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National Institute for Health Research

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Abstract

Clinical effectiveness and cost-effectiveness of interventions for the treatment of anogenital warts: systematic review and economic evaluation

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Background: Typically occurring on the external genitalia, anogenital warts (AGWs) are benign epithelial skin lesions caused by human papillomavirus infection. AGWs are usually painless but can be unsightly and physically uncomfortable, and affected people might experience psychological distress. The evidence base on the clinical effectiveness and cost-effectiveness of treatments for AGWs is limited.

Objectives: To systematically review the evidence on the clinical effectiveness of medical and surgical treatments for AGWs and to develop an economic model to estimate the cost-effectiveness of the treatments.

Data sources: Electronic databases (MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library databases and Web of Science) were searched from inception (or January 2000 for Web of Science) to September 2014. Bibliographies of relevant systematic reviews were hand-searched to identify potentially relevant studies. The World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov were searched for ongoing and planned studies.

Review methods: A systematic review of the clinical effectiveness literature was carried out according to standard methods and a mixed-treatment comparison (MTC) undertaken. The model implemented for each outcome was that with the lowest deviance information criterion. A de novo economic model was developed to assess cost-effectiveness from the perspective of the UK NHS. The model structure was informed through a systematic review of the economic literature and in consultation with clinical experts. Effectiveness data were obtained from the MTC. Costs were obtained from the literature and standard UK sources.

Results: Of 4232 titles and abstracts screened for inclusion in the review of clinical effectiveness, 60 randomised controlled trials (RCTs) evaluating 19 interventions were included. Analysis by MTC indicated that ablative techniques were typically more effective than topical interventions at completely clearing AGWs at the end of treatment. Podophyllotoxin 0.5% solution (Condyline®, Takeda Pharmaceutical Company Ltd; Warticon® solution, Stiefel Laboratories Ltd) was found to be the most effective topical treatment evaluated. Networks for other outcomes included fewer treatments, which restrict conclusions on the comparative effectiveness of interventions. In total, 84 treatment strategies were assessed using the economic model. Podophyllotoxin 0.5% solution first line followed by carbon dioxide (CO_2) laser therapy second line if AGWs did not clear was most likely to be considered a cost-effective use of resources at a willingness to pay of £20,000–30,000 per additional quality-adjusted life-year gained. The result was robust to most sensitivity analyses conducted.

Limitations: Limited reporting in identified studies of baseline characteristics for the enrolled population generates uncertainty around the comparability of the study populations and therefore the generalisability of the results to clinical practice. Subgroup analyses were planned based on type, number and size of AGWs, all of which are factors thought to influence treatment effect. Lack of data on clinical effectiveness based on these characteristics precluded analysis of the differential effects of treatments in the subgroups of interest. Despite identification of 60 studies, most comparisons in the MTC are informed by only one RCT. Additionally, lack of head-to-head RCTs comparing key treatments, together with minimal reporting of results in some studies, precluded comprehensive analysis of all treatments for AGWs.

Conclusions: The results generated by the MTC are in agreement with consensus opinion that ablative techniques are clinically more effective at completely clearing AGWs after treatment. However, the evidence base informing the MTC is limited. A head-to-head RCT that evaluates the comparative effectiveness of interventions used in clinical practice would help to discern the potential advantages and disadvantages of the individual treatments. The results of the economic analysis suggest that podophyllotoxin 0.5% solution is likely to represent a cost-effective first-line treatment option. More expensive effective treatments, such as CO_2 laser therapy or surgery, may represent cost-effective second-line treatment options. No treatment and podophyllin are unlikely to be considered cost-effective treatment options. There is uncertainty around the cost-effectiveness of treatment with imiquimod, trichloroacetic acid and cryotherapy.

Study registration: This study is registered as PROSPERO CRD42013005457.

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Glossary

Cost-effectiveness acceptability curve A graphical representation of the probability of an intervention being considered cost-effective over a range of monetary values for society's willingness to pay for an additional unit of health gain.

Cost-effectiveness analysis A form of economic evaluation comparing the costs and outcomes of two or more courses of action.

Cost-effectiveness plane A diagrammatic presentation of incremental costs and outcomes from the economic evaluation of two interventions, consisting of four quadrants.

Cost–utility analysis A special kind of cost-effectiveness analysis in which outcomes are measured as quality-adjusted life-years.

Electrotherapy Ablative technique in which an electrical current is used to transect or vaporise tissue.

Incremental cost-effectiveness ratio An expression of the additional cost of health gain associated with an intervention relative to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean effects.

Innate immune system First line of defence against invading pathogens. The cells of the innate system recognise and respond to pathogens in a generic way. In contrast to the adaptive immune system, the innate immune system does not confer protection against re-exposure to the same pathogen.

Multiple cost-effectiveness acceptability curve A graphical representation of the probability that a single treatment strategy will have the highest net benefit compared with two or more additional treatment strategies for a given willingness to pay for an additional quality-adjusted life-year gained.

Quality-adjusted life-year A measure of disease burden, capturing both the quality and quantity of life.

Quality of life A concept incorporating all of the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors that might affect his or her physical, mental and social well-being.

List of abbreviations

AE	adverse effect
AGW	anogenital wart
BASHH	British Association for Sexual Health and HIV
BNF	*British National Formulary*
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CO_2	carbon dioxide
CrI	credible interval
DIC	deviance information criterion
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
GP	general practitioner
GUM	genitourinary medicine
HCHS	Hospital and Community Health Services
HIV	human immunodeficiency virus
HPA	Health Protection Agency
HPV	human papillomavirus
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
mCEAC	multiple cost-effectiveness acceptability curve
MeSH	medical subject heading
MTC	mixed-treatment comparison
NHS EED	NHS Economic Evaluation Database
OR	odds ratio
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SE	standard error
SF-6D	Short Form questionnaire-6 Dimensions
SmPC	Summary of Product Characteristics
STI	sexually transmitted infection
TCAA	trichloroacetic acid

Plain English summary

Anogenital warts (AGWs) are small lumps or growths occurring in and around the anus or genital area that can cause local discomfort or bleeding. AGWs are caused by a virus called the human papillomavirus (HPV), which is passed on through close skin-to-skin contact. There are over 100 types of HPV but type 6 and type 11 HPV are the two most common HPVs linked to AGWs. AGWs are one of the most commonly occurring sexually transmitted infections (STIs) in the UK. In 2013, AGWs accounted for 16 out of 100 new STI cases. About 50 out of 100 patients will experience recurrence of AGWs within 1 year of initial clearance of their lesions.

Most people infected with HPV do not develop AGWs. In addition, it can take some time (weeks or months) to develop AGWs after being infected with HPV. Therefore, people can carry the virus without knowing that they are infected and might unknowingly pass on the infection.

Anogenital warts can clear without treatment but the frequency with which the growths clear on their own is not certain. Several treatments are available for AGWs, including creams applied to the skin and more aggressive therapies that break down the growths. AGWs can be difficult to treat and it might take several weeks, or even up to 6 months, of treatment to clear them.

Our review found that, although not the most effective of all of the treatments looked at, podophyllotoxin 0.5% solution (Condyline®, Takeda Pharmaceutical Company Ltd; Warticon® solution, Stiefel Laboratories Ltd) works well at clearing AGWs. It can be applied at home and provides value for money, which makes it a good treatment option. Carbon dioxide laser therapy is a more aggressive therapy that is very effective at clearing AGWs by the end of treatment but it is more expensive and does not offer as much value for money. Other aggressive treatments such as freezing and cutting out the AGWs under a local anaesthetic also work well at clearing AGWs but these are also expensive.

Scientific summary

Background

Typically occurring on the external genitalia, anogenital warts (AGWs) are benign epithelial skin lesions predominantly caused by the human papillomavirus (HPV) subtypes 6 and 11. AGWs are one of the most commonly occurring sexually transmitted infections (STIs) in the UK. In 2011, AGWs accounted for 16 out of 100 new STI cases. Although AGWs are usually painless, they can be unsightly and physically uncomfortable, and affected people might experience psychological distress. Recurrence of AGWs after initial clearance is common, with approximately half of patients experiencing the development of new AGWs within 1 year of clearance of lesions.

Anogenital warts can potentially clear without treatment, most likely in people who are immunocompetent. On this basis, some people may prefer to wait a period of time before starting treatment. However, there is uncertainty around the frequency of spontaneous resolution of lesions, with reports of rates of clearance without treatment ranging between 0% and 50% of people affected. Treatment for AGWs does not treat the viral infection and people can pass on HPV even after treatment or cure of AGWs. As well as increasing the risk of onward transmission, a delay in treatment could result in a worsening of AGWs. First-line treatment is not always successful in achieving complete clearance of AGWs and repeated treatments over a prolonged time period might be required to eradicate large or persistent AGWs.

Multiple medical and surgical treatments are available for the treatment of AGWs, with topical treatments that can be applied by the patient the mainstay of treatment. Of the topical treatments available, imiquimod 5% cream (Aldara®, Meda Pharmaceuticals), podophyllotoxin 0.5% solution (Condyline®, Takeda Pharmaceuticals Company Ltd; Warticon® solution, Stiefel Laboratories Ltd) and podophyllotoxin 0.15% cream (Warticon® cream, Stiefel Laboratories Ltd) are the core treatments for AGWs that are suitable for people to self-apply in their home. There is consensus that ablative techniques such as electrotherapy, cryotherapy and carbon dioxide (CO_2) laser therapy are highly effective in the treatment of AGWs. However, the evidence base on the clinical effectiveness and cost-effectiveness of treatments used in AGWs is limited.

Objectives

To systematically review the evidence on the clinical effectiveness of medical and surgical treatments for AGWs and to develop an economic model to estimate the cost-effectiveness of treatments used in the UK clinical setting.

Methods

Electronic databases (MEDLINE, EMBASE, MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Health Technology Assessment database, Web of Science and NHS Economic Evaluation Database) and trial registries were searched from inception (or January 2000 for Web of Science) to September 2014. Randomised controlled trials (RCTs) and economic evaluations were included based on prespecified inclusion criteria. Two reviewers independently screened all titles and abstracts to identify potentially relevant studies for inclusion in the review. Full-text publications were evaluated independently by two reviewers. Data from included studies were extracted into a standardised

data extraction form by one reviewer and validated by a second. The quality of included studies was assessed independently by two reviewers using standard checklists. The extracted data and quality assessment for each study were presented in structured tables. When sufficient comparable data were available for an outcome measure, mixed-treatment comparisons (MTCs) were performed using a Bayesian Markov chain Monte Carlo simulation. The primary outcomes of the review of clinical effectiveness were complete clearance at the end of treatment and at a subsequent time point and recurrence. Treatment effects were analysed as odds ratios (ORs) for dichotomous data. The weighted average of the baseline treatment was used in combination with the relative treatment effect to calculate probabilities for all treatments included in the analysis of that outcome.

To assess the cost-effectiveness of treatments for AGWs, a de novo economic model was developed. The model structure was informed through a systematic review of the economic literature on treatments for AGWs and in consultation with clinical experts. A simple decision-tree model was developed to capture the key costs and consequences associated with alternative treatments for a single episode of AGWs. The time horizon of the model was 58 weeks, reflecting the maximum possible treatment and follow-up period for up to two lines of therapy for AGWs plus a minimum 12 weeks associated with persistent lesions for those whose AGWs do not clear following two lines of therapy. Because of the short time horizon, costs and consequences were not subject to discounting. Effectiveness data were obtained from the MTC. Costs were obtained from the literature and standard UK sources. Outcomes were expressed using quality-adjusted life-years (QALYs), with health-related quality-of-life data obtained from the literature. Results were captured using probabilistic and deterministic analysis.

Results

A total of 4232 titles and abstracts relating to the clinical effectiveness of interventions were screened for inclusion in the review. Full publications for 155 references were ordered, of which 137 were evaluated [the remainder were either unobtainable ($n = 13$) or published in Chinese ($n = 5$) and translations could not be obtained within the time frame of the project]. Of the 137 full articles evaluated, 70 publications describing 60 studies were relevant to the review. Most full-text publications presented limited details on trial methodology and, as a consequence, most were judged to be at an unclear risk of bias.

Primary and sensitivity MTCs were carried out for complete clearance at the end of treatment and recurrence. Results from the primary MTC for complete clearance at the end of treatment identified CO_2 laser therapy as the treatment with the largest probability of achieving complete clearance [97.1%, 95% credible interval (CrI) 84.8% to 99.9%]. When compared with placebo or no treatment, in both the primary MTC and sensitivity analyses, all treatments evaluated were associated with a statistically significant improvement in complete clearance at the end of treatment. There was no statistically significant difference in complete clearance of AGWs at the end of treatment between most comparisons of active interventions. Of those differences that reached statistical significance, most of the comparisons involved CO_2 laser therapy or podophyllotoxin 0.5% solution.

Carbon dioxide laser therapy was found to be significantly more effective than:

- imiquimod 5% cream (OR 247.0, 95% CrI 3.03 to 1087; OR > 1 favours CO_2 laser therapy)
- trichloroacetic acid (TCAA) (OR 86.15, 95% CrI 4.05 to 415.3; OR > 1 favours CO_2 laser therapy)
- cryotherapy (OR 44.61, 95% CrI 3.30 to 201.7; OR > 1 favours CO_2 laser therapy)
- TCAA plus podophyllin (OR 0.13, 95% CrI 0.003 to 0.59; OR < 1 favours CO_2 laser therapy)
- cryotherapy plus podophyllin (OR 0.22, 95% CrI 0.004 to 0.94; OR < 1 favours CO_2 laser therapy).

Podophyllotoxin 0.5% solution was associated with statistically significant improvements in complete clearance at end of treatment compared with:

- podophyllotoxin 0.5% cream (OR 0.30, 95% CrI 0.04 to 0.99; OR < 1 favours podophyllotoxin 0.5% solution)
- podophyllotoxin 0.3% cream (OR 0.19, 95% CrI 0.007 to 0.874; OR < 1 favours podophyllotoxin 0.5% solution)
- TCAA (OR 0.17, 95% CrI 0.02 to 0.63; OR < 1 favours podophyllotoxin 0.5% solution).

The MTC of recurrence between 3 and 6 months evaluated podophyllin 20–25%, podophyllotoxin 0.5% solution, podophyllotoxin 0.25% solution, TCAA and TCAA plus podophyllin 20–25%. There were no statistically significant differences in recurrence at < 6 months between any comparisons. TCAA was associated with the lowest probability of recurrence (23.4%, 95% CrI 1.5% to 76.6%). By contrast, podophyllotoxin 0.25% solution had the highest probability of recurrence (66.9%, 95% CrI 5.2% to 99.5%). Data for recurrence at ≥ 6 months enabled comparison between podophyllin 20–25%, podophyllotoxin 0.5% solution, imiquimod 5% cream and surgical excision. Only one difference in the MTC was statistically significant. Surgical excision was found to be statistically more effective than podophyllin 20–25% at reducing recurrence at ≥ 6 months (OR 0.14, 95% CrI 0.02 to 0.50). Surgical excision was also associated with the lowest probability of recurrence among the four treatments (15.4%, 95% CrI 4.7% to 33.5%).

Limited reporting of data for other outcomes of interest in available publications led to restricted networks involving few interventions. Additionally, the populations enrolled included a mixture of people who were treatment naive and those who had received previous treatment.

The evidence included in the report was identified through robust systematic review methodology. In addition, the evidence on clinical effectiveness facilitated carrying out a MTC and investigation of the comparative clinical effectiveness of interventions of interest. However, the clinical evidence base identified was weak. Despite identification of 60 studies, most comparisons in the MTC were informed by only one RCT. There is considerable uncertainty around the results generated, as evidenced by the wide CrIs. Because of time constraints it was not possible to assess separately the closed loops within the network, which would have helped to determine whether or not the results generated from 'direct' evidence aligned with the results generated from the 'indirect' evidence on introduction of the wider network.

Additionally, few studies reported full baseline characteristics for the enrolled population. Based on feedback from clinical experts, the project team assumed that the populations enrolled are analogous and are representative of people with AGWs and attending genitourinary medicine clinics. The uncertainty around the comparability of the study populations and, therefore, the generalisability of the results to clinical practice is acknowledged.

A total of 84 treatment strategies were assessed within the economic analysis. The estimated average cost per treatment strategy in probabilistic analysis was found to range between £199 (podophyllotoxin solution followed by CO_2 laser therapy) and £700 (podophyllin 20–25% followed by cryotherapy) per patient. The average QALYs gained per patient per treatment sequence in probabilistic analysis were estimated to range between 1.006 (no treatment followed by podophyllin 20–25%) and 1.040 (CO_2 laser therapy followed by surgical excision) per patient. Results from the deterministic analysis were comparable.

The treatment strategy of podophyllotoxin 0.5% solution followed by CO_2 laser therapy was most likely to be considered a cost-effective use of resources at a willingness to pay of £20,000–30,000 per additional QALY gained, in both probabilistic and deterministic analyses. In probabilistic analysis, at a willingness-to-pay threshold of £20,000 per additional QALY gained, podophyllotoxin 0.5% solution followed by CO_2 laser was found to have a probability of 80.7% of being considered the strategy with the highest net benefit. In deterministic analysis, podophyllotoxin 0.5% solution followed by CO_2 laser therapy was

estimated to be the least expensive treatment strategy, with no other treatment strategy providing a cost-effective alternative to this sequence of treatments at a willingness-to-pay threshold of £20,000–30,000 per additional QALY. This result was robust to the majority of changes in the model parameters.

Conclusions

The evidence base to inform the first-line treatment of AGWs, albeit large, is limited in terms of the number and quality of reporting of studies providing data on the effectiveness of individual interventions. Additionally, the extent of heterogeneity in the baseline characteristics of the populations enrolled is unclear. Analysis by MTC indicated that ablative techniques, and in particular CO_2 laser therapy, are generally associated with higher probabilities of complete clearance at the end of treatment.

As noted earlier, imiquimod 5% cream, podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream are key topical treatments for AGWs. Although these treatments are the mainstay of patient-applied treatments, the evidence to support their use is derived from predominantly small RCTs. Moreover, no study identified assessed the effectiveness of the three treatments in a head-to-head comparison. MTC analysis identified considerable disparity in the probability of achieving complete clearance between podophyllotoxin 0.5% solution and imiquimod 5% cream. Podophyllotoxin 0.5% solution had a 92.6% (95% CrI 81.8% to 98.4%) probability of completely clearing lesions compared with 56.1% (95% CrI 20.3% to 85.0%) for imiquimod 5% cream.

The findings of the de novo economic analysis indicate that the treatment strategy of podophyllotoxin 0.5% solution followed by CO_2 laser therapy is likely to be considered a cost-effective use of resources at a willingness to pay of £20,000–30,000 per additional QALY gained. This finding was robust to the majority of changes in model parameters. Nevertheless, it is noted that there is uncertainty associated with the quality of the clinical data informing the model. Thus, it is considered that the following general conclusions can be drawn from the economic analysis:

- Podophyllotoxin 0.5% solution is an effective and relatively inexpensive treatment. It is therefore likely that prescription of this therapy first line would be considered a cost-effective use of resources.
- Despite their low intervention costs, no treatment and treatment with podophyllin are unlikely to be cost-effective treatment options for AGWs because of the relatively low rates of complete clearance and, in the case of podophyllin, higher estimated rates of recurrence.
- Highly effective treatments such as CO_2 laser therapy or surgical excision may represent a cost-effective treatment option at second line following failure to completely clear with podophyllotoxin 0.5% solution, provided that these treatments are considered clinically appropriate. This is because, despite relatively high initial costs, treatments are likely to be effective and typically require only a single appointment with a clinician.
- There is uncertainty around the cost-effectiveness of imiquimod, TCAA and cryotherapy as second-line treatment. In this economic analysis, these treatments were not found to offer cost-effective alternatives at second line because of the relatively lower rates of complete clearance compared with CO_2 laser therapy and surgical excision. However, it is noted that the clinical systematic review reported uncertainty around treatment effects and rates of recurrence, and thus clinical experience should be taken into account when using these treatments until additional data are available assessing their effectiveness.

A RCT evaluating the interventions predominantly used in clinical practice in a head-to-head comparison would go some way to clarifying the comparative clinical effectiveness of interventions. There is uncertainty around whether effectiveness is different in first episodes or recurrent episodes, and if the type of AGW affects treatment effectiveness. Given this uncertainty, stratification by status of previous treatment and AGW type would help clarify whether or not these factors influence treatment efficacy.

Study registration

This study is registered as PROSPERO CRD42013005457.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Introduction

Anogenital warts (AGWs) are the second most commonly diagnosed sexually transmitted infection (STI) in the UK.[1] In 2013, AGWs made up 16% (approximately 73,000 new cases) of all incident STI cases presenting in genitourinary medicine (GUM) clinics in England.[2] Typically occurring on the external genitalia, AGWs are usually painless but can be unsightly and physically uncomfortable, and affected people may experience psychological distress.[3] Additionally, recurrence of AGWs after initial clearance is common, with approximately half of patients experiencing the development of new AGWs within 1 year after clearance of lesions.[1]

Aetiology and pathology

Anogenital warts are benign epithelial skin lesions and are caused by human papillomavirus (HPV) infection. Over 100 HPV types have been identified, of which about 30 have been found to infect genital epithelium.[4] AGWs are predominantly (approximately 90%) caused by HPV subtypes 6 and 11.[1] Many people who contract HPV do not develop AGWs and it can take some time after infection with HPV before AGWs appear;[5,6] most people will develop AGWs between 3 weeks and 8 months after infection with HPV.[7] Consequently, people might not be aware that they are carrying the virus and could unknowingly pass on the infection. HPV can also be transmitted from a mother to her infant during labour (perinatal transmission), but this is rare.[8] Treatment of AGWs does not eliminate HPV infection, but most people whose lesions clear will become HPV deoxyribonucleic acid (DNA) negative. Cells that remain infected with HPV DNA can stay dormant (latent) for prolonged periods of time and a first episode or a recurrence of symptoms can occur months, or even years, after initial infection. Thus, those who do not become HPV DNA negative can also pass on the virus, even after treatment or clearance of lesions.[5]

Like other papillomaviruses, HPV establishes productive infections in keratinocytes of the skin or mucous membrane.[9] HPV replicates only in the basal cell layer of surface tissues and infected areas are marked by a proliferation of viral DNA and the formation of AGWs. HPV is transferred by close skin-to-skin contact and so areas of skin that are traumatised during sexual intercourse are the sites on which AGWs are most likely to develop.[5,6] AGWs typically appear on the penis, scrotum, urethral meatus and perianal area in men and on the introitus (vaginal opening), vulva, perineum and perianal area in women.[10] AGWs rarely develop on the pubic area, upper thighs and inguinal folds in men and women or on the cervix and vaginal walls in women. Although AGWs most frequently appear on external genital locations, they can also develop in the anal canal[5] and in the oral cavity, larynx, conjunctivae and nasal cavity.[3]

An AGW can occur as a single lesion but cases of AGWs seen in clinical practice frequently consist of from five to 15 lesions of 1–10 mm in diameter.[10] Lesions can be condylomatous, papular, flat or keratotic in appearance.[11] Most AGWs present as soft cauliflower-like growths (condylomatous) of varying size, with flat, plaque-like and pigmented lesions seen less frequently.[12] Condylomatous and papular AGWs are usually soft and located on moist, non-keratinised, non-hair-bearing skin. By contrast, flat and keratotic AGWs are firm and located on dry, keratinised, hairy skin.[13] Soft, non-keratinised AGWs usually respond well to treatment with topical application of, for example, podophyllotoxin, imiquimod 5% cream (Aldara®, Meda Pharmaceuticals) and trichloroacetic acid (TCAA), whereas physical ablative methods are more effective for treating keratinised lesions.[5]

Of those people with HPV who develop AGWs, most will notice painless lumps or growths in the anogenital area.[5,6] Depending on the number, size and location of the AGWs, a few people might

experience local irritation, bleeding, discomfort or pain. Large AGWs can manifest with coincident maceration of the skin (softening of the skin caused by constant exposure to moisture), but this is rare;[7] maceration of the skin increases the risk of secondary infection.[7]

Risk factors for AGWs include a history of unprotected sexual intercourse, a history of STIs, smoking, the use of oral contraceptives and high parity (number of children).[14,15] Susceptibility to the development of AGWs is generally higher among patients who are immunocompromised, such as people who have undergone organ transplantation or those with human immunodeficiency virus (HIV) infection.[14,15] Hormonal factors and male circumcision have also been investigated as risk factors for genital HPV infection, with inconclusive results.[16,17]

Diagnosis

Anogenital warts are typically diagnosed by visual examination and additional investigations are usually unnecessary.[5,6] HPV typing is not routine in the diagnosis of AGWs. European guidelines recommend against HPV typing as no additional information is gained.[6] AGWs with atypical features that are suggestive of precancerous or cancerous lesions should be biopsied.[6,11] When a person presents with perianal AGWs, or with irritation of or discharge from the anus, examination of the anal canal is recommended.[5,6]

Application of acetic acid 5% can turn lesions white.[5,6] Some clinicians use acetic acid 5% to help visualise AGWs and to help diagnose subclinical HPV lesions. However, whitening of lesions is not specific to HPV-associated lesions and use of acetic acid in the diagnosis of AGWs remains controversial.[6]

Prognosis

Anogenital warts can potentially clear without treatment, most likely in people who are immunocompetent.[11] On this basis, some people may prefer to wait a period of time before starting treatment.[10] However, there is uncertainty around the frequency of spontaneous resolution of lesions, with reports of rates of clearance without treatment ranging between 0% and 50% of people affected.[7,13,18,19] As well as increasing the risk of onward transmission, a delay in treatment could result in a worsening of AGWs, with increases in size or number of AGWs or the area affected, particularly in people who have impaired cellular immunity (e.g. as a result of pregnancy or infection with HIV). First-line treatment is not always successful in achieving complete clearance of AGWs and repeated treatments over a prolonged time period might be required to eradicate large or persistent AGWs. The recording of lesions on AGW maps at each visit affords an opportunity to monitor response or lack of response to treatment.[5]

Treatment of AGWs does not necessarily eradicate the underlying HPV infection and the effect of treatment on reducing HPV infectivity is unclear.[20] Recurrence of AGWs after clearance is common. In 2013, GUM clinics diagnosed 73,418 new cases of AGWs and 62,873 cases of recurrent AGWs[2] (an individual could have experienced more than one episode of recurrence). If a person has small, easy-to-treat AGWs, they are still likely to require multiple rounds of treatment. Additionally, it is often unclear whether recurrences are the result of recurrence of infection after a period of remission, a new infection or inadequate treatment during an active episode.[20]

It is estimated that 20% of people with AGWs have a concurrent STI, including chlamydia, HIV infection and syphilis, and screening for other STIs should be discussed.[21–23] Tracing and notification of previous sexual partners is not recommended, but examination of current sexual partners should be considered.[5] There is no evidence to suggest that reinfection from an untreated current partner contributes to recurrence.[20] However, sexual partners may benefit from assessment for infection with HPV and the presence of AGWs and other STIs, and from the opportunity to discuss any concerns about AGWs and the prognosis for their partner.[5,24] From the perspective of the clinician, it would be valuable to convey to

the current partner that they could be infected with HPV and that, if so, although they do not have visible AGWs, they could potentially infect another person.

Consistent condom use might be beneficial in preventing acquisition of HPV in those without HPV infection and is reported to reduce the infection rate by 30–60%.[5] However, the evidence base on the effectiveness of condoms in the prevention of transmission of HPV is of low quality.[11] Current UK guidance recommends that people with AGWs abstain from sex, including anal and oral sex, until their current AGWs have cleared.[5]

Infection with some subtypes of HPV increases the risk of developing anogenital cancers.[25] HPV subtypes 6 and 11, which are the subtypes predominantly associated with AGWs, are classed as low-risk HPVs, that is, lesions resulting from subtypes 6 and 11 are rarely cancerous.[25] HPV subtypes associated with a high risk of cancer include subtypes 16 and 18.[25] Most high-risk HPV infections are transient. Persistent infection with a high-risk HPV subtype is a causal factor for the development of precancerous and cancerous lesions.[25] HPV subtypes 16 and 18 are associated with an increased risk of cervical cancer and are thought to have a causal role in vulval, vaginal and anal cancers;[25] they account for an estimated 70% of all cervical cancers.[26] Co-infection with low- and high-risk HPV subtypes is common.[25]

Epidemiology

Incidence and prevalence

Data from the GUM Activity Dataset [collated by the Health Protection Agency (HPA)] show a steady increase in the reported number of diagnoses of AGWs made in GUM clinics throughout England and Wales since records began in 1971.[27] Cases of first episodes and recurrent and re-registered persistent AGWs rose by 30% between 2000 and 2009 (from 70,414 in 2000 to 91,202 in 2009).[27] A small decline in reported diagnoses of first-episode AGWs has been observed in recent years but a similar reduction in recurrent episodes has not occurred (summarised in *Table 1*).[2] More men than women are diagnosed with AGWs, for both first-episode and recurrent cases (see *Table 1*). Moreover, younger men and women are more likely to present with first-episode AGWs, particularly those aged 20–24 years; trends in diagnoses of first-episode AGWs by age and gender are presented in *Figure 1*.[2] Men who have sex with men are at an increased risk of infection with HPV. In 2013, 8% of diagnoses of first-episode AGWs in men were in men who have sex with men compared with 6% in 2008.[2]

The HPA notes that diagnoses reported by GUM clinics underestimate the total number of cases of AGWs.[27] Current estimates do not account for people with asymptomatic infections who do not attend a GUM clinic, people with symptomatic infections who either self-treat with over-the-counter preparations or receive treatment from their general practitioner (GP), or unrecognised cases of AGWs. Additionally, the HPA identified > 400 other sexual health services offering tests, diagnosis and treatment for STIs, which, as they are not associated with GUM clinics, would not report diagnoses of AGWs to the HPA.[27] Combining data from GUM clinics and other sexual health resources would more closely represent the population affected by AGWs.

TABLE 1 Number of reported diagnoses of first and recurrent episodes of AGWs by gender for 2011–13

	2011			2012			2013		
Episode	Men	Women	Total	Men	Women	Total	Men	Women	Total
First	41,598	34,938	76,547[a]	40,384	33,490	73,879[a]	40,796	32,614	73,418[a]
Recurrent	39,274	22,679	61,968[a]	39,707	21,866	61,576[a]	40,966	21,906	62,873[a]
Total	80,872	57,617	138,245	80,091	55,356	135,455	81,762	54,520	136,291

a Total reported by the HPA.[2]

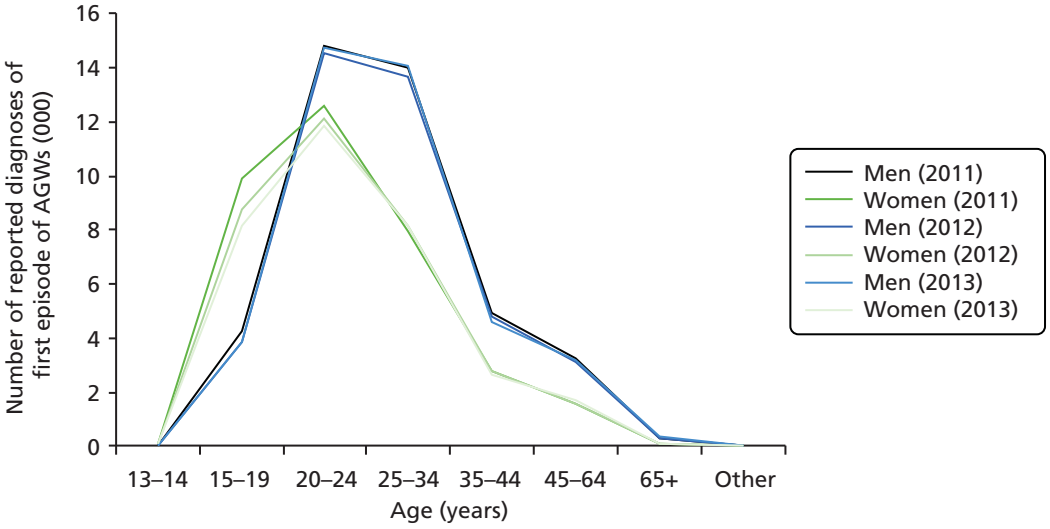

FIGURE 1 Trends in diagnoses of first episode of AGWs by age and gender for 2011–13.[2]

Impact of the health problem

In the long term, HPV subtypes 6 and 11 are not associated with the development of chronic diseases. Although AGWs can cause discomfort, the detrimental impact of a diagnosis of AGWs on psychological health frequently outweighs the effect of AGWs on physical health.[28–31] People with AGWs often feel guilty and ashamed about their diagnosis and frequently experience a considerable degree of stigma at having contracted a STI.[29–34] Feelings of self-loathing, anger and depression are also common.[29–34] Additional psychological stress arises from anxiety about the risk of transmission of infection to others, uncertainty around the success of treatment, the time to clearance of lesions and the risk of recurrence.[31,33,35,36] A small quality-of-life (QoL) study in Denmark evaluating 10 people with AGWs identified that their principal concern was the negative effect of a diagnosis on their relationships and sex lives.[37,38] People with AGWs might be aware of HPV infection as a causal factor for both AGWs and anogenital malignancy but, without an in-depth knowledge of low- compared with high-risk subtypes, are likely to be anxious about the possibility of developing cancer.[37]

Two vaccines against infection with HPVs are available for use in the UK. The bivalent vaccine Cervarix® (GlaxoSmithKline) protects against subtypes 16 and 18 and the quadrivalent vaccine Gardasil® (Sanofi Pasteur) additionally protects against subtypes 6 and 11.[39] Cervarix and Gardasil are licensed for use in female patients from the age of 9 years to protect against cervical cancer and precancerous lesions in the genital area (cervix, vulva or vagina).[40,41] Gardasil is additionally licensed (amendment granted in 2014) to protect against anal cancer, precancerous lesions in the anus and genital warts and can also be used in male patients from the age of 9 years.[41] At this time, the exact duration of the protective effect of Cervarix and Gardasil is unknown. In clinical trials, the vaccines afforded protection for up to 5 years.[42,43] In addition, there is some evidence that both vaccines might offer partial protection against other high-risk HPV subtypes that are not present in the vaccine.[43–45]

In 2008, the Department of Health announced the introduction of a HPV immunisation programme for girls aged 12–13 years starting in September of that year.[46] After an economic evaluation of Cervarix and Gardasil, Cervarix was announced as the vaccine of choice for the first 3 years of the immunisation programme.[46,47] Subsequently, Cervarix was offered to all girls aged 12–13 years with an initial 2-year catch-up campaign for those aged up to 18 years. By 2010, > 84% of girls had received the scheduled three doses of vaccine (given at 0, 1 and 6 months) as part of the routine immunisation programme and

> 47% of girls were vaccinated in the catch-up campaign.[48] Delivery of Cervarix was not expected to reduce the number of cases of AGWs presenting at GUMs. At the end of the initial 3-year immunisation schedule, the vaccine used in the programme was changed from Cervarix to Gardasil. Gardasil is delivered predominantly through secondary schools and was initially given as three injections over 12 months, with the dose reduced to two injections from September 2014.[49] It remains to be seen whether or not boys will be routinely vaccinated with Gardasil.

The effect of HPV vaccination on the incidence of cervical cancer caused by HPV subtypes 16 and 18 is likely to manifest in the long term. By contrast, based on the experience of other programmes, the benefits of vaccination with regard to the incidence of AGWs should be apparent in the near future. Australia introduced a national HPV vaccination programme using Gardasil in 2007, targeted at women aged ≤ 27 years.[50] One year after initiation of the programme the number of women aged ≤ 28 years presenting with AGWs at sexual health clinics declined by 25%. A marked reduction in the number of heterosexual, but not homosexual, men presenting with AGWs was also noted as a result of herd immunity.[50]

The steadily increasing occurrence and high rate of recurrence of AGWs places a significant cost burden on the NHS in terms of disease management. A study based on data collated by the HPA from GUM clinics and primary care estimated the national cost of managing AGWs to be £52.4M in 2010 (£276 per treated AGW episode).[51] By contrast, another study estimated the annual cost of care per AGW episode in England to be £113, with a total cost of £16.8M.[3] With the introduction of a national vaccination programme, a fall in the incidence of AGWs is anticipated, particularly in women. However, no men, and not all women, receive the vaccine routinely. Therefore, a level of risk for contracting HPV infection, and developing AGWs, remains, as does the need for clinically effective and cost-effective treatments for AGWs.

Current service provision

In the UK, AGWs are managed predominantly at GUM clinics. Individuals might seek care directly or be referred to a GUM clinic by their GP. The goal of treatment is to reduce symptoms and visible lesions, not to treat the virus. The evidence base to direct first- and second-line treatment is limited. Although numerous randomised controlled trials (RCTs) are available, few studies compare active interventions against each other and those that do are typically small studies associated with an unclear or high risk of bias (summarised in *Chapter 3*).

Guidelines produced by the British Association for Sexual Health and HIV (BASHH) in 2007 on the management of AGWs[5] recommend that GUM clinics develop their own treatment algorithms that accommodate local practice and the treatments available, a recommendation echoed by European guidelines.[6] Implementation of locally developed and monitored treatment algorithms is reported to improve the management of AGWs.[3] However, development of bespoke treatment pathways has led to variation in clinical practice across the UK in the treatment of AGWs.

An update to the BASHH guidelines became available subsequent to submission of this report.[7] The updated guidelines provide examples of treatment algorithms for the management of AGWs in women and men. The algorithms incorporate a review of treatment effectiveness every 4 weeks,[5] which is also recommended in European guidelines.[6] Guidance from BASHH outlines that algorithms should encompass both initial treatment and the management of cases that do not respond promptly or relapse. The guidance goes on to recommend adoption of a continuous audit cycle to monitor the effectiveness of the algorithm and to ensure alteration of the algorithm if required, for example to incorporate new treatments.

Several treatments are available for the management of AGWs, with choice of treatment determined by morphology, number, localisation and distribution of warts and patient preference.[5,6] BASHH and European guidelines emphasise the importance of providing patients with information about their condition and discussing the treatment options available.[5,6] As noted earlier, not treating AGWs initially is also an option because some people will experience spontaneous clearance over a period of up to 6 months. Active treatments are divided into provider-applied (clinic-based) and patient-applied (home-based) therapy groups. Podophyllotoxin (available as a solution and a cream) and imiquimod 5% cream are the mainstay of the patient-applied therapies, having superseded interferons and 5-fluorouracil, which are no longer recommended for the routine management of AGWs because of their adverse effects (AEs).[5] Other topical treatment options applied by a clinician are TCAA and podophyllin, although the use of podophyllin is no longer recommended.[7] Destructive methods that require administration by a clinician, such as electrosurgery (cautery, hyfrecation), cryotherapy and laser therapy act to debulk the visible lesions. In some settings, topical treatments and ablative therapies might be used in combination. People who are immunocompromised typically have a poorer response to the treatments available. The topical antiviral cream cidofovir (Vistide®, Gilead), which is primarily used to treat cytomegalovirus retinitis, has been investigated as a potential treatment option for those with AGWs who are immunocompromised. As highlighted in BASHH guidance, treatments are associated with high rates of treatment failure and relapse.[5]

When compared with guidance issued in 2007, the updated advice from BASHH provides firmer recommendations on preferred treatments for AGWs, as summarised in *Box 1*.[5,7]

BOX 1 British Association for Sexual Health and HIV guidance on treatment of AGWs[7]

- Soft non-keratinised AGWs respond well to podophyllotoxin and TCAA.
- Keratinised lesions might be better treated with physical ablative methods, such as cryotherapy, excision, TCAA or electrocautery.
- Imiquimod is a suitable treatment for both keratinised and non-keratinised warts.
- People with a small number of low-volume warts, irrespective of type, can be treated with ablative therapy or topical treatment with podophyllotoxin from the outset.
- Podophyllotoxin for 4 weeks or imiquimod for up to 16 weeks is suitable for home treatment by patients. The patient should be given a demonstration on lesion finding and treatment application.
- Very large wart lesions, including Buschke–Löwenstein tumours, should be considered for surgical treatment.
- Injectable local anaesthetic (e.g. 2% lidocaine) should be used before any surgical excision or ablative procedure. Topical anaesthetics [e.g. lidocaine cream (EMLA®, AstraZeneca)] can be used before local anaesthetic injection, or before cryotherapy, particularly when treating larger lesions.
- Caution should be exercised when using any modality of treatment because of the danger of oedema and necrosis of surrounding tissue. This is most pronounced with agents such as TCAA but can also be seen with other treatments, including cryotherapy.
- No treatment may be an option as approximately 30% of patients will experience spontaneous clearance of warts over a period of up to 6 months. However, most patients seek treatment for the discomfort, anxiety, distress or social unacceptability that warts cause.

Description of technologies under assessment

Several topical applications and ablative techniques are available for the treatment of AGWs. Topical treatments for AGWs are available that can be self-applied at home rather than attending a GUM clinic to be treated by a clinician. Patient-applied topical treatments are increasingly prescribed, particularly for mild, early lesions, because of the convenience of use and the increased privacy for the patient. However, only ablative techniques consistently achieve clearance rates approaching 100%.[6] No intervention has emerged as the most clinically effective treatment for AGWs and treatment choice is typically decided after discussion between the treating clinician and the person with AGWs.

Topical interventions

Topical interventions for the treatment of AGWs are available as creams and solutions. Although suitable for the treatment of penile AGWs, solutions are less practical for self-application to genital lesions in women and anal lesions in both men and women. Topical treatments evaluated in this project are those recommended in the BASHH guidelines available at the time of writing of the protocol for the project.[5] Based on clinical expert advice, although not licensed for the treatment of AGWs in the UK, cidofovir was also included because of the potential for use in the treatment of AGWs in people who are immunocompromised and who typically have a poorer response to other treatments. An update to the BASHH guidelines, which are under review at the time of writing, no longer lists podophyllin for the treatment of AGWs.[7] For completeness, and to adhere to the prespecified protocol, podophyllin has been included in the systematic review and analysis of clinical effectiveness.

Patient applied

Imiquimod

Imiquimod is an immunomodulator and acts by modifying the immune response, specifically the response of the innate immune system.[52] Binding of imiquimod to toll-like receptor 7 triggers the cellular release of cytokines. Studies report that treatment with imiquimod leads to increases in levels of the cytokines interferon-alpha, interleukin-1beta, interleukin-6 and tumour necrosis factor-alpha.[52–54] Cytokines act to boost the body's defences by blocking multiplication of invading pathogens, including viruses.

Formulated as a 5% cream (12.5 mg of imiquimod in 250 mg of cream) for application by the patient, imiquimod is licensed by the European Medicines Agency (EMA)[55] and the US Food and Drug Administration (FDA)[56] for the topical treatment of:

- external genital and perianal warts (condylomata acuminata) in adults
- small superficial basal cell carcinomas in adults
- clinically typical, non-hyperkeratotic, non-hypertrophic actinic keratoses on the face or scalp in immunocompetent adult patients when size or number of lesions limits the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate.

In addition, imiquimod 3.75% cream is also licensed by the FDA for the treatment of external AGWs.[57]

According to the Summary of Product Characteristics (SmPC), when treating AGWs, imiquimod 5% cream should be applied topically three times per week on non-consecutive days (e.g. Monday, Wednesday and Friday or Tuesday, Thursday and Saturday) before normal sleeping hours.[58] It is advised that the cream be applied in a thin layer to clean skin involving lesions and, after smoothing completely into the skin, the cream should be left in place for 6–10 hours. After this period, the treated area should be washed with mild soap and water. Application of an excess of cream or prolonged contact with the skin might result in a severe application site reaction.

In studies evaluating the clinical effectiveness of imiquimod, local skin reactions were often the most common AE, with people experiencing erythema (61%), erosion (30%), excoriation/flaking/scaling (23%) and oedema (14%).[58] It is important that people understand that a degree of inflammation is to be expected and represents the local immune response, which is beneficial in clearing the infection. People also reported systemic AEs, including headache, nausea and myalgia.

Imiquimod is contraindicated in people who are hypersensitive to imiquimod or to any of the excipients in the formulation.[58] As imiquimod elicits an effect through stimulating the immune system, caution is advised when using imiquimod in the treatment of people who are receiving immunosuppressive treatments.

The *British National Formulary* (BNF)[39] lists the net price of a pack of 12 sachets of Aldara as £48.60.

Podophyllotoxin

Podophyllotoxin is the most abundant lignan extracted from the resin podophyllin, which is itself isolated from species of the Podophyllum family.[59] Podophyllotoxin inhibits the action of topoisomerase II, an enzyme involved in DNA replication. Blocking topoisomerase II activity prevents cellular division and therefore multiplication of AGW cells. As AGW cells die, they are replaced by non-HPV-infected cells.

Podophyllotoxin has been evaluated in RCTs at various doses in gel, solution and cream formulations.[60–68] No preparation of podophyllotoxin is licensed by the EMA or FDA for the treatment of AGWs, but UK marketing authorisations have been granted for podophyllotoxin 0.5% solution (Condyline®, Takeda Pharmaceuticals Company Ltd; Warticon® solution, Stiefel Laboratories Ltd) and 0.15% cream (Warticon® cream, Stiefel Laboratories Ltd) preparations.

All podophyllotoxin preparations are for the treatment of external AGWs only. The SmPCs for the three podophyllotoxin-based treatments available in the UK indicate that, irrespective of formulation, the preparation should be applied directly to the AGWs twice daily for 3 consecutive days.[69–71] The SmPCs outline that, if required, the treatment schedule can be repeated at weekly intervals for a maximum of 4 weeks in the case of Warticon (cream and solution)[70,71] and 5 weeks in the case of Condyline.[69] Because of the destructive effect of podophyllotoxin on cells, care should be taken to apply the preparation only to the affected area.

Preparations containing podophyllotoxin are contraindicated in people who:

- are hypersensitive to podophyllotoxin or to any of the other ingredients
- have open or bleeding lesions
- are using another podophyllin- or podophyllotoxin-containing preparation.[69–71]

Additionally, Condyline is contraindicated in pregnant or breastfeeding women and children aged < 12 years.[69]

As with imiquimod 5% cream, the most common AEs associated with podophyllotoxin preparations are reactions at the application site, including erythema, pruritus and a skin-burning sensation. Skin erosion is also common with podophyllotoxin-based applications.[69–71]

The BNF[39] lists a net price for Condyline of £14.49 for a 3.5-ml bottle with applicators compared with £14.86 for 3.0 ml (with applicators) of Warticon solution. Podophyllotoxin 0.15% cream is available at a net cost of £17.83 for 5 g, together with a mirror to aid application.

Clinician applied

Cidofovir

Cidofovir is a monophosphate nucleotide analogue.[72] Conversion of cidofovir to the biphosphate form produces a metabolite that is a competitive inhibitor and an alternative substrate for viral DNA polymerases (DNA polymerase is an enzyme that is essential for DNA replication). Incorporation of the biphosphate form of cidofovir into the growing DNA chain in preference to the natural substrate of deoxycytidine triphosphate disrupts further elongation of the chain and thus viral replication.[72] As cidofovir acts directly on viral DNA, it has been proposed that topical cidofovir does not require a competent immune system to be effective and thus could potentially afford greater clinical benefit for people with HIV infection than with other treatments available.[73]

At the time of writing, cidofovir is not licensed for the treatment of AGWs. Cidofovir is licensed by the EMA[74] and FDA[75] for intravenous use in the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome who do not have kidney disease (as cidofovir is associated with nephrotoxicity). As a potent inhibitor of viral DNA polymerase, there is considerable interest in the potential of cidofovir as a treatment for other conditions caused by viruses. Several in vivo and in vitro studies report the effectiveness of cidofovir against a range of DNA virus and retrovirus infections, including papillomavirus, adenovirus and herpes virus.[76] Additionally, small studies and case reports describe the effectiveness of topical and intralesional cidofovir in the treatment of virally induced skin conditions.[76] For the treatment of cutaneous disease, cidofovir has been formulated as a 1% gel and is applied topically to lesions overnight, three times a week for up to 16 weeks.[73]

Podophyllin

Crude podophyllin is obtained as a powder. As noted earlier, the active metabolite in podophyllin is podophyllotoxin. The process to extract podophyllin from species of the Podophyllum family is not standardised and thus the concentration of podophyllotoxin can differ markedly from batch to batch of podophyllin.[59] Additionally, crude podophyllin has not been subject to rigorous investigation and the remaining constituents of the crude product have not been well characterised. Identification of the mutagenic flavenoids quercetin and kaempferol in crude podophyllin led to concern about the potential for exacerbation of oncogenic HPV-associated intraepithelial neoplasia[77,78] (quercetin and kaempferol constitute 3% and 6% of the dry weight of podophyllin powder, respectively[77,79,80]). As a result of the concerns about toxicity and the varying concentration of podophyllotoxin, the use of podophyllin is no longer recommended.[6,7]

For clinical use, crude podophyllin is added to a benzoin tincture to create a resin that is painted onto lesions. Podophyllin resin is not licensed by the EMA or FDA for the treatment of AGWs but has been approved by the Medicines and Healthcare products Regulatory Agency (the UK marketing authority) for the treatment of plantar warts and AGWs.[81] Because of the corrosive nature of the treatment, podophyllin must be applied by a clinician and care must be taken to avoid applying the resin to the surrounding skin; it is recommended that surrounding skin be covered with soft paraffin to protect against treatment. After application, the treated area should be covered with soft paraffin and left for a maximum of 6 hours, after which the podophyllin resin should be washed off.[81] Podophyllin is typically applied once weekly until complete clearance.

Podophyllin should not be used in women who are pregnant or breastfeeding and should not be used to treat facial warts.[81] Severe toxicity associated with absorption of podophyllin has been reported. Consequently, when a person presents with a large number of AGWs, it was recommended that only a few be treated at a time to reduce the risk of systemic toxicity.[81]

Trichloroacetic acid

Trichloroacetic acid is a caustic agent used in various cosmetic treatments including facial peels and tattoo removal as well as for the treatment of AGWs.[82] Typically used at a concentration of 80–90% in the treatment of AGWs, TCAA destroys cellular proteins, which results in cell death. TCAA preparations are not licensed by the EMA or FDA for treatment of AGWs. Despite the lack of a licence, TCAA is recommended for the treatment of AGWs, particularly soft non-keratinised AGWs.[5] Incorrect application of TCAA can damage healthy skin and therefore it is not suitable for home application. If considered an appropriate treatment, TCAA is applied once weekly. Complete clearance of AGWs can occur after a single application, but most people will require multiple courses of treatment. The most common AEs of treatment are pain or burning during administration, with some people experiencing an intense burning sensation for 5–10 minutes after application. Ulceration after application of TCAA can also occur, which makes TCAA unsuitable for the treatment of AGWs of large volume. Despite the listed AEs, TCAA is thought to be the safest of the available topical treatments for use during pregnancy.[1]

Physical ablative techniques

The four main physical ablative techniques used to treat AGWs are:

- carbon dioxide (CO_2) laser therapy
- cryotherapy
- electrotherapy
- surgical excision.

Carbon dioxide laser therapy

Carbon dioxide laser therapy uses a concentrated beam of infrared light energy to heat and ultimately cauterise the affected area. Depending on the number and size of AGWs present, laser surgery can be carried out under either local or general anaesthetic.[5] CO_2 laser therapy is particularly suitable for AGWs of a large volume or those that are located in anatomical sites that are difficult to access for other ablative techniques, such as AGWs deep inside the anal canal or urethra. After laser surgery, people are likely to experience soreness and irritation at the site of the AGWs. Other potential AEs include pain, bleeding and scarring at the site of treatment. Treatment can be repeated if necessary. CO_2 laser surgery is more costly than other ablative techniques and is of limited availability.[5,82]

Cryotherapy

Cryotherapy involves freezing AGWs using liquid nitrogen. Freezing causes permanent dermal and vascular damage, which triggers an immune response leading to the necrosis and clearance of the destroyed cells.[5,82] Cryotherapy is usually most effective for the treatment of multiple small AGWs and particularly those that develop on the shaft of the penis or on, or near, the vulva.[82] Treatment can be applied as a single freeze or a double freeze–thaw technique and is typically carried out once weekly for a maximum of 4 weeks.[5] Cryotherapy should be applied until complete freezing of the lesion is achieved and until a 'halo' of freezing is established a few millimetres around the treated lesion.[5] Achieving complete freezing of the lesion can take as long as 30 seconds, if not longer, and might not be possible if the person cannot tolerate the treatment.

Electrotherapy

Electrotherapy techniques use high-frequency electrical currents to cauterise lesions. There are two types of electrotherapy: electrocautery (also referred to as hyfrecation) and electrical surgery. In electrocautery, a direct or alternating electrical current is passed through a resistant metal wire electrode, which generates heat. Application of the heated electrode to the lesion cauterises the tissue.[83] Direct contact of the electrode with the skin causes electrodessication (coagulation and desiccation without carbonisation) of the lesion, whereas positioning the electrode above the skin with an air gap of 1–3 mm leads to electrofulguration (rapid heating and carbonisation) of the lesion.[83] In contrast to electrocautery, electrosurgery involves passing a high frequency alternating electrical current directly through the living tissue to destroy the lesions. Electrotherapy is particularly effective for treating smaller AGWs located on

the shaft of the penis, the rectum or the vulva or for pedunculated lesions, but is not recommended for the treatment of larger AGWs because of the potential for permanent scarring.[82] Electrotherapy is often combined with excision to treat large AGWs that develop around the anus or vulva and which have failed to respond to topical treatments.[1] Undergoing electrotherapy can be painful and a local or general anaesthetic is usually required.

Surgical excision

Excision of AGWs under local anaesthetic is particularly effective for the removal of condylomatous AGWs and small hardened AGWs that are located in anatomically accessible sites.[5] The use of an anaesthetic cream before injection of local anaesthetic is recommended. Surgical excision can cause scarring and so might not be suitable for large AGWs.[1]

Chapter 2 Definition of the decision problem

Scoping searches were carried out to gain an insight into current recommendations and the evidence base available for the interventions used in UK clinical practice for the treatment of AGWs. At the time of writing, UK guidelines[5] recommend that treatment of AGWs be tailored to the requirements and preferences of the individual patient. From the clinician's perspective, size, location and number of AGWs typically influence treatment recommendations. Interventions for clearing AGWs encompass a diverse range of topical pharmacological agents and ablative techniques and, on occasion, a combination of treatments. There is a marked difference in costs across the various interventions. The initial searches identified multiple studies comparing treatments against each other or placebo but no resource summarising a systematic evaluation of the comparative clinical effectiveness or cost-effectiveness of the various treatments available for clearing AGWs.

The protocol stipulated that studies evaluating any licensed dose or formulation of topical treatments would be eligible for inclusion. Of the topical treatments used for clearing AGWs, only imiquimod has a marketing authorisation for the treatment of AGWs (authorised doses of 5% and 3.75%). To enable comparison of imiquimod with the other prespecified topical interventions, the criterion of licensed dose or formulation was relaxed and studies of any dose or formulation of listed topical treatments were eligible. Studies have evaluated topical treatments in various settings (home vs. clinic) and using different formulations (solutions, creams and gels), doses and application schedules. It is not practical to evaluate all of the diverse treatment options available for clearing AGWs in a single head-to-head RCT. Thus, synthesis of the available clinical data could supplement expert opinion on which treatments are clinically effective. No resource reporting an indirect synthesis of clinical data was identified. To inform the decision problem in terms of clinical effectiveness and cost-effectiveness, and to build on the direct comparative data identified, a key objective of the project, if feasible, was to carry out a mixed-treatment comparison (MTC).

Decision problem

The eligibility criteria pertaining to population, intervention, comparators and outcomes are summarised in *Table 2*.

TABLE 2 Eligibility criteria

PICO criteria	Criteria
Population	Patients aged ≥ 16 years with clinically diagnosed AGWs (irrespective of biopsy confirmation)
Intervention	Topical treatments evaluated: podophyllotoxin, imiquimod, podophyllin, TCAA and cidofovir. Physical ablation methods evaluated: cryotherapy (liquid nitrogen spray or cryoprobe), surgical excision (under local anaesthetic), electrotherapy (electrocautery, hyfrecator surgery) and laser therapy. Combination or sequential therapy (e.g. cryotherapy followed by podophyllotoxin) will also be included
Comparators	The interventions listed above compared with each other (either as monotherapy or combination therapy), placebo or no intervention
Outcomes	Clinical effectiveness (expressed in terms of clearance, recurrence and volume of AGWs), HRQoL and AEs (local and systemic). Specifically: • primary outcomes: AGW clearance at completion of treatment (e.g. up to 16 weeks for imiquimod) and at later time points after completion of treatment (e.g. 3 months, 6 months); recurrence rate (time point reported in RCT) • secondary outcomes: time to complete clearance; volume of wart clearance (e.g. > 50% clearance of original AGWs or > 75% clearance of original AGWs); relief of symptoms during treatment; appearance of new warts during treatment; QoL as reported using a validated QoL rating scale (e.g. EQ-5D, SF-36); AEs; malignancy
Study design	RCTs

EQ-5D, European Quality of Life-5 Dimensions; HRQoL, health-related quality of life; PICO, population, intervention, comparators and outcomes; SF-36, Short Form questionnaire-36 items.

Overall aims and objectives of the assessment

The objectives of this systematic review were to:

- evaluate the clinical effectiveness of medical or surgical treatments for AGWs
- evaluate the cost-effectiveness of medical or surgical treatments for AGWs
- identify key areas for further primary and secondary research.

Adverse effects associated with the various treatments were also assessed and compared.

The review did not cover diagnostic tests or HPV typing as HPV typing is not routine in the diagnosis of AGWs. Omission of HPV typing is unlikely to influence treatment decisions as around 90% of AGWs are caused by HPV types 6 and 11. Health promotion (advice and counselling), prevention of transmission and screening for other STIs were also not addressed by this systematic review.

Interventions not recommended in the BASHH guidelines[5,7] for routine management of AGWs and not typically used in NHS clinical practice were excluded from this review:

- salicylic acid (not used on anogenital skin)
- 5-fluorouracil (rarely used in UK clinical practice because of associated severe ulceration after application)
- interferon (rarely used in UK clinical practice; superseded by imiquimod)
- sinecatechins 10% and 15% ointment (insufficient evidence to support use in treatment of AGWs).

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing effectiveness

Evidence on the clinical effectiveness of interventions to treat AGWs was identified by conducting a systematic review of the published research literature. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination[84] and the Cochrane Collaboration.[85] The protocol for the systematic review is registered on PROSPERO database (registration number CRD42013005457).[86]

Identification of studies

To identify relevant studies, multiple electronic databases were searched:

- Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE
- Ovid EMBASE
- The Cochrane Library [specifically Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects and Health Technology Assessment (HTA) database]
- Web of Science.

Search strategies were designed to include medical subject headings (MeSH) and text terms for AGWs, including 'condyloma acuminata' (the medical term for AGWs). To maximise the number of potentially relevant studies retrieved, no MeSH or text terms were included for interventions of interest. Based on the results of the scoping search and clinical expert advice, it was anticipated that few RCTs meeting the eligibility criteria would be identified, despite the number of studies retrieved. Therefore, searches were simultaneously carried out for prospective observational studies (matched control studies, case series and case–control studies).

Search filters designed to retrieve reports by study design were identified through the InterTASC Information Specialists' Sub-Group search filter resource.[87] Filters developed and validated by the Scottish Intercollegiate Guidelines Network were used to identify RCTs in MEDLINE and EMBASE.[88] Filters devised by *Clinical Evidence* (a collection of systematic overviews covering various conditions) were chosen to retrieve potentially relevant observational studies from MEDLINE and EMBASE.[89] Search terms for AGWs were tailored to the database searched.

Bibliographies of previous overviews, guidelines and retrieved articles were manually reviewed for additional studies. Clinical trial registries (World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov) were also searched to identify planned, ongoing and finalised clinical trials of interest. The website of the US FDA [see www.fda.gov/ (accessed 16 December 2015)] was also searched to identify unpublished data. In addition, clinical experts were contacted with a request for information on any additional studies of which they had knowledge.

No language restriction was applied to the searches. With the exception of Web of Science, electronic databases were searched from inception, with the initial search carried out on 30 August 2013. Search parameters for Web of Science were limited to a search period of 2000 to 1 September 2014, with study type restricted to article, meeting abstract, proceedings paper and corrections. Search results were uploaded into Reference Manager version 11.0 (Thomson ResearchSoft, San Francisco, CA, USA) and deduplicated. Update searches were carried out on 22 April and 1 September 2014. Full details of the search strategies are presented in *Appendix 1*.

Two researchers (SB and one of ET or CK) independently screened the titles and abstracts returned by the search strategy according to prespecified eligibility criteria (see *Table 2*). In cases in which consensus could not be achieved, the full texts of potentially relevant studies were ordered. During abstract appraisal, to facilitate discussion of whether or not sufficient evidence had been identified to restrict inclusion of study type to RCTs, potentially relevant studies were categorised as RCT, observational study or systematic review. Two reviewers (SB and CK) independently assessed full publications for inclusion, with studies classified as RCTs evaluated first. Discrepancies were resolved by discussion, with involvement of a third reviewer (SEd) if consensus could not be reached. After appraisal of full-text publications, the number of RCTs identified as eligible for inclusion in the review of clinical effectiveness and AEs led to the decision to limit reporting to RCTs.

Inclusion and exclusion criteria

Eligibility criteria for the review of clinical effectiveness were as specified in the decision problem (summarised in *Table 2*). The review included only RCTs, with systematic reviews and non-randomised studies excluded. The interventions of interest were topical treatments and ablative techniques, either alone or in combination. RCTs were included if the treatments were evaluated in a population with AGWs and compared with each other, placebo or no treatment. Studies were excluded if none of the outcomes of interest was reported.

Data abstraction

Because of the large number of RCTs identified, in the first instance two reviewers (SB and Victoria Wakefield) independently extracted data from only 10 studies onto a standardised data extraction form; a function of the initial 10 extractions was to pilot the suitability of the data extraction form. Subsequently, one reviewer (various) extracted data from the remaining studies onto a modified data extraction form, with validation of the data by a second reviewer (SB). Information extracted included details on study design and methodology, the baseline characteristics of the population and data on outcomes of interest, both clinical effectiveness outcomes and AEs. Discrepancies were resolved by discussion, with involvement of a third reviewer (SEd) when necessary. During data extraction, if the reviewer(s) identified areas with limited reporting (e.g. aspects of trial conduct) or discrepancies in reporting within the publication (e.g. in event rate), authors were contacted with a request for clarification. If a study was reported as a conference proceeding or an abstract only, study authors were contacted with a request for further details. Studies reporting data on an outcome of interest but for which insufficient methodological details were available to allow full critical appraisal of study quality, even after contact with authors, were included in sensitivity analyses (additional detail provided in *Results*). Data extraction forms for the included studies are provided in *Appendix 2*.

Critical appraisal strategy

Two reviewers independently assessed the quality of the clinical effectiveness studies. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Study quality was assessed according to recommendations of the Centre for Reviews and Dissemination[84] and the *Cochrane Handbook for Systematic Reviews of Interventions*.[85] Study quality was recorded using the Cochrane risk of bias tool[85,90] and was incorporated into the data extraction form (see *Appendix 2*).

Outcome-specific risk of bias was determined for the outcomes for which data were extracted.[90] The three bias assessment categories used were low, unclear and high. A study was deemed to be at low risk of bias when all key domains were associated with low risk of bias, at an unclear risk of bias when one or more key domains had an unclear risk of bias and at a high risk of bias when one or more key domains was thought to be at a high risk of bias.

Methods of data synthesis

Details of the clinical effectiveness results and quality assessment for each included study are presented in structured tables (see *Appendix 2*) and an overall assessment of study quality is provided as a narrative summary (see *Quality assessment*). The possible effects of study quality on the clinical effectiveness data and review findings are discussed where relevant.

Standard pair-wise meta-analysis was performed, where possible, to evaluate clinical effectiveness and was based on intention-to-treat analysis. Intention-to-treat analysis was defined as people being analysed in the treatment group to which they were allocated at randomisation, irrespective of whether they changed treatment, withdrew or were lost to follow-up. Dichotomous outcome data were meta-analysed using Mantel–Haenszel odds ratios (ORs) with 95% confidence intervals (CIs) and a fixed-effects model; meta-analysis with a random-effects model was carried out as a sensitivity analysis. To facilitate comparison and interpretation of estimates of effect across studies, when data from a single trial were available for a comparison of interest, and if appropriate, the trial data were analysed and presented as for meta-analysed data. Missing data were imputed and were analysed as a treatment failure for all outcomes (i.e. for complete clearance, people lost to follow-up were considered not to have achieved clearance and, for recurrence, people lost to follow-up were considered to have recurred).

Meta-analysis was carried out using Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Inconsistency among studies included in the meta-analysis was assessed using the I^2 test and the level for statistically significant heterogeneity was set at $p < 0.10$. Levels of inconsistency were defined as follows: low level, I^2 of 0–25%; moderate level, I^2 of 26–50%; and high level, I^2 of > 50%. In the presence of statistically significant heterogeneity ($p < 0.10$), possible sources were investigated, including differences in study populations, methods or interventions. The low number of studies included in each meta-analysis precluded the evaluation of publication bias and/or small study effects.

Additionally, the comparative clinical effectiveness of interventions was investigated using MTCs. The methods used for MTC followed the guidance described in the National Institute for Health and Care Excellence Decision Support Unit's Technical Support Documents for Evidence Synthesis.[91,92] MTCs were conducted using a Bayesian Markov chain Monte Carlo simulation in WinBUGS (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK). The following were implemented for each analysis:

- uniform priors (also called 'uninformed' or 'flat' priors) were used
- all outcomes were considered independent
- to ensure convergence on the posterior distribution:
    - results for all clinical effectiveness outcomes analysed were based on 50,000 iterations after a 'burn in' of 150,000 iterations
    - results for all safety outcomes analysed had a 'burn in' of 30,000 iterations, with results based on 100,000 iterations
- the OR was used as the summary effect estimate for all outcomes
- a weighted average of the baseline treatment was used in combination with the relative treatment effect to calculate probabilities for all treatments included in the analysis of that outcome
- any results taken forward into the economic model used the posterior sampling to retain the correlation between parameter estimates caused by their joint estimation from a single data set.

When a random-effects model was deemed the best fit, the extent of the between-study heterogeneity was investigated by evaluating the posterior mean of tau-squared.

The potential limitations of the MTC, together with the associated influence on the generated estimates of effect, are discussed in the strengths and limitations of the report (see *Chapter 5*).

Sensitivity analyses were carried out for the outcomes of complete clearance (at the end of treatment and at later time points) and recurrence of AGWs in both standard meta-analysis and the MTC. Sensitivity analyses included studies or individual outcomes deemed to be at an overall high risk of bias, together with studies in people with comorbid HIV infection and a cluster of differentiation 4+ cell count of < 200 cells/mm^3.

As a consequence of the limited reporting of baseline characteristics in the included studies (discussed in greater detail in *Quantity and quality of research available*), planned subgroup analyses were not carried out. Planned analyses included:

- soft, moist, non-keratinised AGWs
- dry, keratinised AGWs
- number of AGWs [to be grouped as single, few (two–five) or multiple (six or more)]
- site of AGWs
- no previous treatment for AGWs ('first attack' patients)
- recurrent AGWs (return of AGW after a complete response to treatment)
- persistent AGWs (treatment is continued for > 6 months)
- immune status (immunosuppressed vs. not immunosuppressed).

Results

Quantity and quality of research available

Searches of electronic databases retrieved 4231 records (post deduplication) that were of possible relevance to the review (*Figure 2*). Manual searching identified one additional reference, giving a total of 4232 records screened for inclusion in the review. Full publications for 155 references were ordered. Of these, 13 publications were unobtainable.[93–105] Five studies published in Chinese were identified for which translations could not be obtained within the time frame of the project.[106–110] An evaluation of RCTs published in Chinese journals found that most studies described as randomised were not truly random.[111] Based on this report and translations obtained for this project for other retrieved studies published in Chinese, the authors of the project consider that most of the studies in Chinese are unlikely to be random

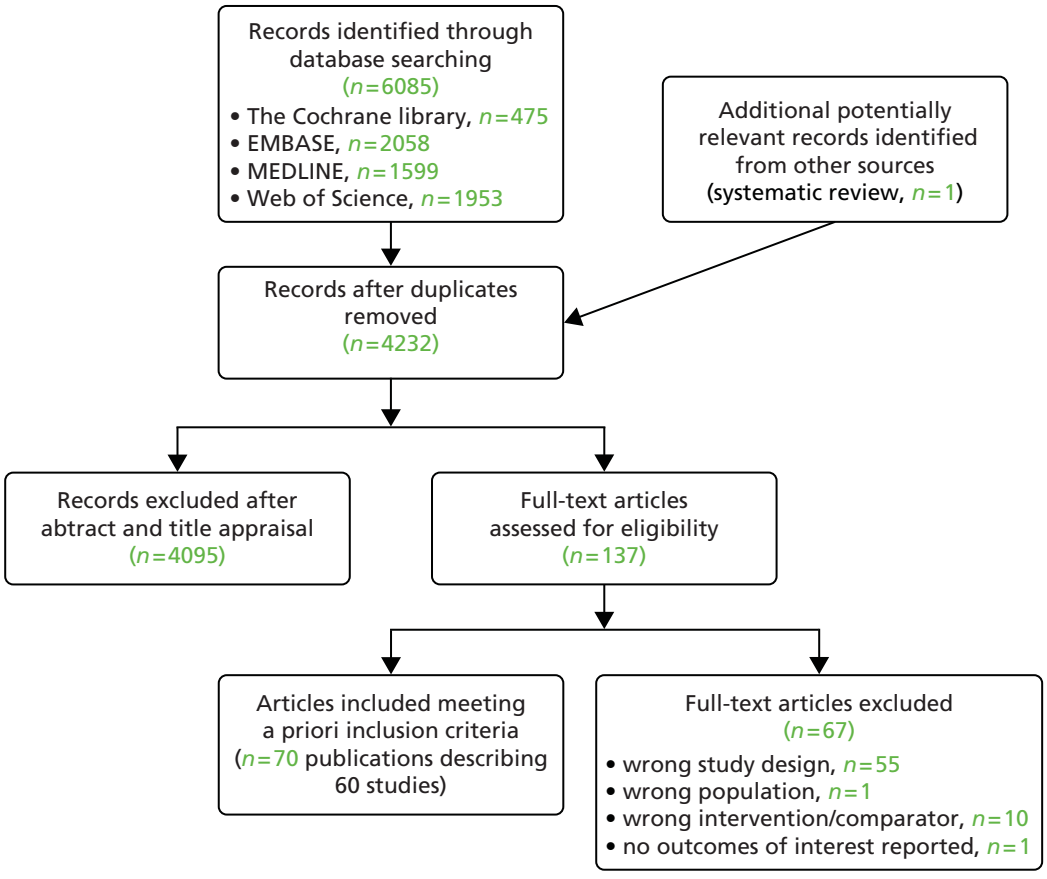

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

and omission of these studies is unlikely to have influenced the assessment of clinical effectiveness. Of the 137 full articles evaluated, 70 publications describing 60 studies (full publications[60–68,112–162]) were relevant to the review. Citation details for conference abstracts related to full publications are provided only when additional information was available in the abstract. A list of publications screened but subsequently excluded (with reasons for exclusion) from the review is available in *Appendix 3*.

Summaries of the studies included in the review are presented by treatments evaluated (*Table 3*) and by key characteristics of studies (*Table 4*).

TABLE 3 Interventions evaluated within the studies included in the review

Intervention	Identified studies evaluating intervention
Placebo	Arican 2004;[112] Baker 2010;[113] Benedetti Panici 1989;[114] Beutner 1989;[115] Beutner 1998;[116] Beutner 1998;[117] Edwards 1998;[118] Gilson 1999;[119] Greenberg 1991;[62] Kirby 1990;[61] Matteelli 2001;[120] Snoeck 2001;[121] Syed 1994;[122] Syed 1995;[123] Syed 1995;[124] Tyring 1998;[125] Tyring 1998;[68] von Krogh 1992;[126] von Krogh 1994[127]
Topical interventions	
Cidofovir	Matteelli 2001;[120] Orlando 2002;[128] Snoeck 2001[121]
Imiquimod	Arican 2004;[112] Baker 2010;[113] Beutner 1998;[116] Beutner 1998;[117] Edwards 1998;[118] Fife 2001;[129] Garland 2006;[130] Gilson 1999;[119] Komericki 2011;[131] Padhiar 2006;[132] Stefanaki 2008;[133] Trofatter 2002;[134] Tuncel 2005;[135] Tyring 1998[125]
Podophyllotoxin	Beutner 1989;[115] Claesson 1996;[65] Edwards 1988;[136] Greenberg 1991;[62] Handley 1992;[67] Hellberg 1995;[137] Kar 2003;[138] Kinghorn 1993;[63] Kirby 1990;[61] Komericki 2011;[131] Lacey 2003;[64] Landthaler 1987;[139] Lassus 1984;[140] Mazurkiewicz 1990;[60] Petersen 1995;[141] Strand 1995;[142] Syed 1993;[143] Syed 1994;[122] Syed 1995;[123] Syed 1995;[124] Tyring 1998;[68] von Krogh 1992;[126] von Krogh 1994;[127] White 1997[144]
Podophyllin	Edwards 1988;[136] Gabriel 1983;[145] Goh 1998;[66] Handley 1992;[67] Hellberg 1995;[137] Jensen 1985;[146] Kar 2003;[138] Kinghorn 1993;[63] Lacey 2003;[64] Landthaler 1987;[139] Lassus 1984;[140] Maiti 1985;[147] Mazurkiewicz 1990;[60] Nath 1990;[148] Padhiar 2006;[132] Sherrard 2007;[149] Simmons 1981;[150] Stone 1990;[151] Tabari 2010;[152] White 1997[144]
TCAA	Abdullah 1993;[153] Godley 1987;[154] Nath 1990;[148] Sherrard 2007;[149] Tabari 2010[152]
Ablative therapies	
Argon plasma coagulation	Viazis 2007[155]
CO_2 laser therapy	Azizjalali 2012;[156] Bar-Am 1993;[157] Ferenczy 1995[158]
Cryotherapy	Abdullah 1993;[153] Azizjalali 2012;[156] Gilson 2009;[159] Godley 1987;[154] Sherrard 2007;[149] Simmons 1981;[160] Stefanaki 2008;[133] Stone 1990[151]
Electrosurgery	Benedetti Panici 1989;[114] Ferenczy 1995;[158] Orlando 2002;[128] Simmons 1981;[160] Stone 1990[151]
Surgical excision	Jensen 1985[146]
Combination treatments	
Argon plasma coagulation plus imiquimod 5% cream	Viazis 2007[155]
Cryotherapy plus imiquimod	Tuncel 2005[135]
Cryotherapy plus podophyllin	Sherrard 2007[149]
Cryotherapy plus podophyllotoxin	Gilson 2009[159]
Electrocauterisation plus cidofovir	Orlando 2002[128]
TCAA plus podophyllin	Gabriel 1983;[145] Sherrard 2007[149]

TABLE 4 Summary of studies included in the systematic review of clinical effectiveness

Study	Sample size (*n*)	Population	Intervention	Comparator	Duration of treatment and follow-up
Abdullah 1993[153]	86	People with definite AGWs for the first time on clinical grounds	TCAA 95%	Cryotherapy	Maximum of six treatments with treatment given on a weekly basis. People with complete clearance of AGWs were followed up for 3 months after the end of treatment
Arican 2004[112]	45	Aged ≥ 18 years, not received any therapies within the 3 months before enrolment and minimum of five AGWs at baseline	Imiquimod 5% cream	Placebo	Treatment period of 12 weeks followed by a treatment-free observation period of 6 months
Azizjalali 2012[156]	160	Lesions with a diameter of ≥ 10 mm and located on the pubis, penis, scrotum, vulva or inguinal area	CO_2 laser therapy	Cryotherapy	3 months
Baker 2010[113]	981 (two trials)	Aged ≥ 12 years and from two to 30 external AGWs with a total AGW area of ≥ 10 mm^2	(1) Imiquimod 3.75% cream, (2) imiquimod 2.5% cream	Placebo	Initial treatment of up to 8 weeks with assessment for complete clearance continued for up to 8 weeks after treatment. Those achieving complete clearance were followed for 12 weeks
Bar-Am 1993[157]	148	Women with benign vulvar and perineal HPV lesions. Men with disseminated foci of penile shaft condylomatous lesions	High-power CO_2 laser	Low-power CO_2 laser	Duration of treatment and follow-up unclear
Benedetti Panici 1989[114]	99	Multiple condyloma lesions (two or more sites affected), aged 18–45 years, no previous therapy, informed written consent	Diathermocoagulation	No treatment	If required, diathermocoagulation was repeated at 3-week intervals. End of study was 6 months after completion of treatment. People with complete clearance of AGWs were also followed up at 12 months
Beutner 1989[115]	109	Men aged ≥ 18 years with a clinical diagnosis of AGWs and with between two and 20 AGWs in an area not exceeding 10 cm^2	Podophyllotoxin 0.5% solution	Placebo	Treatment given for a minimum of 2 and a maximum of 4 weeks. People were also evaluated at 6, 12 and 16 weeks during a follow-up period (i.e. weeks 2, 8 and 12 after treatment)

Study	Sample size (*n*)	Population	Intervention	Comparator	Duration of treatment and follow-up
Beutner 1998[116]	279	Aged ≥ 18 years, seronegative for HIV infection, at least two but no more than 50 AGWs (defined as AGWs in the genital, anal, perineal or perianal area), a biopsy diagnostic or suggestive of condyloma acuminatum and a bidimensional AGW area of at least 10 mm^2	(1) Imiquimod 5% cream, (2) imiquimod 1% cream	Placebo	Treatment given for a maximum of 16 weeks. After treatment, people were followed up for 12 weeks during which time no treatment was given
Beutner 1998[117]	108	Aged ≥ 18 years and seronegative for HIV infection	Imiquimod 5% cream	Placebo	Treatment given over 8 weeks. People achieving complete clearance of AGWs entered into a treatment-free follow-up period of 10 weeks or until recurrence occurred. People with partial response at the end of 8 weeks' treatment were evaluated again at week 2 of follow-up to determine whether or not complete clearance had been achieved
Claesson 1996[65]	180	Men with condylomata acuminata located on the penis shaft and/or within the preputial cavity region. Women with vulval and/or perianal condylomata acuminata	(1) Podophyllotoxin 0.15% cream, (2) podophyllotoxin 0.3% cream	Podophyllotoxin 0.5% solution	Initial treatment period of up to 4 weeks. Those with complete clearance of AGWs were followed up at 16 weeks
Edwards 1988[136]	65	Men with diagnoses, based on clinical appearance, of external penile AGWs	Podophyllotoxin 0.5% solution	Podophyllin 20% (clinician applied)	Initial 6-week treatment period with a subsequent 3-month follow-up period
Edwards 1998[118]	311	Healthy men and women aged ≥ 18 years with a diagnosis of AGW, with a minimum of two but no more than 50 external AGWs and a total wart area of at least 10 mm^2. People were enrolled only when deemed healthy based on medical history, physical examination and laboratory testing	(1) Imiquimod 5% cream, (2) imiquimod 1% cream	Placebo	Treatment period of 16 weeks followed by a treatment-free follow-up period of 12 weeks for those achieving complete clearance during treatment
Ferenczy 1995[158]	282	Presence of vaginal and external anogenital condylomata (diagnosis verified by histology) and a total linear area of AGWs of ≥ 2 cm^2	Electrosurgery	CO_2 laser	Treatment and then follow-up of at least 6 months (maximum 18 months, mean 8 months) after the last treatment received

continued

TABLE 4 Summary of studies included in the systematic review of clinical effectiveness (*continued*)

Study	Sample size (*n*)	Population	Intervention	Comparator	Duration of treatment and follow-up
Fife 2001[129]	110	Men aged ≥ 18 years with from two to 50 AGWs confirmed by biopsy, and a total AGW area of 30–2000 mm^2 after biopsy	(1) Imiquimod 5% cream, once daily, (2) imiquimod 5% cream, twice daily, (3) imiquimod 5% cream, three times daily	Imiquimod 5% cream three times per week	Treatment given over 16 weeks followed by a 4-week observation period for people whose lesions had not cleared by week 16
Gabriel 1983[145]	73	Men with AGWs	TCAA 50% plus podophyllin 25%	Podophyllin 25%	Treatment given over 6 weeks followed by a minimum follow-up of 3 months from beginning of treatment
Garland 2006[130]	120	Women aged ≥ 16 years with from one to 50 visible external genital and/or perianal AGWs with an area of 10–2000 mm^2	(1) Imiquimod 5% cream for 4 weeks, (2) imiquimod 5% cream for 8 weeks, (3) imiquimod 5% cream for 12 weeks	Imiquimod 5% cream for 16 weeks	Initial treatment period of 4–16 weeks, dependent on treatment allocation. All women were followed up until the end of the study at 16 weeks
Gilson 1999[119]	100	Aged ≥ 18 years with a clinical diagnosis of external AGWs and with a minimum of two AGWs with an area totalling at least 10 mm^2. Laboratory-confirmed diagnosis for HIV infection (patients with AIDS were eligible if they had been clinically stable for 4 weeks before enrolment) and a CD4 T-lymphocyte count of ≥ 100×10^6 cells/l	Imiquimod 5% cream	Placebo	Treatment duration of 16 weeks. People experiencing > 80% but < 100% clearance of baseline AGWs continued on blinded treatment for an additional 8 weeks
Gilson 2009[159]	149	Aged 18–70 years with at least two (maximum 30) external AGWs of a combined area of at least 10 mm^2. AGWs were either previously untreated or had not been treated for at least 4 months	Cryotherapy plus podophyllotoxin 0.15% cream	Cryotherapy plus placebo	Initial 12-week treatment period. After 12 weeks treatment was given at the discretion of the clinician. People were followed up until 24 weeks after commencement of treatment
Godley 1987[154]	130	Heterosexual men with penile AGWs	TCAA	Cryotherapy	Weekly treatment until disappearance of AGWs, for up to a maximum of 10 treatments. If complete AGW clearance was achieved, men were followed up for 2 months after the end of treatment
Goh 1998[66]	45	Men aged ≥ 16 years with penile AGWs	(1) Podophyllin 0.5% in ethanol (patient applied), (2) podophyllin 0.25% in ethanol (patient applied)	Podophyllin 25% (clinician applied)	Treatment groups were reviewed weekly for up to 6 weeks

Study	Sample size (*n*)	Population	Intervention	Comparator	Duration of treatment and follow-up
Greenberg 1991[62]	72	Women with clinical diagnosis of exophytic vulvar condylomata and ≤ 25 lesions to be treated. AGWs had a total area of < 10 cm^2 and occupied < 30% of the vulva	Podophyllotoxin 0.5% (solution and cream formulations)	Placebo	Treatment given for a maximum of 4 weeks, with patients followed up until week 10 after the start of treatment
Handley 1992[67]	57	Men with primary AGWs	Podophyllotoxin 0.5% solution	Podophyllin 0.5% solution (patient applied)	Initial treatment period of up to 5 weeks, with follow-up review at 3 months (unclear if this was final follow-up)
Hellberg 1995[137]	60	Women with overt AGWs	Podophyllotoxin 0.5% cream	Podophyllin 20% (clinician applied)	Maximum duration of treatment of 4 weeks. Women with complete clearance were followed up at 3 months (unclear whether 3 months after the end of treatment or 3 months from initiation of trial)
Jensen 1985[146]	60	First episode of AGWs and presence of perianal AGWs (the perianal region was defined as a circle of diameter 6 cm centring on the anus)	Podophyllin 25% (clinician applied)	Surgical excision	Initial assessment occurred 1 week after the final treatment. For podophyllin, treatment was repeated weekly for up to 6 weeks. People were followed up at 3, 6, 9 and 12 months
Kar 2003[138]	72	Presence of AGWs as determined by visual inspection (without biopsy confirmation)	Podophyllotoxin 0.5% solution	Podophyllin 20% (clinician applied)	Initial treatment period of 6 weeks with a subsequent follow-up period of 6 months (unclear whether this is 6 months after the end of treatment or 6 months from start of treatment)
Kinghorn 1993[63]	200	External AGWs (condylomata acuminata) and aged ≥ 16 years	Podophyllotoxin 0.5% cream	Podophyllin 25% (clinician applied)	Treatment period of a maximum of 5 weeks followed by a final assessment at week 13 from the start of the study
Kirby 1990[61]	38	Men aged ≥ 18 years with from two to 20 external AGWs, excluding anal AGWs. Total AGW surface area of < 10 cm^2	Podophyllotoxin 0.5% solution	Placebo	Initial treatment period of 4 weeks with subsequent follow-up at 12 and 16 weeks for those categorised as cured at week 6
Komericki 2011[131]	51	Presence of untreated AGWs	Imiquimod 5% cream	Podophyllotoxin 0.5% solution	People evaluated at end of treatment: 4 weeks with podophyllotoxin 0.5% solution vs. 16 weeks with imiquimod 5% cream
Lacey 2003[64]	354	Aged 18–65 years and current episode of AGWs lasting ≤ 3 months and with no therapy in that time	(1) Podophyllotoxin 0.5% solution, (2) podophyllotoxin 0.15% cream	Podophyllin 25% (clinician applied)	Initial treatment period of a maximum of 4 weeks with follow-up at 12 weeks after trial entry for those with complete clearance at any time point during treatment

continued

TABLE 4 Summary of studies included in the systematic review of clinical effectiveness (*continued*)

Study	Sample size (*n*)	Population	Intervention	Comparator	Duration of treatment and follow-up
Landthaler 1987[139]	39	Unclear	Podophyllotoxin 0.5% (solution for men and cream for women)	Podophyllin 25% (clinician applied)	AGWs were treated until clearance and patients were followed up at 4 weeks (or longer) after clearance. Patients received treatment for a minimum of 2 weeks. It is noted that treatment was stopped early in those not responding to treatment; the criteria used to determine non-response to treatment are unclear
Lassus 1984[140]	100	Men with condylomata acuminata in the preputial cavity	Podophyllotoxin 0.5% solution	Podophyllin 20% solution	Initial treatment period of a maximum of 4 weeks with follow-up at 6 months after the start of treatment for those with complete clearance at the end of treatment
Maiti 1985[147]	100	Male with penile AGWs who had not received treatment for their AGWs in the 6 months before enrolment	(1) Podophyllin 0.5% solution (patient applied), (2) podophyllin 1.0% solution (patient applied)	Podophyllin 2.0% solution (patient applied)	Initial treatment period of 1 week with follow-up at 3 weeks and 3 months for those with complete clearance at end of treatment
Matteelli 2001[120]	12	Aged ≥ 18 years with a clinical diagnosis of external AGWs established by physical examination and a laboratory-confirmed diagnosis of HIV infection	Cidofovir 1% cream	Placebo	Initial treatment period of 2 weeks treatment followed by 2 weeks of observation
Mazurkiewicz 1990[60]	54	Presence of AGWs	(1) Podophyllotoxin 0.5% solution, (2) podophyllotoxin 0.5% cream	Podophyllin 20% (clinician applied)	Initial treatment period of up to 6 weeks with an observation period of 4 weeks after the end of treatment for those whose AGWs had completely cleared after treatment
Nath 1990[148]	100	Presence of AGWs	Podophyllin 25% (clinician applied)	TCAA 50% (clinician applied)	Initial treatment period of 12 weeks with follow-up for 3 months for those categorised as 'cured'
Orlando 2002[128]	74	Presence of AGWs and seropositive for HIV infection	Electrocauterisation plus cidofovir 1%	(1) Electrocauterisation, (2) cidofovir 1% (patient applied)	Initial assessment at the end of treatment (varies with allocated treatment) followed by 6 months' follow-up for those who achieved complete clearance with treatment

Study	Sample size (*n*)	Population	Intervention	Comparator	Duration of treatment and follow-up
Padhiar 2006[132]	60	Aged 12–65 years with at least two but no more than 50 clinically diagnosed external AGWs. Seronegative for HIV infection	Imiquimod 5% cream	Podophyllin 20% (clinician applied)	Initial treatment period (16 weeks with imiquimod 5% vs. 6 weeks with podophyllin 20%) followed by a 6-month follow-up period for those with clearance of AGWs
Petersen 1995[141]	269	Diagnosis of condyloma acuminatum. No topical, systemic antiviral or AGW treatment in the 4 weeks preceding the study	Podophyllotoxin 0.5% solution	Podophyllotoxin 0.5% cream	Initial treatment duration of 2–4 weeks with final follow-up at 12 weeks
Sherrard 2007[149]	409	People with new or recurrent genital AGWs that had not been treated in the preceding 3 months	(1) TCAA plus podophyllin 25%, (2) cryotherapy plus podophyllin 25%	(1) Podophyllin 25% (clinician applied), (2) TCAA, (3) cryotherapy	8 weeks (maximum treatment period); no follow-up period
Simmons 1981[160]	42	Men with AGWs	Electrocautery	Cryotherapy	Up to two treatments at a 2-week interval plus a minimum follow-up for 3 months from start of the trial
Simmons 1981[150]	140	Men with AGWs who had not received treatment in the preceding 3 months	Podophyllin 10% (clinician applied)	Podophyllin 25% (clinician applied)	Initial treatment period of 6 weeks with subsequent follow-up to 3 months after the start of treatment
Snoeck 2001[121]	30	Biopsy-proven genital AGWs, perianal AGWs or both	Cidofovir 1% gel	Placebo	Up to 12 weeks' treatment with subsequent follow-up for 4 weeks after completion of treatment or removal from the study. Those with a complete response were followed up for 6 months (unclear whether or not this is additional to the 4-week observation period)
Stefanaki 2008[133]	120	Immunocompetent men with diagnosis of external genital or perianal AGWs and no previous treatment for AGWs	Imiquimod 5% cream	Cryotherapy	Initial treatment period of 3 months with subsequent follow-up at 6 and 12 months
Stone 1990[151]	450	People with external AGWs that had not been treated in the month preceding trial entry	Podophyllin 25% (clinician applied)	(1) Cryotherapy, (2) electrofulguration	Initial treatment period of up to 6 weeks with follow-up after 3 months for those achieving complete clearance
Strand 1995[142]	90	Men with genital AGWs (acuminata or papular)	(1) Podophyllotoxin 0.15% cream, (2) podophyllotoxin 0.3% cream	Podophyllotoxin 0.5% solution	Initial treatment period of up to 4 weeks with subsequent follow-up at 16 weeks after entry into the study

continued

TABLE 4 Summary of studies included in the systematic review of clinical effectiveness (*continued*)

Study	Sample size (*n*)	Population	Intervention	Comparator	Duration of treatment and follow-up
Syed 1993[143]	60	Men aged 15–40 years with a clinical diagnosis of AGWs	(1) Podophyllotoxin 0.15% cream, (2) podophyllotoxin 0.3% cream	Podophyllotoxin 0.3% solution	Initial treatment for a maximum of 4 weeks with subsequent follow-up at 16 weeks after treatment for those classed as 'cured' during treatment
Syed 1994[122]	90	Asian women between the age of 16 and 40 years with extravaginal AGWs	(1) Podophyllotoxin 0.3% cream, (2) podophyllotoxin 0.5% cream	Placebo	Initial treatment period of up to 4 weeks with subsequent follow-up at 16 weeks for those achieving complete clearance during treatment
Syed 1995[123]	40	Men aged 18–40 years with genital AGWs (on the glans, shaft, corona sulcus or perianal area) and who were HIV negative at baseline	Podophyllotoxin 0.5% cream	Placebo	Initial treatment period of up to 4 weeks with follow-up at 16 weeks for those achieving complete clearance during treatment. Final follow-up was 1 year after the first day of treatment
Syed 1995[124]	40	Women aged 18–40 years with AGWs and who were HIV negative	Podophyllotoxin 0.5% cream	Placebo	Initial treatment period of up to 4 weeks with follow-up at 16 weeks for those achieving complete clearance during treatment. Final follow-up was 1 year after the first day of treatment
Syed 1998[161]	60	Women aged 18–45 years with AGWs	Imiquimod 2% cream	Placebo	Initial treatment period of 6 weeks with subsequent follow-up at 16 weeks from the start of the trial for those achieving complete clearance during treatment. Final follow-up was 11 months after the initial visit
Syed 2000[162]	60	Men aged 18–50 years with AGWs	Imiquimod 2% cream	Placebo	Initial treatment period of 6 weeks with subsequent follow-up at 16 weeks from the start of the trial for those achieving complete clearance during treatment. Final follow-up was 11 months after the initial visit
Tabari 2010[152]	120	People with a diagnosis of genital AGWs as evaluated by physical examination of the lesions	Podophyllin 25% (clinician applied)	TCAA 30% (clinician applied)	Total duration including follow-up of 6 months. Duration of treatment is unclear
Trofatter 2002[134]	90	Women with histologically confirmed external AGWs	(1) Imiquimod 5% cream, once daily, (2) imiquimod 5% cream, twice daily	Imiquimod 5% cream three times per week	Initial treatment period of up to 16 weeks with a subsequent 4-week observational period

Study	Sample size (*n*)	Population	Intervention	Comparator	Duration of treatment and follow-up
Tuncel 2005[135]	60	Presence of recalcitrant AGWs (perianal and/or genital) that were refractory to at least one conventional therapy	Cryotherapy plus imiquimod 5% cream	(1) Imiquimod 5% cream, (2) cryotherapy	Initial treatment period of up to 16 weeks; unclear whether or not there was an additional follow-up period
Tyring 1998[125]	22	Aged ≥ 18 years with a clinical diagnosis of external AGWs, with at least 10 but no more than 50 AGWs	Imiquimod 5% cream	Placebo	Initial treatment period of up to 16 weeks
Tyring 1998[68]	326	Immunocompetent people aged > 18 years with at least two distinct external AGWs (genital and/or perianal). Women had to have a negative pregnancy test	Podophyllotoxin 0.5% gel	Placebo	Initial treatment period of up to 8 weeks followed by assessment after a further 8 weeks to evaluate recurrence (depending on number of treatment cycles, total study time ranged from 9 to 16 weeks)
Viazis 2007[155]	49	Intra-anal AGWs that had not been previously treated with any modality. Absence of AGWs, or previous elimination of AGWs, on the penis, groin, cervix, urethral meatus, vagina or pubis. People with simultaneous perianal AGWs were included	Argon plasma coagulation plus imiquimod 5% cream	Argon plasma coagulation	Argon laser treatment was repeated every 4 weeks until complete clearance of AGW was achieved. After elimination of AGWs, patients were followed up for a mean of 12 months (range 3–21 months)
von Krogh 1992[126]	60	Women with vulvoanal condylomata (acuminata, popular or sessile)	Podophyllotoxin 0.5% cream	Placebo	Initial treatment period of 3 weeks with subsequent follow-up at 3 months for those categorised as cured at any point in the study
von Krogh 1994[127]	57	Men attending sexually transmitted disease outpatient departments who had previously untreated penile AGWs	(1) Podophyllotoxin 0.5% solution, (2) podophyllotoxin 0.25% solution	Placebo	Initial treatment period of a maximum of 2 weeks with follow-up of up to 23 weeks for those considered to have complete clearance
White 1997[144]	315	Men with first-episode, untreated penile AGWs	Podophyllotoxin 0.5% (formulation unclear)	(1) Podophyllin 0.5% (patient applied), (2) podophyllin 2% (patient applied)	Final follow-up occurred at 3 months (initial treatment period unclear)

Study characteristics

Population

Inclusion criteria varied considerably across identified studies, with some studies reporting clinical diagnosis of AGWs as the sole criterion for eligibility (see *Table 4*). The size of studies was also wide-ranging, with the largest study randomising 450 people[151] and the smallest randomising 12 people.[120]

Few identified studies reported comprehensive baseline characteristics for the enrolled study population. Key characteristics of AGWs that potentially influence treatment choice and effectiveness include size, number and location of lesions, together with wart type (keratinised vs. non-keratinised). Of those studies reporting baseline characteristics, most studies included a mixed population in terms of AGW characteristics. AGW morphology was rarely specified as an inclusion criterion and only one study[61] was identified that restricted inclusion by AGW type, specifying that AGWs should be non-keratinised. Most studies evaluated the treatment of external AGWs. One study[155] was identified that evaluated treatment of intra-anal AGWs. Duration of AGWs and line of treatment also varied across studies. Some studies focused on people who were treatment naive or restricted inclusion to those who had not received treatment in a set time period before enrolment, typically the preceding 3 months. As well as varying across studies, duration of disease varied considerably within studies, for example ranging from 1 to 300 weeks in the study by Godley *et al.*[154]

Several studies specified a minimum age for eligibility of 18 years and the reported mean age of people enrolled in studies ranged from 20 to 35 years. Although many studies included both genders, 18[61,66,67,115,123,127,129,133,136,140,142,143,145,147,150,154,160,162] and eight[62,122,124,126,130,134,137,161] studies focused on men and women respectively. Three studies evaluated treatments in people with HIV infection.[119,120,128]

The generally limited reporting of baseline characteristics precludes discussion of the extent of clinical heterogeneity across studies. Given the limited information available, clinical experts were consulted about the potential disparity across studies in populations enrolled. Experts fed back that they considered the population across the studies likely to be representative of people with AGWs and who present to GUM clinics. Thus, the project team considered it appropriate to carry out a MTC.

Interventions and comparators

Studies evaluating all interventions of interest were identified (see *Table 4*). Topical treatments evaluated were the self-applied imiquimod 5% cream and podophyllotoxin, and the clinician-applied TCAA and podophyllin 20–25%. Various concentrations (e.g. podophyllotoxin 0.5% cream and 0.15% cream), formulations (e.g. podophyllotoxin 0.5% cream and podophyllotoxin 0.5% solution) and application schedules of podophyllotoxin were evaluated across studies. Additionally, the duration of treatment with imiquimod 5% cream varied across studies. The licence for imiquimod 5% cream indicates that treatment can be given for up to 16 weeks and recommends an application schedule of three times per week on non-consecutive days.[58] Studies were identified evaluating application of imiquimod 5% for 4, 8, 12 and 16 weeks[130,133] and at application schedules of once daily, twice daily and three times daily.[129,134]

After consultation with clinical experts on the potential influence of treatment duration, dose and formulation (relates to ease of application) on clinical effectiveness, the following assumptions were made for the purposes of carrying out meta-analysis, both direct and indirect:

- Imiquimod 5% cream of any schedule (e.g. three times a week vs. once daily vs. twice daily) applied for 12 weeks is equivalent in clinical effectiveness to imiquimod 5% cream applied for 16 weeks; schedules of < 12 weeks' duration were excluded from the analysis.
- Clinician-applied podophyllin 20% and clinician-applied podophyllin 25% are clinically equivalent.
- Different formulations of podophyllotoxin are of potentially sufficiently dissimilar clinical effectiveness to warrant analysis by preparation.
- With the exception of podophyllotoxin 0.25% and 0.3%, doses of podophyllotoxin are potentially of sufficiently dissimilar clinical effectiveness to warrant analysis by dose.

Outcomes

The outcomes of interest to this review and reported in the included studies are listed in *Table 5*. No study reported data on the outcomes of relief of symptoms, malignancy or QoL. Although most studies presented results on the primary outcome of complete clearance of AGWs at the end of treatment, few studies presented data on complete clearance at subsequent time points. The definition of recurrence of AGWs differed slightly across studies. Most studies defined recurrence as the appearance of AGWs at a site previously cleared of AGWs, whereas some included appearance of AGWs at sites additional to those initially cleared.

Quality assessment

No study was deemed to be at an overall low risk of bias, with the largest proportion of studies categorised as having an overall unclear risk of bias predominantly because of the limited reporting in the full publications (*Table 6*). In an attempt to supplement the information available, study authors were contacted with requests for additional detail on trial methodology. Only two authors replied by the prespecified deadline. Given that it is over 10 years since publication of most of the identified studies, the low response rate was to be expected.

All studies were described as randomised but details on methods used to generate the randomisation sequence were rarely reported. Assessment of clearance and recurrence of AGWs was subjective and thus at risk of bias. Most studies involving topical applications were described as double blinded but, as for randomisation, the full publications provided little information on methods implemented to initially conceal allocation and to subsequently maintain masking of treatment from clinicians and participants. Additionally, for most studies described as double blind, it was unclear whether or not the outcome assessor was the treating clinician and, if not, if the outcome assessor was masked to treatment. Some studies evaluating topical treatments were described as open label in design and thus were categorised as being at high risk of bias for most outcomes reported (see *Table 6*). Differences in setting could make implementation of masking problematic in studies evaluating self-applied against clinician-applied treatments and topical against ablative therapies. However, masking in these studies could be achieved using sham treatments.

Follow-up at the end of treatment was generally high across studies, with several studies categorised as being at low risk of attrition bias for the outcomes evaluated. However, follow-up at later time points to evaluate recurrence was variable, with high rates of loss to follow-up reported in several studies. Authors of some studies suggested that the low rate of return for further assessments could be attributed to treatment success, that is, complete clearance of AGWs without recurrence had been achieved and people felt that they needed no additional treatment or monitoring.

Of the domains relating to study characteristics, selective reporting was the domain most frequently determined to be at a high risk of bias (see *Table 6*). In these cases, results for the primary clinical effectiveness outcomes for this project (complete clearance and recurrence) were either not reported, despite being listed in the publication as a primary outcome, or not reported in a way that facilitated incorporation of the data into meta-analysis.

TABLE 5 Summary of outcomes reported by RCTs included in the review

Study	Complete clearance at end of treatment	Complete clearance at other time points	Recurrence	Time to complete clearance	Volume of clearance	Appearance of new AGWs during treatment	AEs	Included in MTC[a]		
								Complete clearance at end of treatment	Complete clearance at another time point	Recurrence
Abdullah 1993[153]	✓						✓	Primary		
Arican 2004[112]	✓		✓		✓	✓	✓	Primary		
Azizjalali 2012[156]	✓		✓				✓	Primary		
Baker 2010[113]	✓		✓				✓			
Bar-Am 1993[157]							✓			
Benedetti Panici 1989[114]	✓	✓	✓		✓		✓	Sensitivity	Sensitivity	
Beutner 1989[115]	✓		✓				✓	Primary		
Beutner 1998[116]	✓		✓	✓	✓	✓	✓	Primary		
Beutner 1998[117]	✓		✓	✓	✓	✓	✓			
Claesson 1996[65]	✓		✓				✓			
Edwards 1988[136]	✓		✓				✓	Sensitivity		Sensitivity
Edwards 1998[118]	✓		✓	✓	✓	✓	✓	Primary		
Ferenczy 1995[158]	✓		✓				✓			
Fife 2001[129]	✓	✓				✓	✓			
Gabriel 1983[145]	✓		✓				✓	Primary		Primary
Garland 2006[130]	✓						✓			
Gilson 1999[119]	✓				✓	✓	✓	Sensitivity		
Gilson 2009[159]	✓	✓	✓		✓		✓	Primary	Sensitivity	
Godley 1987[154]	✓		✓				✓	Primary		
Goh 1998[66]	✓						✓	Primary		

Study	Complete clearance at end of treatment	Complete clearance at other time points	Recurrence	Time to complete clearance	Volume of clearance	Appearance of new AGWs during treatment	AEs	Included in MTC[a]		
								Complete clearance at end of treatment	Complete clearance at another time point	Recurrence
Greenberg 1991[62]		✓	✓			✓	✓			
Handley 1992[67]	✓	✓	✓				✓	Sensitivity		Sensitivity
Hellberg 1995[137]	✓		✓				✓	Sensitivity		Sensitivity
Jensen 1985[146]	✓		✓				✓	Primary		Primary
Kar 2003[138]	✓		✓			✓	✓	Primary		Primary
Kinghorn 1993[63]	✓		✓				✓	Sensitivity		
Kirby 1990[61]	✓		✓		✓	✓	✓	Primary		
Komericki 2011[131]	✓						✓	Sensitivity		
Lacey 2003[64]	✓		✓				✓	Sensitivity		Sensitivity
Landthaler 1987[139]	✓		✓				✓			
Lassus 1984[140]	✓		✓				✓	Primary		Primary
Maiti 1985[147]	✓		✓				✓			
Matteelli 2001[120]					✓		✓			
Mazurkiewicz 1990[60]	✓		✓				✓	Primary		
Nath 1990[148]	✓		✓				✓	Primary		Primary
Orlando 2002[128]	✓		✓				✓	Sensitivity		
Padhiar 2006[132]	✓		✓	✓	✓		✓	Primary		Primary
Petersen 1995[141]							✓			
Sherrard 2007[149]	✓							Primary		
Simmons 1981[160]		✓					✓		Sensitivity	
Simmons 1981[150]		✓			✓		✓			

continued

TABLE 5 Summary of outcomes reported by RCTs included in the review (*continued*)

Study	Complete clearance at end of treatment	Complete clearance at other time points	Recurrence	Time to complete clearance	Volume of clearance	Appearance of new AGWs during treatment	AEs	Included in MTC[a]		
								Complete clearance at end of treatment	Complete clearance at another time point	Recurrence
Snoeck 2001[121]	✓		✓		✓	✓	✓	Sensitivity		
Stefanaki 2008[133]	✓	✓	✓				✓	Sensitivity	Sensitivity	
Stone 1990[151]	✓		✓				✓	Sensitivity		Sensitivity
Strand 1995[142]	✓		✓				✓	Sensitivity		Sensitivity
Syed 1993[143]	✓		✓		✓		✓	Sensitivity		
Syed 1994[122]	✓		✓				✓	Primary		
Syed 1995[123]	✓		✓				✓	Primary		
Syed 1995[124]	✓		✓		✓			Sensitivity		
Syed 1998[161]	✓		✓		✓		✓			
Syed 2000[162]	✓		✓		✓		✓			
Tabari 2010[152]	✓		✓				✓			
Trofatter 2002[134]	✓	✓		✓	✓		✓			
Tuncel 2005[135]	✓		✓				✓			
Tyring 1998[125]	✓				✓			Sensitivity		
Tyring 1998[68]	✓		✓				✓	Sensitivity		
Viazis 2007[155]	✓		✓	✓			✓			
von Krogh 1992[126]	✓		✓				✓	Primary		
von Krogh 1994[127]	✓		✓				✓	Primary		Primary
White 1997[144]	✓						✓			

a Studies listed as included in the primary analyses were also included in sensitivity analyses.

TABLE 6 Summary of the risk-of-bias assessments of RCTs included in the review

Study	Sources of bias relating to study characteristics				Outcome-specific sources of bias[a]			
					Blinding			
	Random sequence generation	Allocation concealment	Selective reporting	'Other bias'	Participants and personnel	Outcome assessment	Incomplete outcome data	Overall assessment
Abdullah 1993[153]	?	?	?	?	?	?	?	?
Arican 2004[112]	?	?	?	?	?	?	?	?
Azizjalali 2012[156]	✓	?	?	?	?	✓	?	?
Baker 2010[113]	✓	?	✗	?	✓	✓	?	✗
Bar-Am 1993[157]	✓	?	✗	?	?	?	?	✗
Benedetti Panici 1989[114]	?	?	?	?	?	?	✓	?
Beutner 1989[115]	?	?	?	?	?	?	?	?
Beutner 1998[116]	?	?	✓	?	?	?	✓	?
Beutner 1998[117]	?	?	✓	?				?
	AGW clearance at completion of treatment; recurrence of AGWs; time to complete clearance; and volume of wart clearance				?	?	✓	
	Appearance of new AGWs during treatment and AEs				?	?	✗	
Claesson 1996[65]	?	?	✗	?	✗	✗	?	✗
Edwards 1988[136]	✓	?	?	?				✗
	AGW clearance at completion of treatment and AEs				✗	✗	?	
	Recurrence of AGWs				✗	✗	✗	
Edwards 1998[118]	?	?	✓	?				?
	AGW clearance at completion of treatment and volume of AGW clearance				?	?	✓	
	Time to complete clearance; appearance of new AGWs during treatment; and AEs				?	?	?	
	Recurrence of AGWs				?	?	✗	

continued

TABLE 6 Summary of the risk-of-bias assessments of RCTs included in the review (*continued*)

Study	Sources of bias relating to study characteristics				Outcome-specific sources of bias[a]			
					Blinding			
	Random sequence generation	Allocation concealment	Selective reporting	'Other bias'	Participants and personnel	Outcome assessment	Incomplete outcome data	Overall assessment
Ferenczy 1995[158]	✓	?	✗	?	✗	✓	?	✗
Fife 2001[129]	✓	?	?	?	?	?	?	?
Gabriel 1983[145]	?	✓	?	?				?
	Recurrence of AGWs				✓	✓	✓	
	AGW clearance at completion of treatment and AEs				✓	✓	?	
Garland 2006[130]	?	?	✗	?	✗	✗	?	✗
Gilson 1999[119]	?	?	?	?				?
	AGW clearance at completion of treatment				?	?	?	
	Volume of AGW clearance and appearance of new AGWs during treatment				?	?	✗	
	AEs				?	✗	✗	
Gilson 2009[159]	?	✓	?	?				?
	Recurrence of AGWs				?	?	✓	
	AGW clearance at completion of treatment and at other time points and AEs				?	?	?	
Godley 1987[154]	?	?	?	?				?
	Recurrence of AGWs				?	?	✓	
	AGW clearance at completion of treatment and at other time points and AEs				?	?	?	
Goh 1998[66]	?	?	?	?	?	?	?	?
Greenberg 1991[62]	✓	?	✗	?				✗
	AGW clearance at other time points and AEs				?	?	?	
	Recurrence of AGWs and appearance of new AGWs during treatment				?	?	✗	

Study	Sources of bias relating to study characteristics				Outcome-specific sources of bias[a]			
					Blinding			
	Random sequence generation	Allocation concealment	Selective reporting	'Other bias'	Participants and personnel	Outcome assessment	Incomplete outcome data	Overall assessment
Handley 1992[67]	?	?	?	?	?	?	?	?
Hellberg 1995[137]	?	?	?	?	✗	✗	✓	✗
Jensen 1985[146]	?	?	?	?	?	?	✓	?
Kar 2003[138]	?	?	?	?	?	?	?	?
Kinghorn 1993[63]	?	?	?	?	✗	✗	?	✗
Kirby 1990[61]	?	✓	?	?	✓	?	✓	?
Komericki 2011[131]	?	?	?	?	✗	✗	✗	✗
Lacey 2003[64]	?	?	?	?	✗	✗	?	✗
Landthaler 1987[139]	?	?	✗	?	?	?	?	✗
Lassus 1984[140]	?	?	?	?	?	?	?	?
Maiti 1985[147]	?	?	?	?	✓	✓	?	?
Matteelli 2001[120]	?	?	✗	?				✗
	Volume of AGW clearance				✗	✓	?	
	AEs				✗	✗	?	
Mazurkiewicz 1990[60]	?	?	?	?				?
	AEs				?	?	✓	
	AGW clearance at completion of treatment and at other time points and recurrence of AGWs				?	?	?	
Nath 1990[148]	?	?	?	?	?	?	?	?
Orlando 2002[128]	?	?	✗	?				✗
	AGW clearance at completion of treatment and AEs				✗	✗	?	
	Recurrence of AGWs				✗	✗	✗	

continued

TABLE 6 Summary of the risk-of-bias assessments of RCTs included in the review (*continued*)

	Sources of bias relating to study characteristics				Outcome-specific sources of bias[a]			
					Blinding			
Study	Random sequence generation	Allocation concealment	Selective reporting	'Other bias'	Participants and personnel	Outcome assessment	Incomplete outcome data	Overall assessment
Padhiar 2006[132]	?	?	?	?	?	?	?	?
Petersen 1995[141]	?	?	✗	?	?	?	?	✗
Sherrard 2007[149]	?	?	?	?	?	?	?	?
Simmons 1981[160]	✓	?	✗	?	✗	?	?	✗
Simmons 1981[150]	✓	?	✗	?	?	?	?	✗
Snoeck 2001[121]	?	?	?	?	?	?	?	?
Stefanaki 2008[133]	?	?	✗	?				✗
	AGW clearance at completion of treatment and at other time points and AEs				✗	✗	?	
	Recurrence of AGWs				✗	✗	✗	
Stone 1990[151]	✓	?	?	✗	?	?	✓	✗
Strand 1995[142]	?	?	?	?	✗	✗	?	✗
Syed 1993[143]	?	?	✗	?	✗	✗	✓	✗
Syed 1994[122]	?	?	?	?	?	?	✓	?
Syed 1995[123]	?	?	?	?	?	?	✓	?
Syed 1995[124]	?	?	✗	?				✗
	AGW clearance at completion of treatment and at other time points				?	?	✓	
	Recurrence of AGWs				?	?	?	
Syed 1998[161]	?	?	?	?	?	?	✓	?

Study	Sources of bias relating to study characteristics				Outcome-specific sources of bias[a]			
					Blinding			
	Random sequence generation	Allocation concealment	Selective reporting	'Other bias'	Participants and personnel	Outcome assessment	Incomplete outcome data	Overall assessment
Syed 2000[162]	?	?	?	?				?
	AGW clearance at completion of treatment and at other time points and recurrence of AGWs				?	?	✓	
	AEs				?	?	?	
Tabari 2010[152]	✓	?	✗	?				✗
	AGW clearance				?	?	✓	
	Recurrence of AGWs and AEs				?	?	?	
Trofatter 2002[134]	?	?	?	?	✗	✗	?	✗
Tuncel 2005[135]	?	?	✗	?	✗	✗	?	✗
Tyring 1998[125]	?	?	?	✗	?	?	?	✗
Tyring 1998[68]	?	?	✗	?				✗
	Recurrence of AGWs and AEs				?	?	?	
	AGW clearance at completion of treatment and at other time points				?	?	✗	
Viazis 2007[155]	✓	✓	?	?	?	✗	✓	✗
von Krogh 1992[126]	?	?	?	?	?	?	?	?
von Krogh 1994[127]	?	?	?	?	?	?	✓	?
White 1997[144]	✓	✓	✗	?	?	?	✗	✗

✓ = low risk of bias; ? = unclear risk of bias; and ✗ = high risk of bias.
a Unless specified otherwise, outcome-specific risk of bias applies to all outcomes evaluated in the study (summarised in *Table 5*).

Assessment of effectiveness

Complete clearance at the end of treatment

The comparative clinical effectiveness of achieving complete clearance at the end of treatment was evaluated through a MTC and standard pair-wise meta-analysis. It should be noted that, as a consequence of variation in the duration of treatment for active topical interventions, the duration of placebo treatment or no treatment differs across studies. Given the consistently small proportion of people achieving complete clearance without treatment in the included studies, the project team considers variation in duration of placebo treatment to have a minimal impact on relative estimates of comparative clinical effectiveness.

The primary network generated included 22 studies[60,61,66,112,115,116,118,122,123,126,127,132,138,140,145,146,148,149,153,154,156,159] and provided information on 15 treatments; a list of the studies informing the MTC for complete clearance at the end of treatment is presented in *Table 5*. A prespecified sensitivity analysis included studies that (1) were deemed to be at high risk of bias, (2) enrolled people with AGWs who were seropositive for HIV infection and (3) were reported only as conference abstracts. The sensitivity analysis incorporated an additional 17 studies[63,64,67,68,114,119,121,124,125,128,131,133,136,137,142,143,151] and provided information on four extra treatments. The networks of evidence are presented in *Figure 3*. Although no longer recommended as a treatment for AGWs, podophyllin 20–25% (clinician applied) was chosen as the baseline treatment for the MTCs because of the comparatively large number of studies available for analysis.

For the primary and sensitivity MTCs, analysis of model fit identified the random-effects model to be the best-fitting model in each case (*Table 7*). Additionally, the total residual deviance of the random-effects model in each analysis was closer to the number of data points included in the analysis (see *Table 7*). In the primary analysis, the model was a good fit for the data, with a residual deviance close to the number of unconstrained data points. There was evidence of heterogeneity in treatment effects across studies in the primary and sensitivity analyses (see *Table 7*). Codes for fixed- and random-effects models implemented in MTC analyses are supplied in *Appendix 4*.

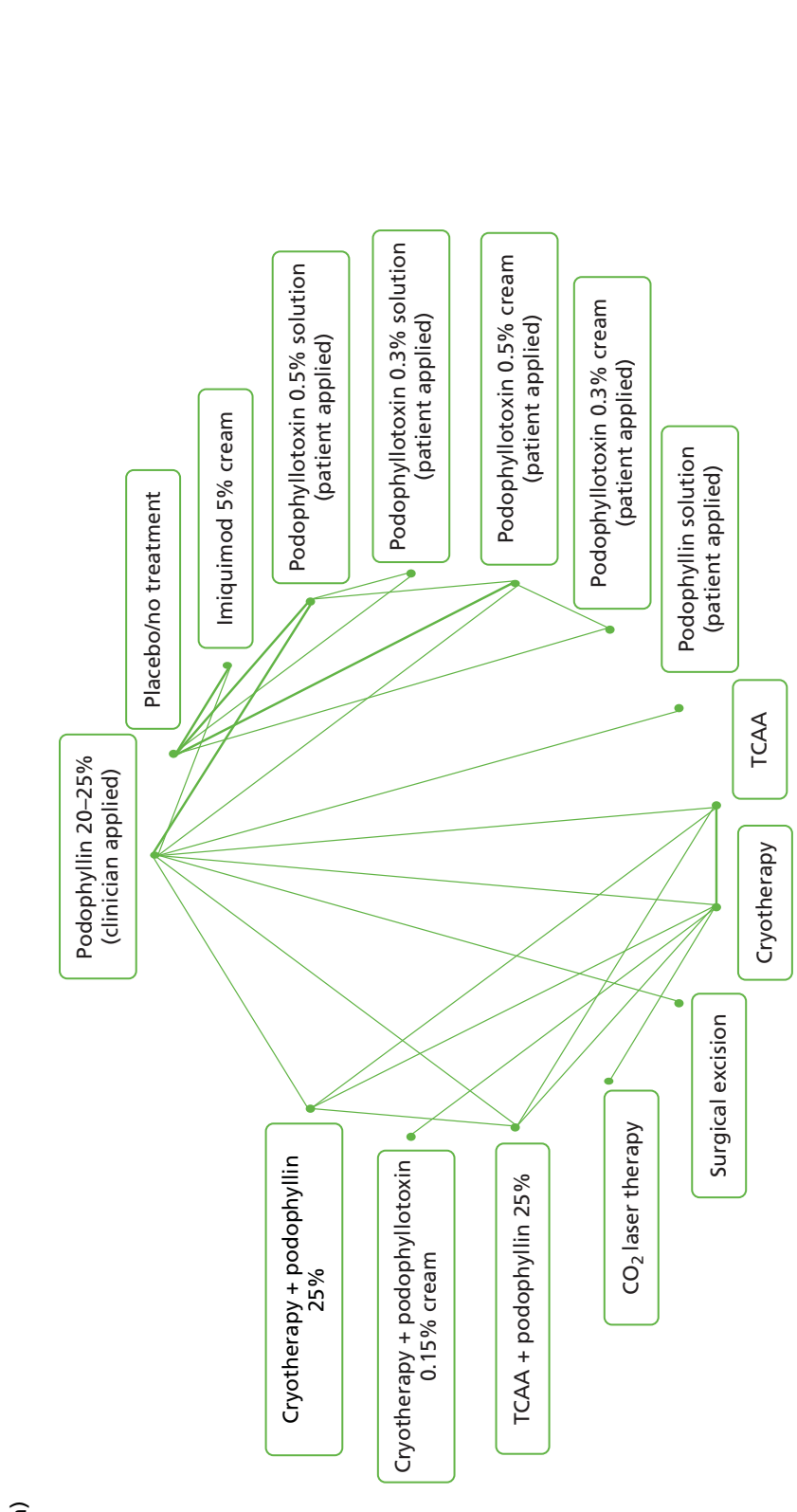

FIGURE 3 Network diagrams of different interventions for complete clearance. The nodes represent the interventions. The thickness of the lines represents the number of studies informing the direct comparison. (a) Primary analysis; and (b) sensitivity analysis. (*continued*)

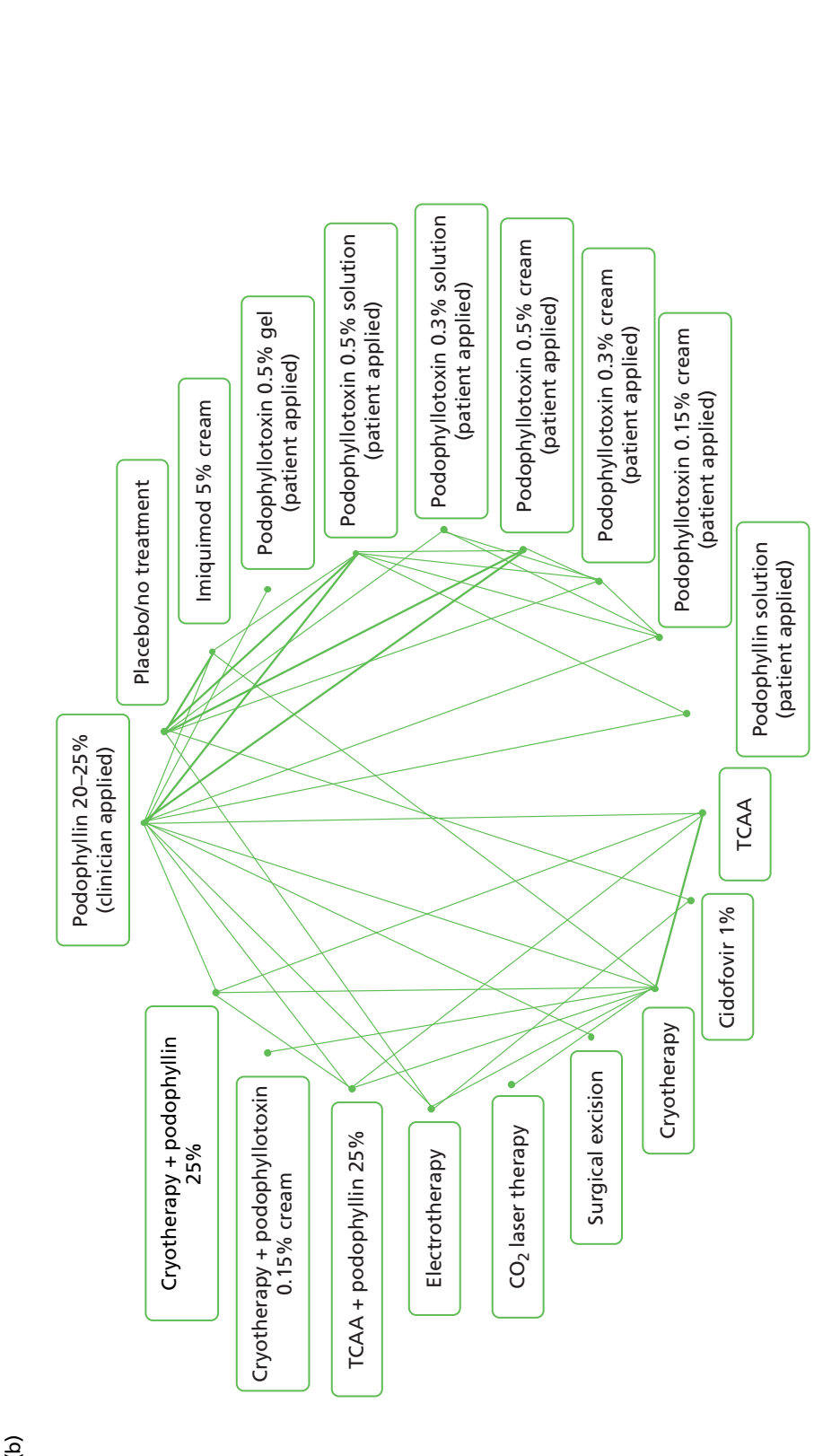

FIGURE 3 Network diagrams of different interventions for complete clearance. The nodes represent the interventions. The thickness of the lines represents the number of studies informing the direct comparison. (a) Primary analysis; and (b) sensitivity analysis.

TABLE 7 Summary of the MTC model characteristics

	Primary analysis		Sensitivity analysis	
Characteristic	Random effects	Fixed effects	Random effects	Fixed effects
Deviance information criterion	267.0	269.8	471.1	508.3
Total residual deviance	53.9	63.7	95.5	152.7
Number of data points	50	50	88	88
Between study variance (95% CrI)	0.72 (0.07 to 1.64)	NA	1.12 (0.62 to 1.76)	NA

CrI, credible interval; NA, not applicable.

Results from the MTCs indicate that ablative techniques, particularly CO_2 laser therapy, have higher probabilities of being the best treatment than most of the topical treatments (summarised in *Table 8*). CO_2 laser therapy is associated with the largest probability of achieving complete clearance at the end of treatment, with probabilities of 97.1% [95% credible interval (CrI) 84.8% to 99.9%] and 96.9% (95% CrI 81.6% to 99.9%) in the primary and sensitivity analyses, respectively. The probabilities of complete clearance at the end of treatment for the primary and sensitivity analyses are summarised in *Figures 4* and *5*, respectively. By contrast, placebo was associated with a probability of clearance of only 7.6% (95% CrI 1.1% to 20.9%) in the primary analysis and 7.1% (95% CrI 1.7% to 17.7%) in the sensitivity analysis, with the duration of treatment with placebo ranging from 2 weeks to 16 weeks. Of the topical treatments, podophyllotoxin 0.5% solution and podophyllotoxin 0.3% solution were associated with the highest probabilities of completely clearing AGWs by the end of treatment (see *Figures 4* and *5*). In the primary analysis, podophyllotoxin 0.5% solution had a marginally higher probability of achieving the outcome than podophyllotoxin 0.3% solution (see *Figure 4*), which was the reverse of the results generated by the sensitivity analysis (see *Figure 5*). Of the topical treatments, podophyllin (clinician applied), imiquimod 5% cream and podophyllotoxin creams were associated with no or a low probability of being the best treatment (see *Table 8*).

TABLE 8 Probability of each treatment being the best treatment for achieving complete clearance at the end of treatment

Treatment	Mean probability (%) of treatment being best treatment (primary analysis)	Mean probability (%) of treatment being best treatment (sensitivity analysis)
Podophyllin 20–25% (clinician applied)	0.0	0.0
Placebo/no treatment	0.0	0.0
Imiquimod 5% cream (patient applied)	0.0	0.0
Podophyllotoxin 0.5% gel (patient applied)	NA	0.5
Podophyllotoxin 0.5% solution (patient applied)	3.8	0.0
Podophyllotoxin 0.3% solution (patient applied)	14.3	8.8
Podophyllotoxin 0.5% cream (patient applied)	0.0	0.0
Podophyllotoxin 0.3% cream (patient applied)	0.0	0.2
Podophyllotoxin 0.15% cream (patient applied)	NA	0.0
Podophyllin solution (patient applied)	1.6	0.4
TCAA	0.0	0.0
Cidofovir 1%	NA	5.6
Cryotherapy	0.0	0.0
Surgical excision	6.7	6.5
CO_2 laser therapy	71.8	62.1
Electrotherapy	NA	13.1
TCAA plus podophyllin 25%	0.0	0.0
Cryotherapy plus podophyllotoxin 0.15% cream	1.0	2.1
Cryotherapy plus podophyllin 25%	0	0.5

NA, not applicable.

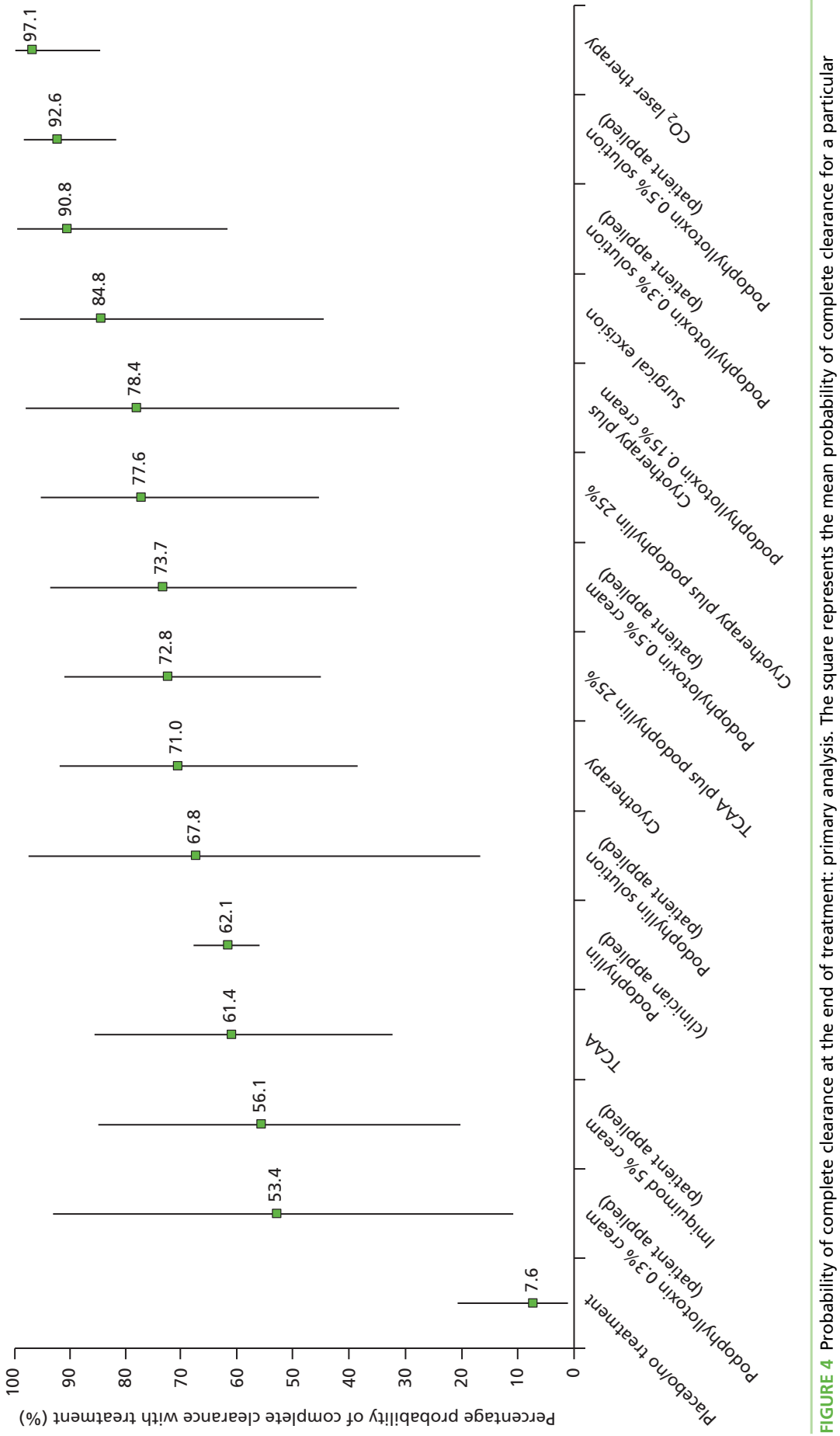

FIGURE 4 Probability of complete clearance at the end of treatment: primary analysis. The square represents the mean probability of complete clearance for a particular treatment. The bar lines indicate the 95% CrI around the estimate of effect.

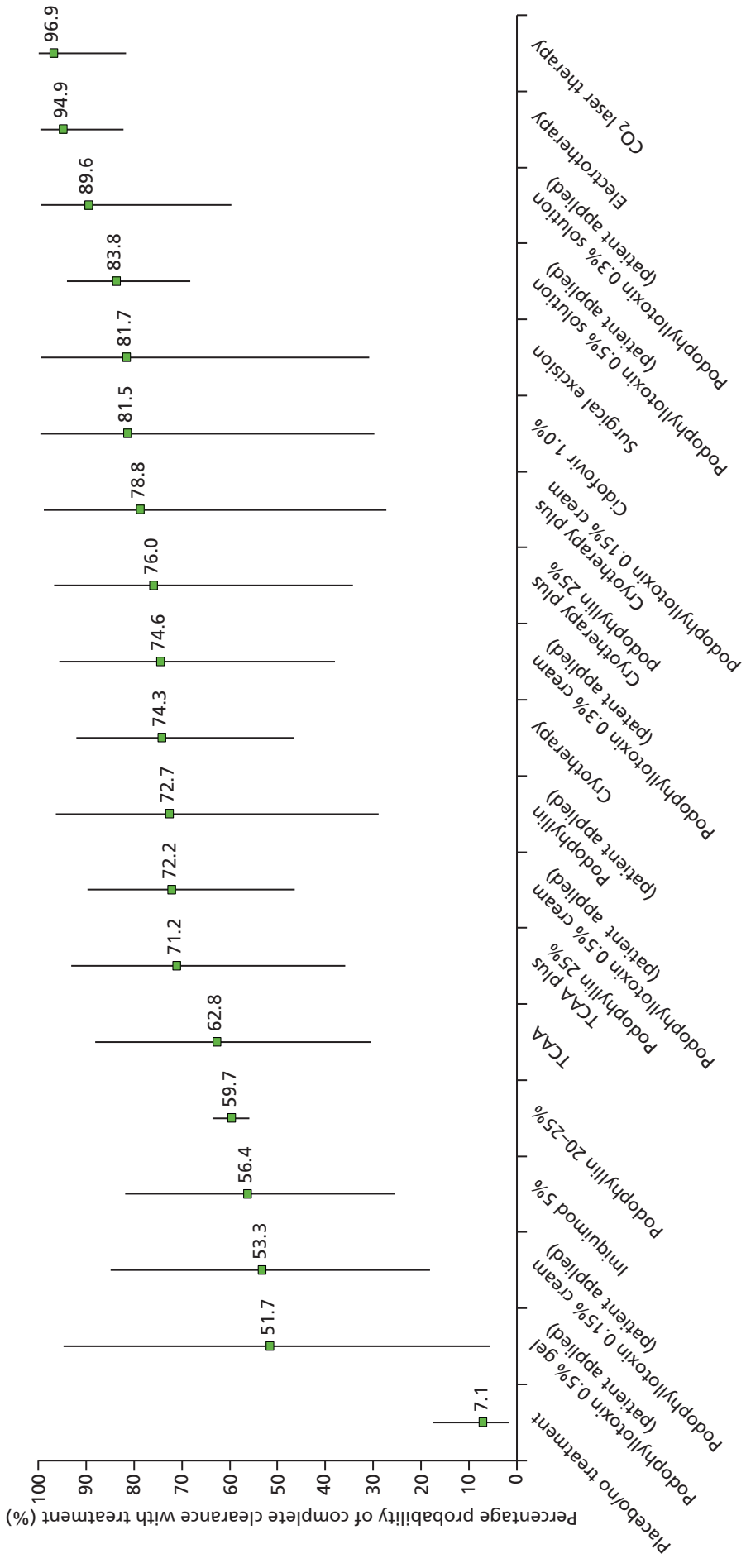

FIGURE 5 Probability of complete clearance at the end of treatment: sensitivity analysis. The square represents the mean probability of complete clearance for a particular treatment. The bar lines indicate the 95% CrI around the estimate of effect.

When compared with placebo or no treatment, in both the MTC primary and sensitivity analyses, all treatments evaluated were associated with a statistically significant improvement in complete clearance at the end of treatment (*Figure 6*) (full results of the MTC are presented in *Appendix 5*). Of the treatments evaluated, CO_2 laser therapy was associated with the largest improvement over placebo or no treatment for this outcome, with an OR of 6533 (95% CrI 65.49 to 25,760) in the primary analysis. The results of the MTC are in agreement with findings from standard pairwise meta-analyses, in which all interventions analysed were found to be statistically significantly more effective than placebo at effecting complete clearance at the end of treatment (*Figure 7*). It should be noted that a high level of statistical heterogeneity was present in the pairwise analysis of imiquimod 5% cream ($I^2 = 53\%$ in the primary analysis) and podophyllotoxin 0.5% cream ($I^2 = 61\%$ in the primary analysis) compared with placebo. Forest plots for individual pairwise meta-analyses are available in *Appendix 6*.

When compared with podophyllin 20–25%, the direction of the effect estimate favoured all other active interventions evaluated in primary and sensitivity analyses. However, most differences between treatments did not reach statistical significance (*Figure 8*). Of the treatments evaluated, CO_2 laser therapy (OR 104.6, 95% CrI 3.35 to 505.2) and podophyllotoxin 0.5% solution (OR 11.65, 95% CrI 2.65 to 38.50) were statistically significantly more effective than podophyllin 20–25% at completely clearing AGWs at the end of treatment (primary and sensitivity analyses). Additionally, sensitivity analyses identified electrotherapy as statistically significantly more effective than podophyllin 20–25% at achieving the outcome (OR 32.72, 95% CrI 3.15 to 150.80). Results from the MTC are predominantly in agreement with findings from standard pairwise meta-analysis. Of the direct evidence available, with the exception of TCAA and podophyllotoxin 0.15% cream, all treatments were associated with a higher probability than podophyllin 20–25% of completely clearing AGWs at the end of treatment (*Figure 9*). Forest plots for individual pairwise meta-analyses are available in *Appendix 6*.

In MTC analyses, there was no statistically significant difference between most treatments for complete clearance of AGWs at the end of treatment. Of those differences that reached statistical significance, most of the comparisons involved CO_2 laser therapy or podophyllotoxin 0.5% or 0.3% solution. CO_2 laser therapy was found to be significantly more effective than imiquimod 5% cream, TCAA and cryotherapy and the combinations of TCAA plus podophyllin and cryotherapy plus podophyllin. Analysis of direct evidence available for the comparison between CO_2 laser therapy and cryotherapy indicated a statistically significant difference between treatments that favoured CO_2 laser therapy (OR 22.08, 95 CI 7.37 to 66.16).

The MTC analysis indicated that podophyllotoxin 0.5% and 0.3% solution were both statistically significantly more effective at effecting complete clearance of AGWs than imiquimod 5% cream. However, analysis of direct evidence found no statistically significant difference between podophyllotoxin 0.5% solution and imiquimod 5% cream for this outcome (OR 1.50, 95% CI 0.47 to 4.76). Results from the MTC also demonstrated that podophyllotoxin 0.5% solution was associated with statistically significant improvements in complete clearance compared with podophyllotoxin 0.5% cream, podophyllotoxin 0.3% cream and TCAA. Full results of the MTC are presented in *Appendix 5*. A summary of the estimates of effect generated by the MTC and standard pairwise meta-analysis is presented in *Table 9*.

The project team acknowledges the considerable uncertainty around the results, as evidenced by the wide CrIs (see *Figures 6* and *8*).

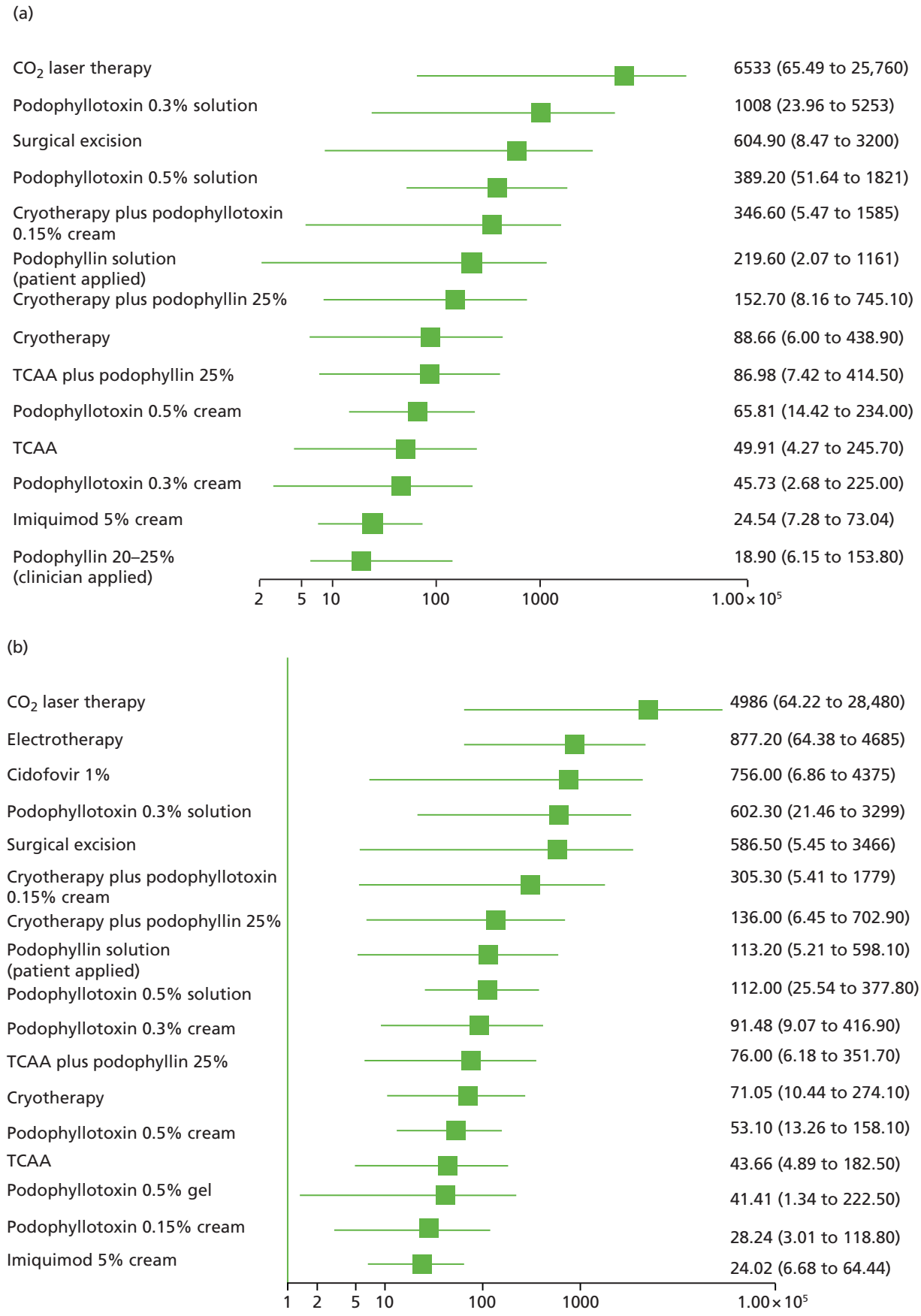

FIGURE 6 Forest plots presenting ORs and accompanying 95% CrIs for complete clearance of AGWs at the end of treatment for the comparison between the active interventions and placebo generated from the MTC. (a) Primary analysis; and (b) sensitivity analysis.

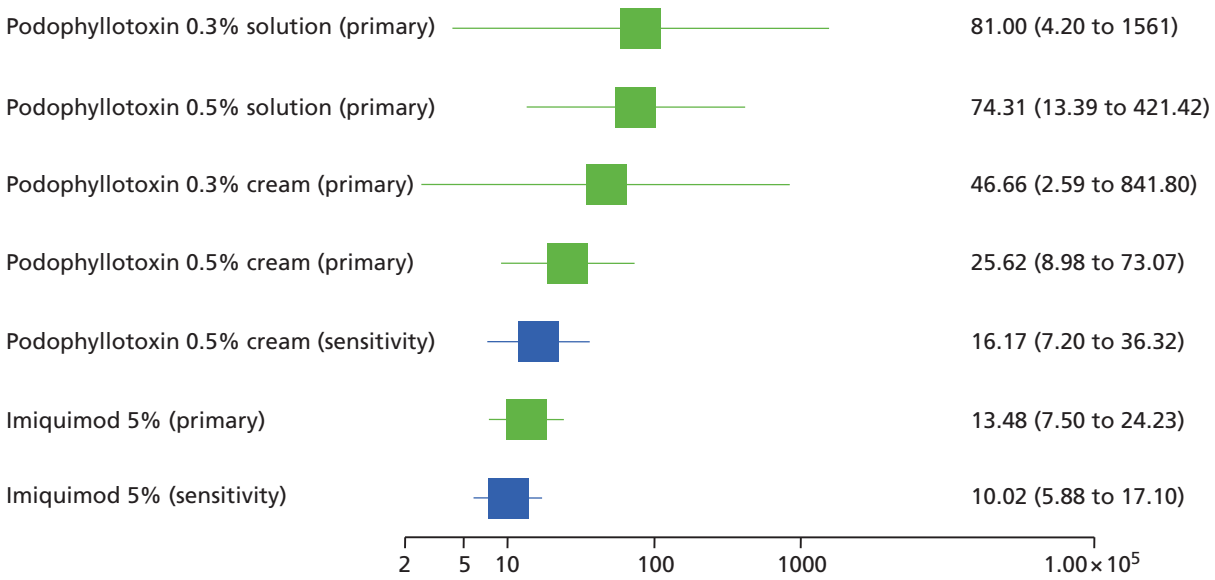

FIGURE 7 Forest plots presenting ORs and accompanying 95% CIs for complete clearance of AGWs at the end of treatment for the comparison between the active interventions and placebo generated from standard pairwise meta-analysis.

(a)

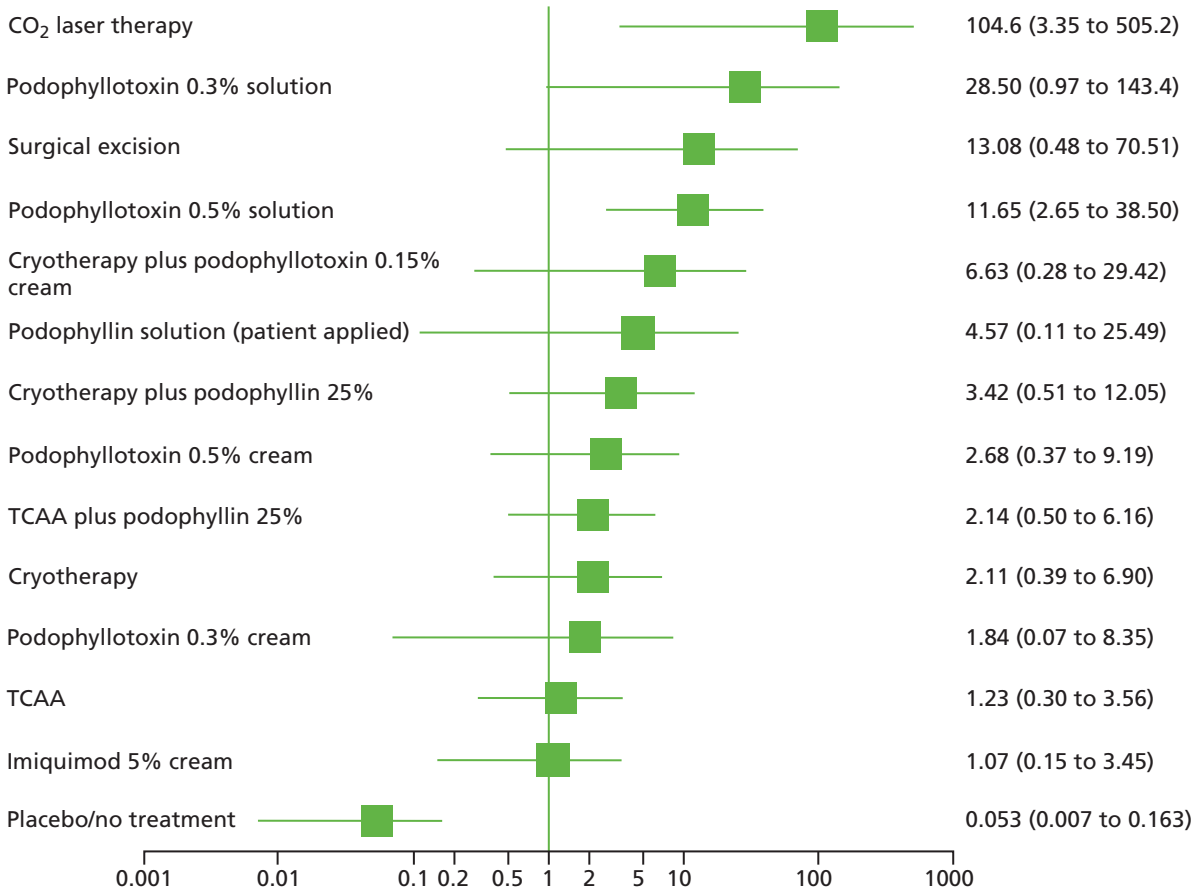

FIGURE 8 Forest plots presenting ORs and accompanying 95% CrIs for complete clearance of AGWs at the end of treatment for the comparison between the interventions and podophyllin 20–25% generated from the MTC. (a) Primary analysis; and (b) sensitivity analysis. (*continued*)

(b)

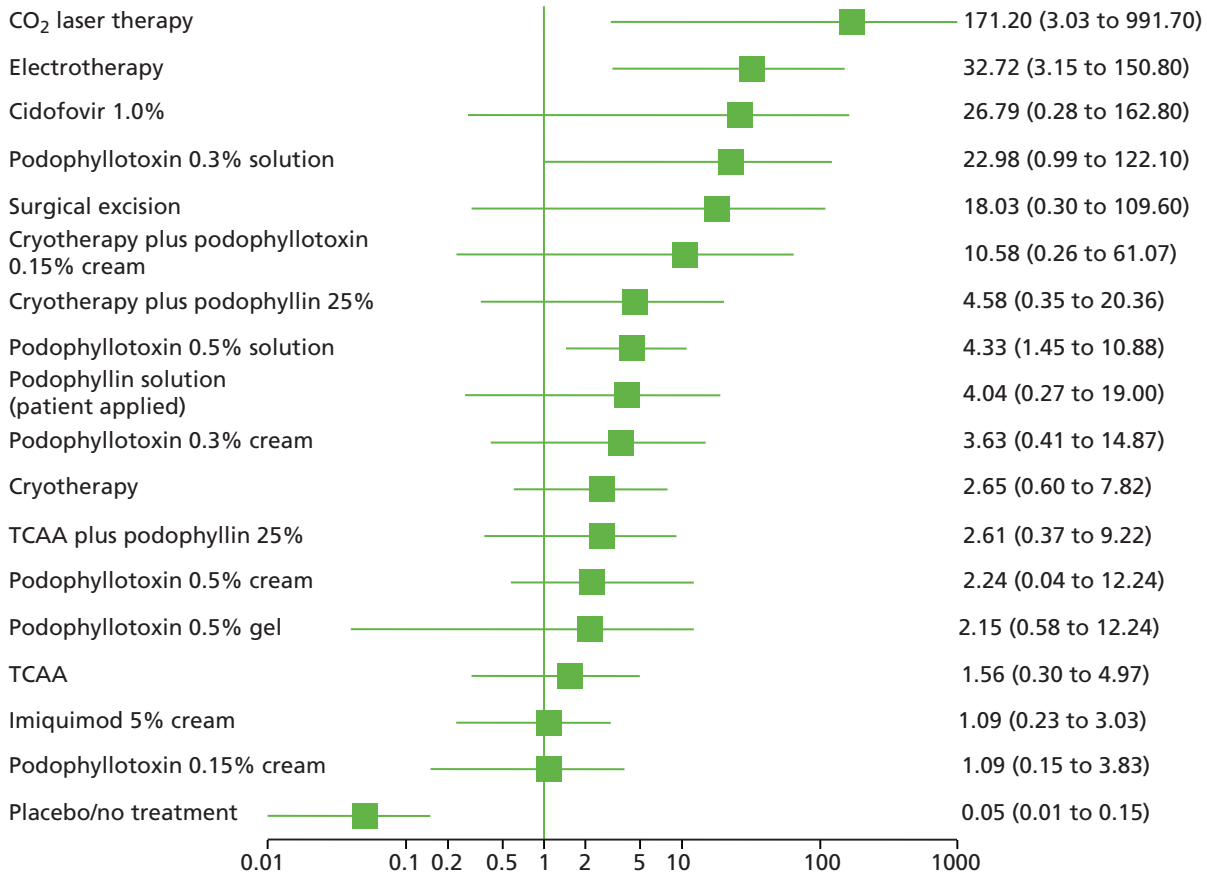

FIGURE 8 Forest plots presenting ORs and accompanying 95% CrIs for complete clearance of AGWs at the end of treatment for the comparison between the interventions and podophyllin 20–25% generated from the MTC. (a) Primary analysis; and (b) sensitivity analysis.

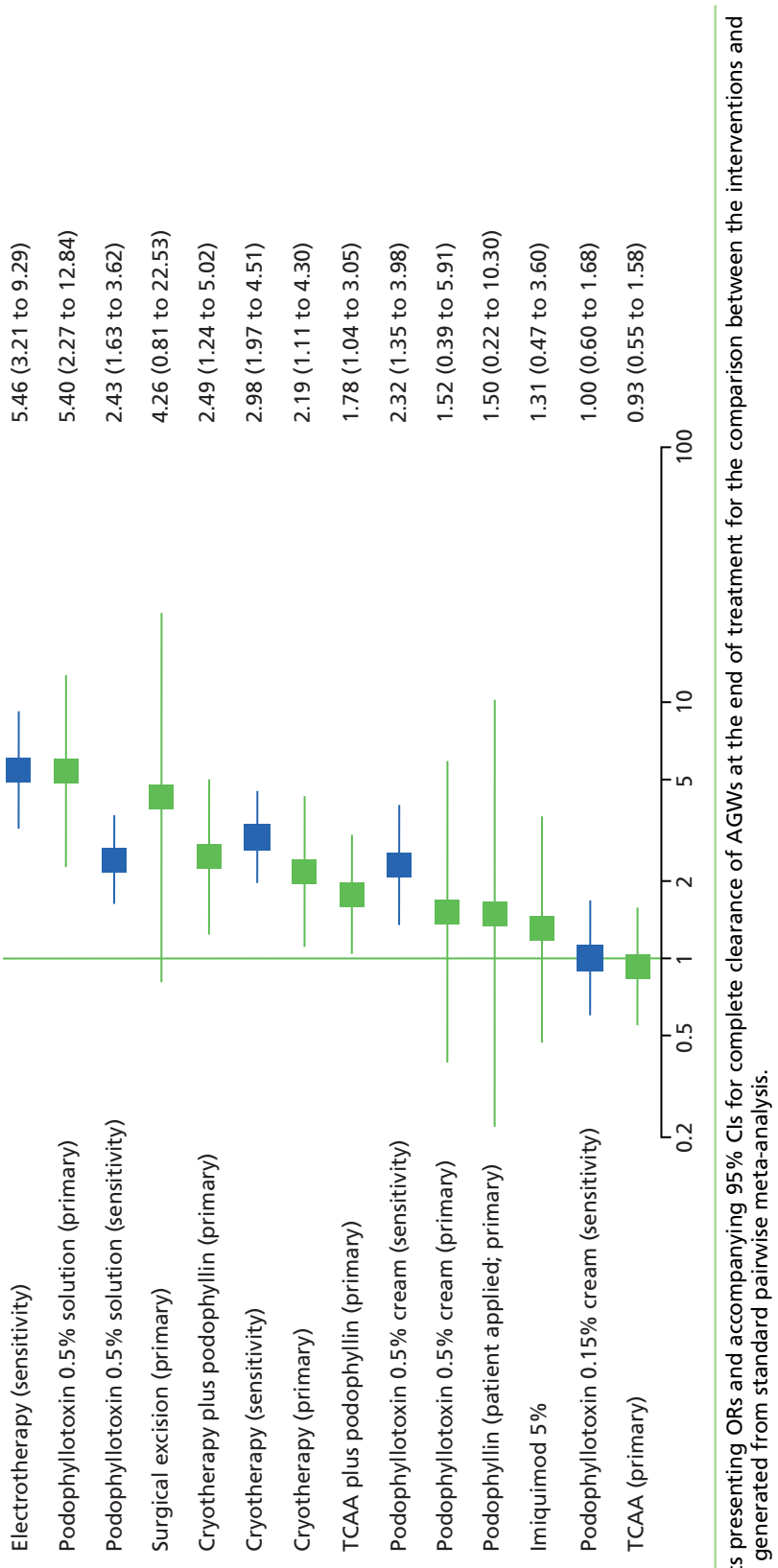

FIGURE 9 Forest plots presenting ORs and accompanying 95% CIs for complete clearance of AGWs at the end of treatment for the comparison between the interventions and podophyllin 20–25% generated from standard pairwise meta-analysis.

TABLE 9 Comparison of estimates of effect generated by the MTC and standard pairwise meta-analysis

Comparison	Pairwise meta-analysis, OR (95% CI)		MTC, OR (95% CrI)	
	Primary	Sensitivity	Primary	Sensitivity
Topical treatments vs. each other				
Podophyllotoxin 0.5% solution vs. imiquimod 5% cream	–	1.50 (0.47 to 4.76)	18.97 (2.27 to 83.18)	5.58 (1.16 to 19.2)
Podophyllin solution (patient applied) vs. podophyllotoxin 0.5% solution	–	0.76 (0.20 to 2.86)	0.61 (0.008 to 3.52)	1.04 (0.07 to 4.69)
Podophyllotoxin 0.5% cream vs. podophyllotoxin 0.5% solution	0.31 (0.08 to 1.22)	–	0.30 (0.04 to 0.99)	0.62 (0.13 to 1.74)
Podophyllotoxin 0.3% cream vs. podophyllotoxin 0.5% solution	–	0.87 (0.23 to 3.22)	0.19 (0.007 to 0.87)	0.91 (0.11 to 3.44)
Podophyllotoxin 0.15% cream vs. podophyllotoxin 0.5% solution	–	0.49 (0.14 to 1.68)	–	0.28 (0.04 to 0.90)
Podophyllotoxin 0.3% solution vs. podophyllotoxin 0.5% solution	1.00 (0.25 to 3.93)	–	2.17 (0.13 to 10.08)	5.32 (0.29 to 27.34)
Podophyllotoxin 0.3% cream vs. podophyllotoxin 0.3% solution	–	1.00	0.31 (0.003 to 1.56)	0.60 (0.02 to 3.29)
Podophyllotoxin 0.15% cream vs. podophyllotoxin 0.3% solution	–	0.05 (0.00 to 1.04)	–	0.18 (0.005 to 0.87)
Podophyllotoxin 0.3% cream vs. podophyllotoxin 0.5% cream	0.23 (0.07 to 0.76)	–	0.66 (0.06 to 2.9)	1.96 (0.23 to 8.14)
Podophyllotoxin 0.15% cream vs. podophyllotoxin 0.3% cream	–	0.33[a] (0.12 to 0.91)	–	0.63 (0.07 to 2.49)
Ablative treatments vs. each other				
CO_2 laser therapy vs. cryotherapy	22.08 (7.37 to 66.16)	–	44.61 (3.30 to 201.7)	63.39 (1.88 to 343.1)
Electrotherapy vs. cryotherapy	–	1.52 (0.97 to 2.39)	–	15.79 (1.39 to 75.41)
Ablative treatments vs. topical treatments				
Cidofovir 1.0% vs. electrotherapy	–	0.25 (0.05 to 1.35)	–	8.71 (0.22 to 48.15)
Cryotherapy vs. imiquimod 5%	–	0.77 (0.37 to 1.59)	4.02 (0.28 to 18.73)	3.36 (0.55 to 12.41)
Cryotherapy vs. TCAA	1.67 (1.09 to 2.57)	–	1.87 (0.55 to 4.73)	2.19 (0.50 to 6.34)
Combination treatments vs. another active treatment				
TCAA plus podophyllin 20–25% vs. cryotherapy	0.94 (0.47 to 1.89)	–	1.53 (0.21 to 5.53)	1.37 (0.14 to 5.42)
Cryotherapy plus podophyllin 20–25% vs. cryotherapy	1.14 (0.54 to 2.38)	–	2.37 (0.25 to 9.36)	2.35 (0.14 to 10.98)
Cryotherapy plus podophyllotoxin 0.15% cream vs. cryotherapy	1.76 (0.92 to 3.37)	–	2.86 (0.27 to 11.39)	3.89 (0.16 to 19.83)
Cryotherapy plus podophyllin 20–25% vs. TCAA	2.76 (1.39 to 5.47)	–	3.56 (0.46 to 13.2)	4.16 (0.26 to 19.44)
Cryotherapy plus podophyllin 20–25% vs. TCAA plus podophyllin 20–25%	1.21 (0.59 to 2.50)	–	2.23 (0.22 to 8.83)	3.15 (0.13 to 15.92)

a Random-effects model generates an effect estimate of 0.26, with accompanying 95% CI of 0.03 to 2.39.

Complete clearance at another time point

Few identified studies reported clinical effectiveness data for complete clearance without recurrence at time points after cessation of treatment. Additionally, some studies reported data on this outcome only for people achieving complete clearance at the end of treatment rather than the full study population. Complete clearance without recurrence is distinct from recurrence as the former outcome accounts for people who clear within a few days of completion of treatment. Here, results for complete clearance evaluated at least 1 month after the end of treatment are reported from those studies aiming to observe all those randomised. Of the 60 studies included in the review, seven studies (based on the clinical assumptions outlined in *Quantity and quality of research available*) presented results on complete clearance at ≥ 1 month.[114,129,133,134,150,159,160] Three studies were not suitable for the MTC as they evaluated various dosing schedules of the same treatment.[129,134,150] Only two[114,159] of the four remaining studies were judged to be of unclear or low risk of bias, with the remaining studies deemed to be at high risk of bias because they were reported only as a conference abstract or enrolled people with HIV infection. Thus, a MTC was feasible only for the preplanned sensitivity analysis.

No study in the MTC evaluated podophyllin 20–25% and so cryotherapy was chosen as the baseline treatment because of the larger number of studies available. The fixed-effects model was the best-fitting model, with a deviance information criterion (DIC) of 47.9 (the DIC for the random-effects model was 48.1). The fixed-effects model was a good fit for the data, with a total residual deviance close to the number of data points analysed (residual deviance of 8.2 compared with eight unconstrained data points analysed).

Five interventions were indirectly compared in the MTC:

1. placebo or no treatment
2. imiquimod 5% cream (three times a week, patient applied)
3. cryotherapy
4. electrotherapy
5. cryotherapy plus podophyllotoxin 0.15% cream.

Of the five interventions analysed, electrotherapy was associated with the highest probability of achieving complete clearance without recurrence 3–6 months after the end of treatment (65.5%, 95% CrI 40.0% to 86.2%; *Figure 10*).

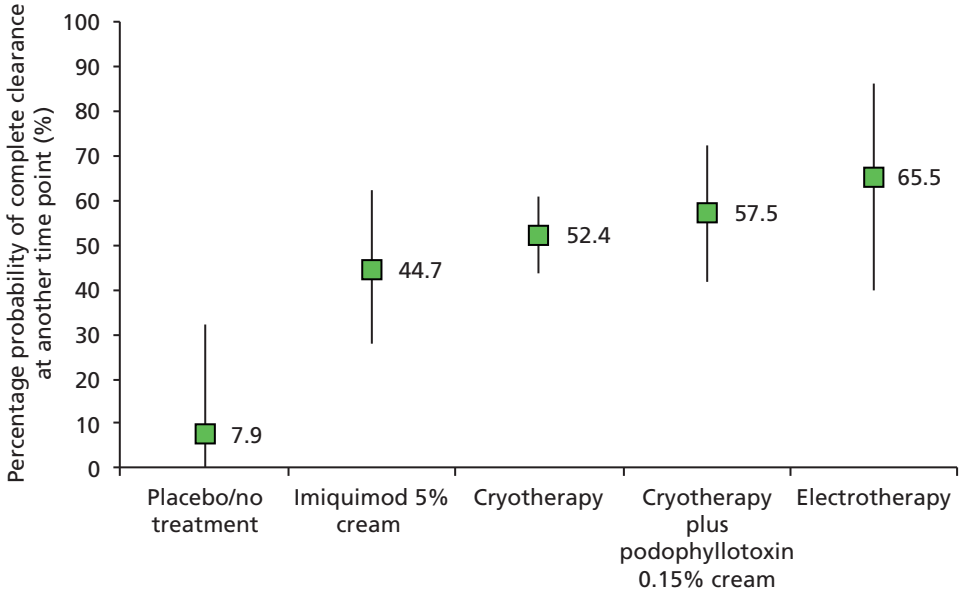

FIGURE 10 Probability of complete clearance at another time point by treatment: sensitivity analysis.

Results of the MTC indicate that the four active interventions are more effective than placebo at improving complete clearance without recurrence, based on median OR (*Table 10*). Mean OR estimates generated for comparisons with placebo/no treatment were unstable and fell outside the 95% CrI. The instability is likely due to the low event rate for placebo informing the analysis (1 event on 48 patients at risk), which leads to extreme values of the ratio of the odds and produces distributions that are highly skewed.

Results from the individual studies informing the MTC are in line with the findings of the MTC (*Table 11*).

Of the three studies not included in the MTC, Fife *et al.*[129] and Trofatter *et al.*[134] compared various dosing schedules of imiquimod 5% cream and Simmons[150] assessed different doses of clinician-applied podophyllin. Meta-analysis of the studies by Fife *et al.*[129] and Trofatter *et al.*[134] found no statistically significant differences between imiquimod 5% cream applied three times weekly, once daily or twice daily (all possible comparisons) (forest plot presented in *Appendix 7*).

Recurrence

Based on advice from clinical experts, for the analysis of clinical effectiveness, recurrence of AGWs has been analysed by period of follow-up. Durations of follow-up assessed are from 3 months up to, but not including, 6 months (hereafter referred to as < 6 months) and ≥ 6 months (maximum reported follow-up of 12 months). A separate analysis of recurrence carried out to inform the cost-effectivness analysis

TABLE 10 Results of the MTC for complete clearance without recurrence

	Comparator, OR[a] (95% CrI)				
Intervention	Cryotherapy	Placebo/no treatment	Imiquimod 5% cream	Electrotherapy	Cryotherapy plus podophyllotoxin 0.15% cream
Cryotherapy	–	–	–	–	–
Placebo/no treatment	0.09 (0.001 to 0.47)	–	–	–	–
Imiquimod 5% cream	0.78 (0.35 to 1.51)	1336 (1.42 to 489.9)[b]	–	–	–
Electrotherapy	2.22 (0.53 to 6.49)	4860 (5.90 to 970.5)[c]	3.27 (0.60 to 10.85)	–	–
Cryotherapy plus podophyllotoxin 0.15% cream	1.31 (0.64 to 2.41)	2120 (2.38 to 811.9)[d]	1.93 (0.63 to 4.62)	0.89 (0.16 to 2.79)	–

a OR > 1 favours the intervention and OR < 1 favours the comparator (listed in the top row of the table, column-defining treatment).
b Median OR = 15.47.
c Median OR = 36.48.
d Median OR = 26.42.
Cells highlighted in green indicate statistically significant results.

TABLE 11 Results of direct evidence for complete clearance without recurrence

Study	Bias rating	Intervention	Comparator	OR (95% CI)
Benedetti Panici 1989[114]	Unclear	Electrotherapy	Placebo/no treatment	25.64 (3.26 to 201.60)
Gilson 2009[159]	Unclear	Cryotherapy plus podophyllotoxin 0.15% cream	Cryotherapy	1.23 (0.63 to 2.39)
Simmons 1981[160]	High	Electrotherapy	Cryotherapy	1.75 (0.51 to 6.01)
Stefanaki 2008[133]	High	Imiquimod 5% cream	Cryotherapy	0.73 (0.35 to 1.52)

included all relevant studies and encompassed recurrence from 3 months onwards. The results of this analysis are not discussed in this section but are presented in *Appendix 8*.

Analyses of recurrence are based on all people reported to have achieved complete clearance of AGWs at the end of treatment. In cases in which fewer people were followed up than cleared their AGWs, a worst-case scenario was implemented and people lost to follow-up were assumed to have undergone recurrence of AGWs.

Many study groups receiving placebo treatment or no treatment included no people with completely cleared lesions at the end of treatment and, consequently, no person could experience recurrence. As such, it was not possible to include placebo treatment in the analysis of recurrence, which restricted the network.

Recurrence at < 6 months

Applying the clinical assumptions outlined earlier identified four studies[127,140,145,148] to inform the primary analysis of recurrence occurring at < 6 months, which facilitated indirect comparison of:

- podophyllin 20–25%
- podophyllotoxin 0.5% solution
- podophyllotoxin 0.25% solution
- TCAA
- TCAA plus podophyllin 20–25%.

The random- and fixed-effects models were similar in terms of goodness of fit (DIC 44.4 vs. 44.4, respectively) and had the same residual deviance (8.3 vs. 8.3, respectively), which was close to the number of unconstrained data points in the analysis (eight data points). However, because of the possibility of clinical heterogeneity in the populations of the trials combined in the network, the random-effects model was preferred.

There were no statistically significant differences between any comparisons for recurrence at < 6 months; results from the MTC are presented in *Appendix 9*. TCAA was associated with the lowest probability of recurrence (23.4%, 95% CrI 1.5% to 76.6%). By contrast, podophyllotoxin 0.25% solution had the highest probability of recurrence (66.9%, 95% CrI 5.2% to 99.5%). The probability of recurrence for all treatments is presented in *Figure 11*.

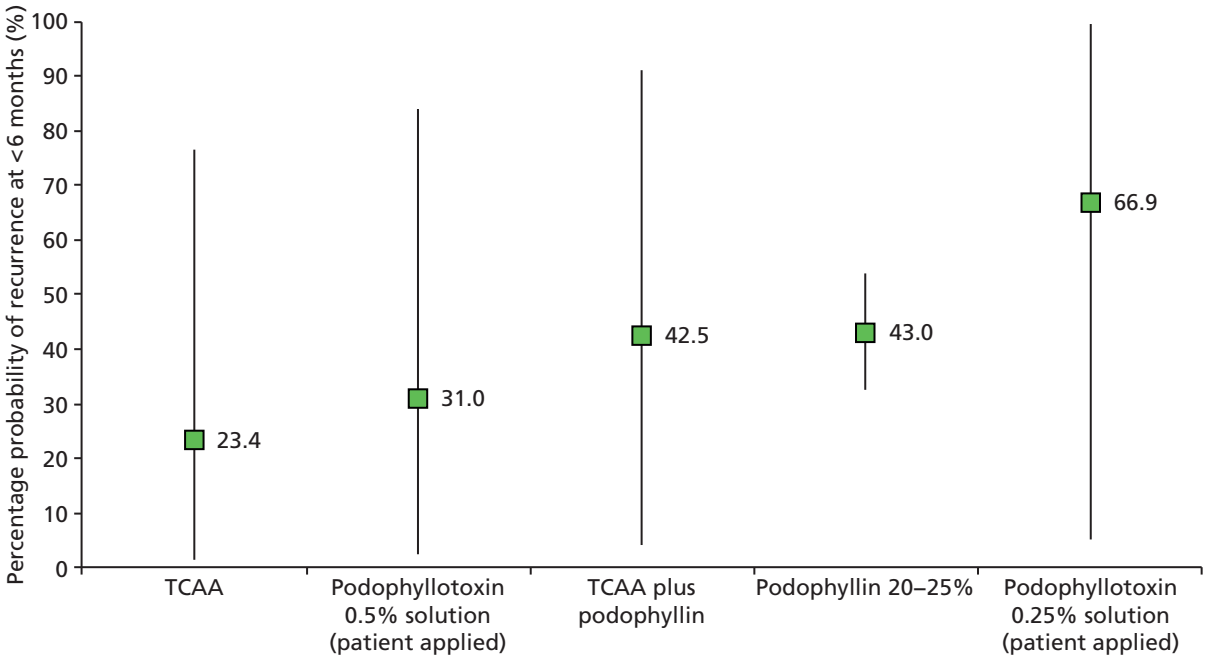

FIGURE 11 Probability of recurrence at < 6 months by treatment: primary analysis.

Sensitivity analysis of recurrence at < 6 months included an additional six studies[64,67,136,137,142,151] and six other interventions:

- podophyllotoxin 0.5% cream
- podophyllotoxin 0.3% cream
- podophyllotoxin 0.15% cream
- podophyllin 0.5% solution (patient applied)
- cryotherapy
- electrotherapy.

The probability of recurrence for all treatments included in the sensitivity analysis is presented in *Figure 12*. Of the 11 interventions analysed, TCAA had the lowest probability of recurrence (24.7%, 95% CrI 8.7% to 46.9%). In marked contrast, podophyllotoxin 0.25% solution (83.3%, 95% CrI 49.5% to 98.5%) and podophyllin 0.5% solution (75.9%, 95% CrI 22.0% to 99.5%) had the highest probabilities of recurrence. The comparatively high probability of recurrence of the two topical treatments is reflected in the results of the MTC. As in the primary analysis, for most comparisons, the differences between interventions did not reach statistical significance. However, six comparisons were statistically significant, with four of these involving podophyllotoxin 0.3% solution and with the direction of effect favouring the comparator (podophyllotoxin 0.5% solution, TCAA, cryotherapy and electrotherapy). Additionally, TCAA was significantly more effective than podophyllin 20–25% (OR 0.35, 95% CrI 0.09 to 0.88) and podophyllotoxin 0.15% cream (OR 0.30, 95% CrI 0.06 to 0.90) at reducing recurrence at < 6 months. Full results of the MTC are presented in *Appendix 9*.

Recurrence at ≥ 6 months

Four studies[132,138,146,155] reported recurrence at ≥ 6 months and informed the primary MTC, three[132,138,146] of which were included in the MTC. No additional studies were identified for inclusion in a sensitivity analysis.

The random- and fixed-effects models had a similar goodness of fit (32.8 vs. 32.8, respectively). However, the fixed-effects model had a slightly lower residual deviance than the random-effects model (6.1 vs. 6.2, respectively), which is close to the number of unconstrained data points in the analysis (six data points).

The network generated evaluated four interventions:

- podophyllin 20–25%
- imiquimod 5% cream
- podophyllotoxin 0.5% solution
- surgical excision.

Of the comparisons evaluated, only two differences were statistically significant. Surgical excision was found to be statistically significantly more effective than podophyllin 20–25% (OR 0.16, 95% CrI 0.03 to 0.43) and podophyllotoxin 0.5% solution (OR 0.14, 95% CrI 0.02 to 0.50) at reducing recurrence at ≥ 6 months. Full results of the MTC are presented in *Appendix 9*. Surgical excision was also associated with the lowest probability of recurrence of the four treatments (15.4%, 95% CrI 4.7% to 33.5%; summarised in *Table 12*).

An additional study not included in the MTC[155] investigated whether or not argon plasma coagulation in combination with imiquimod 5% cream was more effective than argon plasma coagulation alone in the treatment of intra-anal AGWs. Viazis *et al.*[155] found no statistically significant difference between the two treatments for recurrence of AGWs at a mean follow up of 6 months [5/22 people recurred with combination treatment vs. 8/23 people recurred with monotherapy; OR 0.55 (calculated by project authors), 95% CI 0.15 to 2.06].

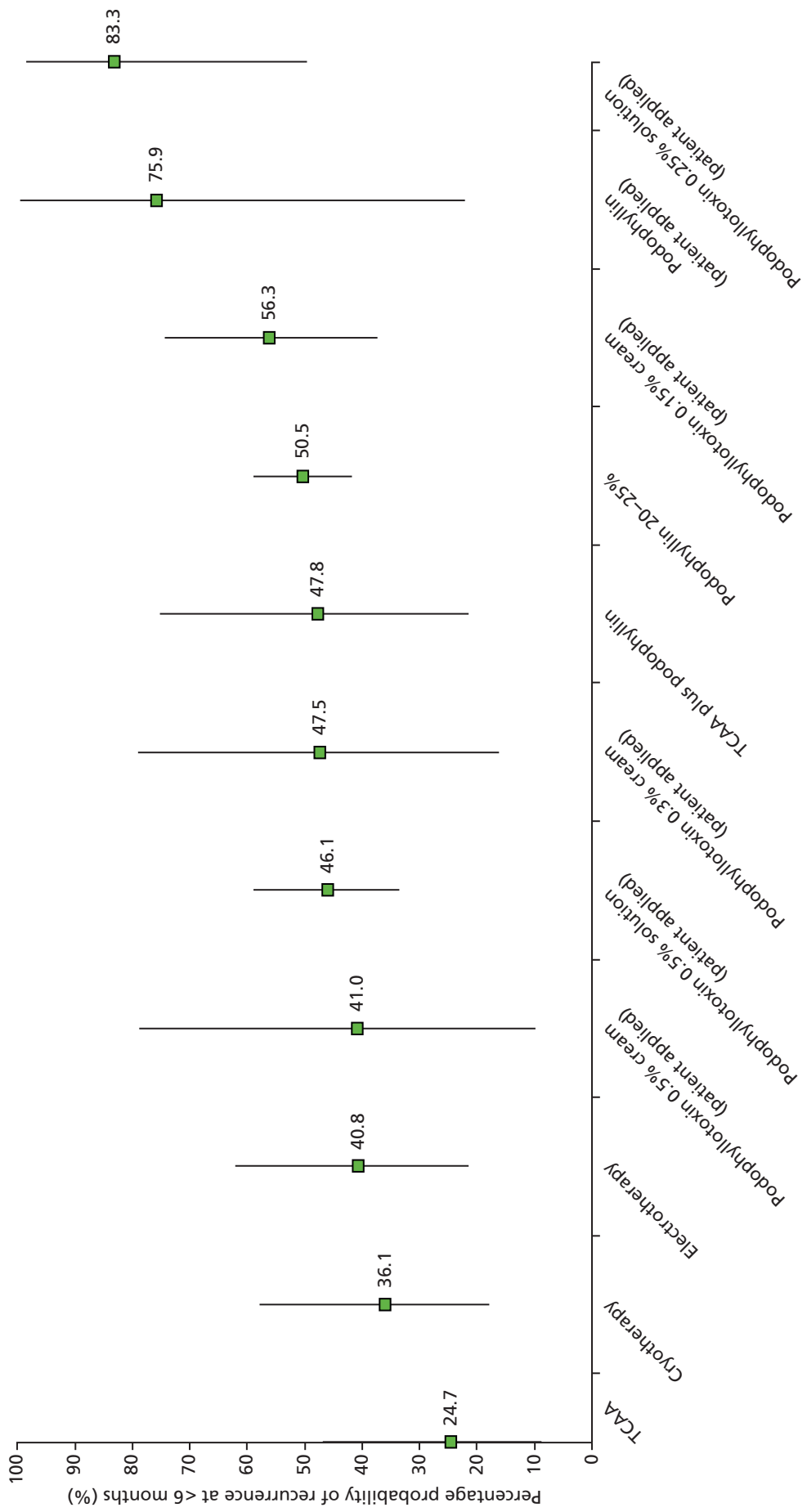

FIGURE 12 Probability of recurrence at < 6 months by treatment: sensitivity analysis.

TABLE 12 Probability of recurrence at ≥ 6 months by treatment

Intervention	Probability (%) of recurrence (95% CrI)
Surgical excision	15.4 (4.7 to 33.5)
Imiquimod 5% cream	24.7 (6.4 to 53.2)
Podophyllin 20–25%	55.9 (42.1 to 69.4)
Podophyllotoxin 0.5% solution (patient applied)	62.1 (37.6 to 82.7)

Time to complete clearance of anogenital warts

No identified study reported time to complete clearance in a format that facilitated inclusion in a standard pairwise meta-analysis or MTC. Six studies[116–118,132,134,155] presented results for time to complete clearance, but only one study[155] reported an accompanying measure of variance and statistical evaluation.

Five studies evaluated imiquimod 5% cream (conventional regimen) compared with placebo,[116–118] podophyllin 20%[132] or alternative application schedules.[134] The median time to complete clearance for imiquimod 5% cream (conventional regimen) varied across the studies, ranging from 7 to 12 weeks.[116–118,132,134] Once daily and twice daily application of imiquimod 5% cream were associated with a median time to complete clearance of 6 and 8 weeks, respectively.[134] Padhiar *et al.*[132] found a median time to complete clearance of 4.85 weeks for podophyllin 20%. Time to complete clearance for placebo ranged from 10 to 12 weeks.[116–118]

Viazis *et al.*[155] found that adding imiquimod 5% cream to argon plasma coagulation significantly reduced the time to complete clearance [62.5 days, standard error (SE) 5.4 days, with argon plasma coagulation plus imiquimod 5% cream vs. 91.2 days, SE 6.4 days, with argon plasma coagulation alone; $p = 0.0016$].

Volume of clearance of anogenital warts

Presented analyses are based on the subgroups reduction in baseline AGW volume by < 50% and reduction in baseline AGW volume by ≥ 50% at the end of treatment. Results for clearance by ≥ 50% exclude those achieving complete AGW clearance, which is evaluated as a separate outcome of interest. Applying the clinical assumptions outlined earlier led to analysis of data from three studies judged to be of unclear or low risk of bias reporting < 50% clearance of AGW volume[112,121,132] and six studies reporting ≥ 50% clearance of AGW volume.[61,112,116,118,121,132] Twelve other studies reporting volume of AGW clearance were not suitable for inclusion in the MTC as they were judged to be at a high risk of bias, evaluated treatments not included in the analysis or did not present data in a format suitable for inclusion in a meta-analysis[114,117,119,120,124,125,134,143,150,159,161,162] (see *Table 5*).

Clearance of anogenital warts of < 50%

Arican *et al.*[112] and Snoeck *et al.*[121] compared imiquimod 5% cream and cidofovir 1% gel, respectively, with placebo. The third study[132] compared imiquimod 5% cream with podophyllin 20–25%.

The fixed-effects model was a slightly better fit than the random-effects model (DIC 28.6 vs. 28.7, respectively). The residual deviance of the fixed-effects model was also similar to the number of unconstrained data points analysed (residual deviance of 6.4 compared with six data points, respectively).

The MTC using the fixed-effects model indicated that the effect estimate for achieving < 50% clearance of AGWs was statistically significantly lower with imiquimod 5% cream than with placebo and cidofovir 1.0% gel (*Table 13*). For the comparison of imiquimod 5% cream and podophyllin 20–25%, the estimate of effect approached 1 and the difference between the treatments did not reach statistical significance.

TABLE 13 Results from the MTC for clearance of < 50% of the volume of AGWs

Intervention	Comparator, OR[a] (95% CrI)			
	Imiquimod 5% cream	Placebo/no treatment	Podophyllin 20–25%	Cidofovir 1% gel
Imiquimod 5% cream	–	–	–	–
Placebo/no treatment	1300 (15.29 to 5560)	–	–	–
Podophyllin 20–25%	0.997 (0.12 to 3.66)	0.01 (< 0.001 to 0.08)	–	–
Cidofovir 1% gel	530.6 (2.28 to 2444)	0.47 (0.04 to 1.86)	1258 (2.11 to 5058)	–

a OR < 1 favours the intervention and OR > 1 favours the comparator.
Cells highlighted in green indicate statistically significant results.

Clearance of anogenital warts of ≥ 50%

Five interventions were evaluated in the MTC:

1. placebo or no treatment
2. imiquimod 5% cream
3. podophyllotoxin 0.5% solution
4. podophyllin 20–25%
5. cidofovir 1% gel.

The fixed-effects model was a better fit than the random-effects model (DIC 64.2 vs. 65.3, respectively). The residual deviance of the fixed-effects model was also similar to the number of unconstrained data points in the analysis (11.7 vs. 12, respectively).

Based on the fixed-effects model, podophyllotoxin 0.5% solution was found to be significantly more effective than imiquimod 5% cream and placebo at reducing the volume of AGWs by ≥ 50% compared with the baseline volume (*Table 14*). No other difference between treatments achieved statistical significance.

TABLE 14 Results from the MTC for clearance of ≥ 50% of the volume of AGWs

Intervention	Comparator, OR[a] (95% CrI)				
	Imiquimod 5% cream	Placebo/no treatment	Podophyllotoxin 0.5% solution	Podophyllin 20–25%	Cidofovir 1% gel
Imiquimod 5% cream	–	–	–	–	–
Placebo/no treatment	0.66 (0.39 to 1.05)	–	–	–	–
Podophyllotoxin 0.5% solution	109.2 (1.46 to 378.9)	167.2 (2.40 to 566.2)	–	–	–
Podophyllin 20–25%	1.80 (0.54 to 4.58)	2.88 (0.75 to 7.84)	0.27 (0.004 to 1.43)	–	–
Cidofovir 1% gel	3.57 (0.30 to 16.9)	5.35 (0.51 to 24.66)	0.50 (0.004 to 3.24)	2.67 (0.15 to 13.76)	–

a OR > 1 favours the intervention and OR < 1 favours the comparator.
Cells highlighted in green indicate statistically significant results.

Appearance of new anogenital warts during treatment

Ten identified studies referred to recording the appearance of new AGWs during treatment.[61,62,112,116–119,121,129,138] Of the 10 studies, three were deemed to be at an unclear or low risk of bias, provided data in a format that could be incorporated into a meta-analysis and evaluated interventions meeting the assumptions outlined earlier.[61,116,118] As per the protocol, sensitivity analysis for this outcome was not planned.

The network generated evaluated imiquimod 5% cream, podophyllotoxin 0.5% solution and placebo or no treatment. Placebo was chosen as the baseline treatment because a placebo or no treatment group was involved in all studies in the MTC. The random-effects model was the best-fitting model, with a DIC of 38.9; the DIC for the fixed-effects model was 41.1. The random-effects model was a good fit for the data, with a total residual deviance close to the number of data points analysed (residual deviance of 6.3 compared with six data points analysed).

No statistically significant differences were found between any comparisons for the probability of developing new AGWs during treatment (*Table 15*). In comparison with placebo or no treatment, the effect estimate favoured imiquimod 5% cream but not podophyllotoxin 0.5% solution (i.e. placebo was favoured over podophyllotoxin 0.5% solution; see *Table 15*).

Imiquimod 5% cream was associated with the lowest probability of new AGWs developing during treatment:

- imiquimod 5% cream: 30.4% (95% CrI 6.7% to 68.5%)
- podophyllotoxin 0.5% solution: 45.4% (95% CrI 5.8% to 91.1%)
- placebo or no treatment: 49.8% (95% CrI 40.8% to 58.7%).

Adverse effects

Given the large number of studies identified, the decision was taken to restrict the comparison and reporting of AEs. After consultation with clinical experts, the project team focused on AEs highlighted as causing discomfort to the patient or being difficult to treat should they occur. The potential for a MTC was investigated for ulceration, blistering, erythema, oedema and itching. Sensitivity analyses for AEs were not planned and reporting of AEs is limited to data from studies deemed to be at low or unclear risk of bias. AEs data were extracted in full from individual studies and are presented in the data abstraction forms in *Appendix 2*.

Ulceration

Abdullah *et al.*[153] and Godley *et al.*[154] compared TCAA with cryotherapy and reported on the occurrence of ulceration. In both studies, a larger proportion of people in the TCAA group than in the cryotherapy group experienced ulceration. Standard pairwise meta-analysis using the fixed-effects model found that TCAA was associated with a significantly higher risk of ulceration than cryotherapy (OR 0.22, 95% CI 0.10 to 0.46; $p < 0.0001$); the forest plot is presented in *Figure 13*. However, the level of heterogeneity in the analysis was high ($I^2 = 68\%$). Using a random-effects model as a sensitivity analysis generated a non-statistically significant difference between treatments (OR 0.13, 95% CI 0.01 to 1.62; $p = 0.11$).

TABLE 15 Results of the MTC for the development of new AGWs during treatment

	Comparator, OR[a] (95% CrI)		
Intervention	**Placebo/no treatment**	**Imiquimod 5% cream**	**Podophyllotoxin 0.5% solution**
Placebo/no treatment	–	–	–
Imiquimod 5% cream	0.57 (0.07 to 2.17)	–	–
Podophyllotoxin 0.5% solution	2.05 (0.06 to 11.00)	8.70 (0.09 to 45.35)	–

a OR < 1 favours the intervention and OR > 1 favours the comparator.

FIGURE 13 Forest plot for the comparison between cryotherapy and TCAA for the outcome of ulceration. df, degrees of freedom; M–H, Mantel–Haenszel.

Blistering

In a comparison of cryotherapy and CO_2 laser therapy, Azizjalali *et al.*[156] found a low occurrence of blistering in each treatment group, with two and no people in the cryotherapy and CO_2 laser therapy groups, respectively, experiencing blistering (80 people were randomised to each group).

Erythema

Seven RCTs informed the MTC of erythema,[60,61,112,116,118,123,132] generating a network incorporating five interventions:

1. placebo or no treatment
2. imiquimod 5% cream
3. podophyllin 20–25%
4. podophyllotoxin 0.5% solution
5. podophyllotoxin 0.5% cream.

The fixed-effects model was found to be a better fit than the random-effects model (DIC 75.0 vs. 76.2, respectively), with a similar residual deviance to the number of unconstrained data points (14.8 vs. 15, respectively).

Using the fixed-effects model with imiquimod 5% cream as baseline, the MTC found that all active interventions were associated with a statistically significant increase in risk of erythema compared with placebo (*Table 16*). However, no statistically significant differences in erythema were identified across the comparisons of active interventions (see *Table 16*).

Of the five interventions compared, podophyllotoxin 0.5% solution was associated with the highest probability of occurrence of erythema:

1. placebo or no treatment: 19.1% (CrI 13.1% to 26.3%)
2. imiquimod 5% cream: 60.3% (95% CrI 52.6% to 67.7%)
3. podophyllin 20–25%: 44.5% (95% CrI 24.3% to 66.1%)
4. podophyllotoxin 0.5% solution: 66.8% (95% CrI 31.8% to 92.0%)
5. podophyllotoxin 0.5% cream: 50.9% (95% CrI 21.2% to 81.7%).

TABLE 16 Results of the MTC for erythema

Intervention	Comparator, OR[a] (95% CrI)				
	Imiquimod 0.5% cream	Placebo/no treatment	Podophyllin 20–25%	Podophyllotoxin 0.5% solution	Podophyllotoxin 0.5% cream
Imiquimod 5% cream	–	–	–	–	–
Placebo/no treatment	0.15 (0.10 to 0.24)	–	–	–	–
Podophyllin 20–25%	0.59 (0.19 to 1.40)	3.93 (1.17 to 9.83)	–	–	–
Podophyllotoxin 0.5% solution	2.1 (0.29 to 7.87)	13.9 (1.89 to 52.32)	3.79 (0.66 to 13.07)	–	–
Podophyllotoxin 0.5% cream	0.91 (0.17 to 3.08)	6.00 (1.10 to 20.58)	1.67 (0.37 to 5.20)	0.59 (0.12 to 1.80)	–

a OR < 1 favours the intervention and OR > 1 favours the comparator.
Cells highlighted in green indicate statistically significant results.

Oedema

The studies by Beutner *et al.*,[116] Edwards *et al.*[118] and Padhiar *et al.*[132] were included in the MTC of oedema, facilitating comparison of imiquimod 5% cream, podophyllin 20–25% and placebo or no treatment.

The best-fitting model was the fixed-effects model, with a DIC of 31.5 compared with 32.3 for the random-effects model. Additionally, the fixed-effects model was a good fit for the data (residual deviance of 5.1 compared with six unconstrained data points in the analysis).

Imiquimod 5% cream and podophyllin 20–25% both statistically significantly increased the risk of oedema compared with placebo:

- imiquimod 5% cream: OR 0.05 (95% CrI 0.01 to 0.13; OR < 1 favours placebo)
- podophyllin 20–25%: OR 316.2 (95% CrI 39.86 to 1304; OR > 1 favours placebo).

Additionally, podophyllin 20–25% was found to statistically significantly increase the risk of oedema compared with imiquimod 5% cream (OR 12.39, 95% CrI 2.74 to 40.21; OR > 1 favours imiquimod 5% cream).

Itching

Three studies informed the MTC of itching,[61,116,132] enabling comparison of imiquimod 5% cream, podophyllin 20–25%, podophyllotoxin 0.5% solution and placebo or no treatment.

The random- and fixed-effects models were similar in terms of goodness of fit (DIC 35.2 vs. 35.2, respectively) and had the same residual deviance (6.1 vs. 6.1, respectively), which was close to the number of unconstrained data points in the analysis (six data points). However, because of the possibility of clinical heterogeneity in the populations of the trials combined in the network, the random-effects model was preferred.

There was no significant difference in the risk of itching between any of the active treatments compared with placebo (*Table 17*). Similarly, there was no significant difference between any of the active treatments compared with one another for this adverse event.

Of the active interventions, podophyllin 20–25% had the highest probability of being associated with itching (51.2%, 95% CrI 6.8% to 93.7%). Imiquimod 5% cream and podophyllotoxin 0.5% solution had similar probabilities of being associated with itching, at 30.7% (95% CrI 21.5% to 40.6%) and 39.9% (95% CrI 0.1% to 96.5%), respectively.

TABLE 17 Results of the MTC for itching

Intervention	Comparator, OR[a] (95% CrI)			
	Imiquimod 0.5% cream	Placebo/no treatment	Podophyllotoxin 0.5% solution	Podophyllin 20–25%
Imiquimod 0.5% cream	–	–	–	–
Placebo/no treatment	1.19 (0.03 to 6.0)	–	–	–
Podophyllotoxin 0.5% solution	18.0 (0.02 to 62.8)	9.21 (0.14 to 52.2)	–	–
Podophyllin 20–25%	6.8 (0.16 to 35.8)	93.6 (0.12 to 230.5)	111.4 (0.02 to 240.8)	–

a OR < 1 favours the intervention and OR > 1 favours the comparator.

Summary of evidence synthesis

Analysis by MTC indicated that, in line with the conclusions outlined in European guidelines,[6] ablative techniques, and in particular CO_2 laser therapy, are generally associated with higher probabilities of complete clearance of AGWs at the end of treatment. There was considerable disparity in the probability of achieving complete clearance between podophyllotoxin 0.5% solution and imiquimod 5% cream, which are the mainstays of topical treatment. Podophyllotoxin 0.5% solution had a 92.6% (CrI 81.8% to 98.4%) probability of completely clearing lesions compared with 56.1% (CrI 20.3% to 85.0%) for imiquimod 5% cream. However, the wide CrIs indicate that there is considerable uncertainty associated with the results and the findings should be interpreted with caution.

In the primary MTC, there was no statistically significant difference between most of the treatments evaluated for complete clearance of AGWs at the end of treatment. Of those differences that reached statistical significance, most of the comparisons involved CO_2 laser therapy or podophyllotoxin 0.5% or 0.3% solution.

CO_2 laser therapy was found to be significantly more effective than:

- imiquimod 5% cream: OR 247.0 (95% CrI 3.03 to 1087; OR > 1 favours CO_2 laser therapy)
- TCAA: OR 86.15 (95% CrI 4.05 to 415.3; OR > 1 favours CO_2 laser therapy)
- cryotherapy: OR 44.61 (95% CrI 3.30 to 201.7; OR > 1 favours CO_2 laser therapy)
- TCAA plus podophyllin: OR 0.13 (95% CrI 0.003 to 0.59; OR < 1 favours CO_2 laser therapy)
- cryotherapy plus podophyllin: OR 0.22 (95% CrI 0.004 to 0.94; OR < 1 favours CO_2 laser therapy).

Podophyllotoxin 0.5% solution was associated with statistically significant improvements in complete clearance at the end of treatment compared with:

- podophyllotoxin 0.5% cream: OR 0.30 (95% CrI 0.04 to 0.99; OR < 1 favours podophyllotoxin 0.5% solution)
- podophyllotoxin 0.3% cream: OR 0.19 (95% CrI 0.007 to 0.874; OR < 1 favours podophyllotoxin 0.5% solution)
- TCAA: OR 0.17 (95% CrI 0.02 to 0.63; OR < 1 favours podophyllotoxin 0.5% solution).

Limited reporting of data in available publications for other outcomes of interest led to restricted networks involving few interventions.

Chapter 4 Assessment of cost-effectiveness

Evidence on the cost-effectiveness of interventions to treat AGWs was identified by carrying out a systematic review of the published research literature (see *Systematic review of existing cost and cost-effectiveness evidence*) and through development of a de novo economic analysis (see *Independent economic assessment: methods* and *Independent economic assessment: results*).

Systematic review of existing cost and cost-effectiveness evidence

Search strategy

A systematic review was carried out in September 2013 to identify relevant published cost-effectiveness and costing studies on the treatment of AGWs. The following databases were searched from inception:

- MEDLINE (Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE)
- EMBASE (Ovid EMBASE)
- HTA database (The Cochrane Library)
- NHS Economic Evaluation Database (NHS EED; The Cochrane Library).

The search strategy combined terms to capture AGWs and terms to capture economic evaluation and costing studies. Full details of the search terms are presented in *Appendix 1*.

In addition to searching the above databases, reference lists of identified studies were reviewed for potentially relevant studies. No restrictions on language or setting were applied to any of the searches. Studies were assessed for inclusion based on the criteria outlined in *Table 18*.

The systematic review was updated in March 2014. The search strategy remained the same as outlined above; however, results were limited from 2013 to March 2014 to identify only additional relevant studies.

Search results

A total of 952 studies were identified from the September 2013 database search as being potentially relevant (*Figure 14*). Two health economists independently appraised the titles and abstracts of these studies; 270 studies were identified as duplicates and 626 studies were excluded on the basis of title and abstract. A total of 56 studies were therefore identified as potential economic evaluations or costing studies and were ordered for full review.

TABLE 18 Inclusion and exclusion criteria for the systematic review of economic evaluation and costing studies

Search	Inclusion criteria	Exclusion criteria
Economic evaluations	Study population with AGWs	Literature reviews
	Any economic evaluation study: cost-effectiveness (including cost–utility) analyses, cost–benefit analyses, cost-minimisation analyses, cost–consequence analyses	
Costing studies	Study population with AGWs	

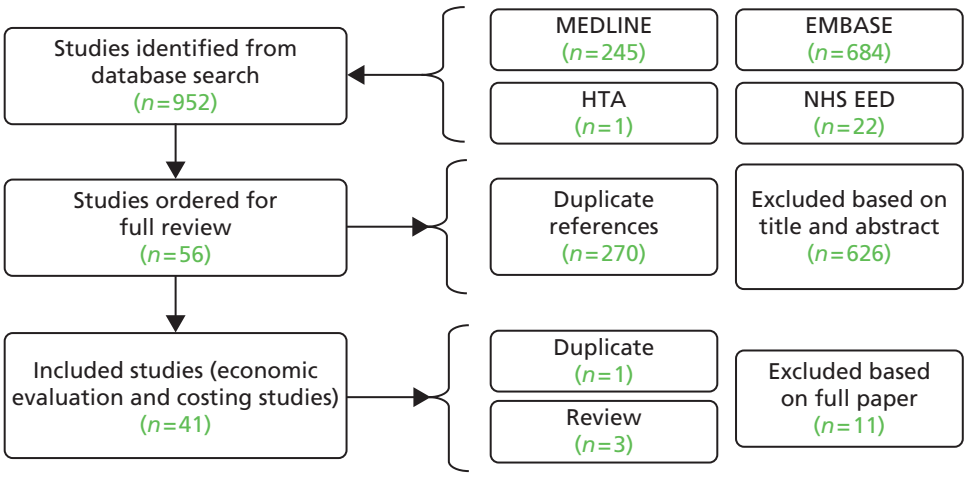

FIGURE 14 Identified economic evaluation and costing studies, September 2013 search.

After review of the full papers, a total of 41 papers were included: 10 were economic evaluations,[64,163–171] seven were UK costing studies[3,51,172–176] and 24 were non-UK costing studies.[177–200] The remaining 15 studies[64,201–214] were excluded for the following reasons:

- duplicate paper (one study)[64]
- literature review (three studies)[201,211,212]
- not a costing study nor an economic evaluation (seven studies)[202,204,206–210,213,214]
- not AGWs (four studies).[203,205]

The updated search carried out in March 2014 identified an additional 102 potentially relevant economic evaluation and costing studies. The title and abstracts of these studies were appraised independently by two health economists. A total of 61 studies were identified as duplicate studies, 40 studies were excluded based on title and abstract and one UK costing study was ordered for full review. This further UK costing study[215] was included in the review (*Figure 15*).

Consequently, a total of 10 economic evaluation studies[64,163–171] and eight UK costing studies[3,51,172–176,215] were identified and reviewed; the results from these studies are summarised in the following sections.

Description of the identified cost-effectiveness studies

A total of 10 economic evaluation studies were identified from the September 2013 search.[64,163–171] A summary of the identified economic evaluations is presented in *Table 19*, with full data extraction tables presented in *Appendix 2*.

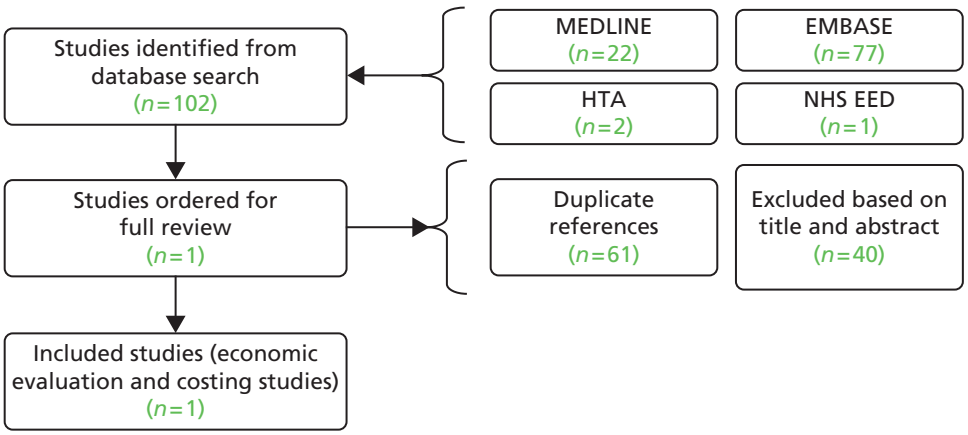

FIGURE 15 Identified economic evaluation and costing studies, March 2014 search.

TABLE 19 Summary of the identified economic evaluations

Author, year, country	Interventions	Analysis, time horizon	Key outcome measure	ICER
Langley 2010,[163] USA	Sinecatechins vs. imiquimod	Decision analysis, < 1 year	Sustained clearance of warts	NR
Walczak 2009,[164] Poland	Imiquimod vs. podophyllotoxin	Decision analysis, < 1 year	Total clearing of warts	Incremental cost per total clearing of warts
Lacey 2003,[64] UK	Clinic-applied 25% podophyllin, patient-applied 0.15% podophyllotoxin cream, patient-applied 0.5% podophyllotoxin solution	Trial-based analysis, < 1 year	Complete remission of warts at 12 weeks	Incremental cost per additional patient cured
Lafuma 2003,[165] France	Imiquimod 5% vs. podophyllotoxin 0.5% first line followed by laser therapy	Decision analysis, < 1 year	Proportion of patients cured	Incremental cost per additional patient cured
Williams 2003,[166] UK	Imiquimod vs. podophyllotoxin	Decision analysis, < 1 year	Sustained clearance of warts	Incremental cost per additional sustained clearance
Alam *et al.* 2001,[167] USA	Podophyllin resin 25%, podophyllotoxin, TCAA, imiquimod, interferon-alpha-2b, cryotherapy, electrodessication, surgical excision and laser	Decision analysis, time horizon NR	Complete clearance	NR
Fagnani 2000,[168] France	Imiquimod 5% vs. podophyllotoxin gel 0.5% first line followed by CO_2 laser therapy	Decision analysis, < 1 year	Patients cured	NR
Langley 1999,[169] USA	Analysis 1: imiquimod 5% first line followed by podophyllin, cryotherapy or TCAA	Decision analysis, < 1 year	Sustained clearance	NR
	Analysis 2: podofilox (podophyllotoxin 0.5% solution) first line followed by podophyllin, cryotherapy or TCAA			
	Analysis 3: cryotherapy first line followed by imiquimod 5%			
Langley 1999,[170] USA	Analysis 1: imiquimod vs. podofilox (podophyllotoxin 0.5% solution)	Decision analysis, < 1 year	Sustained clearance	NR
	Analysis 2: podophyllin, laser surgery, cryotherapy, TCAA second line			
Mohanty 1994,[171] UK	Podophyllin 25% resin vs. podophyllotoxin 0.5% solution first line followed by cryotherapy, TCAA or electrocautery	NA, retrospective analysis of clinic data	Patients cured	NR

ICER, incremental cost-effectiveness ratio; NA, not applicable; NR, not reported.

In general, the analyses presented within the identified studies were non-comparative, with four of the 10 studies reporting an incremental cost-effectiveness ratio (ICER).[64,164–166] The remaining six studies reported the cost per benefit for each intervention but did not compare between therapies.[163,167–171] No studies reported a cost–utility analysis, that is, no economic evaluation used health-related quality of life (HRQoL) as the measure of outcome.

The stated study population varied within the studies and was reported alternatively as those with AGWs,[166] condylomata acuminata,[167] external AGWs,[165] external genital warts,[163,168–170] genital and perianal warts,[164] and genital warts.[64,171] Following consultation with clinical experts, it was advised that the terms 'genital' and 'anogenital' warts are commonly used interchangeably, both within the literature and in clinical practice. Consequently, the distinction between the populations reported in each study is not considered to constitute a significant source of heterogeneity between studies.

Of the 10 identified economic evaluations, eight reported results calculated from simple decision analyses, including one UK study.[163–170] A critique of these analyses is presented in *Appendix 2* using the Philips *et al.*[216] checklist for decision-analytical models. Models took the form of either a one-stage or a two-stage decision tree. The two remaining studies were UK based; one study carried out a trial-based economic evaluation[64] and the remaining study analysed retrospective clinic data.[171] The time horizon for each identified economic evaluation was < 1 year; discounting was not applied to costs or benefits in any of the identified studies.

A one-stage decision tree was described within six of the studies.[163,164,166,167,169,170] In these studies, the cost and outcomes associated with one line of treatment for external genital warts were estimated. The key outcome for these models was complete clearance[164,167] and sustained clearance[163,166,169,170] of lesions. People entering each model were either clear or not clear of lesions at the end of the analysis.

Two-stage decision trees were described within four studies.[165,168–170] In these analyses, a second-line treatment was incorporated, allowing for non-response, relapse or recurrence after first-line treatment. Similar to the one-stage decision analyses, the key outcome for these models was sustained clearance[169,170] and patients cured.[165,168] The two-stage sequential models were characterised by first-line treatment with patient-administered therapy followed by second-line provider-administered ablative therapies.

Of the 10 studies, three were UK based.[64,166,171] A narrative description is presented in *Boxes 2–4* for the included economic evaluation studies adopting a UK perspective.

Description of the identified costing studies

A total of 32 costing studies were identified in the review (31 from the September 2013 search and one from the March 2014 search). Of these 32 studies, eight reported data from the UK.[3,51,172–176,215] UK data were considered to be the most relevant for this economic evaluation; therefore, these eight studies were extracted in full (see *Appendix 2*).

The cost of managing genital warts was reported both at a national level (total cost of treating genital warts)[3,51,172,173,215] and at a micro level (cost per episode of care).[3,51,173–176,215] At a national level, four publications reported three separate analyses that estimated the UK total cost of genital wart treatment. Lanitis[51] and Carroll *et al.*[173] reported the results of one analysis in which the annual UK cost associated with treating genital warts was estimated to be £52.4M. A second analysis, reported by Brown *et al.*,[172] estimated the annual UK cost to be £22.4M. Chapman *et al.*[215] presented results for the UK (£58.4M) and each of the devolved nations (England £41.72M, Scotland £1.90M, Wales £1.87M, Northern Ireland £0.95M). Finally, Desai *et al.*[3] reported total costs for England (£16.8M). The estimated average cost per episode of care ranged from £94,178 to £27,651 (*Table 20*).

BOX 2 Summary of cost-effectiveness data contained within the study by Lacey *et al.*[64]

Results from a trial-based analysis were reported, assessing the cost and effectiveness of self-applied podophyllotoxin 0.5% solution, self-applied podophyllotoxin 0.15% cream and clinic-applied 25% podophyllin for the treatment of genital warts.

The authors carried out an open RCT across 11 sexually transmitted disease clinics in the UK. Patients were included if they were adults, were immunocompetent, had a current episode of AGWs of ≤ 3 months in duration and were not receiving current treatment. In total, 354 patients were analysed. Effectiveness and safety data were obtained from the clinical trial. Effectiveness was captured as complete remission of all warts at 12 weeks. The estimated complete remission rates at 12 weeks were 46.9% for clinic-applied podophyllin solution, 62.2% for patient-applied podophyllotoxin cream and 70.2% for podophyllotoxin solution.

The economic analysis was performed from a societal perspective. Neither costs nor benefits were discounted. The cost year of the analysis was 1998. Both direct and indirect costs were estimated and included the cost of visits to STD clinics (estimated as the average cost across the participating clinics); the cost of drug treatment; the cost associated with patient travel; the cost of treating AEs leading to discontinuation; and production losses when patients were absent from work (estimated using average incomes for women and men in the UK in 1998). The estimated total cost of 12 weeks' treatment was £535 for clinic-applied podophyllin solution, £573 for patient-applied podophyllotoxin cream and £517 for podophyllotoxin solution.

Compared with clinic-applied podophyllin solution, patient-applied podophyllotoxin solution was estimated to be both less costly and more effective. The incremental cost per additional patient cured at 12 weeks for podophyllotoxin cream compared with podophyllin was estimated to be £246.73. The authors did not compare podophyllotoxin cream with podophyllotoxin solution. The authors noted that the conclusions of the analysis were limited because recurrence rates after individual treatments were not included.

The study provides a description of the cost-effectiveness of clinic-applied podophyllin solution and patient-applied podophyllotoxin solution but may be of limited use within this analysis because of its societal perspective, the use of 'patient cured' as the measure of outcome as opposed to quality-adjusted life-years, the lack of a reported sensitivity analysis and restriction to a within-trial analysis.

BOX 3 Summary of cost-effectiveness data contained within the study by Williams and von Krogh[166]

This study assessed the relative cost-effectiveness of podophyllotoxin (either cream or solution) and imiquimod for AGWs in HIV-negative people. A decision model was developed and the analysis was carried out from the perspective of the UK NHS.

The model was a simple decision tree that assessed the percentage of patients with sustained clearance of AGWs after treatment and follow-up. Follow-up was assumed to be 12 weeks in duration. Treatment duration varied between 4 weeks for podophyllotoxin and 16 weeks for imiquimod; therefore, the time horizon of the model was between 16 and 28 weeks. Clinical trial estimates of clearance during treatment were obtained from the literature. Identified estimates were pooled by simple summation, that is, no adjustments were made to account for differences in patient characteristics across studies. The sustained clearance percentage at the end of treatment and follow-up was calculated to be 35.1% for podophyllotoxin and 40.6% for imiquimod.

BOX 3 Summary of cost-effectiveness data contained within the study by Williams and von Krogh[166] (*continued*)

The analysis included costs of drug acquisition and GUM clinic attendance. Drug costs were obtained from the BNF (cost year 2002). GUM clinic costs were obtained from Lacey *et al.*[64] (cost year 1998). Costs were not discounted. The total cost was estimated to be £109.95 for treatment with podophyllotoxin and £245.83 for treatment with imiquimod.

The incremental cost per additional sustained clearance for imiquimod compared with podophyllotoxin was estimated to be £2477. The authors concluded that 'the modest and statistically insignificant incremental effectiveness of imiquimod is thus purchased at enormous cost'.

A series of one-way analyses and probabilistic sensitivity analysis were carried out. In probabilistic analysis, the authors found that, in 9995 of the 10,000 iterations of the model, podophyllotoxin treatment was dominant when compared with imiquimod (i.e. was less costly and more effective). This conclusion implies that only five out of 10,000 simulations resulted in imiquimod having higher efficacy, despite having a higher base-case efficacy (40.6% vs. 35.1%); this seems an unlikely result.

The analysis carried out may be of limited use within this analysis. This is because of the lack of a systematic review to identify all relevant trials and meta-analyses to synthesise the identified effectiveness data, the use of 'sustained clearance' as the measure of outcome as opposed to quality-adjusted life-years and the counterintuitive probabilistic results.

BOX 4 Summary of cost-effectiveness data contained within the study by Mohanty[171]

Results from a retrospective cost-effectiveness analysis using GUM clinic data were reported. Notes from people aged ≥ 16 years who attended St Luke's Hospital GUM clinic in 1991 were reviewed. In total, the notes from 6021 patients were reviewed. Of these people, 742 were diagnosed with genital warts. People who received and completed treatment with either podophyllin 25% resin or podophyllotoxin solution 0.5% first line for their genital warts were included in the analysis; this resulted in a sample size of 683 people. The cost of first- and second-line therapy was incorporated into the analysis. Second-line therapy was cryotherapy, TCAA or electrocautery; the choice of second-line therapy was dependent on the size and number of warts.

Effectiveness of therapy was assessed as 'warts cured'; this was defined as complete clearance of warts by thorough clinical examination under bright light with no recurrence within 3 weeks of clearance. The percentage of patients cured was 34.6% for podophyllin 25% resin and 66% for podophyllotoxin solution 0.5%.

The analysis estimated the costs of drugs and staff associated with the treatment of each patient. The average cost per patient was estimated to be £14.95 for podophyllin 25% resin and £20.75 for podophyllotoxin solution 0.5%. Costs were not discounted.

Incremental cost-effectiveness was not reported. Instead, the authors presented a cost per patient cured of £27.15 for podophyllin 25% and £25.75 for podophyllotoxin solution 0.5%. The authors concluded that, although the cost per patient was higher for podophyllotoxin solution than for podophyllin, because the efficacy of podophyllotoxin was greater than that of podophyllin, the cost per patient cured was lower for podophyllotoxin solution. No sensitivity analysis was reported.

The data reported are of limited use within this analysis; this is because of the use of retrospective case note effectiveness data, a lack of incremental cost-effectiveness analysis and a lack of sensitivity analysis.

TABLE 20 Summary of UK costing studies identified in the literature review

Study	Population	Cost year	Number of episodes (location of episode)	Cost per episode (£)	Total population cost (£)
Chapman 2013[215]	UK and devolved nations	NR	220,779 in the UK; 157,693 (England), 7461 (Scotland), 7091 (Wales), 3619 (Northern Ireland)	265	£58.42M UK; £41.72M (England), £1.90M (Scotland), £1.87M (Wales), £0.95M (Northern Ireland)
Lanitis 2012[51]	UK	2010	173,077 (GUM clinic), 16,782 (primary care)[a]	276	£52.4M
Desai 2011[3]	England	2008–10	141,770 (GUM clinic), 39,645 (primary care), 1978 (hospital)	113	£16.8M
Carroll 2011[173] (linked to Lanitis 2012[51])	UK	2010	173,077 (GUM clinic), 16,882 (primary care)[a]	273 (women); 278 (men)	£52.4M
Woodhall 2011[176]	Seven GUM clinics in the UK	2010	370 (GUM clinic)	94	NR
Woodhall 2009[175]	York GUM clinic	2007	189 (GUM clinic)	139	NR
Brown 2006[172]	UK	2003	132,114 (GUM clinic)	NR	£22.4M
Langley 2004[174]	Six GUM clinics in England and Wales	NR	1200 chart reviews (GUM clinic)	146.37 (women); 135.77 (men)	NR

NR, not reported.
a The number of GP episodes was reported as 16,782 in Lanitis *et al.*[51] and 16,882 in Carroll *et al.*[173]

For studies reporting national-level cost estimates, the population included people attending GUM clinics,[3,51,172,173,215] attending in primary care[3,51,173,215] and receiving hospital treatment.[3] All studies described the patient population as people diagnosed with genital warts. No study identified people with AGWs as a separate population; however, clinical experts advised that the terms 'genital warts' and 'anogenital warts' are often used interchangeably, and the term 'genital warts' is considered appropriate to capture both genital warts and AGWs.

A narrative summary of the eight UK costing studies is provided in *Boxes 5–11*.

Summary of the systematic review of existing cost and cost-effectiveness evidence

A total of 10 economic evaluations and eight UK-based costing studies relevant to an economic analysis of treatments for AGWs were identified from the literature review.

Of the identified costing studies, four reported the total cost of treating genital warts in the UK[51,172,173,215] and two reported the total cost of treating genital warts in England.[3,215] A cost per episode of care was reported in seven of the eight identified costing studies.[3,51,173–176,215] Chapman *et al.*[215] present, in an abstract, the results of an analysis in which the annual UK and devolved national costs of genital warts were estimated; the UK cost was estimated to be £58.42M. Lanitis[51] and Carroll *et al.*[173] present the results of one analysis in which the annual UK cost associated with treating genital warts was estimated at £52.4M. A further analysis, reported by Brown *et al.*,[172] estimated the annual UK cost of treatment for AGWs at £22.4M. The estimated average cost per episode of care ranged from £94[176] to £276.[51]

BOX 5 Summary of cost data contained within the study by Chapman *et al.*[215]

The authors present a conference abstract in which the cost of managing genital warts in the UK and each devolved nation was estimated. The cost per episode of genital warts was estimated to be £265. At a national level the annual UK cost of managing genital warts was estimated to be £58.42M, with costs of £41.72M for England, £1.9M for Scotland, £1.87M for Wales and £0.95M for Northern Ireland. Cost was calculated by multiplying the number of people with genital warts presenting at GUM clinics and primary care in the UK and devolved nations by the expected resource use for these patients (as estimated by GUM experts) and applying UK-specific unit costs.

The number of people with genital warts presenting at GUM clinics was estimated using HPA data for the UK and England and data from the Information Services Division for Scotland, the Communicable Disease Surveillance Centre for Wales and the Public Health Agency for Northern Ireland. The number of people with genital warts presenting in primary care was estimated using data from the Health Improvement Network database extrapolated using population statistics to estimate the number of genital wart cases at national level.

BOX 6 Summary of cost data contained within the studies by Lanitis[51] and Carroll *et al.*[173]

Both studies report the cost of managing genital warts in the UK estimated from the same analysis; Carroll *et al.*[173] is a conference abstract and Lanitis[51] is the full paper publication. Both studies report an estimated UK cost of managing genital warts of £52.4M (cost year 2010). The average cost per episode was estimated to be £276. Cost was calculated by multiplying the number of people with genital warts in the UK by the expected resource use for these patients and applying UK-specific unit costs.

The number of people with genital warts in the UK was estimated by combining the number of people attending GUM clinics with the number of people attending primary care as a result of genital warts. GUM clinic data were obtained from the 2009 HPA surveillance report and primary care data were obtained from the Health Improvement Network database; both were projected to estimate 2010 figures. GUM clinic data were presented by episode type: first episode (96,278 people), recurrent episode (58,109 people) and persistent episode (18,690 people). Primary care data were not divided into categories. To avoid double counting across databases, patients not prescribed treatment by GPs in primary care were assumed to have been referred to a GUM clinic. The number of patients treated in primary care was estimated to be 16,782 in Lanitis[51] and 16,882 in Carroll *et al.*[173] The total number of people with genital warts in GUM clinics and primary care in 2010 was estimated as 189,859.

To estimate treatment utilisation patterns, four GUM clinicians were surveyed and each provided an estimate of the number of visits required per patient, based on type of case (whether first episode, recurrent episode or persistent episode) and type of wart (keratinised or non-keratinised). Most genital wart episodes were found to require two visits, with persistent and hard-to-treat warts requiring three or more and eight to twelve visits, respectively. Keratinised warts were more likely to be treated with cryotherapy or combination therapy than with topical therapy alone, whereas non-keratinised warts were more likely to be treated with topical therapy. The authors considered that the proportion of patients treated with topical compared with ablative therapy 'remained fairly consistent regardless of the episode'.[51]

Unit costs of treatment were applied to the estimated number of episodes and the treatment patterns estimated by the four clinical advisors. A sensitivity analysis was carried out in which costs and patient characteristics were varied; the total cost estimate was most sensitive to the proportion of hard-to-treat patients.

BOX 7 Summary of cost data contained within the study by Desai *et al.*[3]

The authors present an estimated cost of care in 2008 for people with genital warts in England presenting at GUM clinics, general practices and NHS hospitals. The estimated total cost was £16.8M (95% CI £15.5M to £18.0M), with an estimated average cost per episode of care of £113. Cost was calculated by multiplying the estimated number of people with genital warts in England with the expected resource use for these patients and applying UK-specific unit costs.

The number of people presenting with genital warts (new and recurrent cases) was obtained for GUM clinics, GP surgeries and NHS hospitals. The number of people attending GUM clinics for genital warts was obtained from HPA data; data from 2008 and 2009 were averaged to provide an estimate of 141,770 cases each year. To obtain GP surgery data, the General Practice Research Database (GPRD) was reviewed between 2006 and mid-2008; GPRD data were extrapolated to the total population under GP care in England, resulting in an estimated 39,645 episodes of care annually. Hospital data were obtained using Hospital Episode Statistics for people treated in a NHS hospital with a primary diagnosis of 'anogenital (venereal) warts'. In total, 1978 episodes of care were recorded to this code in 2008. To account for overlap between GPRD and HPA data, an episode with a referral code or at least one diagnostic code in the referral table and an episode with no treatment recorded were assumed to have been referred to a GUM clinic. Costs presented by Woodhall *et al.*[176] were applied to the number of people with genital warts.

BOX 8 Summary of cost data contained within the study by Woodhall *et al.*[176]

The authors present an estimated cost of care for people with genital warts in 2010 based on review of the treatment of patients presenting at seven sexual health clinics. The authors carried out a case note review of 370 people aged ≥ 16 years attending six sexual health clinics in England and one clinic in Northern Ireland. Patients were required to have a current diagnosis of genital warts (new or recurring episode) and to have attended the clinic between April and June 2007. Resources used in the care of each participant were recorded and costs were applied through a mixture of standard UK unit costs and clinic estimates of cost.

The case note review implied that patients attended for a mean of 2.5 visits per episode of care. An episode of care lasted for a weighted mean of 36 days (95% CI 27 to 46 days). The percentage of patients attending once was 45% for women and 55% for men. The authors also reported consultation times at clinic by staff involved in the visit. The estimated mean cost per episode of care was £94 without a STI screen and £146 with a STI screen (2010 cost year).

BOX 9 Summary of cost data contained within the study by Woodhall *et al.*[175]

The authors present an estimated cost of care for adults with genital warts in 2007 based on review of the treatment of patients presenting at a York sexually transmitted disease clinic. The authors carried out a case note review of 189 patients registered at the clinic and diagnosed with genital warts (first or recurrent episode) and recorded the resources used by each patient. The time taken for each procedure was estimated through interviews with nine members of the clinical team.

UK costs were applied to the resources used; staff costs were taken from the *Unit Costs for Health and Social Care 2007*, published by the Personal Social Services Research Unit. The costs of treatment carried out in the clinic (cryotherapy, curettage, electrosurgery/hyfrecation, electrosurgery/diathermy, TCAA) were estimated from local costs of equipment and consumables. The cost of home treatment was estimated from the BNF 2007. The authors presented total costs in US dollars, converting from UK cost figures using an exchange rate of £1 = $2.0551. The mean cost of an episode of care was estimated to be $286 (£139).

The mean number of visits per episode of care (both first and recurrent) was estimated to be 2.8 (95% CI 2.4 to 3.2). Nearly half (46%) of all patients had one visit per episode of care; of these patients, > 80% had been provided with home treatment (either podophyllotoxin or imiquimod). The average length of an episode of care was 41 days, with 3% of cases having an episode of care > 6 months.

The authors found that the mean cost for first episodes was greater than the mean cost for recurrent episodes although this was not statistically significant (first episode $296 vs. recurrent episode $266; $p = 0.43$); this was a result of a lower average number of visits to a clinician (first episode 2.9 visits vs. recurrent episode 2.74 visits) and a shorter mean duration of episode of care (first episode 44 days vs. recurrent episode 36 days).

BOX 10 Summary of cost data contained within the study by Brown *et al.*[172]

The authors report an estimated resource use and cost associated with screening and management of cervical dysplasia and cervical cancer, and treatment of genital warts in 2003. For the calculation of costs associated with the treatment of genital warts, the authors estimated the number of people with genital warts in the UK and multiplied this by the estimated resource use and associated costs to estimate a total cost of genital wart treatment in 2003. The total 2003 UK cost was estimated to be £22,402,330.

The number of people with genital warts (first or recurrent) presenting in GUM clinics was obtained from HPA surveillance data. The number of genital wart cases reported by GUM clinics in 2003 in the UK was 76,457 for incident cases, 38,902 for recurrent cases and 16,755 for persistent cases. Data for drug use, procedures and number of visits per episode was obtained from questionnaires sent to six GUM clinicians in Aberdeen, Liverpool, London (two clinicians), Nottingham and Southampton. Telephone interviews were conducted with each respondent to review and clarify responses. Responses were pooled and mean rates of events were used for costing. Length of visit was obtained from the study by Langley *et al.*,[174] which carried out a retrospective chart review. Physician and nurse costs were obtained from the *Unit Costs for Health and Social Care 2001*. For GUM clinic visits for diathermy, cryotherapy or combination therapy (procedure plus drug therapy), an all-inclusive payment was obtained from personal communication with a clinician. Costs of topical treatments were obtained from the BNF, accessed online in February 2006.

BOX 11 Summary of cost data contained within the study by Langley *et al.*[174]

The authors report the results of a retrospective case note review of people with external genital warts, carried out in six GUM clinics in England and Wales in 2000. At each clinic, the case notes of 100 female and 100 male patients, each with a completed episode of care, were evaluated and costs were applied to the resources consumed. The treatment patterns observed in the audit were reported elsewhere.[209]

The following costs were included in the analysis: labour costs, material costs, extra costs (i.e. STI screening) and clinic-related indirect costs. The sources of cost data were not provided within the study. Labour costs were described as being estimated using annual salaries. Indirect costs were described as non-labour expenses, non-patient care expenses and direct patient care costs.

The average total cost of an episode of care across the six study sites was estimated to be £146.37 for women and £135.77 for men. There was a high amount of variability in the average cost per episode of care across study sites; the cost for women varied between £96.78 and £265.31 and the cost for men varied between £66.57 and £195.58.

Of the identified economic evaluation studies, none incorporated HRQoL as the measure of benefit; moreover, only four of the 10 studies reported a fully incremental analysis.[64,164–166] The outcome measure used in all analyses was related to complete clearance or complete curing of AGWs. Of the 10 identified studies, eight reported decision analyses, all of which were simple decision trees restricted to one or two lines of therapy.[163–170] None of the identified decision analyses incorporated costs associated with AEs, and uncertainty was not comprehensively assessed in any of the decision analyses.

Imiquimod and podophyllotoxin were the most widely assessed therapies and were assessed head-to-head in seven studies.[164–170] Three of these seven studies presented ICERs,[164–166] and all reported that imiquimod was associated with an incremental cost and an incremental benefit compared with podophyllotoxin. Ablative therapies were generally assessed at second line of treatment.

Therefore, to obtain an analysis that included HRQoL estimates and assessed as fully as possible the scope of this review (see *Chapter 2*, *Decision problem*), a de novo economic model was developed; the methods are described in the following section, with the results presented in *Independent economic assessment: results*.

Independent economic assessment: methods

Scope

The scope of the independent economic assessment is described in *Table 21* and reflects the decision problem as outlined in *Chapter 2* (see *Decision problem*). When the economic assessment deviates from the decision problem, a rationale is provided within the table.

TABLE 21 Summary of the independent economic assessment

Element	Overview	Comments	Reference section
Type of economic evaluation	Cost-effectiveness analysis; health benefit assessed using quality-adjusted life-years (i.e. cost–utility analysis)	–	*Model structure*
Population	People aged ≥ 16 years with clinically diagnosed AGWs, irrespective of biopsy confirmation	–	*Population*
Interventions	The following interventions were considered in the economic evaluation: • no treatment • topical treatment: imiquimod 5% cream, podophyllin 20–25%, podophyllotoxin 0.5% solution, TCAA • ablative treatment: CO_2 laser therapy, cryotherapy, surgical excision • combination treatment: cryotherapy plus podophyllin 25%, cryotherapy plus podophyllotoxin 0.15% cream, TCAA plus podophyllin 25%	The following interventions were not considered in the economic evaluation because of a lack of any supporting clinical data: • cidofovir • electrotherapy • any combinations of treatments in addition to those listed • podophyllotoxin cream 0.15%	*Interventions*
Model			
Perspective	NHS and PSS	–	*Model structure*
Model type	Decision tree	–	
Time horizon	58 weeks	–	
Discounting	No discounting	No discounting because of the short model time frame (approximately 1 year)	

PSS, Personal Social Services.

Model structure

A simple decision-tree model was developed from the perspective of the UK NHS and Personal Social Services to capture the key costs and consequences associated with alternative treatments for a single episode of AGWs. Costs captured included costs of interventions and resource use associated with AGWs. Consequences were assessed as quality-adjusted life-years (QALYs). The model structure is presented in *Figure 16*.

Within the model structure developed, people with AGWs are initially prescribed a first-line treatment. The aim of treatment is to completely clear AGWs. If AGWs are clear after first-line treatment, there is a probability of recurrence of AGWs within a 12-week period. If AGWs do not recur, the person remains clear of AGWs until the end of the modelled period.

If AGWs recur after first-line treatment, or if AGWs do not clear at the end of first-line treatment, a second-line treatment is prescribed. Again, AGWs either clear or do not clear at the end of second-line treatment. If AGWs clear, there is a probability of recurrence of AGWs within a 12-week period. If AGWs do not recur, the person remains clear of AGWs until the end of the modelled period.

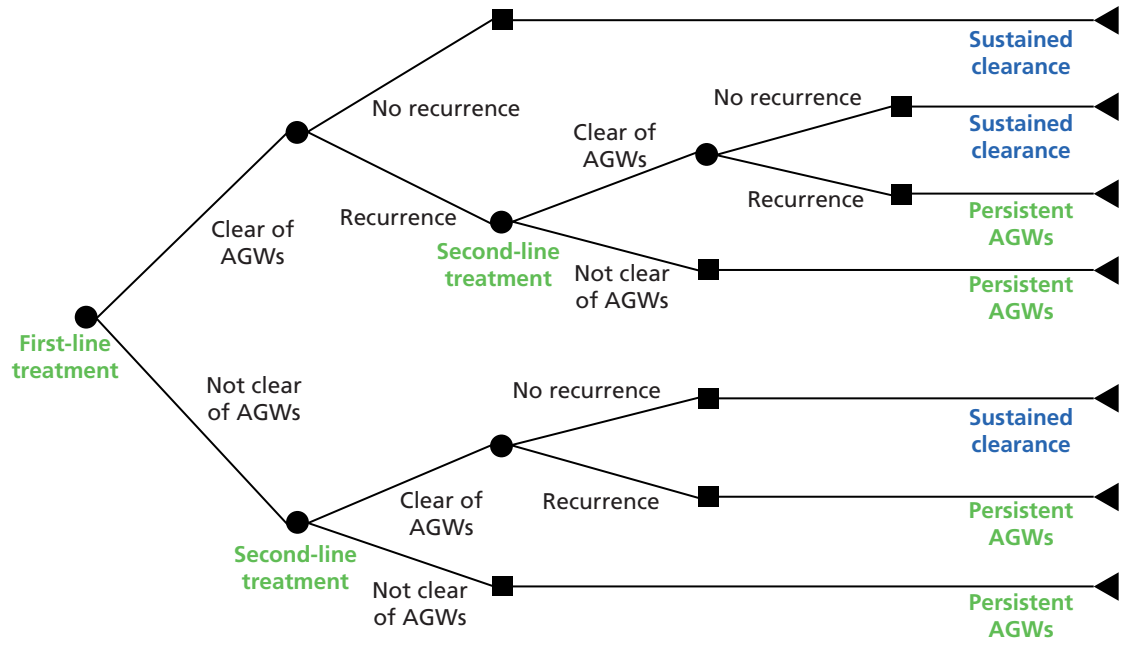

FIGURE 16 De novo model structure. In the base case, complete clearance occurs at the mid-point of treatment and recurrence occurs at the mid-point of follow-up. This was tested in sensitivity analysis.

If AGWs do not clear at the end of second-line treatment, or if AGWs recur after second-line treatment, the person is assumed to have persistent warts. A cost associated with further lines of therapy and a HRQoL decrement associated with continuing AGWs are applied.

The following key features of the model structure are described in greater detail in the following sections:

- a single episode of AGWs rather than multiple episodes of AGWs was modelled
- recurrence of AGWs after clearance is modelled
- persistent warts were defined as AGWs that have not cleared after two lines of therapy
- complete clearance and recurrence were assumed to occur half-way through follow-up.

A single episode of anogenital warts rather than multiple episodes of anogenital warts was modelled

Treatment for AGWs does not affect the underlying HPV infection; instead, treatment for AGWs is limited to treatment of the current presenting AGWs (see *Chapter 1*, *Aetiology and pathology*). Consequently, people who experience one episode of AGWs may experience future episodes of AGWs. For the purposes of this model, it was considered appropriate to capture the costs and QALYs associated with a single episode of AGWs rather than multiple AGW episodes within the economic analysis. This was for several reasons.

First, HRQoL and costs are not expected to differ between first and subsequent AGW episodes (*Box 12*). Therefore, regardless of whether the patient is experiencing a first or a later episode of AGWs, the model is considered appropriate to quantify the differences in costs and QALYs associated with each treatment.

Second, there were insufficient data identified from the literature that were associated specifically with a first or a recurrent episode of AGWs (see *Chapter 3*, *Results*); therefore, it was not possible to model multiple episodes with differing efficacy. Moreover, clinical expert opinion suggested that, for a patient with the same characteristics, the response for a subsequent episode would be expected to be similar to the response for an initial episode.

BOX 12 Health-related quality of life and costs for first and subsequent AGW episodes

Health-related quality of life

Woodhall *et al.*[176] report HRQoL for 895 people with genital warts who presented at eight UK sexual health clinics between August 2009 and February 2010. Of these, 586 were attending for their first episode and 309 for a second or later episode. The authors found no significant difference in the estimate of disutility between people with a first episode of AGWs and those with a subsequent episode.

Costs

Woodhall *et al.*[175] report data on the cost of treatment and duration of episodes of care from a retrospective case note review. The authors reviewed case notes from 189 patients attending the York sexually transmitted disease clinic during two 3-month periods in 2006 and 2007. In total, 127 patients presented for their first episode and 62 presented for a recurrent episode. Results were reported for all patients, by gender and by first or recurrent episode. The average number of visits per episode of care was similar for first and recurrent episodes [2.9 visits (95% CI 2.4 to 3.4 visits) for a first episode vs. 2.74 visits (95% CI 2.1 to 3.4 visits) for a recurrent episode]. The authors found no statistically significant difference in the mean cost between first ($296) and recurrent ($266) episodes ($p = 0.43$).

Finally, previous cost-effectiveness analyses for AGWs have used short-term decision trees to model a single episode of AGWs (see *Systematic review of existing cost and cost-effectiveness evidence*).

Based on the proposed treatment pathway informed by clinical experts, the likely impact of an episode of AGWs and the limitations imposed by the available data from the literature, using a simple decision tree was determined as the most appropriate modelling approach. More complex modelling approaches, such as a state transition Markov model, could have been used but the additional complexity was unlikely to add any benefit in this economic evaluation. In addition, a decision tree model reflects the general approach adopted within the literature.

Recurrence of anogenital warts after clearance is modelled

In clinical practice, a proportion of patients may experience a recurrence of AGWs after initial clearance. Typically, based on consultation with clinical experts, recurrence up to 12 weeks after initial clearance is considered clinically to be an extension of the initial episode of AGWs rather than a new episode. Therefore, it was considered appropriate to include the treatment costs and QALYs for these patients in the economic model.

In addition, of the 10 identified cost-effectiveness analyses (see *Description of the identified cost-effectiveness studies*), one study used clearance of AGWs at the end of treatment as the outcome measure of interest.[167] The remainder (nine studies) incorporated some element of time between clearance at the end of treatment and assessment of clearance.[64,163–166,168–171] It is therefore considered that incorporation of recurrence within the model structure is in line with the majority of the identified economic evaluation studies on this topic.

The clinical data for AGW recurrence during follow-up were analysed using a MTC and are described in greater detail in *Chapter 3* (see *Assessment of effectiveness*). A number of weaknesses associated with the clinical data for recurrence were identified, including a lack of data for some included treatments and differences in the time point at which recurrence was assessed.

Despite limitations of the data, it was considered clinically appropriate to model recurrence within the model structure. The data for recurrence were tested extensively in sensitivity analysis to establish the importance of this variable as a driver for cost-effectiveness. These issues are explored in greater detail in *Recurrence of anogenital warts within 12 weeks of complete clearance*.

Persistent warts were defined as anogenital warts that have not cleared after two lines of therapy

In the model, people with AGWs receive up to two lines of therapy, plus, for those people not clear of AGWs after two lines of therapy, a cost and HRQoL associated with treatment of persistent AGWs.

Although the definition of persistent warts is variable, as a simplifying assumption it was considered appropriate to limit the number of lines of therapy prior to treatment for persistent warts to two. Following the systematic review of the cost literature (see *Systematic review of existing cost and cost-effectiveness evidence*), evidence presented within the studies by Lanitis[51] and Woodhall *et al.*[175,176] implied that the majority of people with AGWs require two or fewer appointments with a clinician whereas patients with persistent warts require additional appointments (*Box 13*).

If at each appointment a new prescription was provided, this would imply that two lines of treatment within the model would capture the treatment pathway for the majority of people with AGWs. Moreover, this could be an overestimate of the number of lines of therapy prescribed in practice, as a proportion of patients may return to the clinician to verify complete clearance rather than receive a new prescription. For people requiring a greater number of appointments, the model captures the costs associated with additional treatment through the 'persistent AGWs' phase of the economic model.

Lanitis,[51] Woodhall *et al.*[175] and Brown *et al.*[172] defined persistent AGWs as an episode of AGWs in which treatment continues for > 3 months. Alternative definitions include AGWs that last beyond two lines of therapy (clinical expert opinion) and AGWs that have not cleared despite numerous applications of multiple therapies after a period of approximately 1 year (clinical expert opinion). Within the protocol for this analysis, persistent AGWs were defined as AGWs that had remained for 6 months.

To reflect the varying interpretations of persistent warts present within clinical practice and the literature, within the model patients are assumed to have persistent AGWs after their AGWs have failed to completely clear with two lines of therapy. The duration of persistent AGWs is set at a minimum of 12 weeks after failure on two lines of therapy. Therefore, all people in the model who go on to have persistent AGWs are assumed to have AGWs for 58 weeks. This assumption is tested in sensitivity analysis.

BOX 13 Average number of clinician appointments required for a single episode of AGWs: results from the systematic review of the AGW cost literature

Lanitis[51] surveyed four clinical experts who observed that the majority of people with AGWs required two clinician visits and that people with persistent warts more commonly required three or more visits.

Woodhall *et al.*[176] reviewed the case notes for 370 patients; patients attended for a mean of 2.5 visits per episode of care, with the majority of patients (45% of women, 55% of men) attending for one visit.

Woodhall *et al.*[175] found that, following review of the case notes for 189 patients, patients attended for a mean of 2.8 visits per episode of care, with the majority (46%) attending for one visit per episode of care.

Complete clearance and recurrence were assumed to occur half-way through follow-up

In the base case it was assumed that people achieving complete clearance of AGWs at the end of treatment were clear at the mid-point of the treatment duration. Similarly, it was assumed that any patient experiencing recurrence of AGWs experienced this at the mid-point of follow-up. This was a simplifying assumption, designed to reflect the fact that some patients would clear/recur immediately and some patients would clear/recur towards the end of treatment/follow-up. This assumption was tested in sensitivity analysis.

Time horizon and discounting

The time horizon of the model was 58 weeks. This reflects the maximum possible treatment and follow-up period (46 weeks; see *Interventions*) plus a minimum 12 weeks of persistent AGWs. Because of the short model time frame (approximately 1 year), costs and consequences were not discounted.

It was considered that a time horizon of 58 weeks (406 days) would capture the costs and consequences of the vast majority of AGW episodes, including episodes of persistent warts. This was based on the systematic review of existing cost and cost-effectiveness evidence. The average duration of an episode of AGWs has previously been estimated as 36 days[176] and 41 days.[175] In the study by Woodhall *et al.*[176] it was estimated that the costs associated with the treatment of genital warts were incurred within 12 months for 98% of cases. In the study by Woodhall *et al.*,[175] it was reported that only 3% of patients had an episode lasting > 6 months. In the study by Desai *et al.*,[3] the average duration of an episode of care was analysed by number of consultations: for episodes requiring two consultations, the median duration of the episode of care was 12 days (range 2–57 days); for episodes requiring three or more consultations, the median duration of the episode of care was 48 days (range 4–331 days).

The time horizon was varied in sensitivity analysis.

Population

The population of interest for this economic assessment was people aged ≥ 16 years with clinically diagnosed AGWs, irrespective of biopsy confirmation.

Following a systematic search of the clinical literature, the data were not sufficient to analyse by subgroup (see *Chapter 3*, *Quantity and quality of research available*); therefore, subgroups were not considered within the economic analysis.

Interventions

Interventions included in the economic analysis

The interventions relevant for this economic assessment of treatments for AGWs were outlined in the protocol as the topical treatments podophyllotoxin, imiquimod, podophyllin, TCAA and cidofovir; the physical ablation methods cryotherapy, surgical excision, electrotherapy and laser therapy; and any combination or sequential treatment with either topical or physical ablation interventions.

Following review of the data identified in the systematic search of the clinical literature and presented in *Chapter 3*, the following interventions were included in the economic analysis:

- placebo
- imiquimod 5% cream
- podophyllin 20–25%
- podophyllotoxin 0.5% solution
- TCAA
- CO_2 laser therapy
- cryotherapy
- surgical excision
- cryotherapy plus podophyllin 25%
- cryotherapy plus podophyllotoxin 0.15% cream
- TCAA plus podophyllin 25%.

Data for 'placebo' were assumed to represent 'no treatment'. This assumption was required because of a lack of clinical data around no treatment. Although acknowledging the weaknesses of this approach, it was considered, on balance, that this was appropriate because of the objective measures of treatment effectiveness used to assess clearance.

No data were obtained for cidofovir, electrotherapy or any sequential treatment sequences as set out in the protocol, nor were any further combinations of treatments identified. In addition, the following interventions identified from the search were not included in the base-case economic analysis:

- podophyllin 0.25–0.5% (patient applied)
- podophyllotoxin solution 0.25%
- podophyllotoxin cream 0.3%
- podophyllotoxin cream 0.5%.

These interventions were excluded from the economic base-case analysis because they are not routinely used or available in UK clinical practice. In sensitivity analysis, complete clearance data for podophyllotoxin cream 0.5% were used as a proxy for podophyllotoxin cream 0.15%, a concentration that is used in clinical practice (see *Chapter 1*, *Current service provision*); however, this was not presented in the base case.

Modelled treatment regimens for included interventions

Duration of treatment

The duration of treatment for trials included in the MTC varied (see *Chapter 3*, *Quantity and quality of research available*). Thus, the average duration of treatment seen in UK clinical practice was modelled based on consultation with clinical experts, ensuring comparability with the range of treatment durations investigated in the included clinical trials. The duration of treatment modelled in the base case for each intervention is presented in *Table 22*, alongside the duration of treatment analysed in the included clinical trials.

It was therefore assumed that the treatment effect estimated from the MTC based on the included clinical trials was independent of treatment duration (see *Chapter 3*, *Assessment of effectiveness*). In addition, as CO_2 laser therapy and surgery are typically carried out in one session, the average duration of treatment modelled is intended to reflect the typical waiting time for the procedure.

Because of the variability in treatment duration, the impact of uncertainty in these parameters was tested in a sensitivity analysis.

TABLE 22 Average duration of treatment modelled in the base-case analysis

Intervention	Number of trials included in the MTC[a]	Duration of treatment (weeks) analysed in clinical trials (range)	Modelled average duration of treatment (weeks)
No treatment	9	4–16	6
Imiquimod 5% cream	4	12–16	16
Podophyllin 20–25%	9	4–12	6
Podophyllotoxin 0.5% cream (sensitivity analysis only)	4	3–6	4
Podophyllotoxin 0.5% solution	6	4–6	4
TCAA	4	6–12	6
CO_2 laser therapy	1	6	6
Cryotherapy	5	6–12	6
Surgical excision	1	NR; up to four visits, average of one visit	6
Cryotherapy plus podophyllin 25%	1	8	6
Cryotherapy plus podophyllotoxin 0.15% cream	1	12	6
TCAA plus podophyllin 25%	2	8	6

NR, not reported.
a See *Chapter 3*, *Quantity and quality of research available*.

Duration of follow-up

Duration of follow-up was assumed to be 12 weeks for all interventions. This was based on clinical expert opinion and was selected to capture any recurrence of AGWs that would be considered part of the original episode of AGWs in clinical practice. This duration was tested in sensitivity analysis.

Treatment sequences

Within the base-case analysis, people with AGWs were assumed to receive up to two lines of treatment for their AGWs before being classed as having persistent AGWs. Complete clearance data at the end of the treatment were available for 11 interventions (see *Complete clearance at the end of the treatment*); thus, the total number of possible treatment sequences equalled 121. However, on the basis of the following assumptions, 84 possible treatment sequences were modelled (*Table 23*):

- 'No treatment' will be prescribed first line only, that is, an active intervention will always be prescribed second line.
- No sequence of treatments will involve the same intervention twice, that is, if a patient fails on one intervention they will not be prescribed that intervention again. This is assumed to include combinations of therapy, for example a patient prescribed podophyllin first line would not receive cryotherapy in combination with podophyllin second line.

These assumptions were verified through consultation with clinical experts.

Model inputs

A summary of all model inputs, the associated uncertainty and sources of data are presented in *Table 24* and described in the remainder of this section. In addition, *Table 25* summarises the key model assumptions.

TABLE 23 Treatment sequences included in the economic analysis

	Second-line intervention										
First-line intervention	**No treatment**	**Imiquimod 5% cream**	**Podophyllin 20–25%**	**Podophyllotoxin 0.5% solution**	**TCAA acid**	**CO_2 laser therapy**	**Cryotherapy**	**Surgical excision**	**Cryotherapy plus podophyllin 25%**	**Cryotherapy plus podophyllotoxin 0.15% cream**	**TCAA plus podophyllin 25%**
No treatment	✗	1	2	3	4	5	6	7	8	9	10
Imiquimod 5% cream	✗	✗	11	12	13	14	15	16	17	18	19
Podophyllin 20–25%	✗	20	✗	21	22	23	24	25	✗	26	✗
Podophyllotoxin 0.5% solution	✗	27	28	✗	29	30	31	32	33	✗	34
TCAA	✗	35	36	37	✗	38	39	40	41	42	✗
CO_2 laser therapy	✗	43	44	45	46	✗	47	48	49	50	51
Cryotherapy	✗	52	53	54	55	56	✗	57	✗	✗	58
Surgical excision	✗	59	60	61	62	63	64	✗	65	66	67
Cryotherapy plus podophyllin 25%	✗	68	✗	69	70	71	✗	72	✗	✗	✗
Cryotherapy plus podophyllotoxin 0.15% cream	✗	73	74	✗	75	76	✗	77	✗	✗	78
TCAA plus podophyllin 25%	✗	79	✗	80	✗	81	82	83	✗	84	✗

1– 84, possible treatment sequences; ✗, not a possible treatment sequence.

TABLE 24 Summary of all model inputs

Input	Mean value	Source	Measure of variance	Lower value	Upper value	Distribution for probabilistic analysis	Comments
Duration of treatment (weeks)							
No treatment	6	Clinical expert opinion	Upper and lower 20% of mean	4.8	7.2	Normal	–
Imiquimod 5% cream	16			12.8	19.2	Normal	
Podophyllin 20–25%	6			4.8	7.2	Normal	
Podophyllotoxin 0.5% cream (sensitivity analysis only)	4			3.2	4.8	Normal	
Podophyllotoxin 0.5% solution	4			3.2	4.8	Normal	
TCAA	6			4.8	7.2	Normal	
CO_2 laser therapy	6			4.8	7.2	Normal	
Cryotherapy	6			4.8	7.2	Normal	
Surgical excision	6			4.8	7.2	Normal	
Cryotherapy plus podophyllin 25%	6			4.8	7.2	Normal	
Cryotherapy plus podophyllotoxin 0.15% cream	6			4.8	7.2	Normal	
TCAA plus podophyllin 25%	6			4.8	7.2	Normal	

Input	Mean value	Source	Measure of variance	Lower value	Upper value	Distribution for probabilistic analysis	Comments
Probability (%) of complete clearance of AGWs at the end of treatment							
No treatment	7.6	MTC (see *Chapter 3*, *Assessment of effectiveness*)	MTC CrIs (see *Chapter 3*, *Assessment of effectiveness*)	1.1	20.9	MTC CODA	The CODA output from WinBUGS provides a list of all values generated from the full posterior distribution. Therefore, for probabilistic analysis, rather than resampling from the posterior distribution, the output itself has been used
Imiquimod 5% cream	56.1			20.3	85.0		
Podophyllin 20–25%	62.1			56.2	68.0		
Podophyllotoxin 0.5% cream (sensitivity analysis only)	73.7			38.9	93.8		
Podophyllotoxin 0.5% solution	92.6			81.9	98.4		
TCAA	61.4			32.5	85.8		
CO_2 laser therapy	97.1			84.7	99.9		
Cryotherapy	71.0			38.8	92.1		
Surgical excision	84.8			44.9	99.1		
Cryotherapy plus podophyllin 25%	77.6			45.7	95.3		
Cryotherapy plus podophyllotoxin 0.15% cream	78.4			31.4	98.0		
TCAA plus podophyllin 25%	72.8			45.3	91.2		
Duration of follow-up (weeks)							
Duration of follow-up	12	Clinical expert opinion	Upper and lower 20% of mean	9.6	14.4	Normal	All treatments were assumed to be associated with the same duration of follow-up

continued

TABLE 24 Summary of all model inputs (*continued*)

Input	Mean value	Source	Measure of variance	Lower value	Upper value	Distribution for probabilistic analysis	Comments
Probability (%) of recurrence of AGWs after follow-up							
Imiquimod 5% cream	16.5	MTC (see *Appendix 8*)	MTC CrIs (see *Appendix 8*)	2.8	43.9	CODA	The CODA output, from WinBUGS provides a list of all values generated from the full posterior distribution. Therefore, for probabilistic analysis, rather than resampling from the posterior distribution, the output itself has been used
Podophyllin 20–25%	41.2			31.3	51.6	CODA	
Podophyllotoxin 0.5% solution	34.6			20.0	51.4	CODA	
TCAA	18.4			6.3	36.4	CODA	
Surgical excision	9.7			2.2	24.7	CODA	
TCAA plus podophyllin 25%	39.4			17.2	65.3	CODA	
No treatment	26.6	Clinical expert opinion	Upper and lower 20% of mean	21.3	31.9	Beta	Equal to the average value estimated from the MTC
Podophyllotoxin 0.5% cream (sensitivity analysis only)	34.6		Set equal to podophyllotoxin solution 0.5%	20.0	51.4	Beta	Set equal to values estimated for podophyllotoxin solution 0.5%
CO_2 laser therapy	9.7		Set equal to surgical excision	2.2	24.7	Beta	Set equal to values estimated for surgical excision
Cryotherapy	33.0		Upper and lower 20% of mean	26.4	39.6	Beta	Clinical expert opinion
Cryotherapy plus podophyllin 25%	33.0		Upper and lower 20% of mean	26.4	39.6	Beta	Clinical expert opinion
Cryotherapy plus podophyllotoxin 0.15% cream	26.6		Upper and lower 20% of mean	21.3	31.9	Beta	Equal to the average value estimated from the MTC

Input	Mean value	Source	Measure of variance	Lower value	Upper value	Distribution for probabilistic analysis	Comments
Structural inputs							
Duration of persistent warts (weeks)	12	Assumption	Upper and lower 20% of mean	9.6	14.4	Normal	–
HRQoL							
With AGWs	0.87	Woodhall *et al.*[176]	95% CI	0.85	0.89	Beta	–
Without AGWs	0.926			0.899	0.953	Beta	
Price per item (£)							
No treatment	0.00	BNF 68[39]	Upper and lower 20% of mean	0.00	0.00	None	Intervention costs are known and are therefore not varied in probabilistic analysis
Podophyllotoxin solution 0.5% (Condyline)	14.49			11.59	17.39	None	
Podophyllotoxin solution 0.5% (Warticon)	14.86			11.89	17.83	None	
Podophyllotoxin cream 0.15%	17.83			14.26	21.40	None	
Imiquimod 5%	48.60			38.88	58.32	None	
Podophyllin 10 ml	0.02			0.02	0.02	None	
TCAA	0.32			0.26	0.38	None	
Cryotherapy	4.27			3.42	5.12	None	
CO_2 laser therapy	125.49			100.39	150.59	None	
Surgical excision	156.03			124.82	187.24	None	

continued

TABLE 24 Summary of all model inputs (*continued*)

Input	Mean value	Source	Measure of variance	Lower value	Upper value	Distribution for probabilistic analysis	Comments
Number of items per treatment period							
Podophyllotoxin solution 0.5% (Condyline)	1	Clinical expert opinion	Upper and lower 20% of mean	0.8	1.2	Gamma	–
Podophyllotoxin solution 0.5% (Warticon)	1			0.8	1.2	Gamma	
Podophyllotoxin cream 0.15%	1			0.8	1.2	Gamma	
Imiquimod 5%	4			3.2	4.8	Gamma	
Podophyllin 10 ml	5			4	6	Gamma	
TCAA	4			3.2	4.8	Gamma	
Cryotherapy	4			3.2	4.8	Gamma	
CO_2 laser therapy	1			0.8	1.2	Gamma	
Surgical excision	1			0.8	1.2	Gamma	
Cost of persistent warts (£)							
Cost of persistent warts	121.89	Average cost estimated as twice the average cost of combination and ablative therapy	Upper and lower 20% of mean	97.51	146.27	None	–
Number of clinician appointments							
To commence second-line treatment	1	Assumption	Upper and lower 20% of mean	0.8	1.2	Gamma	–

Input	Mean value	Source	Measure of variance	Lower value	Upper value	Distribution for probabilistic analysis	Comments
Number of additional clinician appointments							
No treatment	0	Assumption	Upper and lower 20% of mean	0	0	Gamma	–
Imiquimod 5% cream	0			0	0	Gamma	
Podophyllin 20–25%	5			4	6	Gamma	
Podophyllotoxin 0.5% cream	0			0	0	Gamma	
Podophyllotoxin 0.5% solution	0			0	0	Gamma	
TCAA	4			3.2	4.8	Gamma	
CO_2 laser therapy	1			0.8	1.2	Gamma	
Cryotherapy	4			3.2	4.8	Gamma	
Surgical excision	1			0.8	1.2	Gamma	
Cryotherapy plus podophyllin 25%	5			4	6	Gamma	
Cryotherapy plus podophyllotoxin 0.15% cream	4			3.2	4.8	Gamma	
TCAA plus podophyllin 25%	5			4	6	Gamma	
For persistent warts	2			1.6	2.4	Gamma	
Cost of appointments (per hour) (£)							
Cost of doctor	292.00	Curtis[217]	Upper and lower 20% of mean	233.60	350.40	Gamma	–
Cost of nurse	58.00			46.40	69.60	Gamma	

continued

TABLE 24 Summary of all model inputs (*continued*)

Input	Mean value	Source	Measure of variance	Lower value	Upper value	Distribution for probabilistic analysis	Comments
Length of appointments (minutes): general (female)							
Doctor time (no nurse involved)	17	Woodhall *et al.*[176]	Upper and lower 20% of mean	13.6	20.4	Gamma	–
Doctor time (when nurse involved)	18			14.4	21.6	Gamma	
Nurse time (when doctor involved)	13			10.4	15.6	Gamma	
Nurse time (no doctor involved)	14			11.2	16.8	Gamma	
Length of appointments (minutes): general (male)							
Doctor time (no nurse involved)	16	Woodhall *et al.*[176]	Upper and lower 20% of mean	12.8	19.2	Gamma	–
Doctor time (when nurse involved)	16			12.8	19.2	Gamma	
Nurse time (when doctor involved)	10			8	12	Gamma	
Nurse time (no doctor involved)	14			11.2	16.8	Gamma	
Length of appointments (minutes): laser therapy							
Doctor time (no nurse involved)	38	Woodhall *et al.*[176]	Upper and lower 20% of mean	30.4	45.6	Gamma	–
Doctor time (when nurse involved)	38			30.4	45.6	Gamma	
Nurse time (when doctor involved)	45			36	54	Gamma	

Input	Mean value	Source	Measure of variance	Lower value	Upper value	Distribution for probabilistic analysis	Comments
Proportion of appointments with doctor/nurse: general							
Doctor (no nurse involved)	0.33	Assumption	Upper and lower 20% of mean	0.27	0.4	Dirichlet	–
Doctor (with nurse)	0.33			0.27	0.4	Dirichlet	
Proportion of appointments with doctor/nurse: laser therapy							
Doctor (no nurse involved)	0.50	Assumption	Upper and lower 20% of mean	0.4	0.6	Dirichlet	–

CODA, convergence diagnosis and output analysis.

TABLE 25 Summary of key model assumptions

Assumption	Justification	Associated sensitivity analysis (if applicable)
A single episode of AGWs was modelled rather than multiple episodes of AGWs	HRQoL and costs are not expected to differ between first and subsequent AGW episodes; therefore, regardless of whether the patient is experiencing a first or a later episode of AGWs, the model is considered appropriate to quantify the differences in costs and QALYs associated with each treatment There were insufficient data identified from the literature that were associated specifically with a first or recurrent episode of AGWs Previous cost-effectiveness analyses for AGWs have used short-term decision trees to model a single episode of AGWs; therefore, the approach taken reflects the general approach adopted within the literature	NA
Persistent warts were defined as AGWs that have not cleared after two lines of therapy	The definition of persistent warts varies in the literature and in clinical practice	The duration of persistent warts was varied in one-way sensitivity analysis and in probabilistic analysis
People achieving complete clearance of AGWs were assumed to be clear at the mid-point of treatment	A simplifying assumption designed to reflect the fact that some patients will clear immediately and some patients will clear towards the end of treatment	In scenario analysis, complete clearance was alternatively set to occur at the start and the end of the treatment period
People recurring after complete clearance of AGWs were assumed to recur at the mid-point of follow-up	A simplifying assumption designed to reflect the fact that some patients will recur immediately and some patients will recur towards the end of follow-up	In scenario analysis, recurrence was alternatively set to occur at the start and the end of the follow-up period
Follow-up after complete clearance was assumed to be 12 weeks	This assumption was based on clinical expert opinion and was selected to capture any recurrence of AGWs that would be considered part of the original episode of AGWs in clinical practice	The duration of follow-up was varied in one-way sensitivity analysis and probabilistic analysis
Data for 'placebo' were assumed to represent 'no treatment'	This assumption was required because of a lack of clinical data around no treatment. Although acknowledging the weaknesses of this approach, it was considered, on balance, that this was appropriate because of the objective measures of treatment effectiveness used to assess clearance	NA
Treatment sequences: 'no treatment' will be prescribed first line only, that is, an active intervention will always be prescribed second line; no sequence of treatments will involve the same intervention twice, that is, if a patient fails on one intervention they will not be prescribed that intervention again	These assumptions were based on clinical expert opinion	NA
The probability of complete clearance or recurrence for second-line therapy is the same as the probability of complete clearance or recurrence for first-line therapy	This assumption was necessary because of a lack of clinical data available by line of therapy and was verified as reasonable based on clinical expert opinion	NA

TABLE 25 Summary of key model assumptions (*continued*)

Assumption	Justification	Associated sensitivity analysis (if applicable)
The probability of complete clearance and recurrence was assumed to be independent of treatment duration	This assumption was necessary because of a lack of clinical data available by line of therapy and was verified as reasonable based on clinical expert opinion	NA
The duration of follow-up was assumed to be 12 weeks following complete clearance	This assumption was based on clinical expert opinion and was selected to capture any recurrence of AGWs that would be considered part of the original episode of AGWs in clinical practice	This duration was tested in one-way sensitivity analysis
The probabilities of recurrence for treatments not included in the MTC were assumed to be adequately represented by clinical expert opinion	This assumption was necessary because of a lack of clinical data available for a number of interventions	Recurrence rates were tested in scenario analysis, one-way sensitivity analysis and threshold analysis
It was assumed that all appointments take place within GUM clinics	This was a simplifying assumption that is not expected to impact on the model results. In clinical practice, the majority of people with AGWs are treated in GUM clinics; however, a proportion of patients may be treated by their GP or in hospital	NA
People treated with clinician-applied topical or ablative therapies, either as monotherapy or as part of a combination therapy, were assumed to require additional appointments at which the therapy is applied. The number of appointments required was assumed to be adequately captured using clinical expert opinion	This assumption was based on clinical expert opinion and was selected to capture resource costs associated with clinician-applied therapies	The number of appointments required was varied in one-way sensitivity analysis
It was assumed that the type of appointment in GUM clinics (doctor led, nurse led or doctor with nurse) was equally split	This was a simplifying assumption	The proportion of appointments by type was varied in one-way sensitivity analysis

NA, not applicable.

Complete clearance at the end of treatment

Data for complete clearance at the end of treatment were identified, extracted and synthesised as described in the primary analysis in *Chapter 3* (see *Results*). The probability of complete clearance at the end of the treatment period for each included intervention obtained from these analyses are summarised in *Table 26* and presented graphically in *Figure 17*.

Within the model, the same estimates of complete clearance at the end of treatment are used for first- and second-line treatment. It is therefore assumed that the probability of complete clearance at the end of treatment is the same, regardless of line of therapy. This assumption was necessary because of a lack of clinical data available by line of therapy and was verified as reasonable based on clinical expert opinion.

The results of the analysis imply that no treatment, as assessed through placebo treatment in the included clinical trials, is, on average, the least effective treatment for complete clearance of AGWs at the end of treatment. No treatment was associated with an average probability of complete clearance of 7.6% and was statistically significantly less effective at the 95% level when compared with all other interventions included within the analysis, with the exception of imiquimod 5% cream.

TABLE 26 Probability of complete clearance at the end of treatment: random-effects MTC, base-case clinical analysis

Intervention	Mean probability of complete clearance at the end of treatment (%)	CrI around the mean (%)	
		Lower 2.5% CrI	Upper 97.5% CrI
No treatment	7.6	1.1	20.9
Imiquimod 5% cream	56.1	20.3	85.0
Podophyllin 20–25% (clinician applied)	62.1	56.2	68.0
Podophyllotoxin 0.5% cream (sensitivity analysis only)	73.7	38.9	93.8
Podophyllotoxin 0.5% solution	92.6	81.9	98.4
TCAA	61.4	32.5	85.8
CO_2 laser therapy	97.1	84.7	99.9
Cryotherapy	71.0	38.8	92.1
Surgical excision	84.8	44.9	99.1
Cryotherapy plus podophyllin 25%	77.6	45.7	95.3
Cryotherapy plus podophyllotoxin 0.15% cream	78.4	31.4	98.0
TCAA plus podophyllin 25%	72.8	45.3	91.2

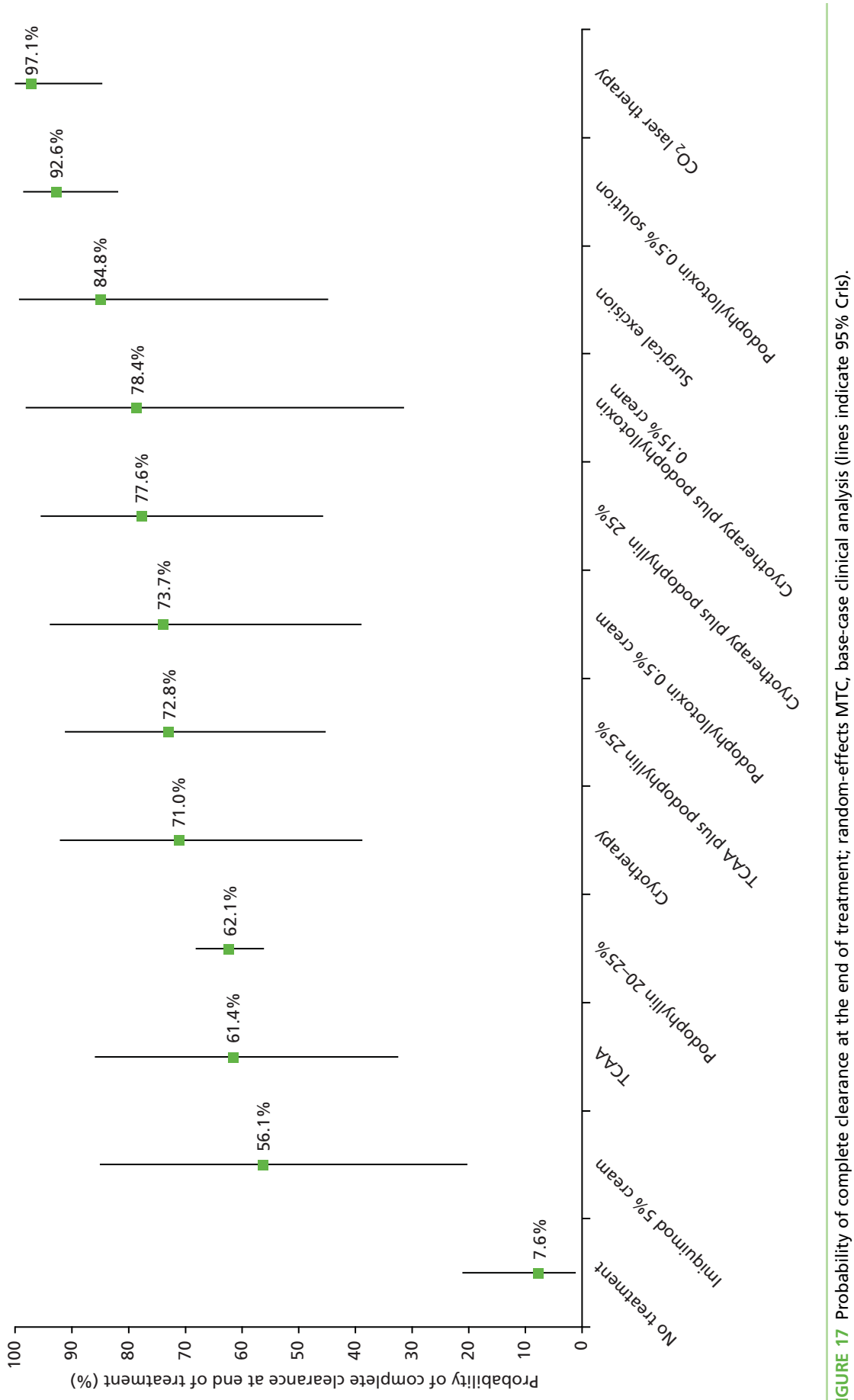

FIGURE 17 Probability of complete clearance at the end of treatment; random-effects MTC, base-case clinical analysis (lines indicate 95% CrIs).

The most effective treatment for complete clearance at the end of treatment, on average, was found to be CO_2 laser therapy. CO_2 laser therapy was associated with an average probability of complete clearance of 97.1%. The probability of complete clearance for CO_2 laser therapy was statistically significantly greater at the 95% level than for podophyllin 20–25% and no treatment.

The CrIs around the estimates of treatment effect were generally wide, with only one further statistically significant difference in treatment effect at the 95% level, with podophyllotoxin 0.5% solution found to be statistically significantly more effective than podophyllin 20–25%.

The findings of this analysis in relation to podophyllotoxin 0.5% solution and imiquimod are of particular interest. Imiquimod was found to be, on average, the second least effective treatment for complete clearance of AGWs at the end of treatment whereas podophyllotoxin 0.5% solution was found to be, on average, the second most effective treatment for complete clearance of AGWs at the end of treatment. These findings contradict the results of cost-effectiveness analyses identified in the cost-effectiveness literature review (see *Systematic review of existing cost and cost-effectiveness evidence*), which would more naturally imply the opposite finding, and the generally held view within clinical practice that imiquimod 5% cream is more effective than podophyllotoxin 0.5% solution.

The discrepancies between the findings of the clinical literature review and synthesis (see *Chapter 3*, *Results*) and the cost-effectiveness analyses identified from the systematic review of the economic literature (see *Systematic review of existing cost and cost-effectiveness evidence*) were investigated and are discussed below.

The following five cost-effectiveness analyses presented in *Systematic review of existing cost and cost-effectiveness evidence* compared the use of imiquimod with the use of podophyllotoxin for AGWs:

1. Walczak[164] (Poland)
2. Lafuma[165] (France)
3. Williams and von Krogh[166] (UK)
4. Alam *et al.*[167] (USA)
5. Fagnani[168] (France).

In four of these analyses, imiquimod was found to be more effective than podophyllotoxin at clearing AGWs by the end of treatment.[164–166,168] The estimated probability of complete clearance at the end of treatment for all five studies and the references used to inform these values are presented in *Table 27*.

It was not possible to verify the figures used in Walczak[164] or Alam *et al.*;[167] in the study by Walczak[164] the references were not provided and in the study by Alam *et al.*[167] the method of reaching a consensus estimate was not described. It is noted that the probabilities of complete clearance reported in Walczak[164] for podophyllotoxin and imiquimod are identical to those presented in Fagnani;[168] however, it is not possible to confirm that these data are from the same sources.

For the remaining studies, no study used systematic review methods to identify their data. In Lafuma[165] and Fagnani[168] two studies were selected without description of how they were identified, with their inclusion justified because the methodology in the two studies was determined to be similar. In the study by Williams and von Krogh,[166] only placebo-controlled trials were identified.

The four studies providing references all included data that were excluded from the analysis described in *Chapter 3*. Data from Greenburg *et al.*[62] and Tyring *et al.*[68] were excluded because of an identified high risk of bias. Data from Syed *et al.*[122] were not included because these data related to podophyllotoxin

TABLE 27 Probability of complete clearance at the end of treatment applied in the identified five cost-effectiveness analyses comparing the use of podophyllotoxin with imiquimod in people with AGWs

Study	Probability of complete clearance at the end of treatment (%)		Source
	Podophyllotoxin	Imiquimod	
Walczak 2009[164]	19.6	42.9	NR
Lafuma 2003[165]	37.0	49.5	Podophyllotoxin: Tyring *et al.*,[68] imiquimod: Edwards *et al.*[118]
Williams 2003[166]	49.1	52.3	Podophyllotoxin: average estimate from nine studies;[61,62,115,122–127] imiquimod: average estimate from six studies[68,115,118,125,161,162]
Alam 2001[167]	63	50	A combination of data from two clinical literature reviews[218,219] and three studies[169,171,220] for podophylloxin and two studies[170,220] for imiquimod
Fagnani 2000[168]	19.6	42.9	Podophyllotoxin: Tyring *et al.*,[68] imiquimod: Edwards *et al.*;[118] using data for 'clear 3 months after treatment'

NR, not reported.

cream rather than podophyllotoxin solution; a decision was made within this analysis (see *Chapter 3*, *Quantity and quality of research available*) to analyse the efficacy of podophyllotoxin cream separately. Data from Syed *et al.*[161,162] were not included because these data related to imiquimod 2% cream rather than imiquimod 5% cream. Data from four further studies[169–171,220] were excluded because these studies were not prospective RCTs. No study included prospective RCT data that were not identified by the systematic review of the clinical literature reported in *Chapter 3*.

In addition, in the studies by Lafuma,[165] Williams and von Krogh[166] and Fagnani,[168] the estimates of the probability of complete clearance were combined using 'naive' indirect comparison, that is, data were taken from a single arm for each trial and compared as if they were from the same trial. In the study by Williams and von Krogh,[166] in which multiple data sources for one treatment were considered, data for the same treatment were pooled to produce a crude average. In the studies by Alam and Stiller[167] and Walczak,[164] no information was provided around how data were combined.

The differences in methodological approach and the included trials may explain the difference in results between this analysis and previous cost-effectiveness analyses. Specifically, for this analysis, a systematic review methodology was followed, data were excluded if they were subject to a high risk of bias and evidence was synthesised using meta-analytical techniques rather than through 'naive' indirect comparison.

Recurrence of anogenital warts within 12 weeks of complete clearance

Data for recurrence of AGWs within 12 weeks of complete clearance were identified, extracted and synthesised as described in *Appendix 8*. The probability of recurrence for each included intervention obtained from these analyses is summarised in *Table 28* and presented graphically in *Figure 18*.

Similar to the results for complete clearance, the CrIs associated with the mean probabilities of recurrence were generally wide, indicating a high degree of uncertainty in the results. The estimated mean probability of recurrence of AGWs ranged from 9.7% (surgical excision) to 41.2% (podophyllin 20–25%). Surgical excision was associated with a statistically significantly (at the 95% confidence level) lower likelihood of recurrence compared with podophyllin 20–25%; no other differences between treatments were found to be statistically significant.

TABLE 28 Network meta-analysis results: probability of recurrence within 12 weeks of complete clearance of AGWs, fixed effects

Intervention	Mean probability of recurrence after 12 weeks (%)	Lower 2.5% CrI (%)	Upper 97.5% CrI (%)
Imiquimod 5% cream	16.5	2.8	43.9
Podophyllotoxin 0.5% solution	34.6	20.0	51.4
Podophyllin 20–25%	41.2	31.3	51.6
TCAA	18.4	6.3	36.4
TCAA plus podophyllin 25%	39.4	17.2	65.3
Surgical excision	9.7	2.2	24.7

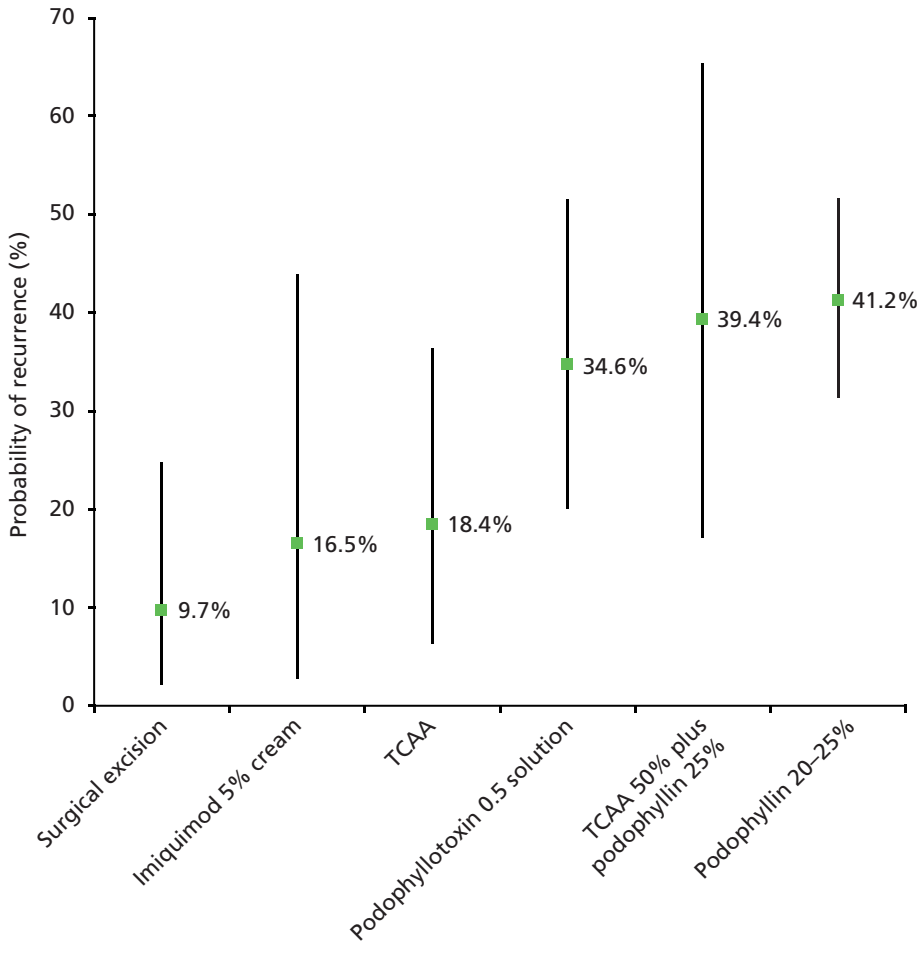

FIGURE 18 Network meta-analysis results: probability of recurrence within 12 weeks of complete clearance of AGWs, fixed effects (lines indicate 95% CrIs).

The data presented for recurrence within 12 weeks of complete clearance were subject to two key limitations:

- data were not identified for all interventions included within the analysis
- data analysed included follow-up periods of 3–12 months, in contrast to the required data for the model including follow-up for up to 3 months.

These issues are discussed in greater detail in the following sections.

Data were not identified for all interventions included within the analysis

The following interventions for which data were identified for the outcome of complete clearance had no data identified for the outcome of recurrence: no treatment, podophyllotoxin cream (sensitivity analysis only), CO_2 laser therapy, cryotherapy, cryotherapy plus podophyllin 25% and cryotherapy plus podophyllotoxin 0.15% cream.

To include recurrence data within the base-case model for these interventions, clinical expert opinion was sought. The resulting probabilities of recurrence used within the base-case economic analysis are presented in *Table 29*.

TABLE 29 Probability of AGW recurrence 12 weeks after complete clearance of AGWs

Intervention	Mean probability of recurrence 12 weeks after complete clearance of AGWs (%)	Lower 2.5% CrI (%)	Upper 97.5% CrI (%)	Source
No treatment	26.6	NA		Clinical opinion (average of values estimated from the MTC)
Imiquimod 5% cream	16.5	2.8	43.9	MTC (see *Appendix 8*)
Podophyllin 20–25%	41.2	31.3	51.6	MTC (see *Appendix 8*)
Podophyllotoxin 0.5% cream (sensitivity analysis only)	34.6	NA		Clinical opinion (equal to value for podophyllotoxin solution 0.5%)
Podophyllotoxin 0.5% solution	34.6	20.0	51.4	MTC (see *Appendix 8*)
TCAA	18.4	6.3	36.4	MTC (see *Appendix 8*)
CO_2 laser therapy	9.7	NA		Clinical opinion (equal to value for surgical excision)
Cryotherapy	33.0	NA		Clinical opinion
Surgical excision	9.7	2.2	24.7	MTC (see *Appendix 8*)
Cryotherapy plus podophyllin 25%	33.0	NA		Clinical opinion
Cryotherapy plus podophyllotoxin 0.15% cream	26.6	NA		Clinical opinion (average of values estimated from the MTC)
TCAA plus podophyllin 25%	39.4	17.2	65.3	MTC (see *Appendix 8*)

NA, not applicable.

Data analysed included follow-up periods of 3–12 months, in contrast to the required data for the model including follow-up for up to 3 months

The data identified from the systematic review of the clinical literature for recurrence of AGWs were limited; thus, to provide a connected network from which data on recurrence could be estimated for use within the economic analysis, data from the assessment of recurrence at 3–12 months were combined in a MTC (see *Appendix 8*).

The baseline treatment effect was estimated using only data from 3 months. However, for the relative effects, it is necessary to assume that the relative difference in probability of recurrence between interventions will not differ over time. This is acknowledged as a weakness of the analysis and an area where further research is considered important.

To test the importance of recurrence data within the model, a number of sensitivity analyses were carried out:

- setting the same probability of recurrence for all interventions:
    - setting the probability of recurrence to the average rate estimated from the MTC
    - setting the probability of recurrence to 0%
    - setting the probability of recurrence to 100%.

The results of these analyses are described in *Sensitivity analysis*.

Adverse events

Adverse events were not included in the economic analysis. This approach was taken after consultation with clinical experts, after review of previous approaches to cost-effectiveness analyses for AGWs and because of a lack of clinical data.

Clinical experts advised that adverse events during the treatment of AGWs are generally mild and reversible, and do not usually require prescribed treatment. In general, it is expected that the clinician would advise the patient experiencing an adverse event to cease using the medication and, if necessary, to apply a soothing cream (available over the counter) to the affected area.

Moreover, only 1 out of 10 cost-effectiveness studies identified from the systematic literature review included adverse events within the economic evaluation.[64] This economic evaluation by Lacey *et al.*[64] was trial based and used adverse event data collected within the trial. The authors concluded that side effects were not a limiting factor for treatments within the trial and accounted for approximately 0.6–6.7% of total direct costs for the treatments analysed within the study.

Finally, the reporting of adverse events within the trials identified in the systematic review of clinical effectiveness was poor (see *Chapter 3*, *Assessment of effectiveness*). Given the absence of reliable data for adverse events, it was considered appropriate to omit these from the economic model.

Health-related quality of life

Systematic review of existing health-related quality-of-life data

A systematic review was carried out in September 2013 to identify relevant published HRQoL evidence to populate the economic model. The following databases were searched from inception:

- MEDLINE (Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE)
- EMBASE (Ovid EMBASE)
- CENTRAL (The Cochrane Library)
- HTA database (The Cochrane Library)
- NHS EED (The Cochrane Library).

The search strategy for all databases combined terms to capture AGWs and HRQoL. Full details of the search terms are presented in *Appendix 1*. In addition to searching the above databases, reference lists of identified studies were reviewed for any potentially relevant studies. No restrictions on language or setting were applied to any of the searches. Studies were assessed for inclusion based on the criteria outlined in *Table 30*.

The systematic review was updated in March 2014. The search strategy remained the same as outlined above; however, results were limited from 2013 to March 2014 to identify only additional relevant studies.

In total, 468 studies were identified from the September 2013 database search (*Figure 19*). Two health economists reviewed all citations. Of these, 148 were identified as duplicates and 201 studies were excluded on the basis of title and abstract. A total of 119 papers were therefore identified as potentially relevant. Of these papers, 12 were identified from the abstract as either reporting condition-specific measures of HRQoL or generic non-preference-based measures of HRQoL, and 107 papers were identified as reporting possible generic, preference-based measures of HRQoL (Q1, see *Table 30*). If it was unclear which type of HRQoL measure was included in the study, the reviewer was inclusive and labelled the study as including a potential generic, preference-based measure of HRQoL.

TABLE 30 Inclusion and exclusion criteria for the HRQoL systematic review

Inclusion criteria	Exclusion criteria
• Q1: possible generic, preference-based measure of HRQoL (e.g. EQ-5D, SF-6D, HUI) or standard gamble/time trade-off studies in any setting (to be as inclusive as possible) • Q2: possible generic, non-preference-based measure of HRQoL (e.g. SF-36) • Q3: possible condition-specific measure of HRQoL	• Abstracts with insufficient methodological details, systematic reviews[a]

EQ-5D, European Quality of Life-5 Dimensions; HUI, Health Utilities Index; SF-36, Short Form questionnaire-36 items; SF-6D, Short Form questionnaire-6 Dimensions.
a Relevant systematic reviews were used as a source of additional studies for consideration.

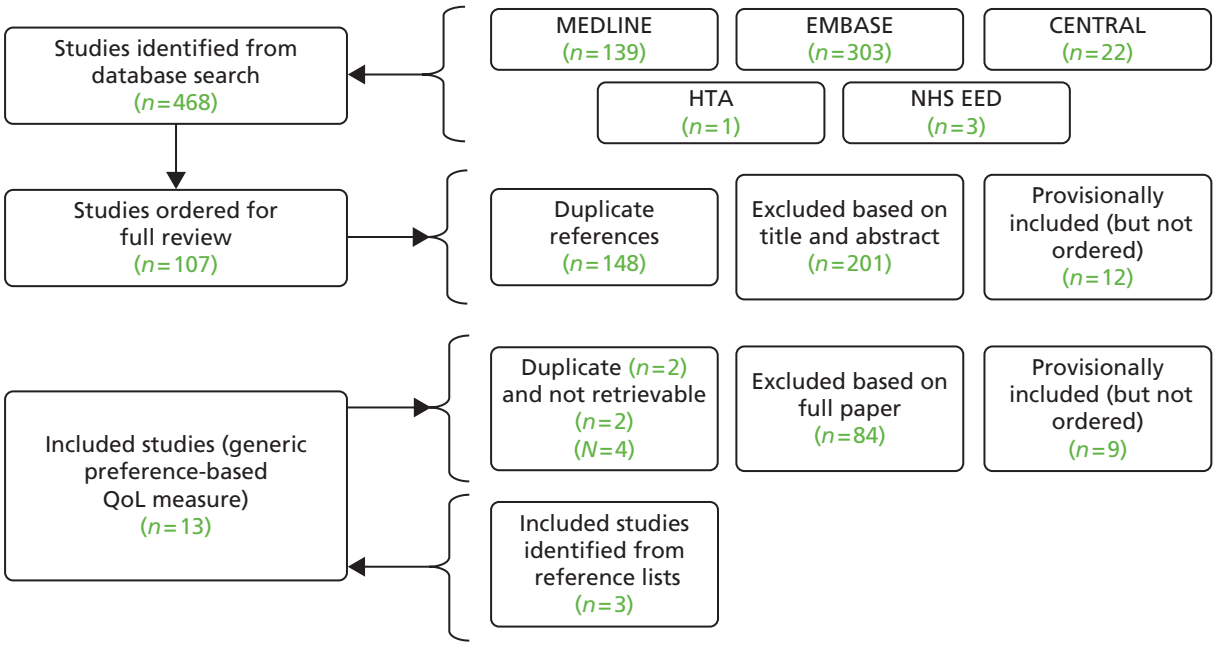

FIGURE 19 Identified HRQoL studies, September 2013 search.

The 12 studies identified as reporting either condition-specific measures of HRQoL or generic, non-preference-based measures of HRQoL were provisionally included, that is, these studies were not ordered in full in the first instance. However, as suitable studies reporting the use of generic, preference-based measures of HRQoL were identified, the 12 studies reporting either condition-specific measures of HRQoL or generic, non-preference-based measures of HRQoL were not included in the review. This is because a generic, preference-based measure of HRQoL, such as the European Quality of Life-5 Dimensions (EQ-5D), was considered preferable for use within an economic evaluation, based on the *NICE Guide to the Methods of Technology Appraisal*.[221] It was therefore considered appropriate to assess the suitability of condition-specific or generic non-preference-based measures of HRQoL, if, and only if, no suitable generic, preference-based measures of HRQoL were identified.

Following review of the 107 studies potentially reporting generic, preference-based measures of HRQoL, 10 studies were included in the review; seven studies[32,176,222–226] were identified as reporting generic non-preference-based measures of QoL and three studies[227–229] were identified as reporting condition-specific measures of QoL. In addition to the studies identified through the database search, three studies[230–232] were identified through review of reference lists as reporting generic, preference-based measures of HRQoL.

A total of 88 studies were excluded. Of these, two were not retrievable; two were duplicate references; 57 did not contain any QoL data; and 27 were excluded on the basis that the study reported a measure of QoL from another study. The most commonly cited reference was a conference abstract by Myers *et al.*[233] The figures within the study were described as being elicited using time trade-off methods and therefore may constitute a generic, non-preference-based measure of HRQoL. The abstract was presented at the 21st International Papillomavirus Conference in Mexico in 2004. Unfortunately, it was not possible to retrieve the full paper for this reference as the study appears to be unpublished. Consequently, it was not possible to verify these QoL values.

A further 49 papers were identified from the updated search in March 2014. Of these, four papers were identified as potentially relevant and ordered for full review, of which three[234–236] were excluded on the basis of the full paper and one[237] was identified as including generic, preference-based HRQoL data.

A total of 14 studies from the September 2013 (13 studies[32,176,222–232]) and March 2014 (one study[237]) searches therefore reported relevant generic, preference-based HRQoL data. Information on the populations, health states, instruments and utility values reported in these studies is presented in *Appendix 2*; a summary of the HRQoL instrument used in each included study is presented in *Table 31*.

Data from the UK were considered to be most relevant for this review in the first instance. Of the 14 identified studies, six contained HRQoL data for people from the UK.[32,176,228,230,231,237] These studies are described in further detail below.

Dominiak-Felden *et al.*[237] reported data from a large, multicentre, observational study carried out in the UK to investigate the impact of HPV-related genital diseases on QoL and psychosocial well-being. A total of 2502 individuals aged 18–64 years from 15 UK centres were screened for inclusion into the study between May 2008 and March 2009. Of those screened, 1512 people met the screening criteria and 1272 were included in the study after confirmation of diagnosis.

A subset of 186 people was found to have a current episode of genital warts. These participants were, on average, aged 28 years and 46% were female. It was not reported what proportion of patients were experiencing their first episode compared with a recurrent episode. People with a current episode of genital warts were invited to complete the EQ-5D questionnaire; the results are presented in *Table 32*.

TABLE 31 Summary of the HRQoL instrument used within each included study

Study	Country	Instrument
Dominiak-Felden 2013[237]	UK	EQ-5D
Mennini 2013[222]	Italy	EQ-5D
Shi 2012[223]	China	EQ-5D
Drolet 2011[227]	Canada	EQ-5D, SF-6D
Mennini 2011[224]	Italy	EQ-5D
Senecal 2011[225]	Canada	EQ-5D
Woodhall 2011[176]	England, Northern Ireland	EQ-5D
Langley 2010[228]	UK, France, Spain, Italy, Germany	SF-6D
Marra 2009[229]	Canada	EQ-5D, SF-6D
Woodhall 2008[32]	England	EQ-5D
Brisson 2007[226]	Canada	EQ-5D
Identified from review of reference lists of identified studies		
Mennini 2010[232]	Italy	Time trade-off
Fiander 2010[230]	UK	EQ-5D
Fiander 2010[231]	UK	EQ-5D

SF-6D, Short Form questionnaire-6 Dimensions.

TABLE 32 Health-related quality-of-life estimates for people with genital warts from the study by Dominiak-Felden *et al.*[237]

	Women			Men		
Estimate	Sample size	Mean estimate	Standard deviation	Sample size	Mean estimate	Standard deviation
EQ-5D index for people with genital warts, unweighted	101	0.84	0.16	85	0.89	0.17

	Women and men		
Estimate	Sample size	Mean estimate	Standard deviation
EQ-5D index for people with genital warts, weighted to reflect the age distribution of the UK general population	186	0.9	0.13
EQ-5D index for the general population	2583	0.89	NR
EQ-5D index for people with genital warts, weighted to reflect the age distribution of the UK general population, aged 18–24 years	NR	0.86	NR
EQ-5D index, mean for the general population aged 18–24 years	NR	0.94	NR
EQ-5D index for people with genital warts, weighted to reflect the age distribution of the UK general population, aged 25–34 years	NR	0.87	NR
EQ-5D index, mean for the general population aged 25–34 years	NR	0.93	NR

NR, not reported.

The authors found that there was no significant difference in the overall EQ-5D score between people with genital warts and the general population when scores were weighted to match the age and sex profile of the general population. However, the authors found that people with genital warts reported, on average, statistically significantly greater issues with anxiety and depression than the age- and sex-matched general population ($p < 0.001$) and fewer issues with the remaining dimensions of the EQ-5D: mobility ($p = 0.007$), self-care ($p = 0.083$), usual activities ($p = 0.005$), pain and discomfort ($p = 0.158$).

The authors considered age subgroups (18–24 years and 25–34 years) and found statistically significant differences in HRQoL compared with the age- and sex-matched general population (see *Table 32*); no sample sizes were stated for these analyses.

Woodhall *et al.*[176] reported a study carried out in seven sexual health clinics in England (six clinics) and Northern Ireland (one clinic). Between August 2009 and February 2010, a total of 895 people aged ≥ 16 years with a current diagnosis of genital warts were invited to complete an EQ-5D questionnaire. The average age of respondents was 28 years (range 16–73 years) and 65% of people were attending for their first episode. EQ-5D scores from people with genital warts were compared with age- and sex-matched average scores from the UK population. The authors noted that HRQoL associated with genital warts differed between women and men; therefore, a utility score for a health state including genital warts was presented by gender, as was an estimate of disutility associated with genital warts (*Table 33*).

Furthermore, Woodhall *et al.*[176] noted that no significant difference in HRQoL was observed between the first and recurrent episodes of AGWs; however, disutility was found to differ between age groups and this difference was statistically significant ($p < 0.0001$). The highest loss of QoL was seen in women aged 16–19 years and men aged 35–44 years. The numbers of patients in each of the different age groups were not presented.

Within the study, a further two UK studies reporting EQ-5D scores for people with AGWs were referenced. Both studies were conference abstracts published as part of the Eurogin 2010 Conference.[230,231] Neither study was identified in the original search; however, these studies were extracted in full and are presented in *Appendix 2*.

Fiander and Cohet[230,231] present data relating to an observational, cross-sectional study in which 1264 subjects (women and men) aged 18–64 years with HPV-related diseases were recruited from 15 community and hospital health-care clinics; the first abstract reports results relating to women[230] and the second reports results relating to men.[231] The study is related to the full paper by Dominiak-Felden *et al.*,[237] described above. The abstacts present EQ-5D data for a subset of the full study population, specifically, women and men aged 18–25 years with genital warts. The sample size for each analysis is not reported. The EQ-5D score for genital warts was estimated to be 0.83 and 0.89 for women and men aged 18–25 years, respectively. No estimates of uncertainty were presented.

TABLE 33 Health-related quality-of-life estimates for people with genital warts contained from the study by Woodhall *et al.*[176]

Estimate	Women ($n = 400$)[a]	Men ($n = 494$)[a]	All ($n = 895$)
EQ-5D index, mean (95% CI) for people with genital warts	0.87 (0.83 to 0.90)	0.88 (0.86 to 0.90)	0.87 (0.85 to 0.89)
Estimated disutility associated with genital warts, mean (95% CI)	0.063 (0.029 to 0.097)	0.043 (0.021 to 0.065)	0.056 (0.038 to 0.074)

a The sample sizes for women and men do not sum to the sample size for the full population.

Langley *et al.*[228] presented a conference abstract in which results from an internet-based survey carried out in the UK, France, Spain, Italy and Germany were published. A reported 53,524 people responded to the survey, with 521 reporting external genital warts. Respondents completed the Short Form questionnaire-6 Dimensions (SF-6D), from which the authors carried out a regression analysis controlling for presence or absence of genital warts, sociodemographic characteristics, health risk factors and the Charlson Comorbidity Index (an index that predicts the 10-year mortality rate for a person who may have a range of comorbid conditions). The disutility associated with external genital warts using the SF-6D (utilities scaled as 0–100) was consequently estimated as –2.47 (95% CI –3.58 to –1.36).

Woodhall *et al.*[32] reported a study of 81 adults attending the York GUM clinic with new, recurrent or persistent genital warts. Participants were invited to complete the EQ-5D questionnaire. EQ-5D scores from participants were compared with those in a control group of 1977 people in the same age range. Unadjusted EQ-5D scores were presented for people with and without genital warts. The authors estimated the mean EQ-5D score with genital warts ($n = 81$) to be 0.90 and the mean EQ-5D score without genital warts ($n = 1977$) to be 0.91. Adjusting for age and gender, the authors estimated a mean difference in EQ-5D score of 0.039 (95% CI 0.005 to 0.078) between people with and people without genital warts.

Health-related quality-of-life data selected for the economic analysis

Data from Woodhall *et al.*[176] were selected as the most relevant HRQoL data for the economic analysis. The baseline characteristics of the population presented in the study by Woodhall *et al.*[176] were considered to be reflective of the characteristics of the population seen in clinical practice in England and Wales. Moreover, the data presented in this study had a UK focus (England and Northern Ireland) and the study provided the largest reported sample of patients (895 vs. 186,[237] 81[32] and 521[228]). In addition, the data were based on the most recent sample; although the data presented by Dominiak-Felden *et al.*[237] were published in 2013 (vs. 2011 for the study by Woodhall *et al.*[176]), the questionnaires were completed in 2009–10 in the study by Woodhall *et al.*[176] and in 2008–9 in the study by Dominiak-Felden *et al.*[237]

The population in Woodhall *et al.*[176] is described as people with 'genital warts'. Although this differs from the focus for this analysis (i.e. both genital warts and AGWs), clinical experts advised that the terms 'genital warts' and 'anogenital warts' are often used interchangeably and the term 'genital warts' is considered appropriate to capture both genital warts and AGWs. It is therefore considered that the population is likely to include those with both genital warts and AGWs.

For the economic analysis, a mean estimate of HRQoL with and without AGWs was required; the estimates used within the economic analysis are presented in *Table 34*.

In the sensitivity analysis, to test the impact of using alternative HRQoL data, a scenario focusing on young adults was carried out. Based on findings from Woodhall *et al.*[176] and Dominiak-Felden *et al.*,[237] HRQoL in young adults appears to be more greatly impacted by AGWs than HRQoL in other age groups. Data for this scenario were taken from the study by Dominiak-Felden[237] for those aged 18–24 years (HRQoL 0.86 with AGWs vs. 0.94 without AGWs).

TABLE 34 Health-related quality-of-life estimates used in the de novo economic analysis

Estimate	Mean	95% CI	Source
Utility score with AGWs	0.87	0.85 to 0.89	Woodhall *et al.*,[176] EQ-5D index for genital warts, women and men ($n = 895$)
Utility score without AGWs	0.926	0.899 to 0.953	Estimate of utility with genital warts from Woodhall *et al.*[176] plus estimate of disutility associated with genital warts, also from Woodhall *et al.*[176]

Costs overview

Costs of intervention acquisition and costs of resource use were incorporated in the analysis and inflated, when required, to 2013 prices; the cost of treating adverse events was not included in the analysis (see *Model inputs*, *Adverse events*). *Table 35* provides a summary of the acquisition costs and resource costs per treatment course for first- and second-line interventions modelled in the base case. In addition, *Table 35* presents the one-off intervention acquisition cost and resource use cost associated with persistent warts. The calculations are described in greater detail in the following sections.

Costs: intervention acquisition costs

No treatment

It is assumed that there is no acquisition cost associated with no treatment.

Patient-applied topical interventions

It is assumed that imiquimod 5% cream, podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream are applied by patients at home. The cost calculations for these treatments are presented in *Table 36*.

TABLE 35 Average cost of course of treatment by intervention

Intervention	Average acquisition cost per course of treatment (£)	Average resource use cost per course of treatment (£)		Average total cost per course of treatment (£)	
		First line	Second line	First line	Second line
No treatment	0	0.00	62.12	0.00	62.12
Imiquimod 5% cream	194.40	0.00	62.12	194.40	256.52
Podophyllin 20–25%	0.11	310.60	372.72	310.71	372.83
Podophyllotoxin 0.5% cream (sensitivity analysis only)	17.83	0.00	62.12	17.83	79.95
Podophyllotoxin 0.5% solution	14.68	0.00	62.12	14.68	76.79
TCAA	1.38	248.48	310.60	249.86	311.98
CO_2 laser therapy	135.07	206.68	268.80	341.75	403.87
Cryotherapy	18.38	248.48	310.60	266.86	328.98
Surgical excision	156.03	206.68	268.80	362.71	424.83
Cryotherapy plus podophyllin 25%	18.49	310.60	372.72	329.09	391.21
Cryotherapy plus podophyllotoxin 0.15% cream	36.21	248.48	310.60	284.69	346.81
TCAA plus podophyllin 25%	1.49	310.60	372.72	312.08	374.20
Persistent warts	121.89	413.37		535.26	

TABLE 36 Acquisition costs of patient-applied topical interventions

Intervention	Brand name	Quantity per item	Number of items per treatment period	Total cost (£)	Source of cost data
Podophyllotoxin 0.5% solution	Condyline	3.5 ml	1	14.49	BNF 68[39]
	Warticon	3 ml	1	14.86	
Imiquimod 5% cream	Aldara	12 sachets	4	194.40	
Podophyllotoxin 0.15% cream	Warticon	5 g	1	17.83	

It was assumed that one item for podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream would be sufficient for the full treatment period. For imiquimod, it was assumed that four items were required per treatment period. It is acknowledged that, in clinical practice, some patients may be prescribed fewer imiquimod items on the basis that a patient may use fewer sachets per week; however, in the base case, the full treatment regimen was modelled. These assumptions were verified with clinicians and varied in a one-way sensitivity analysis to test their impact on the model results.

Provider-applied topical interventions

Podophyllin and TCAA were assumed to be applied by a clinician at a clinic. The cost calculations for these treatments are presented in *Table 37*.

No published list price for podophyllin or TCAA was identified. Thus, the costs for these interventions were estimated using data extracted from the systematic review of the cost and cost-effectiveness literature (see earlier in this chapter).

A cost for podophyllin was reported in two UK cost-effectiveness studies[64,171] and two UK costing studies.[172,176] The most recent study reporting a price for podophyllin was that by Woodhall *et al.*[176] In this study, a cost of £0.02 was estimated for each use of podophyllin. In the model, it was assumed that five sessions would typically be required to apply a course of treatment. This was based on consultation with a clinical expert, who estimated that a typical patient would receive between four and six sessions to apply a course of treatment with podophyllin. This was tested in sensitivity analysis. The cost estimated within the study by Woodhall *et al.*[176] was inflated to current prices using the Hospital and Community Health Services (HCHS) inflation index from the *Unit Costs of Health and Social Care 2013*[217] and was varied in sensitivity analysis.

A cost for TCAA was reported in one UK cost-effectiveness study[171] and one UK costing study.[176] The most recent study reporting a price for TCAA was again that by Woodhall *et al.*[176] In this study, a cost of £0.32 was estimated for each use of TCAA. In the model, it was assumed that four sessions would typically be required to apply a course of treatment. This was on the basis of consultation with a clinical expert, who estimated that a typical patient would receive between three and five sessions to apply a course of treatment with TCAA. As with podophyllin, the cost estimated within the study by Woodhall *et al.*[176] was inflated to current prices using the HCHS inflation index[217] and was varied in sensitivity analysis.

Provider-applied ablative interventions

Cryotherapy, CO_2 laser therapy and surgery were assumed to be carried out by a provider at a clinic. The cost calculations for these treatments are presented in *Table 38*.

The costs applied for these interventions were estimated using data extracted from the systematic review of the cost and cost-effectiveness literature.

TABLE 37 Acquisition costs of provider-applied topical interventions

Intervention	Cost per use (£)	Cost year	Number of uses per treatment period	Total cost in current prices (£)	Source of cost data
Podophyllin 10 ml	0.02	2010	5	0.11	Woodhall *et al.*[176]
TCAA	0.32		4	1.38	

TABLE 38 Acquisition costs of provider-applied ablative interventions

Intervention	Cost per use (£)	Cost year	Number of uses per treatment period	Total cost in current prices (£)	Source of cost data
Cryotherapy	4.27	2010	4	18.38	Woodhall *et al.*[176]
CO_2 laser therapy	125.49	2010	1	135.07	
Surgical excision	156.03	2012/13	1	156.03	Department of Health[238]

A cost for cryotherapy was reported in one UK cost-effectiveness study[171] and two UK costing studies.[175,176] The most recent study reporting a price for cryotherapy was that by Woodhall *et al.*[176] In this study, a cost of £4.27 was estimated for each use of cryotherapy. In the model, it was assumed that four sessions would typically be required to apply a course of treatment. This was on the basis of consultation with a clinical expert, who estimated that a typical patient would receive between three and five sessions of cryotherapy. As before, the cost estimated within the study by Woodhall *et al.*[176] was inflated to current prices using the HCHS inflation index[217] and was varied in sensitivity analysis.

A cost for CO_2 laser therapy was reported in one UK costing study.[176] In this study, a cost of £125.49 was estimated per use. In the model, it was assumed that one treatment would typically be required per treatment period. This was on the basis of consultation with a clinical expert, who estimated that a typical patient would receive one treatment with CO_2 laser therapy. As before, the cost was inflated to current prices using the HCHS inflation index[217] and was varied in sensitivity analysis.

For this analysis, the cost of surgical excision was taken from NHS reference cost values for 2012/13.[238] Specifically, the average cost associated with the outpatient procedure codes MA22Z and MA23Z ('Minor Lower Genital Tract procedures'), weighted by activity, was applied within the model (£156). In the model, it was assumed that one session would typically be required per treatment period. This was on the basis of consultation with a clinical expert. It was assumed that the cost of an appointment in a GUM clinic would also be required. Reference costs were selected in place of national tariff data because reference cost figures are based on the actual reported estimated costs of coded procedures, whereas national tariff data represent the payments received by providers from the Department of Health for the coded procedures.

Combination therapies

The costs applied for combination treatments were estimated as the sum of the costs of each individual element, as shown in *Tables 36–38*. A summary of the applied costs is provided in *Table 39*.

TABLE 39 Acquisition costs of combination interventions

Intervention	Cost per treatment course (£)	Source
Cryotherapy plus podophyllin 25%	18.49	Woodhall *et al.*[176]
Cryotherapy plus podophyllotoxin 0.15% cream	36.21	Woodhall *et al.*,[176] BNF 68[39]
TCAA plus podophyllin 25%	1.49	Woodhall *et al.*,[176] BNF 68[39]

Persistent warts

The one-off intervention cost associated with persistent warts applied in the model was £121.89. The description of how this figure was estimated is provided below.

Following review of the cost papers identified from the economic literature review, it was noted that Lanitis[51] reported data relating to the number of additional appointments required for people with persistent warts. Within the study, a total of four consultants were interviewed. These consultants estimated that people with persistent warts typically required two additional appointments with a clinician compared with those without persistent warts.

Within the model, it was assumed that a further two visits would result in an average of two further lines of prescribed therapy. This is a simplifying assumption based on lack of data, as it is acknowledged that some people with persistent warts may be prescribed more or fewer lines of therapy. Additionally, the therapies prescribed for persistent warts were assumed to consist of either combination treatments or ablative therapies. This was based on the review of cost studies identified in the literature review and on consultation with clinical experts. Two of the identified cost studies presented the results of physician interviews around the likely treatments prescribed for persistent warts.[51,172]

In the study by Lanitis,[51] four consultants were interviewed. These consultants estimated that, for keratinised persistent warts, approximately 37.5% of people would be treated with ablative or combination therapy, with the remainder receiving topical monotherapy. For non-keratinised warts, approximately 25% of people were expected to be treated with ablative or combination therapy, with the remainder receiving topical monotherapy.

In the study by Brown *et al.*,[172] six GUM physicians were interviewed. The expected treatment for people with persistent warts was estimated by the physicians to be:

- cryotherapy (23%)
- diathermy procedure (23%)
- combination of a procedure and topical cream (22%)
- surgery (6%)
- topical cream (27%), of which imiquimod (98%) and podophyllotoxin (2%).

In addition, the clinical experts consulted for this project suggested that, in UK clinical practice, a patient with persistent warts would generally be treated with ablative therapy, most likely CO_2 laser therapy.

To take into account the variation in reported treatment for people with persistent warts, an average cost associated with combination therapies (cryotherapy plus podophyllin 25%, cryotherapy plus podophyllotoxin 0.15% cream, TCAA plus podophyllin 25%) and ablative therapies (cryotherapy, CO_2 laser therapy, surgical excision; for costs see *Table 35*) was used (£60.95) per additional appointment (two in the base case: £121.89). This figure was varied in sensitivity analysis.

Costs: resource use costs

Resource use

The resources modelled within the analysis specifically relate to appointments at GUM clinics. *Table 40* provides a summary of the number of appointments applied within the economic analysis in the base case.

TABLE 40 Summary of resource use applied within the model

Treatment pathway	Number of appointments	Included in model?	Comments
Person with AGWs presents to clinician for diagnosis	1	No	All patients experience this appointment and therefore there are no differences between treatment groups
Additional appointments required for treatment with:			
No treatment	0	Yes	The number of additional appointments required depends on the number of administrations required
Imiquimod 5% cream	0		
Podophyllin 20–25%	5		
Podophyllotoxin 0.5% cream (sensitivity analysis only)	0		
Podophyllotoxin 0.5% solution	0		
TCAA	4		
CO_2 laser therapy	1		
Cryotherapy	4		
Surgical excision	1		
Cryotherapy plus podophyllin 25%	5		
Cryotherapy plus podophyllotoxin 0.15% cream	4		
TCAA plus podophyllin 25%	5		
Person is successfully cleared of AGWs following first-line treatment			
After completion of treatment	0	Yes	No additional appointments required for people successfully treated for AGWs
After 12 weeks' follow-up	0	Yes	
Person is not successfully cleared of AGWs following first-line treatment			
After completion of treatment	1	Yes	An additional appointment is required to review a patient who is not clear of AGWs after first- or second-line treatment
After 12 weeks' follow-up	1	Yes	
Person is prescribed second-line treatment			
Additional appointments required for treatment with:			
No treatment	0	Yes	The number of additional appointments required depends on the number of administrations required
Imiquimod 5% cream	0		
Podophyllin 20–25%	5		
Podophyllotoxin 0.5% cream (sensitivity analysis only)	0		
Podophyllotoxin 0.5% solution	0		
TCAA	4		
CO_2 laser therapy	1		
Cryotherapy	4		
Surgical excision	1		
Cryotherapy plus podophyllin 25%	5		
Cryotherapy plus podophyllotoxin 0.15% cream	4		
TCAA plus podophyllin 25%	5		

TABLE 40 Summary of resource use applied within the model (*continued*)

Treatment pathway	Number of appointments	Included in model?	Comments
Person is successfully cleared of AGWs following second-line treatment			
After completion of treatment	0	Yes	No additional appointments required for people successfully treated for AGWs
After 12 weeks' follow-up	0	Yes	
Person is not successfully cleared of AGWs following second-line treatment			
After completion of treatment	2	Yes	These patients were assumed to have persistent warts and require a further two appointments
After 12 weeks' follow-up	2	Yes	

Within the model it was assumed that all appointments take place within GUM clinics. This was a simplifying assumption that is not expected to impact on the model results. In clinical practice, the majority of people with AGWs are treated in GUM clinics; however, a proportion of patients may be treated by their GP or in hospital. The proportion of people with AGWs treated in GUM clinics is reported by Lanitis[51] to be 91% and by Desai *et al.*[3] to be 77%. Clinical expert opinion considered it likely that approximately 85–90% of appointments take place in GUM clinics, with the vast majority of the remainder carried out at GP practices and a minority carried out in hospital. The clinical experts approached considered that the proportion of patients treated in GUM clinics compared with GP practices would not differ by intervention. Consequently, the assumption that all appointments will be carried out in GUM clinics was not considered to be a key point of difference between interventions and is unlikely to affect the model results.

In clinical practice, all people with AGWs will experience a first appointment with a clinician to diagnose their AGWs; however, this appointment has not been modelled within the analysis. This is because the cost of attendance for the initial appointment will be the same for all interventions modelled and therefore will not affect the incremental results.

People treated first line with clinician-applied topical or ablative therapies, either as monotherapy or as part of a combination therapy, were assumed to require additional appointments in which the therapy is applied; the number of appointments was assumed to directly correlate to the number of required administrations, see *Model structure*. People treated with patient-applied topical therapy, or those who receive no treatment, were assumed to incur no additional appointments for application of their therapy.

All people with recurrence of AGWs after clearance with first-line treatment, or with AGWs that do not clear after first-line treatment, were assumed to return to their clinician and to incur the cost of an appointment. In contrast to the initial appointment, the cost of this appointment has been included in the analysis, because the number of required appointments will vary by treatment because of differences in rates of complete clearance at the end of treatment and rates of recurrence.

As with first-line treatment, people treated second line with clinician-applied topical or ablative therapies, either as monotherapy or as part of a combination therapy, were assumed to require additional appointments in which the therapy is applied; the number of appointments was assumed to directly correlate with the number of required administrations, see *Model structure*. People treated with patient-applied topical therapy were assumed to incur no additional appointments for application of their therapy.

Successful treatment of AGWs was assumed to result in no further appointments. Following review of the studies identified in the systematic review of the cost literature, it was noted that Woodhall *et al.*[176] reported that 45% of women and 55% of men attended their physician once (i.e. the initial appointment). Following consultation with clinical experts, it is considered likely that a majority of patients attending only once at the initial appointment are clear of AGWs and therefore chose not to return to the physician.

It was assumed that people who experience a recurrence of AGWs after second-line treatment, or who do not clear after second-line treatment, had persistent warts and a further two appointments are applied. As described above, this assumption is based on review of the study by Lanitis.[51]

Cost of resources

The cost of attendance at a GUM clinic for an appointment was estimated by multiplying the estimated time per appointment by the cost of clinician time. The estimated time per appointment was taken from the study by Woodhall *et al.*[176] and costs for clinician time were taken from the *Unit Costs for Health and Social Care 2013*[217] for community-based staff.

The study by Woodhall *et al.*[176] reported the results of a case note review of 370 people aged ≥ 16 years attending six sexual health clinics in England and one clinic in Northern Ireland. The authors recorded the resources used in the care of each participant and reported consultation times at clinics by staff involved in the visit. The estimates of consultation time were presented separately in the online appendix for women and men, by type of staff involved in the visit, by first and follow-up appointments and by laser treatment compared with all other treatments.

In the model, data for follow-up appointments were used. This is because the first appointment at a GUM clinic was not modelled (see *Model structure*). In addition, rather than modelling women and men separately, an average appointment time was calculated, which was weighted by the number of women ($n = 157$) and men ($n = 213$) surveyed.

The duration of appointment was assumed to differ by treatment administered. Specifically, the duration of appointment reported for laser therapy in Woodhall *et al.*[176] was used for appointments related to laser therapy, for appointments related to persistent warts and for appointments related to surgical excision. The duration of appointment reported for all other therapies in Woodhall *et al.*[176] was used for the remaining clinician-administered topical and ablative therapies.

For simplicity, it was assumed that, except for CO_2 laser therapy and surgical excision, the type of appointment (doctor led, nurse led or doctor with nurse) was equally split, that is, 33.3% doctor led, 33.3% doctor with nurse and 33.3% nurse led; for CO_2 laser therapy and surgical excision the split was 50% doctor led and 50% doctor with nurse. This was varied in sensitivity analysis.

The cost applied for a doctor and a nurse in the base case was £292 and £58 per hour, respectively.[217] The estimated weighted average cost per consultation for CO_2 laser therapy and surgical excision, and for appointments for persistent warts was £206.68. The estimated weighted average cost per consultation for all other treatments was £62.12. The consultation times and costs included in the analysis are presented in *Table 41*. Costs were varied in sensitivity analysis.

It was considered appropriate to apply the duration of appointment related to laser therapy in Woodhall *et al.*[176] to appointments related to persistent warts to reflect the increased likelihood that clinician-applied ablative therapies would be prescribed at this stage. Similarly, it was considered appropriate to apply the duration of appointment related to laser therapy in Woodhall *et al.*[176] to appointments related to surgical excision because surgical excision was considered by the clinical experts consulted to require a similar length of appointment to that for laser therapy in clinical practice.

Two other UK cost papers identified from the systematic review recorded an estimated time per appointment.[174,175] Both of these papers were published before that by Woodhall *et al.*[176] and involved review of the case notes for fewer people with AGWs (Woodhall *et al.*:[175] 189 people, published 2009; Langley *et al.*:[174] 200 people, published 2004; Woodhall *et al.*:[176] 370 people, published 2011). For these reasons, data from Woodhall *et al.*[176] were considered most appropriate for use within the model in the base case.

TABLE 41 Consultation times and costs modelled in the economic analysis

Staff involved in visit	Average consultation time (minutes), females	Average consultation time (minutes), males	Weighted average consultation time (minutes)	Cost per consultation (£)	Assumed proportion of attendances (%)
For all interventions except CO_2 laser therapy and surgical excision					
Doctor led					
Doctor time	17	16	16.4	79.93	33.3
Doctor with nurse					
Doctor time	18	16	16.8	82.00	33.3
Nurse time	13	10	11.3	10.90	
Nurse led					
Nurse time	14	14	14.0	13.53	33.3
Weighted average cost per consultation				62.12	

Staff involved in visit	Average consultation time (minutes)	Cost per consultation (£)	Assumed proportion of attendances (%)
For CO_2 laser and surgical excision			
Doctor led			
Doctor time	38	184.93	50
Doctor with nurse			
Doctor time	38	184.93	50
Nurse time	45	43.50	
Weighted average cost per consultation		206.68	

Accounting for uncertainty

The impact of parameter uncertainty on the model results was investigated in both probabilistic and deterministic analyses.

Probabilistic analyses

Within the economic model, probabilistic analysis was used to investigate the simultaneous impact of parameter uncertainty on the cost-effectiveness results. Base-case probabilistic results are presented. Probability distributions were assigned to each parameter (except drug acquisition costs) used within the model, from which values were simultaneously sampled 1000 times. There was assumed to be zero uncertainty associated with drug acquisition costs. The type of distribution and rationale for selection of the distribution has previously been described in *Model inputs*.

Traditional head-to-head comparison of incremental results for each individual treatment sequence was considered to be unwieldy for this analysis because of the large number of treatment sequences considered in the base case ($n = 84$; see *Interventions*). Consequently, the results of the probabilistic analysis were presented using multiple cost-effectiveness acceptability curves (mCEACs) and the identified key comparisons investigated incrementally in sensitivity analysis.

Multiple cost-effectiveness acceptability curves enable the graphical presentation of the probability that a strategy will have the highest net benefit compared with all other strategies, for a given willingness to pay for an additional QALY gained.[239] Net benefit is estimated as the total benefit of a treatment strategy expressed in monetary terms less the cost of a treatment strategy. The net benefit is estimated as the QALY gain for the treatment strategy multiplied by the willingness to pay per additional QALY gained. For this analysis, the net benefit for every included treatment strategy was calculated for each of the 1000 simulations, for a range of willingness to pay values from £1000 to £50,000. For each simulation, the strategy with the highest net benefit was identified. These results were then plotted on the mCEAC graph.

Scenario analyses

A variety of assumptions have been made in the construction of the base-case model. Where possible, these have been tested in probabilistic scenario analysis. *Table 42* lists the scenario analyses carried out, the parameters used to inform these scenarios and the rationale for each analysis. For each scenario, 1000 simulations were run and results captured using mCEACs.

TABLE 42 Planned scenario analyses

Scenario analysis	Parameter definition	Rationale
Timing of complete clearance of AGWs	In the base case, if complete clearance occurs, it is assumed to occur, on average, at the mid-point between commencing treatment and assessing response. Two further scenarios were investigated: • complete clearance occurs at the start of treatment • complete clearance occurs at the end of treatment	To investigate the impact of this assumption on model results
Timing of recurrence of AGWs	In the base case, if recurrence occurs, it is assumed to occur, on average, at the mid-point between completing treatment and assessing recurrence. Two further scenarios were investigated: • recurrence occurs at the start of follow-up • recurrence occurs at the end of follow-up	To investigate the impact of this assumption on model results
The probability of recurrence following complete clearance of AGWs	Setting the same probability of recurrence for all interventions to: • the average rate estimated from the MTC • 0% • 100%	To investigate the importance of recurrence for the model results in light of a number of weaknesses associated with the clinical data for recurrence
Alternative HRQoL data	HRQoL for AGWs set to values for young adults aged 18–24 years from the study by Dominiak-Felden[237] (HRQoL 0.86 with AGWs vs. 0.94 without AGWs)	To investigate the impact of AGWs on specific subgroups of patients
Podophyllotoxin 0.5% cream assessed as a proxy for podophyllotoxin 0.15% cream	Complete clearance data for podophyllotoxin 0.5% cream was used in a scenario analysis as a proxy for podophyllotoxin 0.15% cream	To investigate a scenario in which podophyllotoxin 0.15% cream, which is used in clinical practice, was assessed despite a lack of evidence identified from the clinical literature review

Deterministic sensitivity analysis

One-way sensitivity analysis

The key head-to-head comparisons identified from the deterministic and probabilistic analyses were tested using one-way sensitivity analysis.

For each key treatment sequence, all model parameters were varied in a one-way sensitivity analysis. Parameters were assigned low and high values. When available, the low and high values used were the 95% CI or the 95% CrI. When these data were not available, an arbitrary upper and lower 20% value was used. The upper and lower values used have been previously described in *Model inputs*. The deterministic cost-effectiveness result was recorded for each one-way change in each parameter estimate. The variables associated with the greatest impact on the cost-effectiveness results are presented in tornado diagram format later in this chapter (see *Figure 33*).

Threshold analyses

Variables identified from the one-way sensitivity analysis as having the greatest impact on the model results were investigated in threshold analyses for key comparisons. The value for each variable was altered until each relevant ICER reached a threshold of £20,000 or £30,000 per additional QALY.

Independent economic assessment: results

Base-case results

Probabilistic analysis

The following probabilistic base-case results are presented:

- the estimated average cost per patient per treatment strategy, with lower 2.5% and upper 97.5% values (*Table 43*)
- the estimated average QALYs per patient per treatment strategy, with lower 2.5% and upper 97.5% values (*Table 44*)
- a mCEAC presenting the probability of each treatment strategy being considered that with the highest net benefit for varying values for the willingness to pay for an additional QALY gained (from £1000 to £50,000, *Figure 20*)
- a tabular summary of the mCEAC results for willingness-to-pay thresholds of £20,000 and £30,000 per additional QALY gained (*Table 45*).

Quality-adjusted life-years were calculated based on the 58-week time horizon and so the average QALYs per patient, irrespective of treatment sequence, were found to be > 1.

The average cost per treatment sequence was estimated to range between £199 (podophyllotoxin solution followed by CO_2 laser therapy) and £700 (podophyllin 20–25% followed by cryotherapy) per patient. The average QALYs gained per patient per treatment sequence were estimated to range between 1.006 (no treatment followed by podophyllin 20–25%) and 1.040 (CO_2 laser therapy followed by surgical excision) per patient. It is noted that the average cost per patient identified from the systematic review of the cost literature (see *Description of the identified costing studies*) ranged between £94[176] and £276.[51] The results of this analysis imply a larger cost per treatment sequence. However, following consultation with clinical experts, it is noted that in clinical practice podophyllotoxin (solution or cream) is commonly prescribed first line because of its its relatively low cost. The average cost for strategies in which podophyllotoxin solution 0.5% was prescribed first line was estimated in this analysis to range from £199 to £297; thus, it is considered that the estimates of cost from this analysis are generally aligned with the higher end of the range identified from the systematic review of the cost literature.

TABLE 43 Average per-patient costs (£) and lower 2.5% and upper 97.5% values associated with each evaluated treatment sequence: probabilistic analysis

	Second line										
First line	No treatment	Imiquimod 5% cream	Podophyllin 20–25%	Podophyllotoxin 0.5% solution	TCAA	CO_2 laser therapy	Cryotherapy	Surgical excision	Cryotherapy plus podophyllin 25%	Cryotherapy plus podophyllotoxin 0.15% cream	TCAA plus podophyllin 25%
No treatment	NA	511 (335 to 736)	674 (525 to 839)	273 (185 to 392)	550 (384 to 750)	442 (334 to 592)	577 (439 to 762)	520 (381 to 739)	614 (468 to 800)	542 (406 to 740)	636 (458 to 849)
Imiquimod 5% cream	NA	NA	571 (360 to 819)	347 (248 to 474)	502 (323 to 745)	441 (297 to 611)	517 (334 to 755)	485 (316 to 721)	538 (346 to 800)	498 (328 to 748)	550 (349 to 828)
Podophyllin 20–25%	NA	654 (494 to 838)	NA	495 (380 to 638)	682 (518 to 871)	609 (478 to 757)	700 (545 to 892)	662 (516 to 841)	NA	677 (521 to 861)	NA
Podophyllotoxin 0.5% solution	NA	228 (130 to 370)	297 (183 to 444)	NA	244 (151 to 374)	199 (128 to 300)	256 (157 to 390)	232 (141 to 368)	272 (165 to 415)	NA	280 (173 to 427)
TCAA	NA	522 (355 to 745)	610 (416 to 843)	396 (290 to 524)	NA	486 (346 to 658)	562 (373 to 827)	528 (368 to 756)	579 (388 to 810)	542 (368 to 791)	NA
CO_2 laser therapy	NA	407 (310 to 545)	427 (316 to 602)	377 (296 to 477)	412 (312 to 561)	NA	416 (313 to 570)	408 (309 to 552)	420 (315 to 586)	411 (312 to 563)	422 (315 to 593)
Cryotherapy	NA	551 (411 to 757)	643 (478 to 886)	420 (316 to 544)	577 (405 to 836)	514 (389 to 686)	NA	558 (421 to 750)	NA	NA	622 (455 to 856)
Surgical excision	NA	491 (360 to 717)	532 (372 to 820)	431 (337 to 571)	501 (362 to 761)	473 (353 to 663)	508 (365 to 761)	NA	517 (369 to 792)	499 (365 to 743)	522 (372 to 810)
Cryotherapy plus podophyllin 25%	NA	591 (444 to 795)	NA	470 (354 to 612)	613 (448 to 834)	556 (427 to 725)	NA	596 (449 to 807)	NA	NA	NA
Cryotherapy plus podophyllotoxin 0.15% cream	NA	514 (377 to 743)	587 (426 to 841)	NA	535 (374 to 790)	485 (363 to 680)	NA	519 (390 to 733)	NA	NA	571 (413 to 835)
TCAA plus podophyllin 25%	NA	614 (443 to 855)	NA	473 (351 to 618)	NA	574 (422 to 760)	654 (469 to 919)	620 (452 to 854)	NA	633 (457 to 894)	NA

NA, not applicable.

TABLE 44 Average per-patient QALYs and lower 2.5% and upper 97.5% values associated with each evaluated treatment sequence: probabilistic analysis

	Second line										
First line	No treatment	Imiquimod 5% cream	Podophyllin 20–25%	Podophyllotoxin 0.5% solution	TCAA	CO_2 laser therapy	Cryotherapy	Surgical excision	Cryotherapy plus podophyllin 25%	Cryotherapy plus podophyllotoxin 0.15% cream	TCAA plus podophyllin 25%
No treatment	NA	1.008 (0.905 to 1.115)	1.006 (0.900 to 1.113)	1.019 (0.914 to 1.127)	1.011 (0.907 to 1.118)	1.031 (0.925 to 1.142)	1.011 (0.906 to 1.117)	1.025 (0.916 to 1.135)	1.014 (0.908 to 1.121)	1.016 (0.911 to 1.123)	1.010 (0.905 to 1.120)
Imiquimod 5% cream	NA	NA	1.018 (0.914 to 1.126)	1.024 (0.920 to 1.133)	1.020 (0.918 to 1.128)	1.028 (0.923 to 1.139)	1.020 (0.916 to 1.129)	1.026 (0.920 to 1.135)	1.021 (0.918 to 1.130)	1.022 (0.919 to 1.132)	1.020 (0.915 to 1.129)
Podophyllin 20–25%	NA	1.020 (0.916 to 1.129)	NA	1.027 (0.921 to 1.138)	1.022 (0.918 to 1.132)	1.034 (0.927 to 1.146)	1.022 (0.917 to 1.131)	1.030 (0.924 to 1.142)	NA	1.025 (0.919 to 1.134)	NA
Podophyllotoxin 0.5% solution	NA	1.029 (0.924 to 1.140)	1.029 (0.923 to 1.139)	NA	1.031 (0.924 to 1.142)	1.038 (0.930 to 1.150)	1.031 (0.924 to 1.143)	1.035 (0.928 to 1.147)	1.032 (0.925 to 1.144)	NA	1.031 (0.923 to 1.139)
TCAA	NA	1.024 (0.920 to 1.134)	1.023 (0.920 to 1.134)	1.030 (0.924 to 1.141)	NA	1.036 (0.927 to 1.148)	1.026 (0.921 to 1.136)	1.033 (0.925 to 1.144)	1.027 (0.921 to 1.137)	1.028 (0.921 to 1.138)	NA
CO_2 laser therapy	NA	1.038 (0.931 to 1.151)	1.038 (0.931 to 1.151)	1.039 (0.931 to 1.152)	1.038 (0.931 to 1.151)	NA	1.038 (0.931 to 1.151)	1.040 (0.932 to 1.152)	1.038 (0.932 to 1.151)	1.039 (0.931 to 1.151)	1.038 (0.931 to 1.150)
Cryotherapy	NA	1.024 (0.919 to 1.133)	1.023 (0.918 to 1.133)	1.030 (0.923 to 1.141)	1.025 (0.921 to 1.135)	1.035 (0.927 to 1.147)	NA	1.032 (0.926 to 1.143)	NA	NA	1.025 (0.918 to 1.134)
Surgical excision	NA	1.034 (0.927 to 1.145)	1.033 (0.927 to 1.145)	1.036 (0.929 to 1.148)	1.034 (0.927 to 1.145)	1.039 (0.931 to 1.151)	1.034 (0.927 to 1.145)	NA	1.035 (0.927 to 1.146)	1.036 (0.928 to 1.146)	1.034 (0.927 to 1.146)
Cryotherapy plus podophyllin 25%	NA	1.025 (0.920 to 1.136)	NA	1.031 (0.923 to 1.143)	1.027 (0.920 to 1.136)	1.036 (0.928 to 1.148)	NA	1.033 (0.926 to 1.144)	NA	NA	NA
Cryotherapy plus podophyllotoxin 0.15% cream	NA	1.027 (0.922 to 1.137)	1.027 (0.920 to 1.136)	NA	1.029 (0.921 to 1.139)	1.036 (0.927 to 1.149)	NA	1.034 (0.927 to 1.144)	NA	NA	1.028 (0.920 to 1.135)
TCAA plus podophyllin 25%	NA	1.023 (0.916 to 1.132)	NA	1.029 (0.921 to 1.137)	NA	1.035 (0.927 to 1.145)	1.025 (0.917 to 1.134)	1.031 (0.924 to 1.143)	NA	1.027 (0.919 to 1.135)	NA

NA, not applicable.

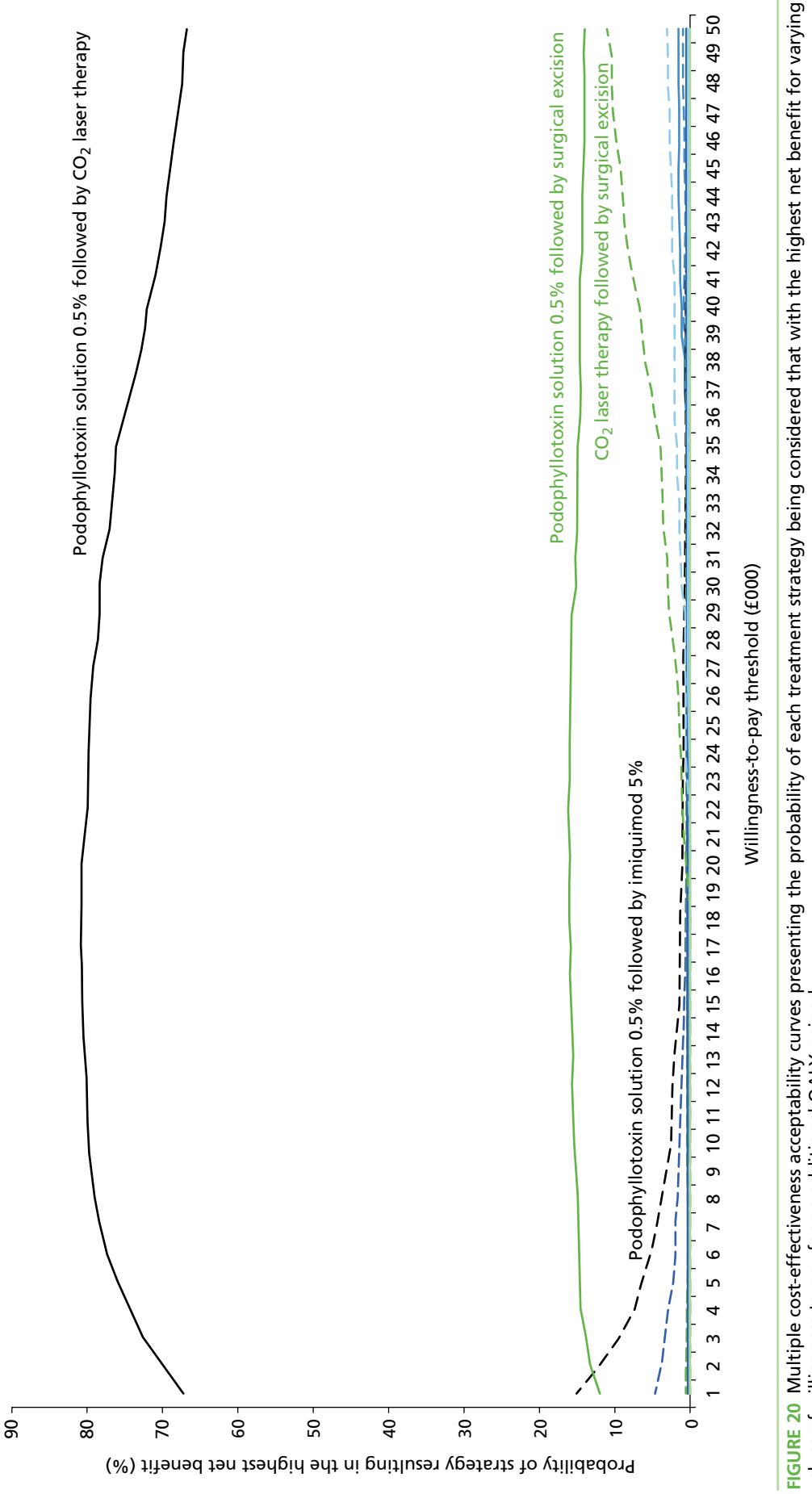

FIGURE 20 Multiple cost-effectiveness acceptability curves presenting the probability of each treatment strategy being considered that with the highest net benefit for varying values of willingness to pay for an additional QALY gained.

TABLE 45 The probability of each treatment strategy being considered that with the highest net benefit, for willingness-to-pay thresholds for an additional QALY gained of £20,000 and £30,000

	Probability (%) of strategy resulting in the highest net benefit, based on a willingness to pay per additional QALY gained of	
Treatment strategy	£20,000	£30,000
Podophyllotoxin 0.5% solution followed by CO_2 laser therapy	80.7	78.3
Podophyllotoxin 0.5% solution followed by surgical excision	15.9	15.1
Podophyllotoxin 0.5% solution followed by imiquimod 5% cream	1.1	0.7
CO_2 laser therapy followed by surgical excision	0.6	3.0
Podophyllotoxin 0.5% solution followed by TCAA	0.5	0.5
Podophyllotoxin 0.5% solution followed by TCAA plus podophyllin 25%	0.4	0.4
Surgical excision followed by cryotherapy plus podophyllotoxin 0.15% cream	0.2	0.1
Podophyllotoxin 0.5% solution followed by cryotherapy	0.1	0.0
Podophyllotoxin 0.5% solution followed by cryotherapy plus podophyllin 25%	0.1	0.0
CO_2 laser therapy followed by cryotherapy plus podophyllotoxin 0.15% cream	0.1	0.3
CO_2 laser therapy followed by TCAA plus podophyllin 25%	0.1	0.1
Surgical excision followed by CO_2 laser therapy	0.1	1.2
Cryotherapy plus podophyllotoxin 0.15% cream followed by surgical excision	0.1	0.1
CO_2 laser therapy followed by podophyllotoxin 0.5% solution	0.0	0.2

The results of the mCEACs show that, at a willingness-to-pay threshold of £20,000 per additional QALY gained, podophyllotoxin solution 0.5% followed by CO_2 laser therapy has a probability of being considered the strategy with the highest net benefit of approximately 80%. Similarly, at a willingness-to-pay threshold of £20,000 per additional QALY gained, podophyllotoxin 0.5% solution followed by surgical excision is associated with a probability of being considered the strategy with the second highest net benefit of approximately 16% (see *Table 45*). Results at a willingness-to-pay threshold of £30,000 per additional QALY gained were very similar (podophyllotoxin solution 0.5% followed by CO_2 laser therapy: 78%; podophyllotoxin 0.5% solution followed by surgical excision: 15%).

These results imply that the treatment strategy of podophyllotoxin solution 0.5% followed by CO_2 laser therapy is highly likely to be the strategy with the highest net benefit at typical UK willingness-to-pay thresholds.

Deterministic analysis

The estimated average costs per patient and average QALYs per patient according to the deterministic analysis are presented in *Table 46* (costs) and *Table 47* (QALYs).

The estimated average cost per treatment sequence ranged between £200 (podophyllotoxin 0.5% solution followed by CO_2 laser therapy) and £698 (podophyllin 20–25% followed by cryotherapy) per patient. The estimated average QALYs per treatment sequence ranged between 0.991 (no treatment followed by podophyllin 20–25%) and 1.024 (CO_2 laser therapy followed by surgical excision) per patient.

TABLE 46 Average per-patient costs (%) associated with each evaluated treatment sequence: deterministic analysis

	Second line										
First line	No treatment	Imiquimod 5% cream	Podophyllin 20–25%	Podophyllotoxin 0.5% solution	TCAA	CO_2 laser therapy	Cryotherapy	Surgical excision	Cryotherapy plus podophyllin 25%	Cryotherapy plus podophyllotoxin 0.15% cream	TCAA plus podophyllin 25%
No treatment	NA	511	673	337	547	444	576	520	612	542	636
Imiquimod 5% cream	NA	NA	573	384	502	444	518	487	539	499	552
Podophyllin 20–25%	NA	654	NA	537	678	609	698	660	NA	675	NA
Podophyllotoxin 0.5% solution	NA	228	296	NA	243	200	255	232	270	NA	280
TCAA	NA	520	605	428	NA	484	554	524	573	536	NA
CO_2 laser therapy	NA	408	429	386	413	NA	417	409	422	412	425
Cryotherapy	NA	550	640	454	570	513	NA	555	NA	NA	620
Surgical excision	NA	489	529	446	498	473	505	NA	514	497	520
Cryotherapy plus podophyllin 25%	NA	589	NA	501	607	555	NA	593	NA	NA	NA
Cryotherapy plus podophyllotoxin 0.15% cream	NA	514	£587	NA	530	484	NA	518	NA	NA	570
TCAA plus podophyllin 25%	NA	614	NA	511	NA	574	652	619	NA	£633	NA

NA, not applicable.

TABLE 47 Average per-patient QALYs associated with each evaluated treatment sequence: deterministic analysis

	Second line										
First line	No treatment	Imiquimod 5% cream	Podophyllin 20–25%	Podophyllotoxin 0.5% solution	TCAA	CO_2 laser therapy	Cryotherapy	Surgical excision	Cryotherapy plus podophyllin 25%	Cryotherapy plus podophyllotoxin 0.15% cream	TCAA plus podophyllin 25%
No treatment	NA	0.993	0.991	1.004	0.996	1.015	0.996	1.009	0.999	1.001	0.995
Imiquimod 5% cream	NA	NA	1.003	1.008	1.005	1.013	1.005	1.010	1.006	1.007	1.004
Podophyllin 20–25%	NA	1.004	NA	1.011	1.007	1.018	1.007	1.015	NA	1.010	NA
Podophyllotoxin 0.5% solution	NA	1.014	1.014	NA	1.015	1.022	1.015	1.020	1.016	NA	1.015
TCAA	NA	1.009	1.008	1.014	NA	1.020	1.011	1.017	1.012	1.013	NA
CO_2 laser therapy	NA	1.022	1.022	1.023	1.023	NA	1.023	1.024	1.023	1.023	1.022
Cryotherapy	NA	1.008	1.008	1.014	1.010	1.019	NA	1.017	NA	NA	1.010
Surgical excision	NA	1.018	1.018	1.021	1.019	1.023	1.019	NA	1.019	1.020	1.019
Cryotherapy plus podophyllin 25%	NA	1.010	NA	1.015	1.012	1.020	NA	1.017	NA	NA	NA
Cryotherapy plus podophyllotoxin 0.15% cream	NA	1.012	1.011	NA	1.013	1.021	NA	1.018	NA	NA	1.013
TCAA plus podophyllin 25%	NA	1.007	NA	1.013	NA	1.019	1.009	1.016	NA	1.012	NA

NA, not applicable.

According to the results of the deterministic analysis, the majority of treatment strategies were dominated by three alternative treatment strategies (were more costly and less effective). Non-dominated (by strict dominance) treatment strategies are presented in *Table 48*.

Similar to the results of the probabilistic analysis, podophyllotoxin 0.5% solution followed by CO_2 laser therapy was found to be the least costly treatment strategy. According to the results of the deterministic analysis, no other treatment strategy provided a cost-effective alternative to podophyllotoxin 0.5% solution followed by CO_2 laser therapy at a willingness to pay per additional QALY of £20,000–30,000.

Discussion of the results

The mean total costs and QALYs estimated from the deterministic and probabilistic analyses were found to be consistent and similar. For both the deterministic and probabilistic analyses, the least expensive treatment strategy was found to be podophyllotoxin 0.5% solution followed by CO_2 laser therapy and the treatment strategy resulting in the greatest QALYs was CO_2 laser therapy followed by surgical excision.

In addition, the main conclusion of the analyses was aligned, with both deterministic and probabilistic analyses implying that podophyllotoxin 0.5% solution followed by CO_2 laser therapy was most likely to be the treatment strategy considered a cost-effective use of resources at a willingness to pay per additional QALY gained of £20,000–30,000.

Based on the results of both the deterministic analysis and the probabilistic analysis, the following comparisons were considered as key and were tested in sensitivity analysis:

- podophyllotoxin 0.5% solution followed by surgery compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy
- CO_2 laser therapy followed by surgery compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy
- CO_2 laser therapy followed by podophyllotoxin 0.5% solution compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy.

Sensitivity analysis

Probabilistic analysis

This section presents the results of the incremental probabilistic analysis for each key comparison using the cost-effectiveness plane.

TABLE 48 Incremental deterministic results excluding strictly dominated strategies

First-line treatment	Second-line treatment	Total cost per patient (£)	Total QALYs per patient	Incremental ICER (£)	Incremental ICER excluding extendedly dominated strategies (£)
Podophyllotoxin 0.5% solution	CO_2 laser therapy	199.96	1.022	–	–
CO_2 laser therapy	Podophyllotoxin 0.5% solution	377.18	1.023	121,483 (extendedly dominated)	–
CO_2 laser therapy	Surgical excision	409.43	1.024	61,599	105,667

Podophyllotoxin 0.5% solution followed by surgery compared with podophyllotoxin 0.5% solution followed by carbon dioxide laser therapy

The results presented in *Figure 21* indicate that the majority of simulations (78%) resulted in podophyllotoxin 0.5% solution followed by surgery being dominated by podophyllotoxin 0.5% solution followed by CO_2 laser therapy, that is, being more costly and less effective. In 13% of simulations, podophyllotoxin 0.5% solution followed by surgery was dominant compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy, that is, less costly and more effective.

According to the results, the probability that podophyllotoxin 0.5% solution followed by surgery would be considered cost-effective compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy at a willingness-to-pay threshold of £20,000 and £30,000 per additional QALY gained was 15% and 16%, respectively.

Carbon dioxide laser therapy followed by surgery compared with podophyllotoxin 0.5% solution followed by carbon dioxide laser therapy

The results presented in *Figure 22* indicate that the majority of simulations (93%) resulted in CO_2 laser therapy followed by surgery being associated with a higher incremental cost and higher incremental QALYs compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy. The average ICER for these simulations was £368,128. No simulations fell into the south-east or south-west quadrants (i.e. lower incremental costs).

According to the results, the probability that CO_2 laser therapy followed by surgery would be considered cost-effective compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy at a willingness-to-pay threshold of £20,000 and £30,000 per additional QALY gained was 1% and 5%, respectively.

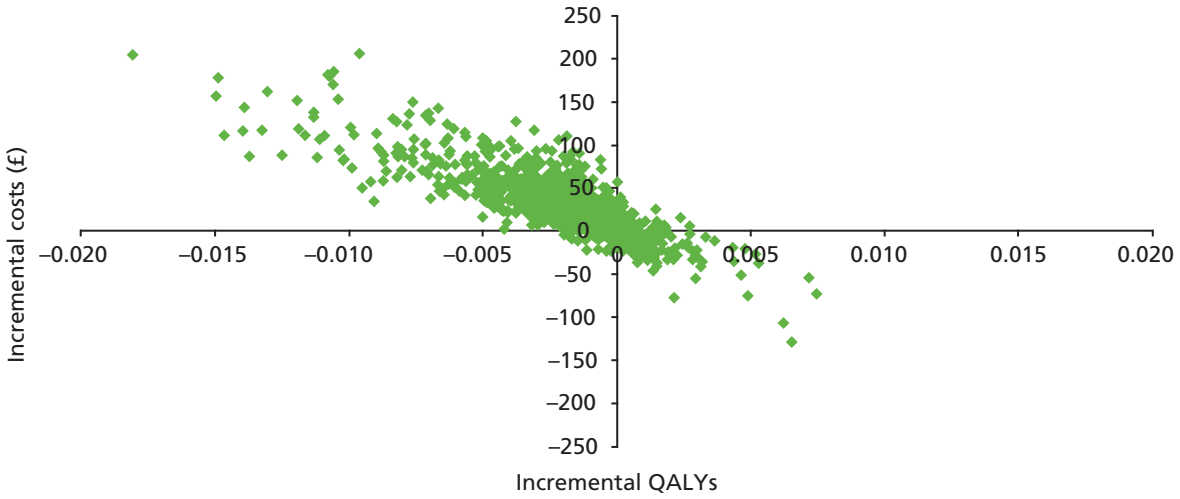

FIGURE 21 Cost-effectiveness plane presenting the incremental costs and QALYs associated with podophyllotoxin 0.5% solution followed by surgery vs. podophyllotoxin 0.5% solution followed by CO_2 laser therapy.

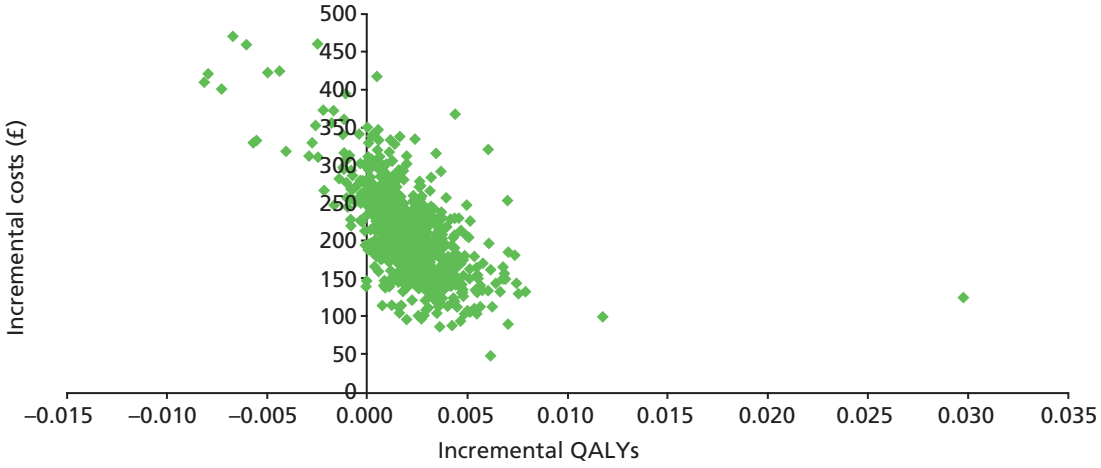

FIGURE 22 Cost-effectiveness plane presenting the incremental costs and QALYs associated with CO_2 laser therapy followed by surgery vs. podophyllotoxin 0.5% solution followed by CO_2 laser therapy.

Carbon dioxide laser therapy followed by podophyllotoxin 0.5% solution compared with podophyllotoxin 0.5% solution followed by carbon dioxide laser therapy

The results presented in *Figure 23* indicate that the majority of simulations (93%) resulted in CO_2 laser therapy followed by podophyllotoxin 0.5% solution being associated with a higher incremental cost and higher incremental QALYs compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy. The average ICER for these simulations was £490,895. No simulations fell into the south-east or south-west quadrants (i.e. lower incremental costs).

According to the results, the probability that CO_2 laser therapy followed by podophyllotoxin 0.5% solution would be considered cost-effective compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy at a willingness-to-pay threshold of £20,000 and £30,000 per additional QALY gained was 0% and 2%, respectively.

Scenario analyses

As described in *Accounting for uncertainty*, scenario analyses were carried out on the probabilistic results, with 1000 simulations run for each scenario and the results presented as mCEACs (*Figures 24–32*).

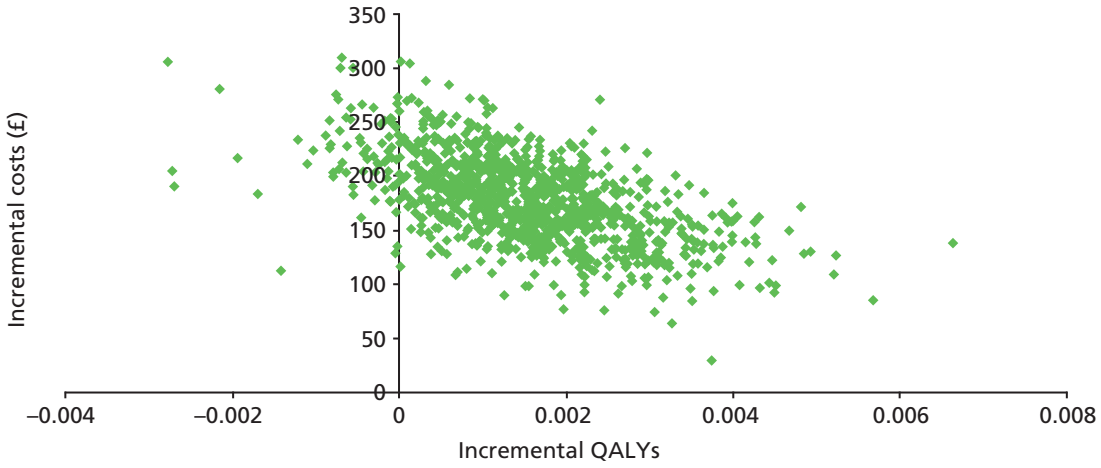

FIGURE 23 Cost-effectiveness plane presenting the incremental costs and QALYs associated with CO_2 laser therapy followed by podophyllotoxin 0.5% solution vs. podophyllotoxin 0.5% solution followed by CO_2 laser therapy.

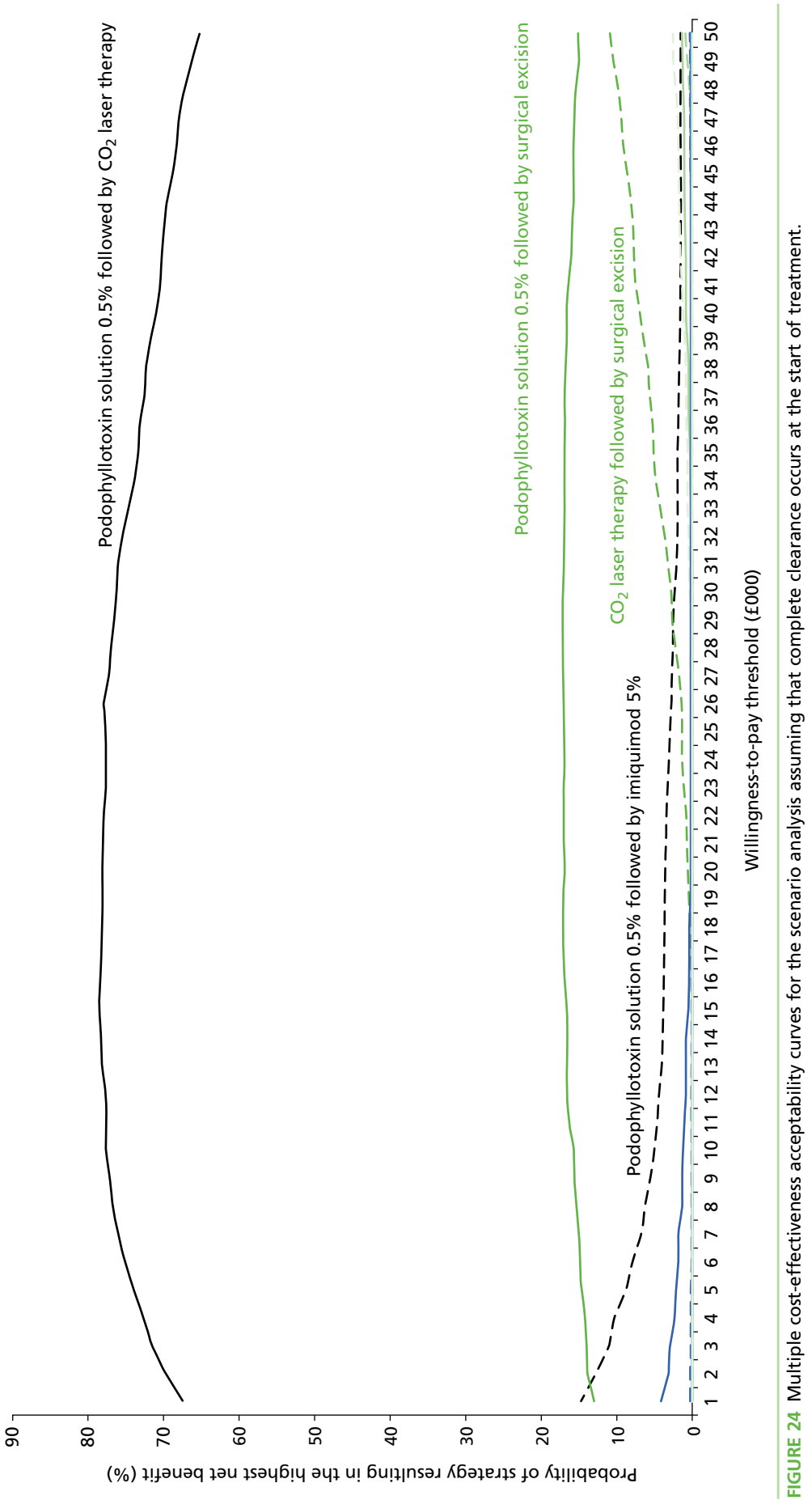

FIGURE 24 Multiple cost-effectiveness acceptability curves for the scenario analysis assuming that complete clearance occurs at the start of treatment.

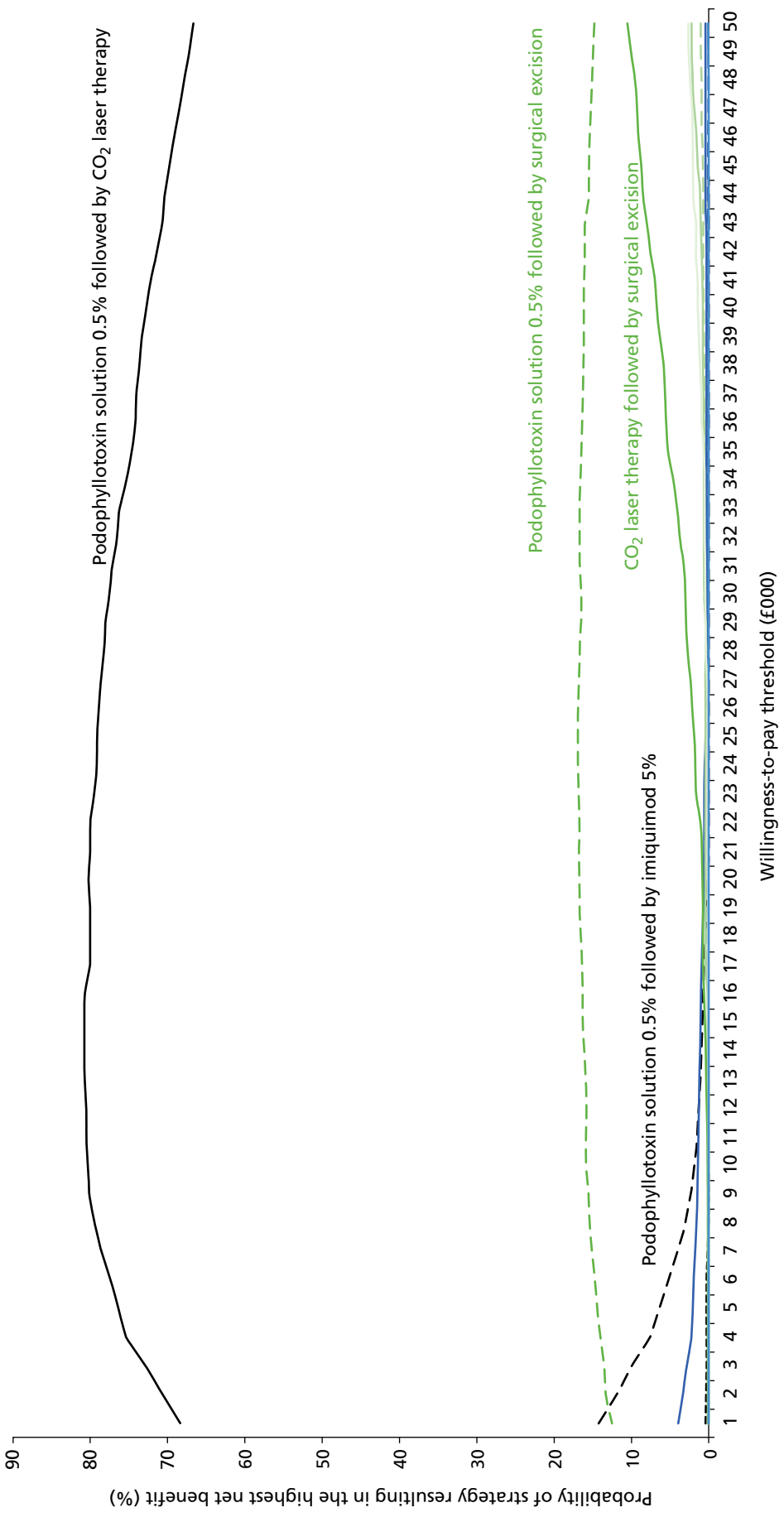

FIGURE 25 Multiple cost-effectiveness acceptability curves for the scenario analysis assuming that complete clearance occurs at the end of treatment.

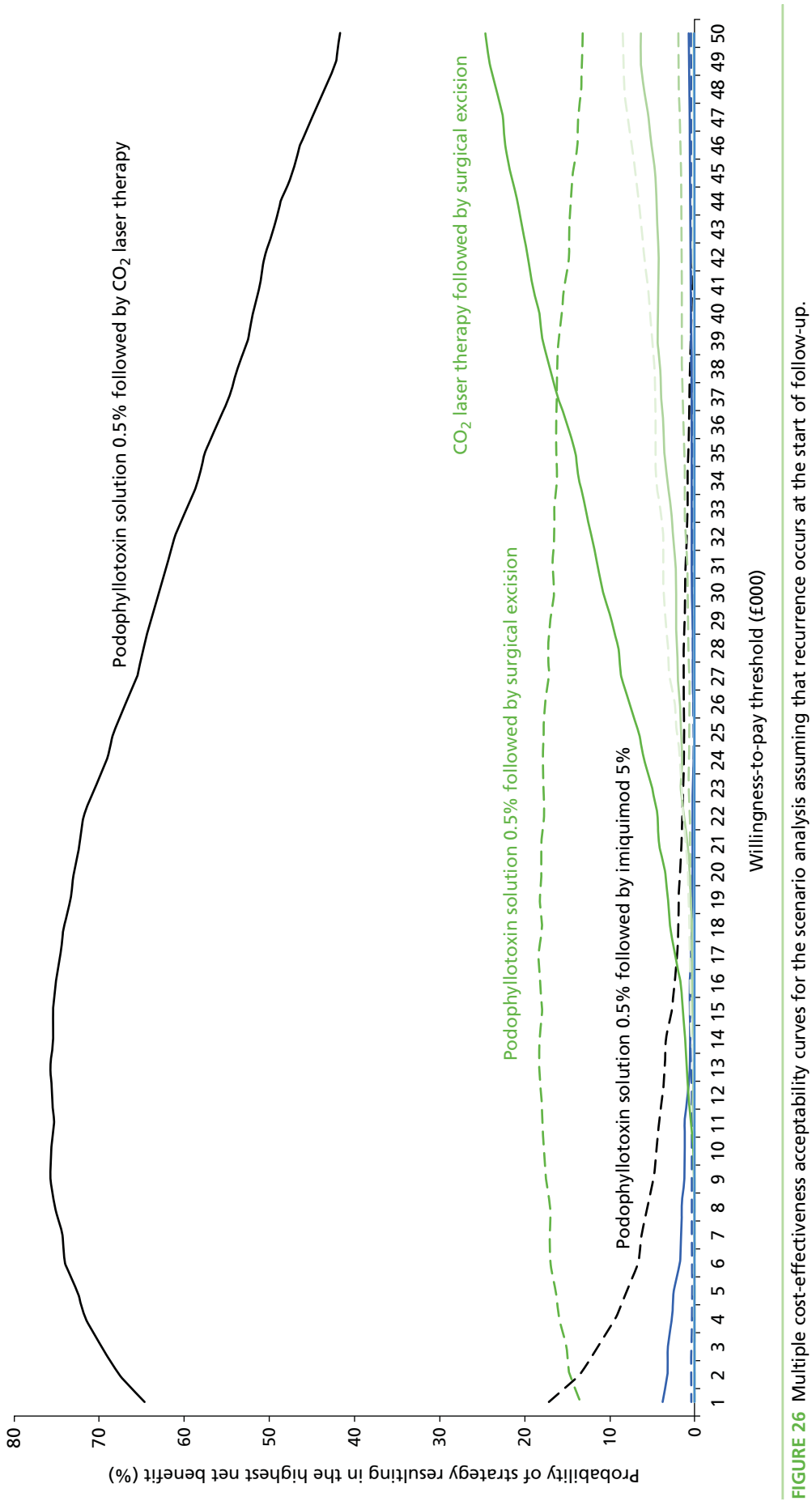

FIGURE 26 Multiple cost-effectiveness acceptability curves for the scenario analysis assuming that recurrence occurs at the start of follow-up.

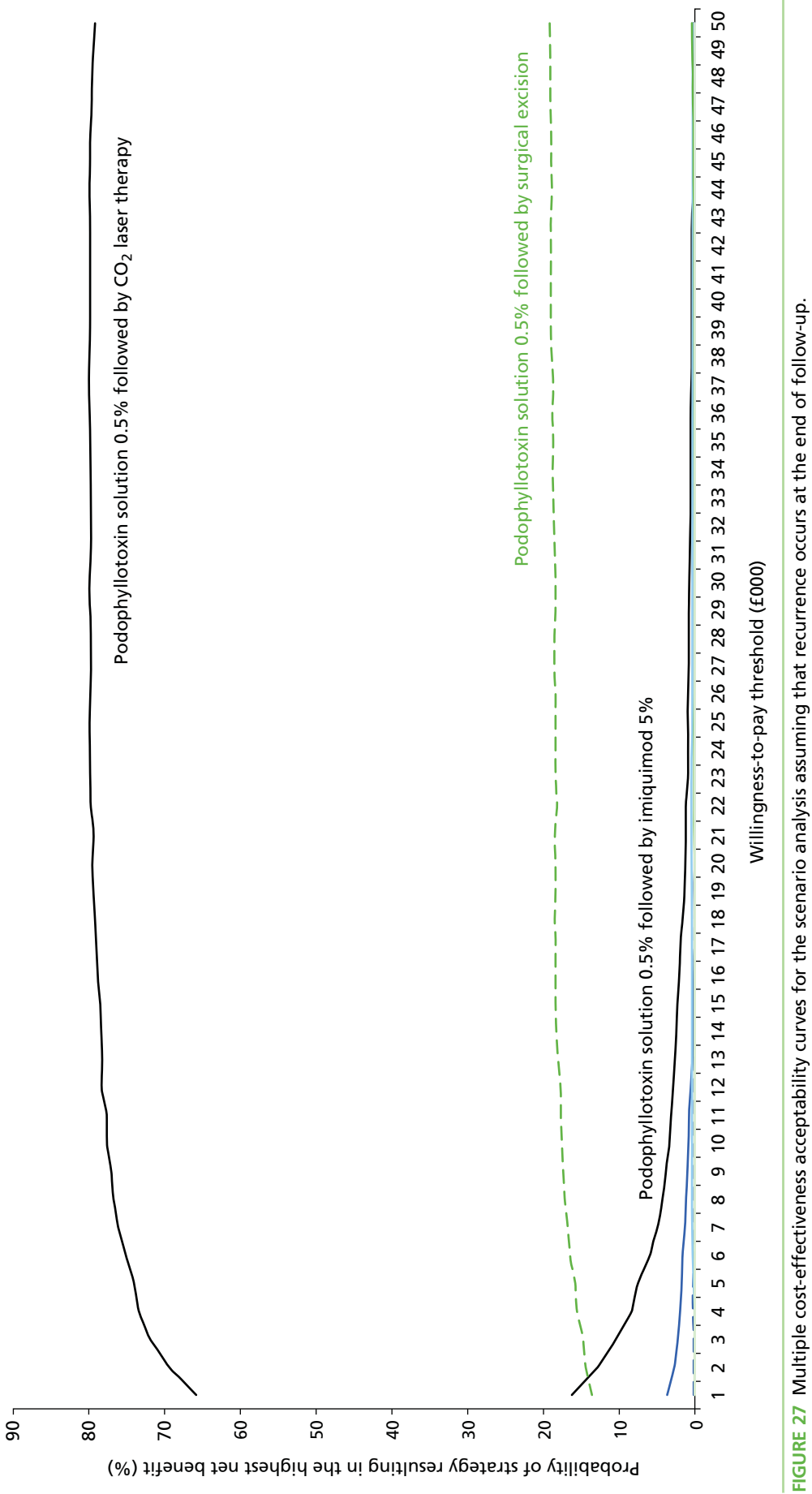

FIGURE 27 Multiple cost-effectiveness acceptability curves for the scenario analysis assuming that recurrence occurs at the end of follow-up.

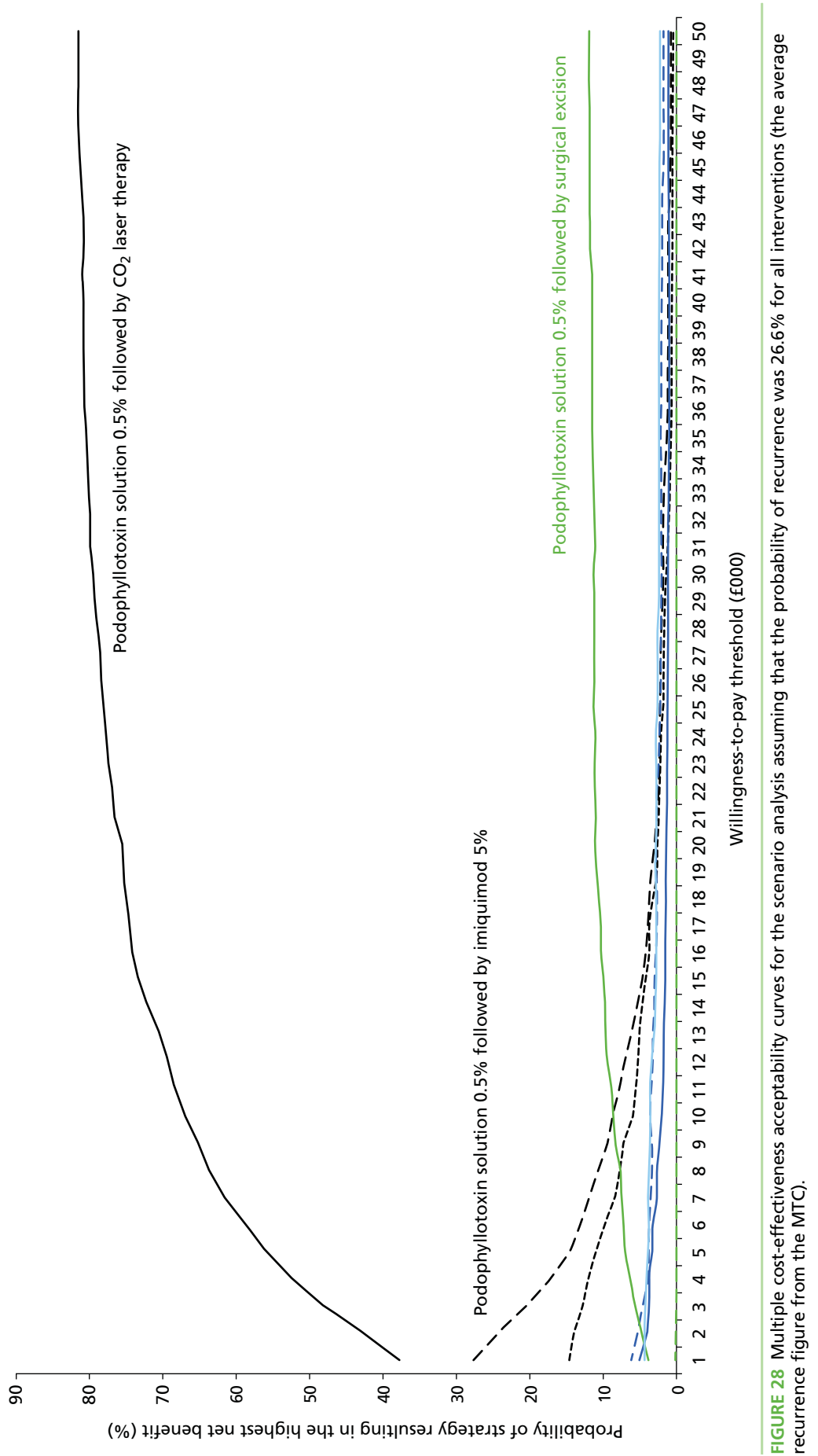

FIGURE 28 Multiple cost-effectiveness acceptability curves for the scenario analysis assuming that the probability of recurrence was 26.6% for all interventions (the average recurrence figure from the MTC).

FIGURE 29 Multiple cost-effectiveness acceptability curves for the scenario analysis assuming that the probability of recurrence was 0% for all interventions.

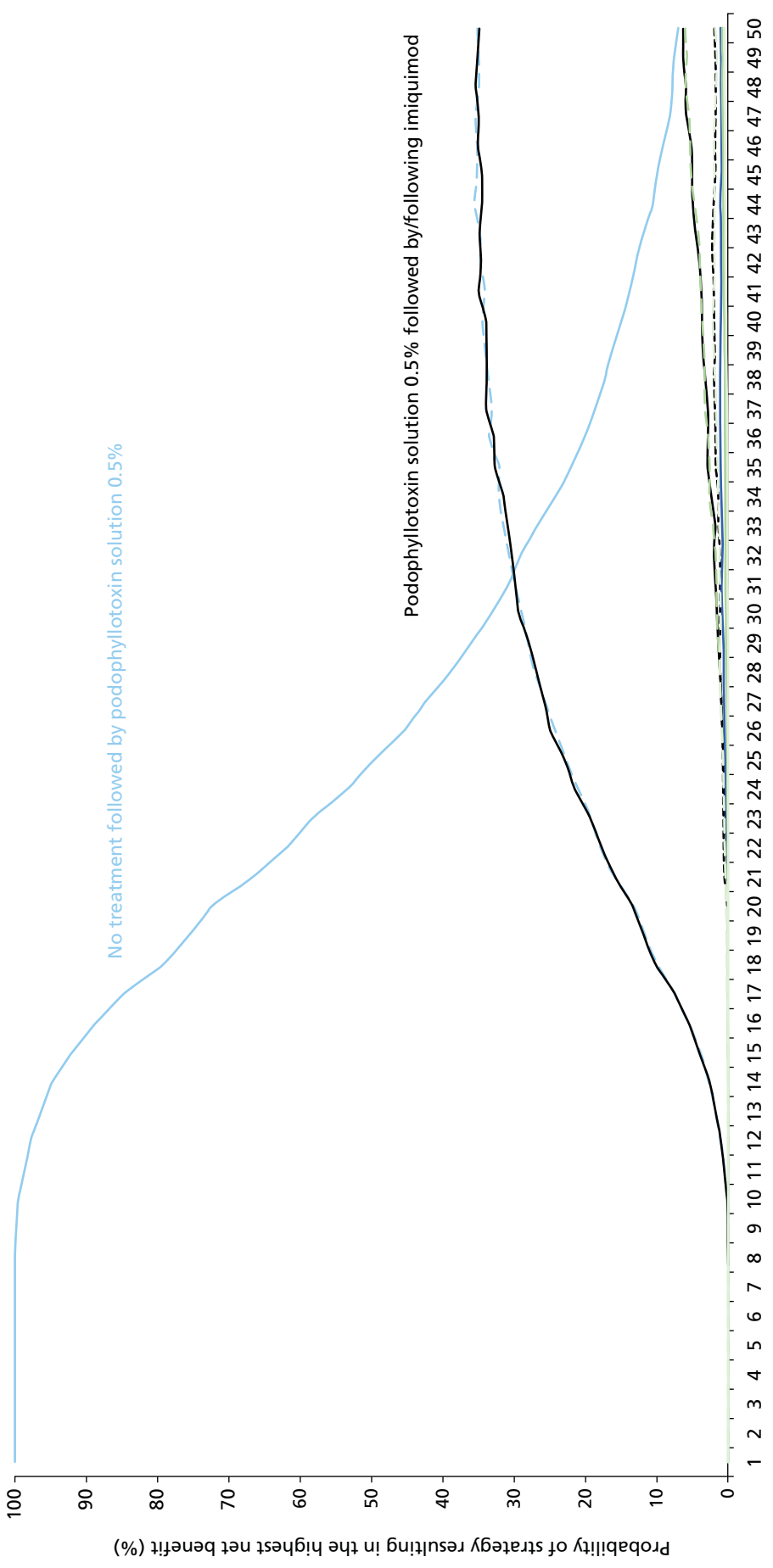

FIGURE 30 Multiple cost-effectiveness acceptability curves for the scenario analysis assuming that the probability of recurrence was 100% for all interventions.

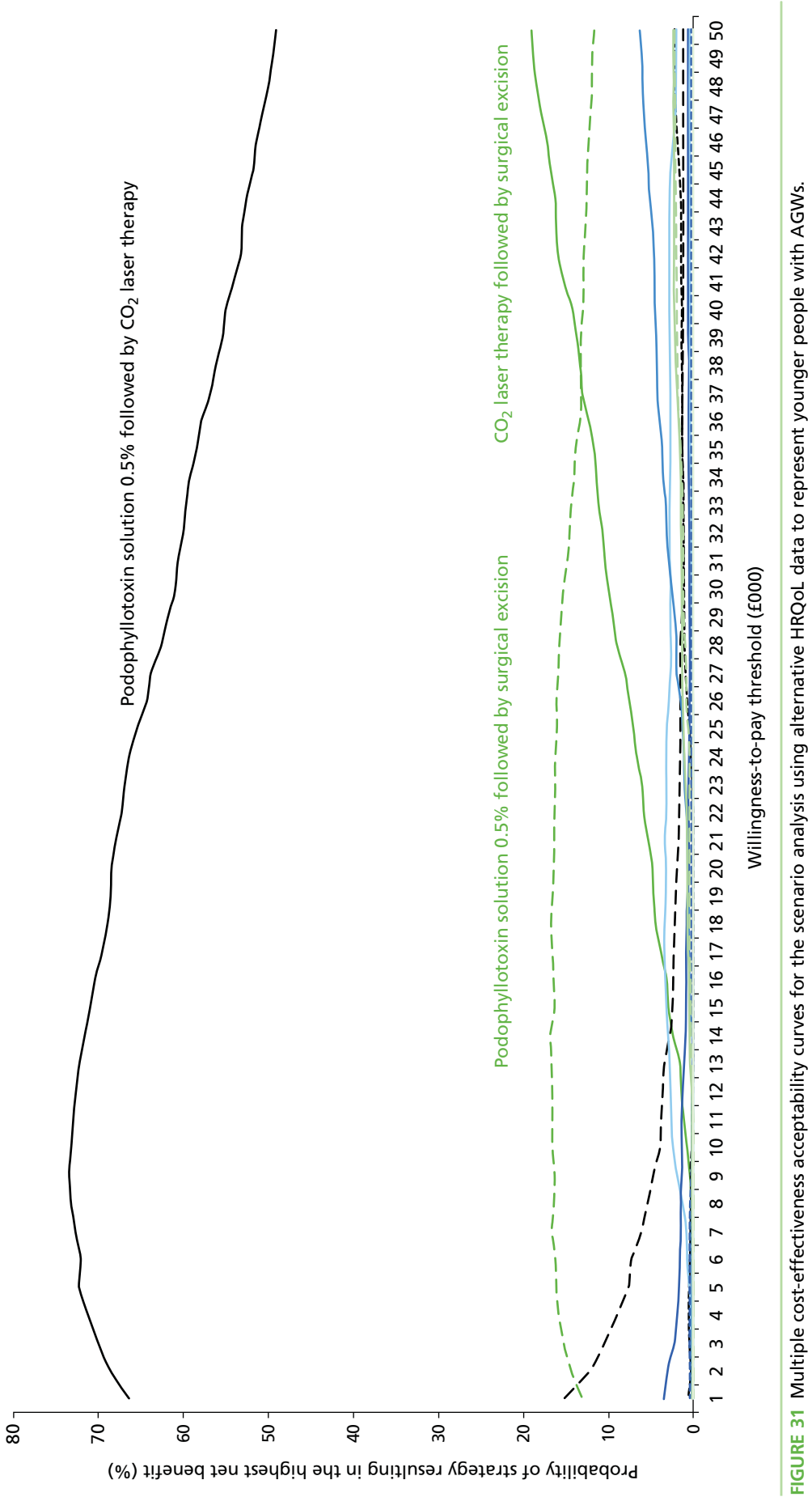

FIGURE 31 Multiple cost-effectiveness acceptability curves for the scenario analysis using alternative HRQoL data to represent younger people with AGWs.

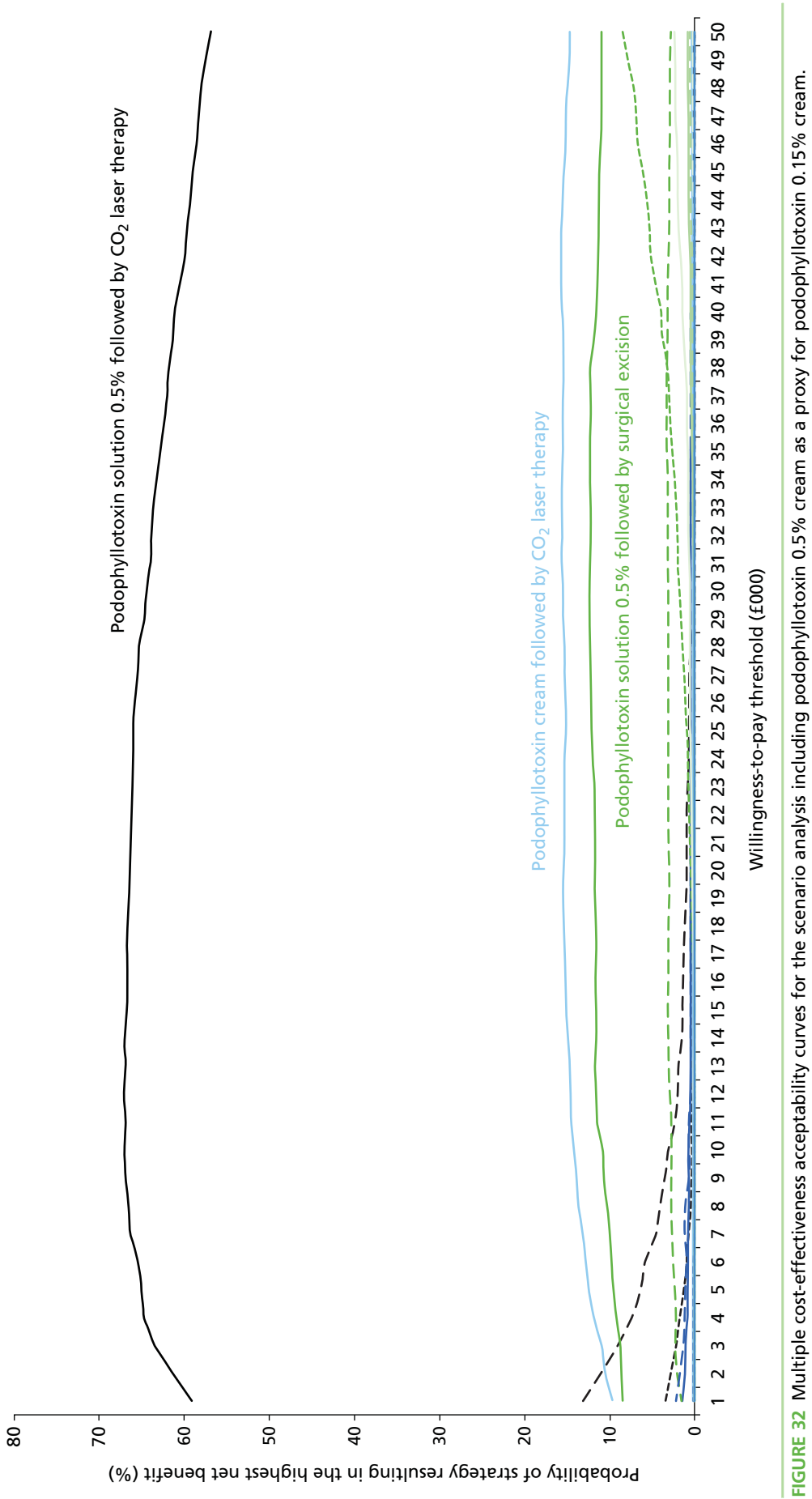

FIGURE 32 Multiple cost-effectiveness acceptability curves for the scenario analysis including podophyllotoxin 0.5% cream as a proxy for podophyllotoxin 0.15% cream.

Only one scenario analysis had a significant impact on the model results. This was the scenario in which the probability of recurrence was set to 100% for all treatments. In this scenario, no treatment followed by treatment with podophyllotoxin 0.5% solution was estimated to be associated with a probability of approximately 73% of being considered the treatment with the highest net benefit at a willingness to pay of £20,000 per additional QALY gained and a 35% probability of being considered the treatment with the highest net benefit at a willingness to pay of £30,000 per additional QALY gained. Podophyllotoxin followed by/following imiquimod 5% cream was associated with a probability of approximately 30% of being considered the treatment with the highest net benefit at a willingness to pay of £30,000 per additional QALY gained.

The results for this scenario are not surprising; the assumption of 100% recurrence means that all people in the model go on to have persistent warts. It therefore is logical that the cheaper treatments are likely to be considered cost-effective, because the scenario automatically assumes that treatment will fail. A scenario in which 100% of people recur is not likely in clinical practice during a single episode (even if many people go on to experience a second or third episode) and therefore this scenario is likely to be extreme. Nevertheless, the results imply that recurrence values are an important driver of the model results.

For all other scenario analyses, the probability of podophyllotoxin 0.5% solution followed by CO_2 laser therapy being considered the treatment strategy with the highest net benefit at a willingness to pay of £20,000 or £30,000 per additional QALY gained varied between approximately 63% and 88%. This implies that the model findings are extremely robust to the analysed scenarios.

One-way deterministic sensitivity analysis

Podophyllotoxin 0.5% solution followed by surgery compared with podophyllotoxin 0.5% solution followed by carbon dioxide laser therapy

In the deterministic base case, podophyllotoxin 0.5% followed by CO_2 laser therapy strictly dominated podophyllotoxin 0.5% solution followed by surgery.

In the one-way sensitivity analysis, podophyllotoxin 0.5% solution followed by surgery remained dominated in all but three scenarios:

1. Using the lower CrI for the probability of complete clearance at the end of CO_2 laser therapy (84.7%) resulted in podophyllotoxin 0.5% solution followed by surgery moving from being strictly dominated by podophyllotoxin 0.5% followed by CO_2 laser therapy (more costly and less effective) to being comparatively more costly and more effective, with an ICER of £628,309.
2. Using the upper CrI for the probability of complete clearance at the end of surgery (99.1%) resulted in podophyllotoxin 0.5% solution followed by surgery moving from being strictly dominated by podophyllotoxin 0.5% followed by CO_2 laser therapy (more costly and less effective) to being comparatively more costly and more effective, with an ICER of £12,925.
3. Using the upper value for the probability of recurrence at the end of follow-up following complete clearance with CO_2 laser therapy (24.7%) resulted in podophyllotoxin 0.5% solution followed by surgery moving from being strictly dominated by podophyllotoxin 0.5% followed by CO_2 laser therapy (more costly and less effective) to being comparatively more costly and more effective, with an ICER of £104,673.

Consequently, the parameter for which the results were most sensitive to change was found to be the probability of complete clearance at the end of surgery. No other parameters varied within the described upper and lower values (see *Model inputs*) affected the conclusions of the analysis.

Carbon dioxide laser therapy followed by surgery compared with podophyllotoxin 0.5% solution followed by carbon dioxide laser therapy

In the deterministic base case, CO_2 laser therapy followed by surgery compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy was associated with an ICER of £105,667.

In the one-way sensitivity analysis, the top five parameters for which the model results were most sensitive were complete clearance at the end of treatment for surgical excision; the probability of recurrence after complete clearance with podophyllotoxin 0.5% solution; HRQoL without AGWs; duration of treatment with podophyllotoxin 0.5% solution; and duration of follow-up following complete clearance (*Figure 33*). No upper or lower parameter value reduced the ICER below £30,000 per additional QALY. The ICER was reduced to £32,969 with the use of the high value for the probability of recurrence after complete clearance with podophyllotoxin 0.5% solution (51.4%).

Consequently, the parameter for which the results were most sensitive to change was found to be the probability of recurrence after complete clearance with podophyllotoxin 0.5% solution. No other parameters varied within the described upper and lower values (see *Model inputs*) affected the conclusions of the analysis.

Carbon dioxide laser therapy followed by podophyllotoxin 0.5% solution compared with podophyllotoxin 0.5% solution followed by carbon dioxide laser therapy

In the deterministic base case, CO_2 laser therapy followed by podophyllotoxin 0.5% solution compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy was associated with an ICER of £121,483.

In the one-way sensitivity analysis, the top five parameters for which the model results were most sensitive were recurrence of treatment after complete clearance with podophyllotoxin 0.5% solution; recurrence of treatment after complete clearance with CO_2 laser therapy; HRQoL without AGWs; complete clearance at the end of CO_2 laser therapy; and HRQoL with AGWs (*Figure 34*). No upper or lower parameter value reduced the ICER below £30,000 per additional QALY. The ICER was reduced to £38,895 with the use of the high value for the probability of recurrence after complete clearance with podophyllotoxin 0.5% solution (51.4%).

Consequently, the parameter for which the results were most sensitive to change was found to be the probability of recurrence after complete clearance with podophyllotoxin 0.5% solution. No other parameters varied within the described upper and lower values (see *Model inputs*) affected the conclusions of the analysis.

Threshold analyses

Variables identified from one-way sensitivity analysis as having the greatest impact on the model results were investigated using threshold analyses for the key comparisons. The value for each parameter was altered until each relevant ICER reached a threshold of £20,000 or £30,000 per additional QALY. The results are presented in *Tables 49–51*.

For the comparison of podophyllotoxin 0.5% followed by CO_2 laser therapy with podophyllotoxin 0.5% solution followed by surgery, threshold analyses indicated that the probability of complete clearance at the end of treatment by surgery would need to increase to approximately 98% to result in an ICER of £20,000–30,000. Similarly, the probability of complete clearance at the end of CO_2 laser therapy would need to decrease to approximately 83% to result in an ICER of £20,000–30,000. It is noted that the probability of complete clearance following treatment by surgical excision required to reduce the ICER to £20,000–30,000 lies within the CrI estimated from the MTC.

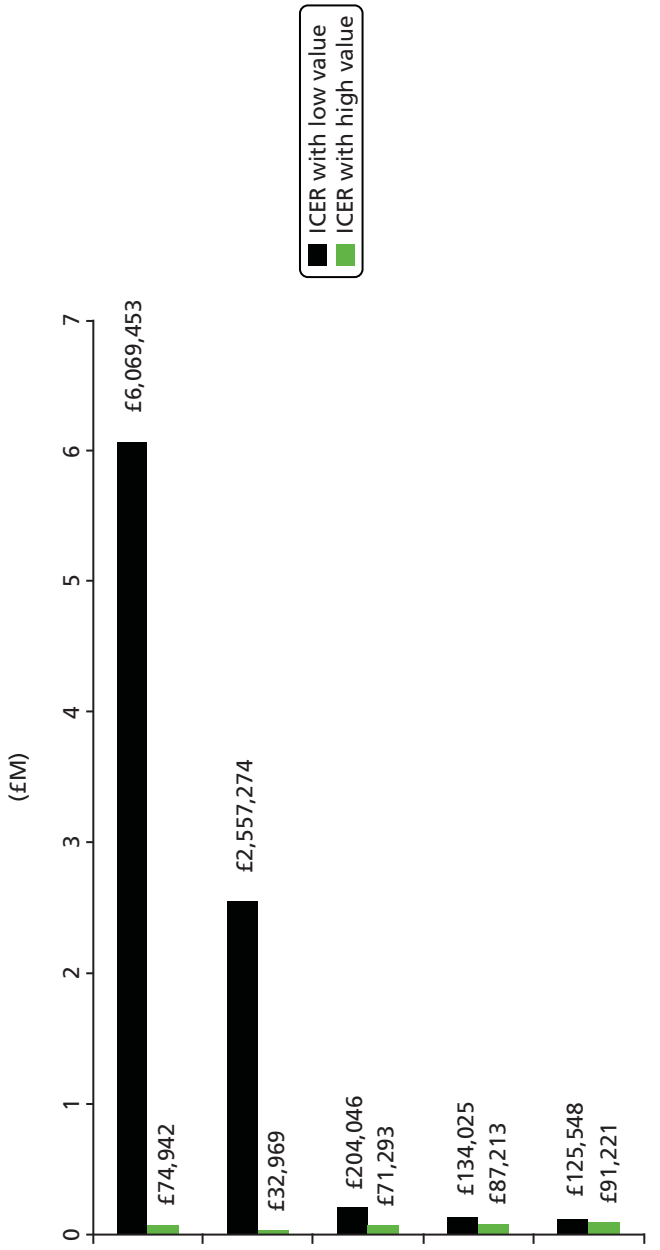

FIGURE 33 Top five parameters for which the model results were most sensitive for the comparison of CO_2 laser therapy followed by surgery with podophyllotoxin 0.5% solution followed by CO_2 laser therapy.

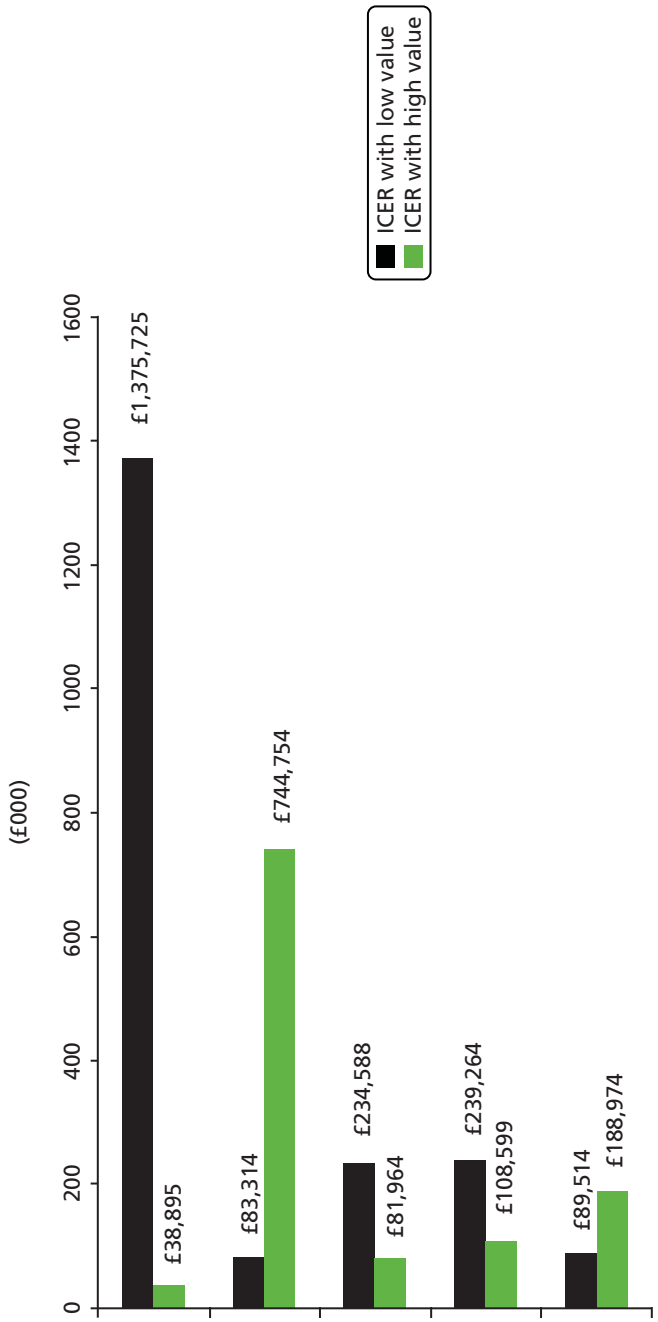

FIGURE 34 Top five parameters for which the model results were most sensitive for the comparison of CO_2 laser therapy followed by podophyllotoxin 0.5% solution with podophyllotoxin 0.5% solution followed by CO_2 laser therapy.

TABLE 49 Threshold analysis of key variables identified in one-way sensitivity analysis for the comparison of podophyllotoxin 0.5% followed by CO_2 laser therapy with podophyllotoxin 0.5% solution followed by surgery

Parameter	Base-case parameter value	Approximate value to reach ICER of £20,000	Approximate value to reach ICER of £30,000
Base-case deterministic ICER (£)	Podophyllotoxin 0.5% followed by CO_2 laser therapy dominates		
Probability of complete clearance at the end of CO_2 laser therapy (%)	97.07	83.18	83.56
Probability of complete clearance at the end of treatment by surgical excision (%)	84.79	98.68	98.29
Probability of recurrence at end of follow-up for CO_2 laser (%)	9.66	24.84	24.79

TABLE 50 Threshold analysis of key variables identified in one-way sensitivity analysis for the comparison of CO_2 laser therapy followed by surgery with podophyllotoxin 0.5% solution followed by CO_2 laser therapy

Parameter	Base-case parameter value	Approximate value to reach ICER of £20,000	Approximate value to reach ICER of £30,000
Base-case deterministic ICER (£)	105,667		
Probability of complete clearance at the end of treatment by surgical excision (%)	84.8	No solution	No solution
Probability of recurrence after complete clearance with podophyllotoxin 0.5% solution (%)	34.6	59.1	52.9
HRQoL without AGWs	0.926	No solution	No solution
Duration of treatment with podophyllotoxin 0.5% solution (weeks)	4	19.6	13.2
Duration of follow-up following complete clearance (weeks)	12	79.6	50.2

TABLE 51 Threshold analysis of key variables identified in one-way sensitivity analysis for the comparison of CO_2 laser therapy followed by podophyllotoxin 0.5% solution with podophyllotoxin 0.5% solution followed by CO_2 laser therapy

Parameter	Base-case parameter value	Approximate value to reach ICER of £20,000	Approximate value to reach ICER of £30,000
Base-case deterministic ICER (£)	121,483		
Probability of recurrence after complete clearance with podophyllotoxin 0.5% solution (%)	34.6	61.5	55.5
Probability of recurrence after complete clearance with CO_2 laser therapy (%)	9.7	No solution	No solution
HRQoL without AGWs	0.926	No solution	No solution
Complete clearance at the end of CO_2 laser therapy (%)	97.1	No solution	No solution
HRQoL with AGWs	0.87	0.586	0.699

Threshold analyses also demonstrated that the probability of recurrence at the end of follow-up for people treated with CO_2 laser therapy would need to be > 24% for the deterministic ICER to reach £20,000–30,000. It is noted that no data were identified for recurrence following clearance with CO_2 laser therapy; thus, this parameter was inferred using clinical expert opinion, with the value for recurrence following surgery used to inform the model parameter. It is therefore considered that the value of this variable is uncertain and this is noted as a potential area of uncertainty.

For the comparison of CO_2 laser therapy followed by surgery with podophyllotoxin 0.5% solution followed by CO_2 laser therapy, threshold analyses indicated that the duration of treatment with podophyllotoxin 0.5% solution and the duration of follow-up following complete clearance would need to increase to > 13 weeks and > 50 weeks, respectively, to reach an ICER of £30,000 per additional QALY. Given current clinical practice, these are unlikely scenarios.

In addition, threshold analyses indicated that the probability of recurrence after complete clearance with podophyllotoxin 0.5% solution would need to increase to approximately 53% from 34.6% to reach an ICER of £30,000 per additional QALY. It is noted that the estimated CrI for the probability of recurrence for podophyllotoxin solution was 20% to 51.4%; therefore this value exceeds the 95% CrI as estimated from the MTC (see *Recurrence of anogenital warts within 12 weeks of complete clearance*).

Threshold analyses indicated that the probability of recurrence after complete clearance with podophyllotoxin 0.5% solution would need to increase to approximately 55.5% from 34.6% to reach an ICER of £30,000 per additional QALY. It is noted that the estimated CrI for the probability of recurrence after complete clearance with podophyllotoxin 0.5% solution was 20–51.4%; therefore, this value exceeds the 95% CrI as estimated from the MTC (see *Recurrence of anogenital warts within 12 weeks of complete clearance*).

For the comparison of CO_2 laser therapy followed by podophyllotoxin 0.5% solution with podophyllotoxin 0.5% solution followed by CO_2 laser therapy, threshold analyses indicated that the HRQoL associated with AGWs would need to fall to 0.699 from 0.87 to reach an ICER of £30,000 per additional QALY gained. Of the UK studies identified that provided HRQoL data,[32,176,228,237] none reported a HRQoL score for people with AGWs at such a value; thus, it is considered that a HRQoL estimate of 0.699 is unlikely in clinical practice.

Summary of the cost-effectiveness findings

Base-case results

Probabilistic analysis of the de novo economic model found that the treatment strategy of podophyllotoxin 0.5% solution followed by CO_2 laser therapy had a probability of 80.7% of being considered the treatment strategy with the highest net benefit at a willingness to pay per additional QALY gained of £20,000. At a willingness to pay per additional QALY gained of £30,000, the probability reduced to 78.3%. The treatment strategy of podophyllotoxin 0.5% solution followed by CO_2 laser therapy was therefore most likely to be considered a cost-effective treatment strategy compared with all other included treatment strategies.

The deterministic analysis of the model found that 81 of the 84 assessed treatment strategies were dominated in the base case, that is, were more expensive and less effective than the remaining three treatment strategies. The non-dominated treatment strategies were podophyllotoxin 0.5% solution followed by CO_2 laser therapy, CO_2 laser therapy followed by podophyllotoxin 0.5% solution and CO_2 laser therapy followed by surgical excision. Of these three strategies, podophyllotoxin 0.5% solution followed by CO_2 laser therapy was the least expensive. The remaining two treatment strategies were associated with ICERs well above the threshold of £20,000–30,000 per additional QALY compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy, at £121,483 (CO_2 laser therapy followed by podophyllotoxin 0.5% solution) and £105,667 (CO_2 laser therapy followed by surgical excision).

Consequently, the deterministic and probabilistic base-case results were aligned and showed that, given the model structure and model inputs used in this analysis, podophyllotoxin 0.5% solution followed by CO_2 laser therapy was likely to be considered the most cost-effective use of resources at a willingness-to-pay threshold of £20,000–30,000 per additional QALY gained.

Results of the sensitivity analysis

Additional probabilistic analysis, one-way sensitivity analysis and threshold analyses were carried out on the key comparisons. The key comparisons were identified as:

- podophyllotoxin 0.5% solution followed by surgery compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy
- CO_2 laser therapy followed by surgery compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy
- CO_2 laser therapy followed by podophyllotoxin 0.5% solution compared with podophyllotoxin 0.5% solution followed by CO_2 laser therapy.

In the head-to-head probabilistic analysis, podophyllotoxin 0.5% solution followed by CO_2 laser therapy continued to be the treatment strategy with the highest probability of being considered cost-effective at a willingness to pay for an additional QALY of £20,000–30,000 when compared individually with podophyllotoxin 0.5% solution followed by surgery, CO_2 laser therapy followed by surgery and CO_2 laser therapy followed by podophyllotoxin 0.5% solution.

In the scenario analysis, only one scenario significantly affected the base-case probabilistic results. This was the scenario in which it was assumed that 100% of people with AGWs recur following complete clearance. In this scenario, the treatment option of no treatment followed by podophyllotoxin 0.5% solution was estimated to be associated with a probability of approximately 73% of being considered the treatment strategy with the highest net benefit at a willingness to pay of £20,000 per additional QALY gained and with a 35% probability of being considered the treatment strategy with the highest net benefit at a willingness to pay of £30,000 per additional QALY gained. Podophyllotoxin followed by/following imiquimod 5% cream was associated with a probability of approximately 30% of being considered the treatment strategy with the highest net benefit.

In the one-way sensitivity analysis for the comparisons of CO_2 laser therapy followed by surgery with podophyllotoxin 0.5% solution followed by CO_2 laser therapy and CO_2 laser therapy followed by podophyllotoxin 0.5% solution with podophyllotoxin 0.5% solution followed by CO_2 laser therapy, no upper or lower value assigned to each variable resulted in an ICER below £30,000. In the comparison of podophyllotoxin 0.5% solution followed by surgery with podophyllotoxin 0.5% solution followed by CO_2 laser therapy, one variable change resulted in an ICER of £12,925; this was use of the upper value for complete clearance at the end of surgery.

In the threshold analyses, the results were generally robust to changes in key parameters for the key comparisons of interest; however, the probability of the recurrence of AGWs following complete clearance with CO_2 laser therapy was identified as a variable of possible interest.

Overall, it is considered that uncertainty in the effectiveness data is the key driver of the model results, in particular, the recurrence data.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness

Analysis by MTC indicated that, in line with conclusions outlined in European guidelines,[6] ablative techniques, and in particular CO_2 laser therapy, are generally associated with higher probabilities of complete clearance at the end of treatment. CO_2 laser therapy was associated with a probability of clearance of 97.1% (95% CrI 84.8% to 99.9%) in the primary MTC. By contrast, placebo was associated with a probability of clearance of only 7.6% (95% CrI 1.1% to 20.9%) in the primary MTC analysis.

Of the topical treatments evaluated, imiquimod 5% cream, podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream are the core treatments for AGWs that are suitable for people to self-apply in their home. Although these treatments are the mainstay of patient-applied treatments, the evidence to support their use is derived from predominantly small RCTs. Moreover, no study identified assessed the effectiveness of the three treatments in a head-to-head comparison. MTC analysis (primary) identified considerable disparity in the probability of achieving complete clearance between podophyllotoxin 0.5% solution and imiquimod 5% cream. Podophyllotoxin 0.5% solution had a 92.6% (95% CrI 81.8% to 98.4%) probability of completely clearing lesions whereas imiquimod 5% cream had a 56.1% (CrI 20.3% to 85.0%) probability of completely clearing lesions. However, the wide CrIs indicate that there is considerable uncertainty associated with the results and the findings should be interpreted with caution.

In the primary MTC there was no statistically significant difference in complete clearance of AGWs at the end of treatment between most of the treatments evaluated. Of those differences that reached statistical significance, most of the comparisons involved CO_2 laser therapy or podophyllotoxin 0.5% solution.

Carbon dioxide laser therapy was found to be significantly more effective than:

- imiquimod 5% cream (OR 247.0, 95% CrI 3.03 to 1087)
- TCAA (OR 86.15, 95% CrI 4.05 to 415.3)
- cryotherapy (OR 44.61, 95% CrI 3.30 to 201.7)
- TCAA plus podophyllin (OR 0.13, 95% CrI 0.003 to 0.59; OR <1 favours CO_2 laser therapy)
- cryotherapy plus podophyllin (OR 0.22, 95% CrI 0.004 to 0.94; OR <1 favours CO_2 laser therapy).

Podophyllotoxin 0.5% solution was associated with statistically significant improvements in complete clearance at the end of treatment compared with:

- podophyllotoxin 0.5% cream (OR 0.30, 95% CrI 0.04 to 0.99; OR <1 favours podophyllotoxin 0.5% solution)
- podophyllotoxin 0.3% cream (OR 0.19, 95% CrI 0.007 to 0.874; OR <1 favours podophyllotoxin 0.5% solution)
- TCAA (OR 0.17, 95% CrI 0.02 to 0.63; OR <1 favours podophyllotoxin 0.5% solution).

The MTC of recurrence between 3 and 6 months evaluated podophyllin 20–25%, podophyllotoxin 0.5% solution, podophyllotoxin 0.25% solution, TCAA and TCAA plus podophyllin 20–25%. There were no statistically significant differences in recurrence at <6 months between any comparisons. TCAA was associated with the lowest probability of recurrence (23.4%, 95% CrI 1.5% to 76.6%). By contrast, podophyllotoxin 0.3% solution had the highest probability of recurrence (66.9%, 95% CrI 5.2% to 99.5%). Data for recurrence at ≥ 6 months facilitated comparison between podophyllin 20–25%, podophyllotoxin 0.5% solution, imiquimod 5% cream and surgical excision. Only one difference in the

MTC was statistically significant. Surgical excision was found to be statistically more effective than podophyllin 20–25% at reducing recurrence at ≥ 6 months (OR 0.14, 95% CrI 0.02 to 0.50). Surgical excision was also associated with the lowest probability of recurrence out of the four treatments (15.4%, 95% CrI 4.7% to 33.5%).

Few identified studies reported clinical effectiveness data on complete clearance without recurrence at time points after the cessation of treatment. Additionally, some studies reported data for this outcome only for people achieving complete clearance at the end of treatment rather than the full study population. Complete clearance without recurrence at time points after the completion of treatment is distinct from recurrence as the former outcome accounts for people who clear within a few days of completion of treatment and who continue to be free of lesions. Five interventions were indirectly compared in a MTC: placebo or no treatment; imiquimod 5% cream (three times a week, patient applied); cryotherapy; electrotherapy; and cryotherapy plus podophyllotoxin 0.15% cream. Electrotherapy was associated with the highest probability of achieving complete clearance without recurrence at 3–6 months after the end of treatment (65.5%, 95% CrI 40.0% to 86.2%). Compared with placebo or no treatment, the four active interventions were associated with a statistically significant improvement in complete clearance without recurrence. However, there were no statistically significant differences between any of the active interventions.

Limited reporting of data for other outcomes of interest in available publications led to restricted networks involving few interventions. A network comprising five treatments evaluated the comparative effectiveness of treatments for clearing > 50% of the baseline volume of AGWs (excluding complete clearance). Analysis identified podophyllotoxin 0.5% solution as being significantly more effective than imiquimod 5% cream and placebo at reducing the volume of AGWs by ≥ 50% compared with baseline volume.

Evaluation of AEs focused on those that cause discomfort to the patient or that are difficult to treat should they occur: ulceration, blistering, erythema, oedema and itching. For ulceration, the results from two studies comparing TCAA with cryotherapy were meta-analysed, which indicated that TCAA was associated with a significantly higher risk of ulceration than cryotherapy (OR 0.22, 95% CI 0.10 to 0.46).

A MTC of four active interventions (imiquimod 5% cream, podophyllin 20–25%, podophyllotoxin 0.5% solution and podophyllotoxin 0.5% cream) enabled an evaluation of their association with an increased risk of erythema. All interventions statistically significantly increased the risk of erythema compared with placebo but not compared with each other.

In summary, the evidence base to inform first-line treatment of AGWs, albeit large, is limited in terms of the number and quality of reporting of studies providing data on the effectiveness of individual interventions. Analyses indicate that ablative techniques, and in particular CO_2 laser therapy, are generally associated with higher probabilities of complete clearance at the end of treatment. Although topical treatments such as imiquimod 5% cream, podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream are the mainstay of patient-applied treatments, the evidence to support their use is limited, with analyses identifying considerable variation across topical treatments in the probability of achieving complete clearance.

Cost-effectiveness

The findings of the de novo economic analysis indicate that the treatment strategy of podophyllotoxin 0.5% solution followed by CO_2 laser therapy is likely to be considered a cost-effective use of resources at a willingness to pay of £20,000–30,000 per additional QALY gained. This finding was robust to the majority of changes in the model parameters.

Despite a robust conclusion from the economic analysis, it is noted that there is uncertainty associated with the clinical data informing the model and therefore the results and conclusions. The main sources of uncertainty have previously been described in detail and include:

- a concern regarding the quality of available clinical evidence, with no studies deemed to be at an overall low risk of bias
- a lack of reporting of baseline characteristics and therefore uncertainty over the comparability of populations assessed in each clinical trial (e.g. size, number, location of lesions and wart type)
- a lack of identified data for recurrence and therefore a reliance on assumptions.

With these concerns in mind, it is considered that the following general conclusions can be drawn from the economic analysis:

- *Cost-effectiveness finding 1*. Podophyllotoxin 0.5% solution is an effective and relatively inexpensive treatment. It is therefore likely that prescription of this therapy first line would be considered a cost-effective use of resources.
- *Cost-effectiveness finding 2*. No treatment and treatment with podophyllin are unlikely to be cost-effective treatment options for AGWs because of their relatively low rates of complete clearance and, in the case of podophyllin, higher estimated rates of recurrence, despite their low costs.
- *Cost-effectiveness finding 3*. Highly effective treatments such as CO_2 laser therapy or surgical excision are likely to represent a cost-effective treatment option at second line following failure to completely clear with podophyllotoxin solution, provided that these treatments are considered clinically appropriate. This is because, despite their relatively high initial costs, these treatments are likely to be effective and typically require only a single appointment with a clinician.
- *Cost-effectiveness finding 4*. There is uncertainty around the cost-effectiveness of treatment with imiquimod, TCAA and cryotherapy at second line. In this economic analysis, these treatments were not found to offer cost-effective alternatives at second line because of their relatively lower rates of complete clearance compared with CO_2 laser therapy and surgical excision. However, it is noted that the clinical systematic review reported uncertainty around treatment effects and rates of recurrence and, thus, clinical experience must be taken into account when using these treatments.

Strengths and limitations of the assessment

Clinical effectiveness

The evidence included in the report was identified through robust systematic review methodology. In addition, the evidence on clinical effectiveness facilitated carrying out a MTC and investigation of the comparative clinical effectiveness of the interventions of interest. However, the clinical evidence base identified was weak. The limited details available on methods implemented for randomisation and allocation concealment led to classification of most studies identified as being at unclear risk of bias. Additionally, few studies reported comprehensive baseline characteristics for the enrolled populations. Among those studies providing details on baseline characteristics, many enrolled a mixture of people who were treatment naive and people who had previously received treatment. It is thought that treatment of recurrent AGWs is more difficult than treatment of a first episode of AGWs. Based on feedback from clinical experts, the project team assumed that the populations enrolled are analogous and are representative of people with AGWs and attending GUM clinics. However, the uncertainty around the comparability of the study populations and therefore the generalisability of the results to clinical practice is acknowledged. Subgroup analyses were planned based on type, number and size of AGWs, all of which are factors thought to influence treatment effect. However, lack of data on clinical effectiveness based on these characteristics precluded analysis of the differential effects of treatments in the subgroups of interest. Determination of the effect of AGW morphology, if any, on treatment effect could contribute to the development of more clinically effective and cost-effective treatment algorithms for AGWs.

Despite identification of 60 studies, most comparisons in the MTC are informed by only one RCT. Additionally, a lack of head-to-head RCTs comparing key treatments, together with minimal reporting of results in some studies, precluded comprehensive analysis of all treatments for AGWs. As a consequence of these limitations in the available evidence, there is considerable uncertainty around the results generated, as evidenced by the wide CrIs. Because of time constraints it was not possible to assess separately the closed loops within the network, which would have helped to determine whether or not the results generated from 'direct' evidence aligned with the results generated from the 'indirect' evidence on introduction of the wider network. Additionally, it has been proposed that in MTCs of studies with variable periods of follow-up, the hazard ratio rather than the OR would be a more appropriate estimate of effect.[240] It is known that ORs change over time and use of a hazard ratio would account for the variable time horizons across the studies.[241] Given that the duration of treatment varied across the studies, particularly for the topical interventions, further analyses using the hazard ratio as the estimate of effect would be of interest.

Cost-effectiveness

Strengths of the analysis

The economic analysis has been carried out in accordance with the International Society for Pharmacoeconomics and Outcomes Research good modelling practice guidance.[242] The model structure was developed following review of the existing economic literature, and in conjunction with clinical experts.

Compared with existing analyses, this study analyses the greatest number of treatment options for AGW. Data sources for the economic model were systematically identified and standard UK sources of cost data were used. The clinical data included in the analysis were systematically identified and synthesised. This study incorporated HRQoL as the measure of benefit and is thus the first cost–utility analysis relating to treatments for AGWs.

The model results were tested extensively in sensitivity analysis including scenario analysis, one-way sensitivity analysis and threshold analysis.

Weaknesses of the analysis

The weaknesses of the analysis relate largely to the uncertainties in the clinical effectiveness data included within the model. Recurrence data were limited and a number of model assumptions were required for the base-case analysis. In particular, the following simplifying assumptions were made:

- Complete clearance occurs at the mid-point of treatment.
- Recurrence occurs at the mid-point of follow-up.
- The number of lines of therapy prior to treatment for persistent warts is two.
- All appointments take place within a GUM clinic.
- The types of appointment in the GUM clinic (doctor led, nurse led or doctor with nurse) were equally split.

However, with the exception of all appointments taking place within a GUM clinic, which was not considered to be a key point of difference between interventions, these assumptions were comprehensively tested in sensitivity analysis.

Additionally, it was not possible to analyse data by characteristics of AGWs; thus, the findings of the analysis have limited applications to specific types of AGWs (e.g. keratinised vs. non-keratinised warts). In addition, based on the limited information provided in the clinical trials, it was not possible to specifically assess the effectiveness of treatments for those large and persistent AGWs requiring repeated treatments over a prolonged time period.

The economic analysis also omitted comparison of a number of treatment options of interest because of a lack of clinical data. These included cidofovir, electrotherapy, any combination of treatments in addition to those included and podophyllotoxin cream 0.15%.

Suggested research priorities

The evidence base to inform the first-line treatment of AGWs, albeit large, is limited in terms of the number of studies providing data on the effectiveness of individual interventions. A RCT evaluating the interventions predominantly used in clinical practice would go some way to clarifying the comparative clinical effectiveness of interventions. The inclusion of a simultaneous cost-effectiveness component would be beneficial. A search of the World Health Organization International Clinical Trials Registry Platform identified one trial, which, at the time of writing, is listed as having completed recruitment with a projected trial completion date of 31 March 2017.[243] The RCT is designed to evaluate whether imiquimod 5% cream or podophyllotoxin 0.15% cream is most effective at clearing AGWs and preventing recurrence. The trial will simultaneously evaluate whether or not HPV vaccine started at the time of initiating topical treatment increases the effectiveness of the cream in either clearing AGWs or preventing recurrence. A search of ClinicalTrials.gov identified no additional trials. Considering the findings from the MTC presented here, the project team considers that a RCT also including podophyllotoxin 0.5% solution would be warranted. In addition, people with either a first episode or a recurrent episode of AGWs are eligible for inclusion in the ongoing RCT.[243] A study stratifying by status of previous treatment would help to clarify whether or not the clinical effectiveness of an intervention varies according to whether it is used in the treatment of a first episode or a recurrent episode of AGWs. Assessment of a topical intervention in combination with an ablative technique would also help to inform the evidence base.

Limited data on recurrence were available. Given the propensity of AGWs to recur, clarification of the maintenance effect of interventions, if any, would be beneficial. Imiquimod 5% cream elicits an effect through modification of the immune system. One potential area for investigation is whether or not complete clearance achieved through an enhanced immune response after treatment with imiquimod 5% cream might be longer lasting than complete clearance using other interventions.

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Contributions of authors

Elizabeth Thurgar provided project management; devised and carried out the literature searches for the review of cost-effectiveness and HRQoL; carried out the appraisal of abstracts retrieved from the clinical effectiveness, cost-effectiveness and HRQoL literature searches; carried out study selection and data extraction; designed and developed the economic model; wrote the sections of the report relating to the health economics and cost-effectiveness analysis; and contributed to the editing of the report.

Samantha Barton provided project management; devised and carried out the literature searches for the systematic review of clinical effectiveness; carried out the appraisal of abstracts retrieved from the literature searches; assessed full publications for inclusion; contributed to data extraction and validation; carried out meta-analysis; wrote the sections of the report relating to clinical effectiveness; and contributed to the editing of the report.

Charlotta Karner contributed to the appraisal of abstracts retrieved from the literature searches; assessed the full publications for inclusion; and contributed to the editing of the report.

Steven J Edwards contributed to the meta-analysis; contributed to the editing of the report; and was overall director of the project and guarantor of the report.

All authors read and commented on draft versions of the report.

Data sharing statement

All available data can be obtained from the corresponding author.

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Appendix 1 Literature search strategies

Systematic review of the clinical literature

TABLE 52 Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE (1946 to April 2014)

Number	Search terms	Results
1	exp Condylomata Acuminata/	4578
2	(genital$ adj3 wart$).tw.	1931
3	(anogenital$ adj3 wart$).tw.	458
4	(peni$ adj3 wart$).tw.	67
5	(venereal adj3 wart$).tw.	89
6	(condyloma$ adj3 acuminat$).tw	2010
7	(anal adj3 wart$).tw	157
8	or/1-7	6258
9	exp cohort studies/	1,347,723
10	cohort$.tw.	274,812
11	controlled clinical trial.pt.	88,946
12	epidemiologic methods/	30,812
13	limit 12 to yr=1966-1989	11,256
14	exp case-control studies/	652,799
15	(case$ and control$).tw.	330,295
16	(case$ and series).tw.	120,299
17	or/9-11,13-16	1,945,365
18	8 and 17	1128
19	Randomized Controlled Trials as Topic/	100,978
20	randomized controlled trial/	383,304
21	Random Allocation/	80,905
22	Double Blind Method/	129,566
23	Single Blind Method/	19,164
24	clinical trial/	500,196
25	clinical trial, phase i.pt	15,918
26	clinical trial, phase ii.pt	26,494
27	clinical trial, phase iii.pt	9907
28	clinical trial, phase iv.pt	955
29	controlled clinical trial.pt	88,946
30	randomized controlled trial.pt	383,304
31	multicenter study.pt	178,695

continued

TABLE 52 Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE (1946 to April 2014) (*continued*)

Number	Search terms	Results
32	clinical trial.pt	500,196
33	exp Clinical Trials as topic/	292,888
34	(clinical adj trial$).tw	221,850
35	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw	132,283
36	PLACEBOS/	33,402
37	placebo$.tw	165,785
38	randomly allocated.tw	16,922
39	(allocated adj2 random$).tw	19,489
40	or/19-39	1,205,342
41	case report.tw	200,047
42	letter/	819,925
43	historical article/	298,131
44	or/41-43	1,306,776
45	40 not 44	1,175,409
46	8 and 45	619
47	18 or 46	1536

TABLE 53 Ovid EMBASE (1974 to April 2014)

Number	Search terms	Results
1	exp condyloma acuminatum/	6357
2	(genital$ adj3 wart$).tw.	2376
3	(anogenital$ adj3 wart$).tw.	550
4	(peni$ adj3 wart$).tw.	81
5	(venereal adj3 wart$).tw.	89
6	(condyloma$ adj3 acuminat$).tw	2578
7	(anal adj3 wart$).tw	174
8	or/1-7	8340
9	exp cohort analysis/	157,222
10	exp longitudinal study/	64,218
11	exp prospective study/	248,369
12	exp follow up/	740,825
13	cohort$.tw.	358,710
14	exp case control study/	89,112
15	(case$ and control$).tw.	417,625

TABLE 53 Ovid EMBASE (1974 to April 2014) (*continued*)

Number	Search terms	Results
16	exp case study/	21,092
17	(case$ and series).tw.	155,445
18	or/9-17	1,764,753
19	8 and 18	1116
20	Clinical trial/	892,502
21	Randomized controlled trial/	357,457
22	Randomization/	63,312
23	Single blind procedure/	18,161
24	Double blind procedure/	119,800
25	Crossover procedure/	38,256
26	Placebo/	237,167
27	Randomi?ed controlled trial$.tw.	93,520
28	Rct.tw.	12,481
29	Random allocation.tw.	1333
30	Randomly allocated.tw.	19,810
31	Allocated randomly.tw.	1942
32	(allocated adj2 random).tw.	813
33	Single blind$.tw.	14,112
34	Double blind$.tw.	146,330
35	(treble or triple) adj (blind$).tw.	351
36	Placebo$.tw.	199,821
37	Prospective study/	248,369
38	or/20-37	1,390,848
39	Case study/	21,092
40	Case report.tw.	261,040
41	Abstract report/ or letter/	902,640
42	or/39-41	1,179,449
43	38 not 42	1,353,441
44	8 and 43	1094
45	19 or 44	1903

TABLE 54 The Cochrane Library (CENTRAL, Database of Abstracts of Reviews of Effects and NHS EED; searched from inception to April 2014)

Number	Search terms	Results
1	MeSH descriptor: [Condylomata Acuminata] explode all trees	227
2	genital* near/3 wart*:ti,ab,kw	166
3	anogenital* near/3 wart*:ti,ab,kw	57
4	peni* near/3 wart*:ti,ab,kw	11
5	venereal near/3 wart*:ti,ab,kw	5
6	condyloma* near/3 acuminat*:ti,ab,kw	374
7	anal near/3 wart*:ti,ab,kw	6
8	#1 or #2 or #3 or #4 or #5 or #6 or #7	458

TABLE 55 Web of Science (searched from 1 January 2000 to 29 August 2013 and updated 22 April 2014)

Number	Search terms	Results
1	(condylom* acumin* or anogenital wart* or genital* wart*)	1636
Publication type limited to articles, meeting abstracts, proceedings papers and corrections.		

Economic evaluation and costing studies

TABLE 56 Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE (1946 to March 2014)

Number	Search terms	Results: 16 September 2013	Results: 21 March 2014
1	exp Condylomata Acuminata/	4583	4561
2	(genital$ adj3 wart$).tw.	1938	1899
3	(anogenital$ adj3 wart$).tw.	461	447
4	(peni$ adj3 wart$).tw.	68	67
5	(venereal adj3 wart$).tw.	89	83
6	(condyloma$ adj3 acuminat$).tw	2012	2021
7	(anal adj3 wart$).tw	158	150
8	Health Economics	2051	2086
9	Economic evaluation	5310	5139
10	exp Costs and Cost Analysis/	41,817	41,415
11	cost benefit analysis/	60,999	59,011
12	exp models economic/	10,234	9945
13	exp fees/	26,970	26,731
14	exp budgets/	11,975	11,984
15	(economic adj2 burden).tw.	4407	4336
16	(expenditure* not energy).tw.	18,604	18,171
17	Cost Effectiveness Analysis	5727	5492
18	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.	21,755	21,273
19	Cost Minimization Analysis	372	342
20	(cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw.	98,718	96,427
21	(decision adj1 (tree* or analys* or model*)).tw.	8849	8599
22	(econom* or price* or pricing or financ*or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw.	191,380	188,735
23	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.	4278	4206
24	Markov*.tw	14,411	13,331
25	or/1-7	6272	6238
26	or/8-24	393,780	387,425
27	25 and 26	245	229
28	limit 27 to yr="2013 -Current"	–	22

TABLE 57 Ovid EMBASE (1974 to March 2014)

Number	Search terms	Results: 13 September 2013	Results: 24 March 2014
1	exp Condyloma Acuminatum/	6370	6253
2	(genital$ adj3 wart$).tw.	2379	2348
3	(anogenital$ adj3 wart$).tw.	552	548
4	(peni$ adj3 wart$).tw.	81	79
5	(venereal adj3 wart$).tw.	89	85
6	(condyloma$ adj3 acuminat$).tw.	2583	2499
7	(anal adj3 wart$).tw.	175	182
8	exp health economics/	601,472	605,634
9	exp economic evaluation/	204,598	207,979
10	exp "Costs and Cost Analysis"/	246,649	250,939
11	exp cost benefit analysis/	65,949	63,714
12	exp models, economic/	108,598	99,561
13	(fee or fees).tw.	14,662	14,905
14	budget$.tw.	23,432	23,894
15	(economic adj2 burden).tw.	6188	6639
16	(expenditure* not energy).tw.	23,187	23,439
17	Cost effectiveness analysis/	90,520	95,868
18	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.	28,829	29,852
19	Cost minimization analysis/	2297	2426
20	(cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw.	124,323	126,576
21	(decision adj2 (tree$ or analys$ or model$)).tw.	14,571	14,966
22	(econom$ or price$ or pharmacoeconomic$ or pharmaeconomic$ or pharmaco-economic$).tw.	234,842	238,368
23	(unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.	28,829	29,852
24	((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.	5463	5530
25	markov$.tw.	14,987	15,397
26	or/1-7	8355	8174
27	or/8-25	984,178	982,805
28	26 and 27	684	699
29	limit 28 to yr="2013 -Current"	–	77

TABLE 58 The Cochrane Library (NHS EED)

Number	Search terms	Results: 11 September 2013	Results: 24 March 2014
1	MeSH descriptor: [Condylomata Acuminata] explode all trees	21	22
2	genital* near/3 wart*:ti,ab,kw in Economic Evaluations	5	5
3	anogenital* near/3 wart*:ti,ab,kw in Economic Evaluations	3	3
4	peni* near/3 wart*:ti,ab,kw in Economic Evaluations	1	1
5	venereal near/3 wart*:ti,ab,kw in Economic Evaluations	0	0
6	condyloma* near/3 acuminat*:ti,ab,kw in Economic Evaluations	21	22
7	anal near/3 wart*:ti,ab,kw in Economic Evaluations	0	0
8	#1 or #2 or #3 or #4 or #5 or #6 or #7 in Economic Evaluations	22	22
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 Publication Date from 2013 to 2014 in Economic Evaluations	–	1

TABLE 59 The Cochrane Library (HTA database)

Number	Search terms	Results: 11 September 2013	Results: 24 March 2014
1	MeSH descriptor: [Condylomata Acuminata] explode all trees	1	2
2	genital* near/3 wart*:ti,ab,kw in Technology Assessments	0	0
3	anogenital* near/3 wart*:ti,ab,kw in Technology Assessments	1	3
4	peni* near/3 wart*:ti,ab,kw in Technology Assessments	0	0
5	venereal near/3 wart*:ti,ab,kw in Technology Assessments	0	0
6	condyloma* near/3 acuminat*:ti,ab,kw in Technology Assessments	1	2
7	anal near/3 wart*:ti,ab,kw in Technology Assessments	0	0
8	#1 or #2 or #3 or #4 or #5 or #6 or #7 in Technology Assessments	1	3
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 Publication Date from 2013 to 2014, in Technology Assessments	–	2

Health-related quality of life

TABLE 60 Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE (1946 to March 2014)

Number	Search terms	Results: 11 September 2013	Results: 24 March 2014
1	exp Condylomata Acuminata/	4582	4561
2	(genital$ adj3 wart$).tw.	1936	1899
3	(anogenital$ adj3 wart$).tw.	461	447
4	(peni$ adj3 wart$).tw.	68	67
5	(venereal adj3 wart$).tw.	89	83
6	(condyloma$ adj3 acuminat$).tw.	2012	2021
7	(anal adj3 wart$).tw.	157	150
8	Quality of Life/	118,500	114,259
9	((quality adj3 life) or life quality or QOL).ti,ab.	154,139	150,091
10	(HRQL or HRQOL or HRQol).ti,ab.	9896	9514
11	(value adj2 life).ti,ab. or Value of Life/	5944	5834
12	(life adj2 qualit$3).tw.	151,305	147,305
13	(quality-adjusted life year$1 or QALY or QALYs or quality adjusted life year$1).ti,ab. or Quality-Adjusted Life Years/	10,465	10,009
14	daly.ti,ab.	807	781
15	(disabilit$3 adj2 life).ti,ab.	2106	2031
16	Health Status Indicators/	20,775	19,646
17	(sf36 or sf-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw.	16,478	15,787
18	(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.	1343	1352
19	(sf6d or sf 6d or sf-6d or short form 6d or shortform 6d or sf six dimension$1 or short form six dimension$1).tw	434	424
20	(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw.	2843	2725
21	(sf16 or sf 16 or sf-16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.	23	22
22	(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw.	336	329
23	(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.	4102	4011
24	(hye or hyes or health$ year$ equivalent$).tw.	64	64
25	hui$1.tw.	1147	1099
26	(willing$ adj2 pay).tw.	2844	2805
27	(willing$ adj2 accept).tw.	1037	1031
28	standard gamble$.tw.	691	667
29	(health adj3 (utilit$3 or value$2 or preference$2)).tw.	7099	6938
30	(visual analog$3 scale or VAS).tw.	38,725	38,478
31	patient preference$2.tw.	4730	4547

TABLE 60 Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE (1946 to March 2014) (*continued*)

Number	Search terms	Results: 11 September 2013	Results: 24 March 2014
32	(person$ trade-off or person$ trade off or PTO).ti,ab.	610	575
33	(Contingent value or contingent valuation).ti,ab.	407	412
34	discrete choice.ti,ab.	623	641
35	health status.ti,ab. or Health Status/	85,172	82,068
36	((quality adj3 wellbeing index) or QWB).ti,ab.	175	166
37	(health utilities index or HUI).ti,ab.	1080	1041
38	(time trade off or time tradeoff or TTO or time trade-off).ti,ab.	1202	1168
39	(utility or utilities).ti,ab.	121,289	116,788
40	disutil$.ti,ab.	227	215
41	disability.tw.	87,199	85,941
42	(wellbeing or well-being or well being or qwb).ti,ab.	44,695	44,284
43	quality of well being.tw.	358	328
44	quality of wellbeing.tw.	8	7
45	or/1-7	6270	6239
46	or/8-44	544,260	530,627
47	45 and 46	139	129
48	limit 47 to yr="2013-2014"	–	9

TABLE 61 Ovid EMBASE (1974 to March 2014)

Number	Search terms	Results: 11 September 2013	Results: 24 March 2014
1	exp condyloma acuminatum/	6369	6252
2	(genital$ adj3 wart$).tw.	2379	2348
3	(anogenital$ adj3 wart$).tw.	552	548
4	(peni$ adj3 wart$).tw.	81	79
5	(venereal adj3 wart$).tw.	89	85
6	(condyloma$ adj3 acuminat$).tw.	2583	2498
7	(anal adj3 wart$).tw.	175	182
8	exp Quality of Life/	246,790	258,667
9	((quality adj3 life) or life quality or QOL).ti,ab.	208,667	216,752
10	(HRQL or HRQOL or HRQol).ti,ab.	12,942	13,580
11	(value adj2 life).ti,ab. or exp Value of Life/	174,421	173,944
12	(life adj2 qualit$3).tw.	203,586	211,313
13	(quality-adjusted life year$1 or QALY or QALYs or quality adjusted life year$1).ti,ab. or exp Quality-Adjusted Life Years/	14,706	15,315
14	daly.ti,ab.	951	963

continued

TABLE 61 Ovid EMBASE (1974 to March 2014) (*continued*)

Number	Search terms	Results: 11 September 2013	Results: 24 March 2014
15	(disabilit$3 adj2 life).ti,ab.	2361	2448
16	exp Health Status Indicators/	3434	5418
17	(sf36 or sf-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw.	21,489	22,280
18	(sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.	1507	1472
19	(sf6d or sf 6d or sf-6d or short form 6d or shortform 6d or sf six dimension$1 or short form six dimension$1).tw	604	667
20	(sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw.	3737	4032
21	(sf16 or sf 16 or sf-16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.	33	36
22	(sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw.	320	322
23	(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.	5968	6571
24	(hye or hyes or health$ year$ equivalent$).tw.	96	101
25	hui$1.tw.	1463	1521
26	(willing$ adj2 pay).tw.	3719	3931
27	(willing$ adj2 accept).tw.	1283	1321
28	standard gamble$.tw.	761	765
29	(health adj3 (utilit$3 or value$2 or preference$2)).tw.	8425	8686
30	(visual analog$3 scale or VAS).tw.	52,398	54,573
31	patient preference$2.tw.	5902	6132
32	(person$ trade-off or person$ trade off or PTO).ti,ab.	608	601
33	(Contingent value or contingent valuation).ti,ab.	526	537
34	discrete choice.ti,ab.	766	836
35	health status.ti,ab. or exp Health Status/	148,028	151,822
36	((quality adj3 wellbeing index) or QWB).ti,ab.	186	191
37	(health utilities index or HUI).ti,ab.	1296	1344
38	(time trade off or time tradeoff or TTO or time trade-off).ti,ab.	1476	1506
39	(utility or utilities).ti,ab.	145,629	148,499
40	disutil$.ti,ab.	327	355
41	disability.tw.	110,507	113,748
42	(wellbeing or well-being or well being or qwb).ti,ab.	54,684	56,406
43	quality of well being.tw.	366	367
44	quality of wellbeing.tw.	19	18
45	or/1-7	8354	8172
46	or/8-44	890,258	911,589
47	45 and 46	303	308
48	limit 47 to yr="2013 -Current"	–	37

TABLE 62 The Cochrane Library (NHS EED)

Number	Search	Results: 11 September 2013	Results: 24 March 2014
1	MeSH descriptor: [Condylomata Acuminata] explode all trees	21	22
2	genital* near/3 wart*:ti,ab,kw in Economic Evaluations	5	5
3	anogenital* near/3 wart*:ti,ab,kw in Economic Evaluations	3	3
4	peni* near/3 wart*:ti,ab,kw in Economic Evaluations	1	1
5	venereal near/3 wart*:ti,ab,kw in Economic Evaluations	0	0
6	condyloma* near/3 acuminat*:ti,ab,kw in Economic Evaluations	21	22
7	anal near/3 wart*:ti,ab,kw in Economic Evaluations	0	0
8	#1 or #2 or #3 or #4 or #5 or #6 or #7 in Economic Evaluations	22	22
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 Publication Date from 2013 to 2014 in Economic Evaluations	–	1

TABLE 63 The Cochrane Library (HTA database)

Number	Search	Results: 11 September 2013	Results: 24 March 2014
1	MeSH descriptor: [Condylomata Acuminata] explode all trees	1	2
2	genital* near/3 wart*:ti,ab,kw in Technology Assessments	0	0
3	anogenital* near/3 wart*:ti,ab,kw in Technology Assessments	1	3
4	peni* near/3 wart*:ti,ab,kw in Technology Assessments	0	0
5	venereal near/3 wart*:ti,ab,kw in Technology Assessments	0	0
6	condyloma* near/3 acuminat*:ti,ab,kw in Technology Assessments	1	2
7	anal near/3 wart*:ti,ab,kw in Technology Assessments	0	0
8	#1 or #2 or #3 or #4 or #5 or #6 or #7 in Technology Assessments	1	3
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 Publication Date from 2013 to 2014, in Technology Assessments	–	2

TABLE 64 The Cochrane Library (CENTRAL)

Number	Search	Results: 11 September 2013	Results: 24 March 2014
1	MeSH descriptor: [Condylomata Acuminata] explode all trees	194	229
2	genital* near/3 wart*:ti,ab,kw in Trials	148	159
3	anogenital* near/3 wart*:ti,ab,kw in Trials	46	48
4	peni* near/3 wart*:ti,ab,kw in Trials	10	10
5	venereal near/3 wart*:ti,ab,kw in Trials	2	2
6	condyloma* near/3 acuminat*:ti,ab,kw in Trials	339	352
7	anal near/3 wart*:ti,ab,kw in Trials	5	5
8	#1 or #2 or #3 or #4 or #5 or #6 or #7 in Trials	416	434
9	MeSH descriptor: [Quality of Life] explode all trees	10,964	13,581
10	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	468	3524
11	quality near/3 life:ti,ab,kw in Trials	20,755	23,884
12	qol:ti,ab,kw in Trials	2639	3089
13	hrqol or hr qol or hrql or hr ql:ti,ab,kw in Trials	1179	1379
14	QALY or quality adjusted life year or quality-adjusted life year:ti, ab,kw in Trials	1140	1368
15	SF 6d or SF-6d or sf6d or short form 6d or short form six dimension*:ti,ab,kw in Trials	81	99
16	SF 36 or SF-36 or SF36 or short form 36 or short form thirty six:ti, ab,kw in Trials	3235	3754
17	eq-5d or eq5d or eq 5d or euroqol:ti,ab,kw in Trials	711	850
18	hui or health utilities index:ti,ab,kw in Trials	1985	2296
19	standard gamble:ti,ab,kw in Trials	70	71
20	time trade off or TTO or time trade-off:ti,ab,kw in Trials	115	124
21	utilit*:ti,ab,kw in Trials	3777	4315
22	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 in Trials	26,949	30,940
23	#8 and #22 in Trials	3	3
24	#8 and #22 Publication Date from 2013 to 2014, in Trials	–	0

Appendix 2 Data abstraction tables and quality assessment

Clinical data abstraction and quality assessment

TABLE 65 Abdullah *et al.*[153]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Vicky Wakefield and Sam Barton
Study ID	Abdullah 1993
Study details	*Sex Trans Dis* 1993;**20**:344–5
Language of publication	English
Type of report	Full paper
Section 2: Study information	
Location and number of sites	Department of Genitourinary Medicine at Coventry and Warwickshire Hospital (one site)
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	People attending the Department of Genitourinary Medicine were enrolled between November 1990 and June 1991
Trial design	RCT
Trial duration	Maximum of six treatments with treatment given on a weekly basis. People with complete clearance of AGWs were followed up for 3 months after the end of treatment
Line of therapy	First
Inclusion criterion	People with definite AGWs for the first time on clinical grounds
Exclusion criteria	Women who were pregnant and people with internal AGWs (cervical, vaginal and rectal) or Buschke–Lowenstein lesions
All outcomes reported in paper	Complete clearance of AGWs by the end of up to six treatments; complete clearance of AGWs after more than six treatments; AEs (ulceration due to treatment)
Subgroups evaluated	Gender (male vs. female)
Stratification	Trial does not report that randomisation was stratified. It is stated that the area and size of AGWs were matched on clinical grounds as closely as possible to avoid bias in either treatment group
Baseline measurement of disease	Not reported; people enrolled based on the presence of AGWs

continued

TABLE 65 Abdullah *et al.*[153] (*continued*)

Item	Details		
Treatment	*TCAA 95%*	*Cryotherapy (liquid nitrogen)*	
Randomised, *n*	33	53	
Withdrawals	3 lost to follow-up (9.1%; reasons for withdrawals not reported)	10 lost to follow-up (18.9%; reasons for withdrawals not reported)	
Treatment regimen	TCAA 95% was applied by a clinician with a pointed plastic probe once a week	Cryotherapy using liquid nitrogen was administered by a clinician using a tapered cotton pledget on a wooden applicator stick. The pledget was applied for a period of time sufficient to freeze the AGW and a 1-mm margin of the surrounding skin. Individual AGWs were frozen twice, using different applicators and disposable small containers of liquid nitrogen for different people. Cryotherapy was applied weekly	
Duration/number of administered treatment	Planned treatment schedule was to continue treatment either until all AGWs cleared or for a maximum of six treatments had been administered. Number of treatments applied not reported		
Baseline patient characteristics	*TCAA 95%*	*Cryotherapy (liquid nitrogen)*	p-*value*
Mean age (with SD/SE if given), years (range)	Not reported		
Duration of disease	Not reported		
Site of AGWs, *n* (%)	Not reported		
Type of AGWs, *n* (%)	Not reported		
Mean number of AGWs (with SD/SE if given)	Not reported		
Mean area of AGWs, mm^2	Not reported		
Sex, *n* (%)			
Men	18 (54.5)	30 (56.6)	Not reported
Women	15 (45.5)	23 (43.4)	Not reported
Any previous treatment, *n* (%)	0	0	Not reported
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Treatment given either until all AGWs cleared or for a maximum of six treatments had been administered, whichever occurred first. However, some people received more than six treatments (results not extracted for this group)		
AEs	Ulceration at site of treatment		

TABLE 65 Abdullah *et al.*[153] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*TCAA 95%, n/N*	*Cryotherapy (liquid nitrogen), n/N*	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	Up to six cycles of treatment	21/33	37/53	Not reported	
AEs: ulceration	Up to six cycles of treatment	9/33	0/53	Not reported	
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation?		?	It is stated that 'people enrolled at random according to a randomisation schedule' (p. 344). Further detail not provided	
	Allocation concealment		?	No details provided	
	Selective reporting		?	Information on prespecified outcomes not reported	
	'Other bias'		?	Insufficient information reported to assess other potential risks of bias	
AGW clearance at completion of treatment	Blinding (participants and personnel)		?	Details on level of masking not provided. Given the difference in the treatments administered, it could be envisaged that masking of key study personnel and participants might not be feasible. It is unclear whether the outcome assessor was masked to treatment. If the outcome assessor was masked to treatment, the probability of masking being broken is unclear	
	Blinding of outcomes assessment		?		
	Incomplete outcome data		?	Number of people lost to follow-up was disclosed but reasons for loss to follow-up were not reported. It is stated that it had been 'presumed that people lost to follow-up had moved out of the area, or their AGWs had cleared, or they had not tolerated the treatment' (p. 345). Larger proportion of people lost to follow-up from the cryotherapy group. Impact of imbalance on results is unclear	

continued

TABLE 65 Abdullah *et al.*[153] (*continued*)

Item	Details		
AEs: ulceration	Blinding (participants and personnel)	?	Details on level of masking not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients might not be feasible
	Blinding of outcomes assessment	?	Unclear whether clinician assessing ulceration was masked to treatment
	Incomplete outcome data	?	Number of people lost to follow-up was disclosed but reasons for loss to follow-up were not reported. It is stated that it had been 'presumed that people lost to follow-up had moved out of the area, or their AGWs had cleared, or they had not tolerated the treatment' (p. 345). Larger proportion of people lost to follow-up from the cryotherapy group. Ulceration is more likely to occur with TCAA, but influence of imbalance on rate of ulceration is unclear
Overall rating of bias		?	Reflects limited information provided in full publication
Section 6: Additional comments			
Additional comments	• Limited methods reported in the paper • Subgroup data by gender reported for all outcomes • It is stated that people did not express any difference in the degree or frequency of subjective discomfort associated with the two treatments. Some people expressed discomfort but there was no pain to justify discontinuing treatment		

SD, standard deviation.
a ?, unclear risk of bias.

TABLE 66 Arican *et al.*[112]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Vicky Wakefield and Sam Barton
Study ID	Arican 2004
Study details	*J Dermatol* 2004;**31**:627–31
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Trial carried out in Turkey; number of sites unclear
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Unclear. It is stated that people enrolled in the trial were volunteers but no other details are provided
Trial design	RCT
Trial duration	Treatment period of 12 weeks followed by a treatment-free observation period of 6 months
Line of therapy	Unclear. People enrolled had not received any therapies in the 3 months before enrolment

TABLE 66 Arican *et al.*[112] (*continued*)

Item	Details		
Inclusion criteria	People with AGWs aged ≥ 18 years of age and who had not received any therapies within the 3 months before enrolment. Minimum number of AGWs at baseline was five		
Exclusion criteria	People were excluded if they had a pathological condition; were aged < 18 years; had an immunosuppressive or a serious systemic disorder; misused alcohol or drugs; had frequently recurrent genital herpes; or had undergone a local or systemic therapy within the previous 3 months		
All outcomes reported in paper	Clearance of AGWs at completion of treatment; volume of AGW clearance at completion of treatment (based on groups with AGW clearance of 0–10%, 11–50% and 51–99% of baseline volume); recurrence at 6 months' follow-up; appearance of new AGWs during treatment; AEs		

Subgroups evaluated	• Gender
	• Location of AGWs based on gender:
	  ○ for women: vulva; perianal area; and vulval and perianal area
	  ○ for men: perianal area; pubis; penis; penis and scrotum; penis, scrotum and perianal area; pubis and penis; scrotum, penis and pubis		

Stratification	Not reported		
Baseline measurement of disease	Regional lesions were determined and mapped at first examination (no other details provided)		
Treatment	*Imiquimod 5% cream (patient applied)*	*Placebo (vaseline)*	
Randomised, *n*	34	11	
Withdrawals, *n* (%)	1 (2.9; reason for withdrawal not reported)	1 (9.1; reason for withdrawal not reported)	
Treatment regimen	Imiquimod 5% cream or placebo was applied by the patient three times a week (every other day in the evenings) using the tip of a stick. When AGWs had cleared, treatment was interrupted. The importance of applying the medication to a dry region, of adhering to the application schedule and of subsequent cleaning of the skin (in the evenings, 8 ± 2 hours after application) was stressed		
Duration/number of administered treatment	Details on the number of treatments administered not provided		
Baseline patient characteristics	*Imiquimod 5% cream (patient applied)*	*Placebo (vaseline)*	p-*value*
Age (years), mean ± SD (range)	30.3 ± 6.1 (18–41)	32.3 ± 6.8 (20–42)	Not reported
Duration of disease (months), mean ± SD	11.9 ± 22.5	12.1 ± 24.2	Not reported

continued

TABLE 66 Arican *et al.*[112] (*continued*)

Item	Details		
Site of AGWs			
Women			
Vulva	5	1	Not reported
Perianal area	5	1	Not reported
Vulva and perianal area	1	0	Not reported
Men			
Perianal area	7	1	Not reported
Pubis	3	2	Not reported
Penis	7	1	Not reported
Penis and scrotum	1	0	Not reported
Penis, scrotum and perianal area	1	1	Not reported
Pubis and penis	2	2	Not reported
Scrotum, penis and pubis	1	1	Not reported
Type of AGWs, *n* (%)	Not reported		
Mean number of AGWs (with SD/SE if given)	Not reported		
Mean area of AGWs (mm^2)	Not reported		
Sex, *n/N* (%)			
Men	23/34 (67.6)	9/11 (81.8)	Not reported
Women	11/34 (32.4)	2/11 (18.2)	Not reported
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	100% clinical clearance of AGWs after 12 weeks of treatment		
Recurrence of AGWs	Appearance of new lesions or recurrence of AGWs in the 6-month follow-up period after the end of treatment. Details on methods to distinguish new lesions from existing lesions and to determine recurrence not reported		
Volume of wart clearance	Proportion of people with 0–10%, 11–50% and 51–99% clinical clearance of AGWs at the end of treatment		
Appearance of new warts during treatment	New AGWs appearing during treatment		
AEs	Definition of AEs not provided. Data presented for occurrence of erythema, erosion, burning sensation and itching		

TABLE 66 Arican *et al.*[112] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Imiquimod 5% cream (patient applied),* n/N	*Placebo (vaseline),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	12 weeks	23/33	1/10		$p < 0.001$
Recurrence of AGW (includes new lesions)	6 months after end of treatment	6/23	1/1		Not reported
Volume of wart clearance	12 weeks				
0–10%		0/33	8/10		Not reported
11–50%		1/33	0/10		Not reported
51–99%		9/33	1/10		Not reported
Appearance of new warts during treatment	12 weeks	0/33	Not reported		
AEs	12 weeks				
Mild-severity erythema		3/33	2/10		Not reported
Moderate-severity erythema		4/33	0/10		Not reported
Erosion		1/33	0/10		Not reported
Erythema and erosion		6/33	0/10		Not reported
Erythema and excoriation		2/33	0/10		Not reported
Burning sensation		1/33	0/10		Not reported
Itching		0/33	2/10		Not reported
Influenza-like symptoms		1/33	0/10		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	It is stated that the study was planned as a randomised trial but details on method of randomisation are not provided	
	Allocation concealment		?	No details provided	
	Selective reporting		?	Information on prespecified outcomes not reported	
	'Other bias'		?	Insufficient information reported to assess other potential risks of bias	

continued

TABLE 66 Arican *et al.*[112] (*continued*)

Item	Details		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	Described as double blinded but insufficient information provided to determine who was masked
	Blinding of outcomes assessment	?	Described as double blinded but insufficient information provided to determine who was masked
	Incomplete outcome data	?	Although number of withdrawals disclosed, reasons for withdrawal are not reported. Analysis of AGW clearance at end of treatment was carried out on a modified ITT population (two people, one from each group, not included in analysis)
Recurrence of AGWs	Blinding (participants and personnel)	?	Described as double blinded but insufficient information provided to determine who was masked
	Blinding of outcomes assessment	?	Described as double blinded but insufficient information provided to determine who was masked
	Incomplete outcome data	?	Although number of withdrawals disclosed, reasons for withdrawal are not reported. Analysis of recurrence at end of follow-up was carried out on a modified ITT population (two people, one from each group, not included in analysis)
Volume of wart clearance	Blinding (participants and personnel)	?	Described as double blinded but insufficient information provided to determine who was masked
	Blinding of outcomes assessment	?	Described as double blinded but insufficient information provided to determine who was masked
	Incomplete outcome data	?	Although number of withdrawals disclosed, reasons for withdrawal are not reported. Analysis of volume of AGW clearance was carried out on a modified ITT population (two people, one from each group, not included in analysis)
Appearance of new warts during treatment	Blinding (participants and personnel)	?	Described as double blinded but insufficient information provided to determine who was masked
	Blinding of outcomes assessment	?	Described as double blinded but insufficient information provided to determine who was masked
	Incomplete outcome data	?	Although number of withdrawals disclosed, reasons for withdrawal are not reported. Analysis of appearance of new AGWs during treatment was carried out on a modified ITT population (two people, one from each group, not included in analysis)

TABLE 66 Arican *et al.*[112] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	?	Described as double blinded but insufficient information provided to determine who was masked
	Blinding of outcomes assessment	?	Described as double blinded but insufficient information provided to determine who was masked
	Incomplete outcome data	?	Although number of withdrawals disclosed, reasons for withdrawal are not reported. Analysis of AEs was carried out on a modified ITT population (two people, one from each group, not included in analysis)
Overall rating of bias		?	Reflects limited description of methods and results in the full publication
Section 6: Additional comments			
Additional comments	• There is a comment in the methods section that the importance of applying treatment three times a week was stressed. However, the methods section also reports that 'during the duration of the therapy, the individuals were encouraged to apply the medicament for a period of 12 weeks and twice a week' (p. 628) • In the description of the results it is stated that the control patient with 51–99% improvement was not included in the study, but reported results suggest that the individual has been included in the results table and another patient seems to have been excluded from the analysis • People were followed up for 6 months to evaluate recurrence. It is stated that 'classical treatments' were given to those with the appearance of new AGWs; however, no definition provided for 'classical treatments' • Recovery was observed most frequently between week 6 and week 12 of treatment • Response to treatment was statistically significantly faster for AGWs in the perianal area in both women and men ($p < 0.001$); no other details were provided • People experiencing erythema were reported to have statistically significant 'better and faster' improvement ($p = 0.021$); further details not reported		

SD, standard deviation.
a ?, unclear risk of bias.

TABLE 67 Azizjalali *et al.*[156]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Vicky Wakefield and Sam Barton
Study ID	Azizjalali 2012
Study details	*Iran J Microbiol* 2012;**4**:187–90
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Hazrat Rasool Akram Hospital, Tehran, Iran
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Between November 2009 and December 2010, all people with documented lower genital AGWs who visited the Hazrat Rasool Akram Hospital were eligible for inclusion

continued

TABLE 67 Azizjalali *et al.*[156] (*continued*)

Item	Details		
Trial design	RCT		
Trial duration	3 months		
Line of therapy	Unclear		
Inclusion criteria	People with lesions with a diameter of ≥ 10 mm located on the pubis, penis, scrotum, vulva or inguinal area		
Exclusion criteria	Exclusion criteria were history of immunosuppressive status; history of immune modulator drug use in the past 4 weeks; history of local antiviral agent use in the past 2 weeks; pregnancy; breastfeeding; destructive therapies; presence of any other concomitant sexually transmitted disease. In addition, the trial did not treat or evaluate vaginal and cervical lesions		
All outcomes reported in paper	Clearance of AGWs at completion of treatment; recurrence; AEs: postprocedure hypopigmentation and blistering		
Subgroups evaluated	None		
Stratification	None reported		
Baseline measurement of disease	Dermatologist evaluation of location of AGWs and duration of disease		
Treatment	*CO_2 laser therapy*	*Cryotherapy*	
Randomised, *n*	80	80	
Withdrawals, *n* (%)	Not reported		
Treatment regimen	After routine decontamination of the lesion area and local anaesthesia, the AGW and a 2-mm surrounding margin of normal skin were evaporated in focal distance of laser light using a unixel CO_2 laser unit, 30-W fluence, with continuous mode wavelength of 10,600 nm with a fluency of 4.5 J/cm^2	The AGW and 2 mm of the normal surrounding margin were frozen using liquid nitrogen (–196°C) and open-spray mode in two freeze/thaw cycles. After lesion removal, tetracycline ointment was applied on the area for 24 hours	
Duration/number of administered treatment	In both groups, lesions were evaluated after 2 weeks and then 3 months later. Second and third applications were performed every 2 weeks to completely clear the lesions		
Baseline patient characteristics	*CO_2 laser therapy*	*Cryotherapy*	p-*value*
Age (years), mean	Not reported		
Duration of disease (months), *n* (%)			
≤ 4	61 (76.3)	56 (70.0)	
≥ 9	1 (1.3)	1 (1.3)	
Site of AGWs, *n* (%)			
Penis	18 (22.5)	14 (17.5)	
Scrotum	23 (28.8)	28 (35.0)	
Vulva	22 (27.5)	19 (23.8)	
Inguinal	17 (21.3)	19 (23.8)	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	Not reported		

TABLE 67 Azizjalali *et al.*[156] (*continued*)

Item	Details				
Area of AGWs (mm^2), mean	Not reported				
Sex, *n* (%)	Not reported				
Any previous treatment, *n* (%)	Not reported				
Ethnicity, *n* (%)	Not reported				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Complete eradication of AGWs (time frame unclear). AGWs were evaluated at 2 weeks and subsequently after a further 3 months. It is unclear whether complete clearance of AGWs refers to initial treatment at 2 weeks or after subsequent treatments, when appropriate				
Recurrence of AGWs	Recurrence rate reported but definition not provided. It is reported that AGWs were evaluated after 2 weeks and then 3 months later				
AEs	Postprocedure hypopigmentation and blistering				
Section 4: Data extraction form					
Outcome	*Time frame*	*CO_2 laser therapy*, n/N	*Cryotherapy*, n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	Unclear	76/80	37/80		$p < 0.001$
Recurrence of AGWs	14 weeks	4/76	7/37		Not reported
AEs					
Blistering	During treatment	0/80	2/80		$p = 0.99$
Postprocedure hypopigmentation	During treatment	Difference between groups reported to be not statistically different. Absolute numbers not reported			Not significant
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		✓	It is stated that randomisation was 'computerised'. Additional information not reported	
	Allocation concealment		?	No details provided	
	Selective reporting		?	Information on prespecified outcomes not reported	
	'Other bias'		?	Insufficient information reported to assess other potential risks of bias	
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		?	Unclear whether clinician administering treatment and/or patient were masked to treatment	
	Blinding of outcomes assessment		✓	It is stated that 'the study group and the type of treatment has been blinded to the dermatologists who examined the patients after treatment to evaluate the lesions' (p. 188)	
	Incomplete outcome data		?	Loss to follow-up was not reported. Analysis of AGW clearance was based on all people randomised, but it is unclear whether there was an imbalance between the groups in the number of people who withdrew from the trial	

continued

TABLE 67 Azizjalali *et al.*[156] (*continued*)

Item	Details		
Recurrence of AGW	Blinding (participants and personnel)	?	Unclear whether clinician administering treatment and/or patient were masked to treatment
	Blinding of outcomes assessment	✓	It is stated that 'the study group and the type of treatment has been blinded to the dermatologists who examined the patients after treatment to evaluate the lesions' (p. 188)
	Incomplete outcome data	?	Loss to follow-up was not reported. Analysis of recurrence seemed to be based on all people with complete clearance of AGWs, but it is unclear whether there was an imbalance between the groups in the number of people who withdrew from the trial
AEs	Blinding (participants and personnel)	?	Unclear whether clinician administering treatment and/or patient were masked to treatment
	Blinding of outcomes assessment	✓	It is stated that 'the study group and the type of treatment has been blinded to the dermatologists who examined the patients after treatment to evaluate the lesions' (p. 188)
	Incomplete outcome data	?	Loss to follow-up was not reported. Analysis of AEs seemed to be based on all people randomised, but it is unclear whether there was an imbalance between the groups in the number of people who withdrew from the trial
Overall rating of bias		?	Reflects limited information presented in trial
Section 6: Additional comments			
Additional comments	• Reporting of results is in terms of lesions not people randomised. Unclear whether people with only one AGW were enrolled or whether only one AGW was treated per person • Considering complete clearance of AGWs, the authors state that 'In cryotherapy group, second and third treatment were needed for complete treatment in 12% and 12.2% of lesions, respectively, while in CO_2 laser therapy, all lesions showed clearance after a single treatment' (p. 188). However, based on the reported results, the clearance rate was not 100% in the group treated with CO_2 laser therapy [76/80 (95%)] • The authors state that the 'Effectiveness index was defined as complete clearance of lesions and was calculated as the number of cleared lesions divided by total number of lesions multiplied by 100' (p. 188). The effectiveness index is not referred to elsewhere in the publication		

SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 68 Baker *et al.*[113]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Sam Barton and Charlotta Karner
Study ID	Baker 2010
Study details	*Contraception* 2010;**82**:211 Related publication in *Infect Dis Obstet Gynecol* 2011:806105 (presents results on clinical effectiveness in women);[244] additional information on the two trials is available from ClinicalTrials.gov[245,246]
Language of publication	English
Type of report	Conference abstract
Section 2: Study information	
Location and number of sites	Not reported
Trial sponsor	Not reported
Conflicts of interest	D Baker, D Ferris, M Martens, S Tyring, L Edwards, A Nelson, K Ault and K Trofatter have been consultants and/or advisory board members for Graceway Pharmaceuticals, LLC (trial sponsor). T Liu was an employee of Graceway and a consultant. S Levy and J Wu are employees of Graceway
Patient enrolment	Not reported
Trial design	RCT (publication describes the combined results from two RCTs)
Trial duration	People were initially treated for up to 8 weeks, with assessment for complete clearance continued for up to 8 weeks after treatment. Those achieving complete clearance were followed for 12 weeks
Line of therapy	Unclear
Inclusion criteria	People were eligible for inclusion if they were aged ≥ 12 years and had 2–30 external AGWs with a total AGW area of ≥ 10 mm^2
Exclusion criteria	Not reported in Baker *et al.*[113] Exclusion criteria reported in Baker *et al.*:[244] known HIV infection; infection, immunosuppression or other genital infections; allergy to imiquimod or cream excipients; history of high-risk-type HPV infection; high-grade pathology on Papanicolaou smear; pregnancy or lactation; imiquimod or HPV vaccination within 1 year; sinecatechins within 12 weeks; cytotoxics, immunomodulators/immunosuppressives, systemic antivirals (excluding oral antiherpes agents and oseltamivir), investigational therapies and any treatments procedures within the anogenital area within 4 weeks
All outcomes reported in paper	Complete clearance at the end of treatment; recurrence; AEs
Subgroups evaluated	Not reported
Stratification	Not reported
Baseline measurement of disease	AGWs were diagnosed clinically; histological confirmation was not required (taken from Baker *et al.*[244])

continued

TABLE 68 Baker *et al.*[113] (*continued*)

Item	Details			
Treatment	*Imiquimod 3.75% cream*	*Imiquimod 2.5% cream*	*Placebo*	
Randomised, *n*	It is stated that 981 people were enrolled and that randomisation was carried out in a 2 : 2 : 1 ratio (imiquimod 3.75% cream : imiquimod 2.5% cream : placebo). The number of people randomised to each group is not reported in the conference abstract. Details taken from ClinicalTrials.gov[245,246]			
Study 1[245]	195	178	97	
Study 2[246]	204	202	105	
Withdrawals, *n* (%)				
Non-completers				
Study 1[245]	59 (30.3)	57 (32.0)	32 (33.0)	
Study 2[246]	55 (27.0)	63 (31.2)	28 (26.7)	
Discontinued early because of safety-related issues: both trials (%)	1.5	1.6	0.5	
Treatment regimen	Allocated treatment was applied once daily until complete clearance of all (baseline and new) AGWs or for a maximum of 8 weeks, whichever occurred earlier			
Duration/number of administered treatment	Not reported			
Baseline patient characteristics	*Imiquimod 3.75% cream*	*Imiquimod 2.5% cream*	*Placebo*	p-*value*
Age (years), mean (SD)				
Study 1[245]	32.5 (11.6)	32.7 (11.3)	30.5 (10.6)	
Study 2[246]	32.8 (11.0)	33.1 (10.1)	33.3 (10.8)	
Duration of disease	Mean duration of disease across all groups: 4.9 years; not reported separately by treatment group			
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean (with SD/SE if given)	Mean number of AGWs across all groups: 8.7; not reported separately by treatment group			
Area of AGWs (mm^2), mean	Mean AGW area across all groups: 158.8; not reported separately by treatment group			

TABLE 68 Baker *et al.*[113] (*continued*)

Item	Details				
Sex (M/F), *n*					
Study 1[245]	95/100	83/95	47/50		
Study 2[246]	88/116	85/117	49/56		
Any previous treatment, *n* (%)	Not reported				
Ethnicity, *n* (%)	Not reported				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Not defined				
Recurrence of AGWs	Those achieving complete clearance were followed and monitored for recurrence				
AEs	Data reported on severe local skin reactions				
Section 4: Data extraction form					
Outcome	*Time frame*	*Imiquimod 3.75% cream,* n/N	*Imiquimod 2.5% cream,* n/N	*Placebo,* n/N	*Estimate of effect* p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment: absolute event rates not reported separately for the two trials	Up to 8 weeks	102/399	74/380	13/202	Imiquimod 3.75% and 2.5% vs. placebo: $p < 0.001$; imiquimod 3.75% vs. imiquimod 2.5%: $p = 0.025$
Recurrence of AGW	12 weeks' follow-up	71/102	44/74	12/13	Not reported
AEs					
Severe local skin reactions (%)	Up to 8 weeks	16.3	15.0	1.0	Not reported
Local skin reactions					
Study 1[245]	Up to 8 weeks	144/195	110/178	29/97	Not reported
Study 2[246]	Up to 8 weeks	148/205	123/201	41/105	Not reported

continued

TABLE 68 Baker *et al.*[113] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	✓	The studies are described as randomised. Details on method used to generate random sequence not available in the conference abstract. In the related publication it is stated that women were randomised using a computer-generated sequence. It is assumed that men were subject to the same randomisation procedure
	Allocation concealment	?	Details on method to conceal allocation not available
	Selective reporting	✗	Data on effectiveness for key clinical outcomes are not reported as absolute events rates in the identified publications or on ClinicalTrials.gov. Results presented cannot be incorporated in a meta-analysis
	'Other bias'	?	Insufficient information available to evaluate other potential sources of bias
AGW clearance at completion of treatment	Blinding (participants and personnel)	✓	In the related publication, it is stated that women received identically appearing prepackaged study kits. The treatment assignment was concealed from the participant, the investigators and their staff and the clinical research team
	Blinding of outcomes assessment	✓	
	Incomplete outcome data	?	The proportion of people not completing the trial is reported in the entries on ClinicalTrials.gov; however, reasons for withdrawal are not specified. It is unclear whether there is an imbalance across the groups in withdrawal for a particular event
Recurrence of AGWs	Blinding (participants and personnel)	✓	In the related publication it is stated that women received identically appearing prepackaged study kits. The treatment assignment was concealed from the participant, the investigators and their staff and the clinical research team
	Blinding of outcomes assessment	✓	
	Incomplete outcome data	?	The proportion of people not completing the trial is reported in the entries on ClinicalTrials.gov. However, reasons for withdrawal are not specified. It is unclear whether there is an imbalance across the groups in withdrawal for a particular event
AEs	Blinding (participants and personnel)	✓	In the related publication it is stated that women received identically appearing prepackaged study kits. The treatment assignment was concealed from the participant, the investigators and their staff and the clinical research team
	Blinding of outcomes assessment	✓	
	Incomplete outcome data	?	The proportion of people not completing the trial is reported in the entries on ClinicalTrials.gov. However, reasons for withdrawal are not specified. It is unclear whether there is an imbalance across the groups in withdrawal for a particular event
Overall rating of bias		✗	Reflects lack of reporting of the number of people randomised to each group and absolute event rates

TABLE 68 Baker *et al.*[113] (*continued*)

Item	Details	
Section 6: Additional comments		
Additional comments	It is stated that complete clearance was higher in women than in men. The related publication identified in the literature search[244] discusses the results in women	
Further information that could be requested from authors	Methodological information	
	Method of randomisation	✓
	Level of masking (if masked, who was masked)	✓
	Method for allocation concealment	✓
	Method for maintaining masking during the trial	✓
	Baseline characteristics	
	Mean and median age of people in each group (with accompanying measure of variation)	✓
	Breakdown by site of AGW in each group	✓
	Mean number and area of AGWs at baseline in each group	✓
	Proportion of people with (i) single, (ii) few (two to five) or (iii) multiple (six or more) AGWs at baseline in each group	✓
	Breakdown of type of AGWs (non-keratinised vs. keratinised) in each group	✓
	Immune status (immunosuppressed vs. not immunosuppressed) in each group	✓
	Any previous treatment	✓
	Ethnicity	✓
	Trial conduct	
	Was there a trial sponsor?	✓
	Did any of the authors have a conflict of interest?	✓
	When was complete clearance recorded?	✓
	Number of people lost to follow-up in each group	✓
	Number of people who withdrew from each group and reasons for withdrawal	✓
	Is the reported analysis based on an ITT population?	✓
	Any concomitant medications received in each group?	✓
	Did both groups receive the same care except for the allocated treatment?	✓
	Results	
	Complete clearance in each group based on subgroups of:	
	site of AGWs	✓
	number of AGWs at baseline [subgroups of few (two to five) and multiple (six or more)]	✓
	type of AGWs (non-keratinised vs. keratinised)	✓
	immune status (immunosuppressed vs. not immunosuppressed)	✓
	Miscellaneous	

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 69 Bar-Am *et al.*[157]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Shannon Amoils and Sam Barton
Study ID	Bar-Am 1993
Study details	*J Reprod Med* 1993;**38**:455–8
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Not reported
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Not reported
Trial design	RCT evaluating high- vs. low-power CO_2 laser treatment in three distinct subgroups of people, only two of whom are relevant to this review; data extracted only for the relevant patient populations
Trial duration	Treatment duration unclear; it is possible that people undergo a single laser procedure. Duration of follow-up not reported; it is stated that 'follow up visits were scheduled weekly until complete healing was observed' (p. 456)
Line of therapy	Not reported
Inclusion criteria	Inclusion criteria for the two groups of interest to this review: women with benign vulvar and perineal HPV lesions; men with disseminated foci of penile shaft condylomatous lesions
Exclusion criteria	Not reported
All outcomes reported in paper	• Treatment duration • Healing time • Cosmetic healing • Local infection
Subgroups evaluated	Randomisation was performed separately in the three distinct groups of people. No subgroups reported
Stratification	Not reported
Baseline measurement of disease	Not reported

TABLE 69 Bar-Am *et al.*[157] (*continued*)

Item	Details			
Treatment				
	High-power CO_2 laser treatment		*Low-power CO_2 laser treatment*	
	Women	*Men*	*Women*	*Men*
Randomised, *n*	Number of people randomised in each group of participants not reported. Results are based on number of people analysed			
Number of people evaluated	41	33	42	32
Withdrawals, *n* (%)	Not reported			
Treatment regimen	Laser beam with an output of 60 W and a spot size of 1–1.5 mm, creating high power density ranging between 3400 and 7640 W/cm^2. Treatments were performed on an outpatient basis under local anaesthesia with 1–2% lidocaine injected intracervically or subcutaneously. Lesions were treated with laser vaporisation, including shallow ablation of 3–5 mm of the surrounding unaffected epithelium. Postprocedure care included application of 3% chloramphenicol skin ointment. All treatments were carried out by the same laser surgeon		Laser beam with an output of 20 W and a spot size of 1–1.5 mm, creating low power density ranging between 1136 and 2547 W/cm^2. Treatments were performed on an outpatient basis under local anaesthesia with 1–2% lidocaine injected intracervically or subcutaneously. Lesions were treated with laser vaporisation, including shallow ablation of 3–5 mm of the surrounding unaffected epithelium. Postprocedure care included application of 3% chloramphenicol skin ointment. All treatments were carried out by the same laser surgeon	
Duration of treatment (minutes), mean (SD):	12.1 (3.2)	17.8 (2.7)	13.5 (3.3)	12.2 (13.2)
Baseline patient characteristics				
	High-power CO_2 laser treatment		*Low-power CO_2 laser treatment*	p-*value*
	Women	*Men*	*Women* *Men*	
Age (years), mean	Not reported			
Duration of disease	Not reported			
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean (with SD/SE if given)	Not reported			
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% female in one subgroup and 100% male in the second subgroup			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AEs	Local infection (no further details reported)			

continued

TABLE 69 Bar-Am *et al.*[157] (*continued*)

Item	Details					
Section 4: Data extraction form						
Outcome	*Time frame*	*High-power CO_2 laser treatment,* n/N		*Low-power CO_2 laser treatment,* n/N		*Estimate of effect* p-*value*
		Women	*Men*	*Women*	*Men*	
Dichotomous outcomes						
AEs: local infection	Not reported	3/41	1/33	2/42	2/32	Difference between treatment groups reported to be not significant for both populations
Section 5: Clinical trial quality						
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*			
	Random sequence generation	✓	It is stated that groups were divided into two treatment groups according to a previously prepared computerised randomisation sequence			
	Allocation concealment	?	Detail on method used to conceal allocation not available			
	Selective reporting	✗	Results for clinical effectiveness of treatments, such as complete clearance and recurrence, are not reported			
	'Other bias'	?	Baseline characteristics for each population are not reported. It is unclear whether there are any imbalances between the treatment groups that would influence the estimates of effect			
AEs	Blinding (participants and personnel)	?	Details on level of masking of personnel are not provided. It is reported that all laser treatments were carried out by the same laser surgeon and so masking of personnel administering laser treatment is not possible. It is unclear whether participants and the outcome assessor were masked to treatment			
	Blinding of outcomes assessment	?				
	Incomplete outcome data	?	The numbers of people randomised to each group and withdrawing from each group (both by population and by treatment group) are not reported. It is unclear whether there is an imbalance in withdrawals from the groups that could influence assessment of local infection			
Overall rating of bias		✗	Reflects lack of reporting of clinical effectiveness outcomes			
Section 6: Additional comments						
Additional comments	None					

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 70 Benedetti Panici *et al.*[114]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Vicky Wakefield and Sam Barton	
Study ID	Benedetti Panici 1989	
Study details	*Obstet Gynecol* 1989;**74**:393–7	
Language of publication	English	
Type of report	Full paper	
Section 2: Study information		
Location and number of sites	Department of Gynaecology, Catholic University, Rome, Italy	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Women attending the Department of Gynaecology were enrolled between September 1986 and August 1987. In total, 203 women entered the trial	
Trial design	Four-arm trial. Two arms evaluated two different schedules of interferon-alpha-2b and a third arm evaluated cauterisation. The fourth arm included people who received no treatment. Only the cauterisation and no treatment groups are of interest to this review	
Trial duration	End of study was 6 months after completion of treatment. People with complete clearance of AGWs were also followed up at 12 months	
Line of therapy	First (inclusion criterion that people had not received previous treatment)	
Inclusion criteria	Multiple condyloma lesions (two or more sites affected); aged 18–45 years; no previous therapy; informed written consent; feasible follow-up	
Exclusion criteria	Moderate or severe intraepithelial neoplasia of the cervix, vagina or vulva; pregnant or breastfeeding; systemic or immunological disease; anaemia (haemoglobin < 10 g/dl); leukopenia (< 4,000/µl); thrombocytopenia (< 100,000/µl); serum creatinine > 1 mg/dl); hepatic dysfunction	
All outcomes reported in paper	Overall clinical response (combination of complete response and partial response) at completion of treatment; complete response at end of treatment and other time points; partial response at end of treatment and other time points (evaluated by recording change in extension of areas affected by AGWs: ≥ 50% or < 50%); disease progression (increase of > 50% in diffusion of disease); recurrence of AGWs; AEs	
Subgroups evaluated	None	
Stratification	Not reported	
Baseline measurement of disease	Colposcopic evaluation of the lower anogenital tract (anus, vulva, vagina and cervix) was carried out. Cytological and histological examinations were also performed	
Treatment	*Diathermocoagulation*	*No treatment*
Randomised, *n*	51	48
Withdrawals, *n* (%)	0 (0)	0 (0)
Treatment regimen	Diathermocoagulation with bipolar electrodes. Procedure carried out under local anaesthetic. If required, repeat procedures were carried out at 3-week intervals	No treatment
Duration of administered treatment	47 people required two or more sessions for apparent elimination of AGWs (median number of sessions 2; range 2–4)	No treatment given

continued

TABLE 70 Benedetti Panici *et al.*[114] (*continued*)

Item	Details		
Baseline patient characteristics	*Diathermocoagulation*	*No treatment*	p-*value*
Age (years), median	25	26	All differences between groups reported to be not significant; *p*-values not reported
Duration of disease	Not reported		
Site of AGWs, *n* (%)			
Vulva	51 (100)	48 (100)	
Cervix	32 (63)	29 (58)	
Urethra	27 (53)	29 (58)	
Vagina	24 (47)	22 (46)	
Perianal and canal	18 (35)	18 (37)	
Number of sites affected, *n* (%)			
2	5 (10)	7 (15)	
≥ 2	46 (90)	41 (85)	
Type of AGWs, *n* (%)			
Warts	20 (39)	20 (42)	
Flat	22 (43)	20 (42)	
Spiked	11 (22)	9 (19)	
Inverted	1 (2)	0 (0)	
Mixed	27 (53)	23 (48)	
Number of AGWs, mean (with SD/SE if given)	Not reported		
Area of AGWs (mm^2), mean (with SD/SE if given)	Not reported		
Sex (M/F), *n* (%)	Not reported		
Any previous treatment, *n* (%)	0 (0)	0 (0)	
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Clearance was evaluated by colposcopy, vaginovulvoscopy and anoscopy. Response was recorded at end of treatment		
AGW clearance at other time points	Response was evaluated by colposcopy, vaginovulvoscopy and anoscopy. Response was recorded at 1, 3 and 6 months after completion of treatment. Complete response was defined as total disappearance of condyloma for at least 4 weeks and had to be confirmed by three different colposcopists		
Recurrence	Recurrence of AGWs in people who had experienced a complete response to treatment (i.e. those people with a complete response 1 month after treatment), recorded at 3, 6 and 12 months after treatment		
Volume of wart clearance	Partial response was defined as a ≥ 50% reduction in condyloma extension. No change was defined as < 50% reduction in lesion extension		
AEs	Not defined for cauterisation technique		

TABLE 70 Benedetti Panici *et al.*[114] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Diathermocoagulation,* n/N	*No treatment,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	End of treatment	51/51	0/48		Not reported
AGW clearance at other time points	1 month after treatment	31/51	0/48		Not reported
	3 months after treatment	18/51	1/48		Not reported
	6 months after treatment	18/51	1/48		$p < 0.001$
Recurrence	3 months after end of treatment	15/31	NA/NA		Not reported
	12 months after end of treatment	17/31	NA/NA		Not reported
Volume of wart clearance					
≥ 50% reduction in condyloma extension	After therapy	0/51	0/48		
≥ 50% reduction in condyloma extension	1 month after treatment	16/51	1/48		
≥ 50% reduction in condyloma extension	3 months after end of treatment	25/51	3/48		
≥ 50% reduction in condyloma extension	12 months after end of treatment	24/51	3/48		
< 50% reduction in condyloma extension	After therapy	0/51	0/48		
< 50% reduction in condyloma extension	1 month after treatment	4/51	44/48		
< 50% reduction in condyloma extension	3 months after end of treatment	8/51	32/48		
< 50% reduction in condyloma extension	12 months after end of treatment	8/51	28/48		
AEs					
Local oedema and pain	Unclear	17/51	0/48		Not reported
Dyspareunia	Unclear	2/51	0/48		Not reported
Slow cicatrisation	Unclear	9/51	0/48		Not reported

continued

TABLE 70 Benedetti Panici *et al.*[114] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	Randomisation was carried out 'using a simple randomisation method as outlined by Armitage' (p. 394);[247] no further details reported
	Allocation concealment	?	The paper comments that the investigator assessing response was masked to treatment given but details on method of allocation concealment not available
	Selective reporting	?	No details reported as to which outcomes were prespecified
	'Other bias'	?	No details reported with regard to whether one surgeon performed all of the diathermocoagulation procedures. Variation in technique could potentially introduce performance bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	The paper comments that the investigator assessing response was masked to treatment given but details on the method of maintaining masking during the trial not provided. It is unclear whether the assessing clinician was an independent clinician or a member of the trial personnel. It might be difficult to mask clinicians to treatment given the variation in techniques (an ablative therapy vs. no treatment)
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✓	Losses to follow-up in the cauterisation and no treatment groups were reported (0 in each group)
Recurrence of AGWs	Blinding (participants and personnel)	?	The paper comments that the investigator assessing response was masked to treatment given but details on the method of maintaining masking during the trial not provided. It is unclear whether the assessing clinician was an independent clinician or a member of the trial personnel. It might be difficult to mask clinicians to treatment given the variation in techniques (an ablative therapy vs. no treatment)
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✓	Analysis based on all people with complete clearance at end of treatment

TABLE 70 Benedetti Panici *et al.*[114] (*continued*)

Item	Details		
Volume of wart clearance	Blinding (participants and personnel)	?	The paper comments that the investigator assessing response was masked to treatment given but details on the method of maintaining masking during the trial not provided. It is unclear whether the assessing clinician was an independent clinician or a member of the trial personnel. It might be difficult to mask clinicians to treatment given the variation in techniques (an ablative therapy vs. no treatment)
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✓	Losses to follow-up in the cauterisation and no treatment groups were reported (0 in each group)
AEs	Blinding (participants and personnel)	?	The paper comments that the investigator assessing response was masked to treatment given but details on the method of maintaining masking during the trial not provided. It is unclear whether the assessing clinician was an independent clinician or a member of the trial personnel. It might be difficult to mask clinicians to treatment given the variation in techniques (an ablative therapy vs. no treatment)
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✓	Losses to follow-up in the cauterisation and no treatment groups were reported (0 in each group)
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	• Extension of areas affected by AGWs was evaluated by measuring the two largest perpendicular dimensions. Partial response was defined as a ≥ 50% decrease in condyloma extension. No change was defined as any modification of < 50% in lesion extension • AEs in the diathermocoagulation group lasted a median of 2 weeks (range 1–8 weeks). In respect to slow cicatrisation, median time to healing was 41 days (range 30–50 days) • Most recurrences occurred within the first 3 months after treatment and could be considered reinfections rather than recurrence		

M/F, male/female; NA, not applicable; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 71 Beutner *et al.*[115]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Sam Barton and Vicky Wakefield	
Study ID	Beutner 1989	
Study details	*Lancet* 1989;**1**:831–4	
Language of publication	English	
Type of report	Full paper	
Section 2: Study information		
Location and number of sites	USA; number of sites unclear	
Trial sponsor	Oclassen Pharmaceuticals, Inc.	
Conflicts of interest	Not reported	
Patient enrolment	Not reported	
Trial design	RCT	
Trial duration	Treatment could be given for a minimum of 2 weeks and a maximum of 4 weeks. Participants were also evaluated at 6, 12 and 16 weeks during a follow-up period (i.e. weeks 2, 8 and 12 after treatment)	
Line of therapy	Unclear	
Inclusion criteria	Men aged ≥ 18 years who had a clinical diagnosis of AGWs; number of warts between two and 20 in an area not exceeding 10 cm^2	
Exclusion criteria	People were excluded if they had untreated syphilis; had frequent genital herpes; had a history of bowenoid papulosis; gave unreliable answers to questions about history; had been treated for AGWs within a month of study entry; were thought to be immunocompromised based on history and physical examination	
All outcomes reported in paper	AGW clearance; reduction in AGW area; reduction in number of AGWs; recurrence; appearance of new AGWs, defined as a AGW that arose during the course of the study at a site distinct from that of the original AGWs (recorded during follow-up period after treatment, not during treatment); AEs	
Subgroups evaluated	Duration of present episode of AGWs (< 12 months vs. ≥ 12 months)	
Stratification	Randomisation prestratified by duration of present episode of AGWs	
Baseline measurement of disease	Site, number and size of AGWs before study entry were recorded	
Treatment	*Podophyllotoxin 0.5% (patient applied)*	*Placebo*
Randomised, *n*	56	53
Withdrawals	Not reported. Note: most patients who had new lesions or who had not responded to treatment were withdrawn from the study at the end of week 2. In addition, patients with recurrent or new AGWs at week 12 were excluded from further evaluations. All patients in the placebo group had withdrawn by week 12; reported that this was generally becase of non-response to therapy	
Treatment regimen	Podophyllotoxin (0.5%) in lactate-buffered USP alcohol. Treatment cycle consisted of application of podophyllotoxin (0.5%) by the patient twice daily (morning and evening) to external AGWs for 3 consecutive days followed by a 4-day period without treatment. At the end of the treatment cycle the patient returned to the investigator for evaluation and instruction about further treatment. The minimum number of treatment cycles administered was two, with a maximum number of allowed treatment cycles of four. Podophyllotoxin (0.5%) was applied only to intact lesions, avoiding adjacent uninvolved skin or bleeding or inflamed lesions	Placebo was vehicle alone
Mean number of treatment cycles	3.2	3.3

TABLE 71 Beutner *et al.*[115] (*continued*)

Item	Details		
Baseline patient characteristics	*Podophyllotoxin 0.5% (patient applied)*	*Placebo*	p-*value*
Age (years), mean (SD)	30.0 (0.9)	31.7 (0.9)	Not reported
Duration of disease, *n* (%)			
≤ 12 months	29 (51.8)	26 (49.1)	Not reported
> 12 months	27 (48.2)	27 (50.9)	Not reported
Site of AGWs (%)			
Penile shaft	88.4	85.4	Not reported
Other	11.6	14.6	Not reported
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean (SE)	7.1 (0.7)	7.8 (0.7)	
Area of AGWs (mm^2), mean (SE)	87.4 (18.3)	101.9 (21.0)	
Sex (M/F), *n* (%)	All men	All men	NA
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Defined as complete clearance of AGWs at end of treatment (week 4). People who showed no change or showed progression at week 2 were considered to be treatment failures and were dropped from the study		
Recurrence of AGWs	AGW(s) that appeared near the site of an original baseline AGW after complete healing. Patients with recurrent or new AGWs at week 12 were not evaluated at week 16		
AEs	Systemic safety and toxicity were evaluated by patient reports, by investigator reports of systemic AEs and by baseline and follow-up laboratory tests. Local adverse reactions (including pain, burning, inflammation, erosion and others to be specified by the investigator after examination of the patient) were classified as none, mild, moderate or severe. Evaluated at each visit during treatment (weeks 1–4) and at the first follow-up visit (week 6)		
Section 4: Data extraction form			
Outcome	*Time frame*	*Podophyllotoxin 0.5% (patient applied),* n/N	*Placebo,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	Week 4	25/56	0/53		$p < 0.001$
Recurrence of AGWs	Week 12	15/25	N/A		
AEs					
Inflammation	Week 6	37/56	3/53		Not reported
Erosion	Week 6	35/56	2/53		Not reported
Burning	Week 6	33/56	19/53		Not reported
Pain	Week 6	26/56	7/53		Not reported
Other	Week 6	19/56	4/53		Not reported

continued

TABLE 71 Beutner *et al.*[115] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	Described as randomised but no details on method of randomisation provided
	Allocation concealment	?	Details of method of allocation concealment not provided
	Selective reporting	?	Insufficient information to determine level of risk
	'Other bias'	?	Insufficient information to assess whether an important risk of bias exists
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	Described as double blinded but insufficient information provided to determine who was masked
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	ITT analysis but unclear how many people were lost to follow-up and whether losses are balanced between the two trial arms
Recurrence of AGWs	Blinding (participants and personnel)	?	Described as double blinded but insufficient information provided to determine who was masked
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	ITT analysis but unclear how many people were lost to follow-up and whether losses are balanced between the two trial arms
AEs	Blinding (participants and personnel)	?	Described as double blinded but insufficient information provided to determine who was masked
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	ITT analysis but unclear how many people were lost to follow-up and whether losses are balanced between the two trial arms
Overall rating of bias		?	Insufficient information provided to determine overall risk of bias

TABLE 71 Beutner *et al.*[115] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	• Study reports that, at the end of treatment (week 4), 73.8% (234/317) of all podophyllotoxin-treated AGWs had cleared compared with 8.2% (13/158) of placebo-treated AGWs; difference between groups was statistically significant ($p = 0.0001$) • At week 6, 82% (260/317) of all podophyllotoxin-treated AGWs had cleared compared with 13% (20/158) of placebo-treated AGWs; difference between groups was statistically significant ($p = 0.0001$). Of cleared AGWs, there was evidence of recurrence in 34% (88/260) of AGWs treated with podophyllotoxin compared with 5% (1/20) of AGWs to which placebo had been applied • Total AGW area was reduced by 82.3% in people who received podophyllotoxin 0.5% compared with 4.2% in people who received placebo; difference between groups was statistically significant ($p = 0.0001$) • Authors comment that duration of infection (< 12 months vs. ≥ 12 months) did not influence therapeutic response (no other details provided) • The most common 'other' AE reported was itching; other AEs included in 'other' were dyspareunia, insomnia, tingling, bleeding, tenderness, chaffing, malodour, scarring, vesiculation, crusting and xerosis. All local adverse reactions were transient and reversible

M/F, male/female; NA, not applicable; SD, standard deviation.
a ?, unclear risk of bias.

TABLE 72 Beutner *et al.*[116]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Victoria Wakefield and Sam Barton
Study ID	Beutner 1998a
Study details	*Antimirob Agents Chemother* 1998;**42**:789–94
Language of publication	English
Type of report	Full paper
Section 2: Study information	
Location and number of sites	USA; seven centres (number of sites not reported)
Trial sponsor	Research was supported by a grant from 3M Pharmaceuticals
Conflicts of interest	Not reported
Patient enrolment	Not reported
Trial design	RCT
Trial duration	Treatment administered for a maximum of 16 weeks. After treatment, people were followed up over a 12-week period during which no treatment was given
Line of therapy	Mixed population (approx. 30% of people were treatment naive)
Inclusion criteria	Aged ≥ 18 years; seronegative for HIV infection; at least two but no more than 50 AGWs (defined as warts in the genital, anal, perineal or perianal area); had a biopsy diagnostic or suggestive of condyloma acuminatum and a bidimensional AGW area of at least 10 mm^2
Exclusion criteria	People were excluded if they had received AGW therapy in the 4 weeks before treatment initiation. Women were excluded if they were pregnant or lactating; had not agreed to use effective birth-control measures; or had a prestudy Papanicolaou smear that showed presence of a high-grade squamous intraepithelial lesion
All outcomes reported in paper	Complete clearance; proportion of people with at least a 50% reduction in AGW area; median time to complete clearance of baseline AGWs; appearance of new warts during treatment; recurrence; AEs

continued

TABLE 72 Beutner *et al.*[116] (*continued*)

Item	Details			
Section 2: Study information				
Subgroups evaluated	Men vs. women			
Stratification	It is stated that 'patients were randomised by study centre and by gender' (p. 789)			
Baseline measurement of disease	At baseline, AGW assessment included photographs, measurement, count and location. The assessment was repeated at each evaluation visit during and after treatment			
Treatment	*Imiquimod 5% cream*	*Imiquimod 1% cream*	*Placebo (vehicle cream)*	
Randomised, *n*	94	90	95	
Withdrawals, *n*	25	19	28	
Lost to follow-up, non-compliance or had an intercurrent illness, among other reasons, *n*	24	11	20	
Treatment-related reasons, *n*				
Local skin reactions	1	1	0	
Lack of therapeutic effect	0	4	2	
Clinically significant increase in wart area	0	3	6	
Treatment regimen	Before bedtime, participants rubbed their allocated treatment into clean, dry AGW-area skin until the treatment disappeared. They were instructed to wash the area with soap and water 8 ± 2 hours after application. Evaluations took place weekly for the first 4 weeks and every 2 weeks thereafter for the remainder of the treatment period and the 12-week follow-up period. At any point during treatment, if all AGWs cleared, treatment was stopped and the participant entered the 12-week follow-up period			
Duration/number of administered treatment	Not reported. It was reported that, when local skin reactions made continued application of treatment difficult, participants were allowed to take rest periods of 1–7 days. The mean number of rest days per patient was 11 days (14 days for female patients vs. 9 days for male patients)			
Baseline patient characteristics	*Imiquimod 5% cream*	*Imiquimod 1% cream*	*Placebo (vehicle cream)*	p-*value*
Age (years), mean (SD)	30 (10)	33 (11)	30 (9)	Not reported
Duration of current episode (months), median (range)	7.3 (0.2–484.3)	12.2 (0.3–388.1)	8.7 (0.3–246.8)	Not reported
Site of AGWs, *n* (%)[a]				
Women				
Vulva	35 (83)	37 (90)	38 (90)	Not reported
Perianal	17 (40)	21 (51)	21 (50)	Not reported
Perineum	1 (2)	2 (5)	1 (2)	Not reported
Other	4 (9)	2 (4)	0 (0)	Not reported
Men				
Penile	50 (96)	41 (84)	47 (89)	Not reported
Perianal	4 (8)	12 (24)	5 (9)	Not reported
Scrotum	2 (4)	3 (6)	4 (8)	Not reported
Groin	2 (4)	7 (14)	3 (6)	Not reported
Other	4 (8)	8 (16)	4 (8)	Not reported

TABLE 72 Beutner *et al.*[116] (*continued*)

Item	Details			
Type of AGWs (e.g. non-keratinsed, keratinised), *n* (%)	Not reported	Not reported	Not reported	
Number of AGWs, median (range)	7 (1–47)	8 (1–50)	8 (1–45)	Not reported
Area of AGWs (mm^2), median (range)	137 (2–9588)	148 (10–13,461)	121 (4–2603)	Not reported
Sex, *n* (%)				
Male	52 (55)	49 (54)	53 (56)	Not reported
Female	42 (45)	41 (46)	42 (44)	Not reported
No previous treatment, *n* (%)	31 (33)	24 (27)	23 (24)	Not reported
Ethnicity, *n* (%)				
White	89 (95)	84 (93)	93 (98)	Not reported
Other	5 (5)	6 (6)	2 (2)	Not reported
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Primary outcome. Defined as complete clearance of baseline AGWs during the treatment period			
Recurrence of AGWs	Reappearance of AGWs during the follow-up period in people with complete clearance during treatment			
Time to complete clearance	Median time to complete clearance of baseline AGWs			
Volume of wart clearance	Proportion of people with a reduction in AGW area of at least 50%			
Appearance of new warts during treatment	Appearance of AGWs that were not present at initiation of treatment			
AEs	Local skin reactions were assessed by patients and study personnel using a 4-point scale from 0 (no reaction) to 3 (severe)			

continued

TABLE 72 Beutner *et al.*[116] (*continued*)

Item	Details					
Section 4: Data extraction form						
Outcome	*Time frame*	*Imiquimod 5% cream,* n/N	*Imiquimod 1% cream,* n/N	*Placebo (vehicle cream),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	At end of and during treatment	49/94	13/90	3/95		$p < 0.001$ for imiquimod 5% vs. imiquimod 1% and placebo
Recurrence of AGWs	12 weeks after end of treatment	9/48	2/12	0/3		Not reported
Volume of wart clearance (proportion of patients with at least 50% reduction in wart area; includes those with 100% clearance)	End of treatment	64/69	32/79	17/75	Based on group of people not lost to follow-up	Not reported
Appearance of new warts during treatment	During treatment	27/92	44/86	58/92		Not reported
AEs						
Erythema						
Mild		15/92	–	26/92		Not reported
Moderate		40/92	–	8/92		Not reported
Severe		21/92	–	0/92		Not reported
Excoriation or flaking						
Mild		20/92	–	10/92		Not reported
Moderate		16/92	–	3/92		Not reported
Severe		3/92	–	1/92		Not reported
Erosion						
Mild		15/92	–	4/92		Not reported
Moderate		26/92	–	1/92		Not reported
Severe		3/92	–	0/92		Not reported
Oedema						
Mild		19/92	–	2/92		Not reported
Moderate		13/92	–	1/92		Not reported
Severe		4/92	–	0/92		Not reported
Scabbing						
Mild		14/92	–	5/92		Not reported
Moderate		12/92	–	0/92		Not reported
Severe		5/92	–	0/92		Not reported
Induration						
Mild		17/92	–	3/92		Not reported
Moderate		5/92	–	0/92		Not reported
Severe		0/92	–	0/92		Not reported

TABLE 72 Beutner *et al.*[116] (*continued*)

Item	Details				
Ulceration					
Mild		3/92	–	0/92	Not reported
Moderate		8/92	–	0/92	Not reported
Severe		1/92	–	0/92	Not reported
Vesicles					
Mild		4/92	–	0/92	Not reported
Moderate		3/92	–	0/92	Not reported
Severe		0/92	–	0/92	Not reported
Most common application site reactions					
Itching		30/92	20/86	17/92	$p = 0.084$
Pain		32/92	11/86	2/92	$p = 0.0001$
Burning		15/92	12/86	1/92	$p = 0.0003$
Tenderness		11/92	11/86	2/92	$p = 0.0120$
Other symptoms					
Headache		27/92	26/86	30/92	$p = 0.892$
Upper respiratory tract infection		13/92	23/86	25/92	$p = 0.053$
Continuous outcomes					
Time to complete clearance (weeks), median	During treatment	9 ($n = 49$)	7 ($n = 13$)	12 ($n = 3$)	Not reported

Section 5: Clinical trial quality

Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*
	Random sequence generation	?	Described as randomised but details of method of randomisation not provided
	Allocation concealment	?	Details of method of allocation concealment not provided
	Selective reporting	✓	The study protocol is not available; however, the publication reports results for all expected clinical outcomes
	'Other bias'	?	Insufficient information to assess whether another important risk of bias exists

continued

TABLE 72 Beutner *et al.*[116] (*continued*)

Item	Details		
Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	Described as double blinded but details on who was masked to treatment and methods to maintain masking during the study not provided
	Blinding of outcomes assessment	?	Described as double blinded but details on who was masked to treatment not provided; unclear whether the physician assessing the outcome was also the treating physician
	Incomplete outcome data	✓	Missing outcome data balanced across intervention groups, with similar reasons for missing data across groups. In addition, analysis of complete clearance is based on all people randomised
Recurrence of AGWs	Blinding (participants and personnel)	?	Described as double blinded but details on who was masked to treatment and methods to maintain masking during the study not provided
	Blinding of outcomes assessment	?	Described as double blinded but details on who was masked to treatment not provided; unclear whether the physician assessing the outcome was also the treating physician
	Incomplete outcome data	✓	Missing outcome data balanced across intervention groups, with similar reasons for missing data across groups. In addition, analysis of recurrence is based on all people with complete clearance of AGWs
Time to complete clearance	Blinding (participants and personnel)	?	Described as double blinded but details on who was masked to treatment and methods to maintain masking during the study not provided
	Blinding of outcomes assessment	?	Described as double blinded but details on who was masked to treatment not provided; unclear whether the physician assessing the outcome was also the treating physician
	Incomplete outcome data	✓	Missing outcome data balanced across intervention groups, with similar reasons for missing data across groups. In addition, analysis of time to complete clearance is based on all people randomised

TABLE 72 Beutner *et al.*[116] (*continued*)

Item	Details		
Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*
Volume of wart clearance	Blinding (participants and personnel)	?	Described as double blinded but details on who was masked to treatment and methods to maintain masking during the study not provided
	Blinding of outcomes assessment	?	Described as double blinded but details on who was masked to treatment not provided; unclear whether the physician assessing the outcome was also the treating physician
	Incomplete outcome data	✓	Missing outcome data balanced across intervention groups, with similar reasons for missing data across groups. In addition, analysis of complete clearance is based on all people randomised
Appearance of new warts during treatment	Blinding (participants and personnel)	?	Described as double blinded but details on who was masked to treatment and methods to maintain masking during the study not provided
	Blinding of outcomes assessment	?	Described as double blinded but details on who was masked to treatment not provided; unclear whether the physician assessing the outcome was also the treating physician
	Incomplete outcome data	✓	Missing outcome data balanced across intervention groups, with similar reasons for missing data across groups
AEs	Blinding (participants and personnel)	?	Described as double blinded but details on who was masked to treatment and methods to maintain masking during the study not provided
	Blinding of outcomes assessment	?	Described as double blinded but details on who was masked to treatment not provided; unclear whether the physician assessing the outcome was also the treating physician
	Incomplete outcome data	✓	Missing outcome data balanced across intervention groups, with similar reasons for missing data across groups
Overall rating of bias		?	Reflects uncertainty around masking of treatment allocation and maintenance of masking during the study

continued

TABLE 72 Beutner *et al.*[116] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	• *New warts*. New AGWs that developed during the treatment period were treated with study medication and were followed separately from baseline AGWs • *Recurrence*. Of the 11 people who experienced a recurrence during the follow-up period, three of these recurrences were noted at week 4, four were noted at week 6, two were noted at week 8, one was noted at week 10 and one was noted at week 12 • *Subgroup analysis*. Results of the ITT analysis by subgroup based on gender indicate that complete clearance was higher in women than in men [imiquimod 5%: men 22/52 (42%), women 27/42 (64%); imiquimod 1%: men 2/49 (4%), 11/41 (27%); vehicle: men 0/53 (0%), women 3/42 (7%)]. Comparisons of imiquimod 5% with imiquimod 1% and placebo were statistically significant in both men and women ($p < 0.05$). The difference between imiquimod 1% and placebo was also statistically significant in the female subgroup ($p = 0.02$) but there was no statistically significant difference between treatments in men ($p = 0.228$). In addition, the median time to clearance of baseline warts was shorter for female patients than for male patients (8 vs. 10 weeks for the imiquimod 5% cream group and 6 vs. 11 weeks for the imiquimod 1% cream group)

SD, standard deviation.
a Some people had AGWs in more than one location.
b ✓, low risk of bias; ?, unclear risk of bias.

TABLE 73 Beutner *et al.*[117]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Victoria Wakefield and Sam Barton
Study ID	Beutner 1998b
Study details	*J Am Acad Dermatol* 1998;**38**:230–9
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Three outpatient centres comprising one public health clinic, one university-based clinic and one private practice (carried out in the USA)
Trial sponsor	Trial supported by a grant from 3M Pharmaceuticals
Conflicts of interest	Not reported; three of six authors are listed as being based at 3M Pharmaceuticals
Patient enrolment	Details on recruitment and dates of enrolment of participants not provided
Trial design	RCT
Trial duration	Treatment was carried out over 8 weeks. People who experienced complete clearance of AGWs entered into a treatment-free follow-up period of 10 weeks or until recurrence occurred. People with a partial response at the end of 8 weeks' treatment were evaluated again at week 2 of follow-up to determine whether complete clearance had been achieved
Line of therapy	Mixed; about 30% of patients were treatment naive
Inclusion criteria	People aged ≥ 18 years who were HIV seronegative
Exclusion criteria	Pregant and lactating women were excluded as were women with vaginal warts or low- or high-grade cervical squamous intraepithelial lesions

TABLE 73 Beutner *et al.*[117] (*continued*)

Item	Details		
All outcomes reported in paper	Complete clearance; recurrence; median time to complete clearance; reduction in volume of AGWs; appearance of new AGWs during treatment; AEs		
Subgroups evaluated	None reported		
Stratification	Not clear		
Baseline measurement of disease	Diagnosis of AGWs was established by physical examination and confirmed by histopathology when indicated. Only clinically visible external AGWs were evaluated and treated. AGW area was determined by multiplying the two greatest perpendicular dimensions of each AGW. Total wart area was the sum of areas of individual AGWs		
Treatment	*Imiquimod 5%*	*Placebo*	
Randomised, *n*	51	57	
Withdrawals, *n*	7	12	
Lost to follow-up	4	6	
Discontinued because of local skin reaction	2	0	
Discontinued because of increase/no change in AGW area	1	5	
Personal reason	0	1	
Treatment regimen	Treatment or placebo was applied by participants. A clinician supervised the first dose of treatment or placebo applied by the participant. Placebo was physically indistinguishable from imiquimod 5% cream. Participants were instructed to bathe or shower before drug application and to avoid bathing/showering for 24 hours when the cream was on the skin. Sufficient cream was applied to cover the AGW, with application three times per week (Monday, Wednesday and Friday or Tuesday, Thursday and Saturday). Treatment was carried out for 8 weeks. Participants were assessed at initiation of treatment and once per week thereafter		
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Imiquimod 5%*	*Placebo*	p-*value*
Age (years), mean (SD)	29 (8)	30 (9)	$p > 0.50$
Duration of disease (months since onset), mean (range)	28 (2–181)	14 (1–277)	$p = 0.18$
Site of AGWs, *n* (%)	It is reported that, in men, the most frequent location of AGWs was the shaft of the penis (90–91%), with warts less commonly occurring on the perianal, scrotal, inguinal, pubic, thigh and perineal areas. In women, AGWs were located on the vulvar, perineal and perianal areas as well as the mons pubis and thigh. Some people had AGWs at multiple sites		Not reported
Type of AGWs	Not reported		
Number of AGWs, median (range)	6 (1–29)	7 (1–105)	$p > 0.50$
Area of AGWs (mm^2), median (range)	47 (6–1785)	63 (4–8784)	$p = 0.14$
Sex: male, *n* (%)	46 (90)	52 (91)	$p > 0.50$

continued

TABLE 73 Beutner *et al.*[117] (*continued*)

Item	Details		
Any previous treatment, *n* (%)			
None	16 (31)	18 (32)	$p > 0.50$
Podophyllin resin	26 (51)	21 (37)	$p = 0.18$
Cryotherapy	18 (35)	20 (35)	$p > 0.50$
Surgical excision	0 (0)	1 (2)	$p > 0.50$
Electrocautery	4 (8)	3 (5)	$p > 0.50$
Laser therapy	0 (0)	1 (2)	$p > 0.50$
TCAA	4 (8)	8 (14)	$p = 0.37$
Condylox	0 (0)	2 (4)	$p = 0.50$
Cornstarch	0 (0)	1 (2)	$p > 0.50$
Unknown/other	2 (4)	4 (7)	$p > 0.50$
Number of previous treatments, mean (SD)	1.06 (0.91)	1.05 (0.93)	$p > 0.50$
Ethnicity, *n* (%)			$p = 0.29$
White	48 (94)	54 (95)	
Black	3 (6)	1 (2)	
Asian/Pacific islander	0 (0)	2 (4)	
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	People with complete clearance during the treatment period. People with a partial response (> 0% to < 100% reduction) at the end of the 8-week treatment period were evaluated again at week 2 of the follow-up period to determine whether they had achieved complete clearance. Analysis of AGW clearance included people with complete clearance at this time point		
Recurrence of AGW	In people with complete clearance, reappearance of AGWs during the 10-week follow-up period		
Time to complete clearance	Median time to complete clearance, including those with initial partial clearance at the end of treatment and subsequent clearance at 2 weeks after the end of treatment		
Volume of wart clearance	Proportion of people with various reductions in baseline wart area (≥ 0%, ≥ 10%, ≥ 20%, ≥ 30%, ≥ 40%, ≥ 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, 100%)		
Appearance of new warts during treatment	Not defined		
AEs	People were asked to quantify symptoms (itching, pain and burning at site of application or adjacent area) as mild, moderate or severe. Objective evidence of inflammation at site of application and adjacent sites was evaluated using a scale from 0 to 6 (0 = no visible reaction; 1 = equivocal response; 2 = mild erythema; 3 = moderate erythema; 4 = intense erythema; 5 = intense erythema with oedema; and 6 = intense erythema with oedema and vesicles). Skin irritation at wart site was reported by week of treatment rather than as the total number of people experiencing the event. In addition, although application-site reactions (e.g. pain, itching, erythema) were reported for the imiquimod 5% group, equivalent data were not reported for the placebo group. Data are not presented in a format that can be used in prespecified analysis		

TABLE 73 Beutner *et al.*[117] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Imiquimod 5%*, n/N	*Placebo*, n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	2 weeks after end of treatment	19/51	0/57		$p < 0.001$
Recurrence of AGW	10 weeks after end of treatment	3/16	0/0		
Volume of wart clearance (proportion of patients with ≥ 50% clearance; includes those with 100% clearance)	2 weeks after end of treatment	34/45	4/50		$p \leq 0.001$
Appearance of new warts during treatment	8 weeks	14/48	20/55		$p > 0.50$
Continuous outcomes					
Time to complete clearance (weeks), median	2 weeks after end of treatment	7 ($n = 18$)	NA ($n = 0$)		
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	It is stated that 'fifty-one patients were randomly selected to receive 5% imiquimod cream; 57 patients were randomly chosen to receive placebo cream' (p. 233). Details on the method of randomisation are not provided	
	Allocation concealment		?	Details on the method of allocation concealment are not reported	
	Selective reporting		✓	The study protocol is not available but the report provides data on all expected clinical outcomes	
	'Other bias'		?	Insufficient detail reported to evaluate risk of other bias	
AGW clearance at completion of treatment	Blinding (participants and personnel)		?	The study is described as double blinded but details on who is masked to treatment are unclear	
	Blinding of outcomes assessment		?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment	
	Incomplete outcome data		✓	Loss to follow-up reported. AGW clearance is based on an ITT analysis	

continued

TABLE 73 Beutner *et al.*[117] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart recurrence is masked to treatment
	Incomplete outcome data	✓	Analysis of recurrence is based on all people with complete clearance at a defined time point
Time to complete clearance	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment
	Incomplete outcome data	✓	Analysis of time to complete clearance is based on all people with complete clearance at a defined time point
Volume of wart clearance (proportion of patients with ≥ 50% clearance)	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment
	Incomplete outcome data	✓	Number of people lost to follow-up is reported. Although proportion of people with reduction in wart clearance is not based on an ITT analysis, a similar proportion of people is excluded from each treatment group
Appearance of new warts during treatment	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment
	Incomplete outcome data	✗	Although number of people lost to follow-up is reported, it is unclear how the number of people included as the denominator in this analysis has been derived (does not correspond to analysis outlined in the paper)

TABLE 73 Beutner *et al.*[117] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment
	Incomplete outcome data	✗	Absolute numbers of AEs not reported for the placebo group. Authors state that 'Each symptom occurred significantly more frequently ($p < 0.05$) in imiquimod recipients than in placebo recipients' (p. 235)
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	The primary analysis reported in the paper excludes people who were lost to follow-up, who discontinued for a personal reason or who were judged to be non-compliant with dosing schedules. People who discontinued because of local skin reactions and for increase/no change in AGW area were considered treatment failures and were included in the analysis of efficacy		

NA, not applicable; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 74 Claesson *et al.*[65]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Sjokvist Garcia-Stewart and Sam Barton
Study ID	Claesson 1996
Study details	*Int J STD AIDS* 1996;**7**:429–34
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study was carried out at multiple European sites: two sites in Sweden (Garnisonssjukhuset T2 and Vastadens Lakarmottgn); one site in Finland (Department of Dermatology and Venereology, University Hospital, Helsinki); one site in France (Institut Alfred Fournier, Paris)
Trial sponsor	Perstorp Pharma, Lund, Sweden
Conflicts of interest	None reported
Patient enrolment	Participants were recruited from those with AGWs attending the study sites. Dates of enrolment not reported
Trial design	RCT (three arms). Publication reports results from two RCTs, one involving men and one involving women
Trial duration	Initial treatment period of up to 4 weeks. Those with complete clearance were followed up at 16 weeks

continued

TABLE 74 Claesson *et al.*[65] (*continued*)

Item	Details						
Line of therapy	Unclear						
Inclusion criteria	Inclusion criterion for the trial evaluating treatments in men: diagnosis of condylomata acuminata located on the penis shaft and/or within the preputial cavity region. Inclusion criterion for the trial evaluating treatments in women: diagnosis of vulval and/or perianal condylomata acuminata						
Exclusion criteria	Exclusion criteria for both RCTs were aged < 18 years; presence of untreated gonorrhoea, syphilis, herpes and/or chlamydia infection; period of < 3 months elapsed since previous treatment for condylomata acuminata						
All outcomes reported in paper	Response to treatment; complete clearance; recurrence; appearance of new AGWs during follow-up; AEs						
Subgroups evaluated	None reported within the individual RCTs						
Stratification	None reported						
Baseline measurement of disease	Not reported						
Treatment	*Podophyllotoxin 0.15% cream (patient applied)*		*Podophyllotoxin 0.3% cream (patient applied)*		*Podophyllotoxin 0.5% solution (patient applied)*		
	Trial 1 (men)	*Trial 2 (women)*	*Trial 1 (men)*	*Trial 2 (women)*	*Trial 1 (men)*	*Trial 2 (women)*	
Randomised, *n*	30	30	30	30	30	30	
Withdrawals, *n* (%)	Not reported for either trial						
Treatment regimen	Treatment schedules were the same in the two RCTs. Participants self-applied their allocated treatment (podophyllotoxin 0.15% cream, podophyllotoxin 0.3% cream or podophyllotoxin 0.5%) twice a day at home for 3 consecutive days. If a cure was not achieved, the treatment cycle was repeated with a 4-day break between cycles. The total number of applications did not exceed 24. Thus, treatment was repeated until complete clearance of AGWs was achieved or for a maximum of 4 weeks, whichever occurred earlier						
Duration/number of administered treatment	Not reported						
Baseline patient characteristics	*Podophyllotoxin 0.15% cream (patient applied)*		*Podophyllotoxin 0.3% cream (patient applied)*		*Podophyllotoxin 0.5% solution (patient applied)*		p-*value*
Age (years), mean	25.7	25	25.9	26.7	24.6	27.7	Not reported
Duration of disease (months), mean	1.6	2	1.3	1.9	1.7	2.7	Not reported
Site of AGWs, *n* (%)	Men: penis shaft and/or within the preputial cavity region; women: vulval and/or perianal areas						
Type of AGWs, *n* (%)	Not reported						
Number of AGWs							
1–5	9	13	12	10	10	12	Not reported
6–10	2	3	6	6	7	5	
> 10	19	14	12	14	13	13	

TABLE 74 Claesson *et al.*[65] (*continued*)

Item	Details
Area of AGWs (mm^2), mean	Not reported
Sex (M/F), *n* (%)	Trial 1: 100% men; trial 2: 100% women
Any previous treatment, *n* (%)	Not reported
Ethnicity, *n* (%)	Not reported
Section 3: Outcomes	
Outcome	*Definition*
AGW clearance at completion of treatment	Cure defined as elimination of all original warts. Evaluated during treatment
AGW clearance at other time points	Results presented for complete clearance at 1, 2 and 3 weeks of treatment
Recurrence of AGWs	In those with complete clearance, recurrence was defined as appearance of AGWs at the follow-up visit in an earlier treated and completely cured area
AEs	At follow-up visits, participants were asked by the clinician whether they had experienced itching, a burning sensation, tenderness, pruritus, erythema or erosion. Symptoms were evaluated numerically as not present (0), mild (1), moderate (2) and severe (3). An overall adverse symptom score was calculated to summarise the worst adverse symptoms recorded for each patient. Definitions of mild, moderate and severe were not available

Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllotoxin 0.15% cream (patient applied),* n/N	*Podophyllotoxin 0.3% cream (patient applied),* n/N	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	4 weeks	No absolute numbers reported for complete clearance at any time point for the two trials. Response rate[a] reported and presented graphically. Number of people achieving complete clearance cannot be determined from graphs				Not reported
AGW clearance at other time points	1, 2 and 3 weeks					Not reported
Recurrence of AGWs[b]	16 weeks after end of treatment	6%	8.6%	8.6%		Not reported
AEs	4 weeks	Absolute numbers not reported for mild, moderate or severe AEs for the two trials. Most data presented graphically				Not reported
Moderate to severe recorded AEs in women (no further definition provided)	4 weeks	12/30	18/30	18/30		Not reported

continued

TABLE 74 Claesson *et al.*[65] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[c]	*Comments*
	Random sequence generation	?	It is stated that men and women were randomised to treatment but details on the method used to generate the random sequence are not available
	Allocation concealment	?	Details of the method of allocation concealment not available
	Selective reporting	✗	Data for most outcomes are reported or presented in such a way that precludes incorporation into a meta-analysis (percentages with no denominator or graphically). Results for complete clearance in both trials, although recorded, are not reported. Recurrence is reported as a percentage combining men and women, but the number of people with complete clearance is not available and so the number of people with recurrence cannot be back calculated
	'Other bias'	?	Insufficient information to determine potential additional sources of bias. The study was carried out at multiple sites but randomisation was not stratified by site to investigate whether similar results were obtained at each site
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence by lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	?	The number of people withdrawing or lost to follow-up is not reported. It is unclear whether there is an imbalance across the groups in the number of people withdrawing or lost to follow-up
Recurrence of AGWs	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW recurrence is likely to be subjective and open to influence by lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	?	The number of people withdrawing or lost to follow-up is not reported. The number of people returning for evaluation at 16 weeks is not reported. It is unclear whether there is an imbalance across the groups in the number of people withdrawing or lost to follow-up

TABLE 74 Claesson *et al.*[65] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence by lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	?	The number of people withdrawing or lost to follow-up is not reported. The number of people included in the evaluation of AEs is not reported. It is unclear whether there is an imbalance across the groups in the number of people withdrawing or lost to follow up
Overall rating of bias		✗	Reflects the open-label nature of the trial and the limited reporting of results for clinical outcomes and AEs
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation.
a Response rate calculated using the equation $100 \times (C/(C + N))$, where C = number of original AGWs completely cured and N = number of original AGWs that did not change.
b Rate of recurrence is presented for men and women combined, not by trial. Number of men and women with complete clearance not reported in either trial and so it is not possible to estimate event rate.
c ?, unclear risk of bias; ✗, high risk of bias.

TABLE 75 Edwards *et al.*[136]

Item	Details
Section 1: Reviewer and study information	
Reviewer name	Sam Barton and Victoria Wakefield
Study ID	Edwards 1988
Study details	*Genitourin Med* 1988;**64**:263–5
Language of publication	English
Type of report	Full paper
Section 2: Study information	
Location and number of sites	One site (St Thomas' Hospital, London, UK)
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Not reported
Trial design	RCT; participants randomised 2 : 1 to podophyllotoxin 0.5% and podophyllin 20%
Trial duration	Initial 6-week treatment period with a subsequent 3-month follow-up period
Line of therapy	Not reported
Inclusion criterion	Men with a diagnosis, based on clinical appearance, of external penile AGWs

continued

TABLE 75 Edwards *et al.*[136] (*continued*)

Item	Details		
Exclusion criteria	Men were excluded if they had had treatment for AGWs in the preceding 28 days or if the area to be treated exceeded 10 cm^2		
All outcomes reported in paper	Complete clearance of AGWs; recurrence; AEs		
Subgroups evaluated	None		
Stratification	Not reported		
Baseline measurement of disease	Not reported		
Treatment	*Podophyllotoxin 0.5% (patient applied)*	*Podophyllin 20% (clinician applied)*	
Randomised, *n*	42	23	
Withdrawals, *n* (%)	10 (23.8) (reasons for withdrawal not reported). In addition, four patients whose AGWs had not resolved after 6 weeks were withdrawn from the trial and regarded as treatment failures	4 (17.4) (reasons for withdrawal not reported). In addition, seven patients whose AGWs had not resolved after 6 weeks were withdrawn from the trial and regarded as treatment failures	
Treatment regimen	Podophyllotoxin 0.5% solution was patient applied, with only the first treatment applied by a clinician. Participants were instructed to continue application morning and evening to complete 3 consecutive days of treatment and were asked to return a week later for further assessment. If AGWs were still present, they continued treatment each week for up to 6 weeks. Those experiencing side effects were advised to stop treatment until they were reviewed, at which time the clinician decided whether to continue treatment. If AGWs had not resolved after 6 weeks, they were withdrawn from the trial and classed as treatment failures	Podophyllin 20% in alcohol was applied by a doctor once a week for up to 6 weeks. If AGWs had not resolved after 6 weeks, participants were withdrawn from the trial and classed as treatment failures	
Duration/number of administered treatment	Up to 6 weeks of treatment; further details not reported		
Baseline patient characteristics	*Podophyllotoxin 0.5% (patient applied)*	*Podophyllin 20% (clinician applied)*	p-*value*
Age (years), mean (range)	27 (20–42)	29 (19–45)	Not reported
Duration of disease	Not reported		Not reported
Site of AGWs, *n* (%)	Penile AGWs; no further details reported		Not reported
Type of AGWs, *n* (%)	Not reported		Not reported
Number of AGWs, mean (with SD/SE if given)	Not reported		Not reported
Area of AGWs (mm^2), mean (with SD/SE if given)	Not reported		Not reported
Sex (M/F), *n* (%)	All men	All men	Not reported
Any previous treatment, *n* (%)	Not reported		Not reported
Ethnicity, *n*			
Black	3	1	Not reported
White	36	23	Not reported
Asian	2	0	Not reported

TABLE 75 Edwards *et al.*[136] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Resolution was defined as the disappearance of the AGW(s) as assessed by a doctor at 6 weeks				
AGW clearance at other time points	Resolution (disappearance) of AGWs at 4 weeks and 3 months. Data for 3 months were not reported as follow-up was low at this time point, which the authors commented precluded comparison between treatments				
Recurrence of AGWs	Relapse was defined as resolution followed by reappearance of the AGW(s) during the 3 months of follow-up				
AEs	Not defined. AEs reported were side effects resulting in treatment disruption and transient side effects (trivial irritation, mild erythema) not requiring treatment discontinuation				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% (patient applied),* n/N	*Podophyllin 20% (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	6 weeks	28/32	12/19		$p < 0.05$
AGW clearance at other time points	4 weeks	24/32	8/19		$p < 0.02$
Recurrence of AGWs	12 weeks after end of treatment	5/13	4/8		Not reported
AEs					
AEs that interrupted treatment	6 weeks	2[a]/32	1[a]/19		Not reported
Transient side effects (trivial irritation and mild erythema)	6 weeks	21/32	15/19		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*		
	Random sequence generation	✓	'Patients were allocated treatment by means of a computer generated randomisation code' (p. 263)		
	Allocation concealment	?	Method of allocation concealment not described		
	Selective reporting	?	Insufficient information available to evaluate whether all prespecified outcomes have been reported		
	'Other bias'	?	Insufficient information available to determine potential additional sources of bias		

continued

TABLE 75 Edwards *et al.*[136] (*continued*)

Item	Details		
AGW clearance at completion of treatment	Blinding (participants and personnel)	✗	Described as an open comparison. Masking people to self-applied treatment three times per week vs. clinician-applied treatment once weekly could prove difficult
	Blinding of outcomes assessment	✗	Assessing clinician not masked to treatment. Given the subjective nature of the assessment of AGW clearance, outcome measurement is likely to be influenced by lack of masking
	Incomplete outcome data	?	Number of people lost to follow-up from each group is reported but information on reasons for loss to follow-up is not available. A similar proportion of people is lost from each treatment group. Efficacy analysis not based on the ITT population
Recurrence of AGWs	Blinding (participants and personnel)	✗	Described as an open comparison. Masking people to self-applied treatment three times per week vs. clinician-applied treatment once weekly could prove difficult
	Blinding of outcomes assessment	✗	Assessing clinician not masked to treatment. Given the subjective nature of the assessment of AGW reappearance, outcome measurement is likely to be influenced by lack of masking
	Incomplete outcome data	✗	Number of people lost to follow-up from each group is reported but information on reasons for loss to follow-up is not available. A large proportion of people did not return for assessment, with differences between groups in the proportion of people returning for reassessment. Analysis of recurrence is not based on all people with complete clearance of AGW
AEs	Blinding (participants and personnel)	✗	Described as an open comparison. Masking people to self-applied treatment three times per week vs. clinician-applied treatment once weekly could prove difficult
	Blinding of outcomes assessment	✗	Assessing clinician not masked to treatment. Assessment of extent of irritation and other AEs is likely to be influenced by lack of masking
	Incomplete outcome data	?	Number of people available for analysis of safety is not reported
Overall rating of bias		✗	Reflects open-label nature of trial and incomplete outcome data for recurrence
Section 6: Additional comments			
Additional comments	Recurrence of AGWs: the authors comment that reattendance at 3 months' follow-up was unsatisfactory and the default rate was too high to allow comparison		

M/F, male/female; SD, standard deviation.
a In the podophyllotoxin group, one person had erythema that persisted for 3 weeks and one had penile swelling. In the podophyllin group, one person developed erythema with preputial tightening.
b ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 76 Edwards *et al.*[118]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Victoria Wakefield and Sam Barton
Study ID	Edwards 1998. Related publication: Ferenczy[248]
Study details	*Arch Dermatol* 1998;**134**:25–30
Language of publication	English
Type of report	Full paper
Section 2: Study information	
Location and number of sites	Eleven ambulatory offices, including both private physician offices and referral medical centres
Trial sponsor	Not reported
Conflicts of interest	Not reported; study personnel included staff from 3M Pharmaceuticals, which is the developer of imiquimod
Patient enrolment	Participants were recruited from the practices of investigators, referring physicians and advertisements
Trial design	RCT; three-arm trial evaluating two doses of imiquimod cream (5% and 1%) vs. a placebo cream
Trial duration	Treatment period of up to 16 weeks followed by a treatment-free follow-up period of up to 12 weeks for those with complete clearance of their AGWs during the treatment period
Line of therapy	Unclear
Inclusion criteria	Healthy men and women aged ≥ 18 years and with a diagnosis of AGWs. People were enrolled only when deemed to be healthy based on medical history, physical examination and laboratory testing, which included complete blood cell count; serum screening multiphasic chemistry panel; serum pregnancy test (women); and determination of HIV status. People had a minimum of two and a maximum of 50 external AGWs, with a total wart area no less than 10 mm^2
Exclusion criteria	People were excluded if they were immunosuppressed by virtue of disease or use of medication; had current chemical or alcohol dependency; had treated their AGW within 4 weeks of enrolment (skin must have returned to normal after any previous therapy); had skin disease in the area to be treated, including frequently recurrent herpes simplex virus infection; or were using any local medications for any purpose, including topical corticosteroids, in the target area during the 2 weeks before enrolment. Women were excluded if they were found to have high-grade squamous intraepithelial lesions (greater than moderate dysplasia) after a Papanicolaou smear; were pregnant or lactating; or were not using contraception
All outcomes reported in paper	Complete clearance; recurrence; proportion with ≥ 50% reduction in area of baseline AGWs; appearance of new AGWs during treatment; time to complete clearance of AGWs; AEs
Subgroups evaluated	By gender (men vs. women)
Stratification	Not reported
Baseline measurement of disease	People underwent a skin biopsy test at baseline that was 'interpreted as diagnostic or suggestive of AGWs and without evidence of dysplasia' (p. 26). AGWs were photographed, measured and mapped at the initiation visit and subsequently every 2 weeks during the treatment and follow-up periods. AGW size was expressed as total area in square metres and determined by the product of the two longest perpendicular dimensions

continued

TABLE 76 Edwards *et al.*[118] (*continued*)

Item	Details			
Treatment	*Imiquimod 5%*	*Imiquimod 1%*	*Placebo (vehicle cream)*	
Randomised, *n*	109	102	100	
Withdrawals, *n* (%)	19 (17)	31 (30)	27 (27)	
Discontinuation because of an AE or lack of therapeutic effect	6 (6)	8 (8)	8 (8)	
Withdrawal because of non-compliance, personal reasons or unavailability for follow-up	13 (12)	23 (23)	19 (19)	
Treatment regimen	Participants were instructed carefully in the use of the test medication and were asked to maintain a diary to record dosing and to ensure compliance. After cleaning and drying the area, the allocated treatment was applied to all external lesions in an amount that could be rubbed in until the cream disappeared. Participants were told to allow the cream to dry before dressing and to leave the medication on during their normal sleeping time. The cream was washed off with soap and water after an application time of 6–10 hours. Treatment was to be applied three times each week until all baseline AGWs were confirmed to have disappeared or for 16 weeks, whichever occurred first. Medication was to be applied every other day for three doses per week with individual applications separated by no less than 36 hours and no more than 96 hours. After the third dose, there was a 2-day pause (60–120 hours) before the next week's dosing. No other topical preparations of any kind were allowed during the treatment period. At any time during the treatment phase, if AGWs were no longer visible, treatment was stopped and the person entered the follow-up phase of the study. Participants were seen weekly for the first 2 weeks, after which they were seen biweekly until their AGWs cleared or for the remainder of the 16-week treatment period			
Duration/number of administered treatment	Not reported			
Baseline patient characteristics	*Imiquimod 5%*	*Imiquimod 1%*	*Placebo (vehicle cream)*	p-*value*
Age (years), mean (SD)	32 (12)	30 (10)	31 (10)	$p > 0.50$
Duration of disease (months), median (range)	4.2 (0.4–375)	6.6 (0–182)	5.8 (0–270)	$p = 0.23$
Male	6.7 (0.4–375)	26.4 (0–182)	7.9 (0.7–270)	$p = 0.01$
Female	3.4 (0.7–168)	3.1 (0.2–90)	4.4 (0–220)	$p > 0.50$
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean (with SD/SE if given)	Not reported			
Area of AGWs (mm^2), median (range)	69 (8–5525)	74 (10–4271)	77 (5–5000)	$p > 0.50$
Male	92 (8–5525)	75 (10–2184)	87 (10–5000)	$p > 0.50$
Female	58 (15–2294)	58 (10–4271)	71 (7–1468)	$p > 0.50$

TABLE 76 Edwards *et al.*[118] (*continued*)

Item	Details			
Sex, *n* (%)				
Male	63 (58)	57 (56)	60 (60)	$p > 0.50$
Female	46 (42)	45 (44)	40 (40)	$p > 0.50$
Any previous treatment, *n* (%)	Not reported			
Ethnicity (%)				
White	85	81	83	$p > 0.50$
Black	13	17	17	
Asian/Pacific Islander	2	2	0	
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Complete clearance of baseline AGWs at any point during the 16-week treatment period			
Recurrence of AGWs	Recorded during the 12-week treatment-free follow-up period. Reappearance of one or more baseline AGWs in people with complete clearance of AGWs during the treatment period			
Time to complete clearance	Taken from Ferenczy;[248] time to complete clearance of AGWs			
Volume of wart clearance	Proportion of patients with ≥ 50% reduction in area of baseline AGWs			
Appearance of new warts during treatment	New AGWs appearing during the treatment period. New AGWs could be treated with the study treatment but were tracked separately and were not evaluated in the clearance of baseline AGWs			
AEs	Local reactions were graded independently by the patient and the investigator using the following scale: none, mild (visible irritation with minimal or no discomfort that did not disrupt daily activity), moderate (caused considerable discomfort but did not disrupt normal activities) or severe (substantially interfered with the patient's normal daily activities)			
Section 4: Data extraction form				
Outcome	*Time frame*	*Imiquimod 5%,* n/N	*Imiquimod 1%,* n/N	*Placebo (vehicle cream),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	16 weeks	54/109	21/102	11/100		Imiquimod 5% vs. placebo: $p < 0.001$; imiquimod 1% vs. placebo: $p = 0.08$
Recurrence of AGWs	12 weeks after end of treatment	6/45	0/18	1/10		Difference reported to be not significant
Time to complete clearance	16 weeks	Median time to clearance for those in the imiquimod 5% and placebo groups of 10 weeks (combined analysis; reported in Ferenczy[248])				Not reported

continued

TABLE 76 Edwards *et al.*[118] (*continued*)

Item	Details				
Volume of wart clearance (proportion of patients with ≥ 50% reduction in baseline AGW area; includes those with 100% clearance)	16 weeks	83/109	36/102	28/100	Imiquimod 5% vs. placebo: $p < 0.001$; imiquimod 1% vs. placebo: $p = 0.29$
Appearance of new warts during treatment	16 weeks	33/106	44/97	41[a]/100	$p = 0.20$
AEs[a] (assessed by investigator)					
Erythema					
None	16 weeks	35/106	72/97	72/95	
Mild	16 weeks	29/106	21/97	20/95	
Moderate	16 weeks	36/106	4/97	3/95	
Severe	16 weeks	6/106	0/97	0/95	
Erosion					
None	16 weeks	72/106	92/97	87/95	
Mild	16 weeks	22/106	4/97	6/95	
Moderate	16 weeks	11/106	1/97	2/95	
Severe	16 weeks	1/106	0/97	0/95	
Excoriation or flaking					
None	16 weeks	80/106	93/97	93/95	
Mild	16 weeks	19/106	4/97	2/95	
Moderate	16 weeks	6/106	0/97	0/95	
Severe	16 weeks	1/106	0/97	0/95	
Oedema					
None	16 weeks	89/106	94/97	94/95	
Mild	16 weeks	14/106	3/97	1/95	
Moderate	16 weeks	2/106	0/97	0/95	
Severe	16 weeks	1/106	0/97	0/95	
Scabbing					
None	16 weeks	90/106	94/97	93/95	
Mild	16 weeks	11/106	1/97	2/95	
Moderate	16 weeks	5/106	1/97	0/95	
Severe	16 weeks	0/106	1/97	0/95	
Induration					
None	16 weeks	97/106	93/97	92/95	
Mild	16 weeks	7/106	4/97	2/95	
Moderate	16 weeks	2/106	0/97	1/95	
Severe	16 weeks	0/106	0/97	0/95	

TABLE 76 Edwards *et al.*[118] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*
	Random sequence generation	?	Described as a randomised study but details on method of randomisation not provided
	Allocation concealment	?	Details on method of allocation concealment not provided
	Selective reporting	✓	The study protocol is not available but the report provides data on most expected clinical outcomes
	'Other bias'	?	Insufficient detail reported to evaluate risk of other bias
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment
	Incomplete outcome data	✓	Number of people withdrawing from the trial, with reasons for withdrawal, are reported. Although a larger proportion of people withdrew from the imiquimod 1% (data not reported here) and placebo groups, the number of people withdrawing because of an AE or lack of therapeutic effect is similar for each group. AGW clearance is based on an ITT analysis
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart recurrence is masked to treatment
	Incomplete outcome data	✗	Number of people withdrawing from the trial, with reasons for withdrawal, is reported. Analysis of recurrence is not based on all people with complete clearance at a defined time point, and a larger proportion of people with complete clearance in the imiquimod 5% group was lost to follow-up for recurrence
Time to complete clearance	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment
	Incomplete outcome data	?	Results for time to complete clearance reported as a combined analysis for only two of the treatment groups (imiquimod 5% and placebo)

continued

TABLE 76 Edwards *et al.*[118] (*continued*)

Item	Details		
Volume of wart clearance (proportion of patients with ≥ 50% reduction in baseline AGW area)	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment
	Incomplete outcome data	✓	Number of people withdrawing from the trial, with reasons for withdrawal, is reported. Although a larger proportion of people withdrew from the imiquimod 1% (data not reported here) and placebo groups, the number of people withdrawing because of an AE or lack of therapeutic effect is similar for each group. Volume of AGW clearance is based on an ITT analysis
Appearance of new warts during treatment	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing wart clearance is masked to treatment
	Incomplete outcome data	?	Number of people withdrawing from the trial, with reasons for withdrawal, is reported. Appearance of new warts during treatment is not based on an ITT analysis, but proportion of people excluded from analysis is low
AEs	Blinding (participants and personnel)	?	The study is described as double blinded but details on who is masked to treatment are unclear
	Blinding of outcomes assessment	?	The study is described as double blinded but it is unclear whether the person assessing AEs is masked to treatment
	Incomplete outcome data	?	Number of people withdrawing from the trial, with reasons for withdrawal, is reported. Reported AEs are not based on an ITT population, but proportion of people excluded from analysis is low
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a AEs reported as percentages in full publication. Absolute event rate imputed by reviewer (SB).
b ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 77 Ferenczy *et al.*[158]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Shannon Amoils and Sam Barton	
Study ID	Ferenczy 1995	
Study details	*J Gynecol Surg* 1995;**11**:41–50	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Study carried out at two sites in Montreal (Sir Mortimer B Davis–Jewish General Hospital and Reddy Memorial Hospital), Canada	
Trial sponsor	Not reported	
Conflicts of interest	Not declared	
Patient enrolment	All patients attending the colposcopy/androscopy clinics of the two locations who were eligible and who gave written consent were enrolled in the study. Enrolment dates not reported	
Trial design	RCT in which each patient acted as the internal control (randomisation of 'side' to be treated with technique rather than randomisation of people)	
Trial duration	Treatment and then follow-up of at least 6 months (maximum 18 months, mean 8 months) after the last treatment received	
Line of therapy	Not reported	
Inclusion criteria	Presence of vaginal and external anogenital condylomata (diagnosis verified by histology); AGW total linear area of ≥ 2 cm^2	
Exclusion criteria	Pregnanc; aged ≤ 18 years	
All outcomes reported in paper	Time to complete ablation (minutes); proportion of people with complete response by number of treatments; recurrence; healing; complications	
Subgroups evaluated	Men vs. women, but results for clinical outcomes not reported by treatment group	
Stratification	None reported	
Baseline measurement of disease	Total linear area of AGWs at baseline was measured by recording the length and width of each condyloma and calculating the total area. Clinical and colposcopic impressions were verified histologically. Measuring the volume of AGWs was attempted but abandoned because of the considerable observed variation in height	
Treatment	*Electrosurgery*	*Continuous-wave CO_2 laser therapy*
Randomised, *n*[a]	282	282
Withdrawals, *n* (%)	74 (26)	
Treatment regimen	Electrosurgery consisted of thin wire electrosurgical excision and fulguration procedures. A square-shaped loop electrode was used for excising larger lesions from the vagina, external anogenital skin and anal canal. A 5-mm ball electrode was used for fulgurating smaller lesions and bleeding sites. Patients with extensive disease (two-thirds of the vagina or external anogenital skin) and those with intra-anal involvement were treated under general anaesthesia at one site, whereas those with less extensive disease were treated under local anaesthesia at the other site	'CO_2 laser densities ranged from 350 W/cm^2 to 1000 W/cm^2 of continuous wave' (p. 42). Patients with extensive disease (two-thirds of the vagina or external anogenital skin) and those with intra-anal involvement were treated under general anaesthesia at one site, whereas those with less extensive disease were treated under local anaesthesia at the other site

continued

TABLE 77 Ferenczy *et al.*[158] (*continued*)

Item	Details		
Duration/number of administered treatment	Mean time to complete treatment: 12 minutes when data controlled for total linear area treated (cm^2); mean time to complete treatment of lesions $\geq 1\ cm^2$ (controlled for total areas treated and proportion of lesions excised): 7 (2.5–36) minutes	Mean time to complete treatment: 6 minutes when data controlled for total linear area treated (cm^2); mean time to complete treatment of lesions $\geq 1\ cm^2$ (controlled for total areas treated and proportion of lesions excised): 9 (4–31) minutes	
Baseline patient characteristics	*Electrosurgery*	*Continuous-wave CO_2 laser therapy*	p-*value*
Age (years), mean	Men 27.5; women 23.6		
Duration of disease	Not reported		
Site of AGWs, *n* (%)			
Women			
Vagina only	8 (4)		
Vulva only	89 (47)		
Anus only	16 (9)		
All	75 (40)		
Men			
Penis only	46 (49)		
Anus only	26 (28)		
Both	22 (23)		
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	Not reported		
Area of AGWs (mm^2), mean	Not reported		
Sex, *n* (%)	Men 94 (33); women 188 (64)		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance	Not defined. Number of men and women achieving 'complete response' is reported by number of treatments required to achieve complete response. Evaluation was by physical examination, including colposcopy		
Recurrence of AGWs	Reported as proportion of people with recurrence; 'recurrence' not further defined		
AEs	Pain–discomfort level was assessed using Melzack's McGill Pain Questionnaire. Participants were instructed to record their discomfort level using numerical headings: 0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain. Physician's assessment of pain was based on the level of vocalisation and perineal movements (score range 0–3) and was recorded independently at the third and sixth post-treatment visits. Participants' and physicians' scores were averaged and analysed separately. No other AEs were reported by treatment group		

TABLE 77 Ferenczy *et al.*[158] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Electrosurgery,* n/N	*Continuous-wave CO_2 laser therapy,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance[b]	Unclear	Not reported			
Recurrence of AGWs[c]	Unclear	Not reported			
AEs					
Pain: physician assessment	Unclear				
Mild		106/208	114/208	Differences between groups reported to be non-significant	
Moderate		83/208	79/208		
Severe		19/208	15/208		
Pain: participant assessment	Unclear				
Mild		101/208	110/208	Differences between groups reported to be non-significant	
Moderate		84/208	76/208		
Severe		23/208	22/208		
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[d]	*Comments*	
	Random sequence generation		✓	It is stated that people were randomised by computer-generated numbers as to which side was treated with electrosurgery or CO_2 laser therapy. The same randomisation schedule was applied to intra-anal condylomata	
	Allocation concealment		?	Details on method used to conceal allocation not available	
	Selective reporting		✗	Data on effectiveness for key clinical outcomes are not reported as absolute events rates by treatment group. Results presented cannot be used in a meta-analysis	
	'Other bias'		?	Insufficient information reported to determine presence of additional sources of bias	

continued

TABLE 77 Ferenczy *et al.*[158] (*continued*)

Item	Details		
AGW clearance	Blinding (participants and personnel)	✗	Participants and personnel are not masked to treatment. Given that the techniques evaluated are surgical and the participant undergoes both techniques, it might not be feasible to mask key study personnel and participants to treatment. AGW clearance is a subjective outcome and is liable to bias by lack of masking
	Blinding of outcomes assessment	✓	It is reported that 'the assessors were blinded at follow-up to the method of treatment used in a specific area in each patient. Each patient was assessed by a physician who was not directly involved in the treatment of that patient' (p. 43). Given that the participant is treated with both electrosurgery and CO_2 laser therapy, it is unlikely that masking of the outcome assessor would be broken
	Incomplete outcome data	?	Number of participants lost to follow-up is reported. However, it is unclear whether any participants withdrew from treatment but continued to be followed up. Reasons for loss to follow-up are not reported
Recurrence of AGWs	Blinding (participants and personnel)	✗	Participants and personnel are not masked to treatment. Given that the techniques evaluated are surgical and the participant undergoes both techniques, it might not be feasible to mask key study personnel and participants to treatment. AGW recurrence is a subjective outcome and is liable to bias by lack of masking
	Blinding of outcomes assessment	✓	It is reported that 'the assessors were blinded at follow-up to the method of treatment used in a specific area in each patient. Each patient was assessed by a physician who was not directly involved in the treatment of that patient' (p. 43). Given that the participant is treated with both electrosurgery and CO_2 laser therapy, it is unlikely that masking of the outcome assessor would be broken

TABLE 77 Ferenczy *et al.*[158] (*continued*)

Item	Details		
	Incomplete outcome data	?	Number of participants lost to follow-up is reported. However, it is unclear whether any participants withdrew from treatment but continued to be followed up. Reasons for loss to follow-up are not reported
AEs	Blinding (participants and personnel)	✗	Participants and personnel are not masked to treatment. Given that the techniques evaluated are surgical and the participant undergoes both techniques, it might not be feasible to mask key study personnel and participants to treatment. Evaluation of pain is a subjective outcome and is liable to bias by lack of masking
	Blinding of outcomes assessment	✓	It is reported that 'the assessors were blinded at follow-up to the method of treatment used in a specific area in each patient. Each patient was assessed by a physician who was not directly involved in the treatment of that patient' (p. 43). Given that the participant is treated with both electrosurgery and CO_2 laser therapy, it is unlikely that masking of the outcome assessor would be broken. It is unlikely that a person would be able to discriminate between pain generated from two areas of treatment
	Incomplete outcome data	?	Number of people lost to follow-up is reported. However, it is unclear whether any participants withdrew from treatment but continued to be followed up. Reasons for loss to follow-up are not reported
Overall rating of bias		✗	Reflects lack of masking of key study personnel and participants and limited reporting of key clinical outcomes
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a Randomisation determined which 'side' of the genital area received electrosurgery and which received CO2 laser therapy (i.e. the participant received both types of surgery).
b It is stated that 'complete clearance of AGWs in women and men after a single and multiple treatments were similar in the areas treated with electrosurgery and CO_2 laser' (p. 41). Absolute numbers by treatment group not reported.
c It is reported that, at any given time during the period of follow-up, lesions recurred as often in the laser-treated areas as in the electroexcised or fulgurated areas.
d ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 78 Fife *et al.*[129]

Item	Details			
Section 1: Reviewer and study information				
Reviewers' names	Fatima Salih and Sam Barton			
Study ID	Fife 2001			
Study details	*Sex Transm Dis* 2001;**28**:226–31			
Language of publication	English			
Type of report	Full publication			
Section 2: Study information				
Location and number of sites	Nine clinical sites in the USA and Canada			
Trial sponsor	3M Pharmaceuticals			
Conflicts of interest	None reported			
Patient enrolment	Details on how people were recruited at the clinical sites not available			
Trial design	RCT			
Trial duration	16-week treatment period followed by a 4-week observation period for people whose lesions had not cleared by week 16			
Line of therapy	Mixed population; 70% of men enrolled had received previous treatment for AGWs			
Inclusion criteria	Male gender; healthy except for AGWs; aged ≥ 18 years; presence of 2–50 AGWs confirmed by biopsy; total AGW area of 30–2000 mm^2 after biopsy. To be eligible for enrolment, participants had to have AGWs that were either previously untreated or, if treated, had not been treated with other methods for at least 4 weeks before study entry			
Exclusion criterion	People previously treated with imiquimod were excluded			
All outcomes reported in paper	Complete clinical clearance of AGWs at end of treatment; decrease in volume of AGWs; time to complete clearance; appearance of new lesions during treatment; AEs			
Subgroups evaluated	Not reported			
Stratification	Not reported			
Baseline measurement of disease	Biopsy of a single representative AGW was carried out to confirm clinical diagnosis. At baseline, AGWs were enumerated, measured and photographed			
Treatment	*Imiquimod 5% three times per week*	*Imiquimod 5% once daily*	*Imiquimod 5% twice daily*	*Imiquimod 5% three times a day*
Randomised, *n*	26	29	29	26
Withdrawals, *n* (%)	A total of 35 people (31.8%) withdrew from the trial; data for each group not reported separately. It is reported that there was no difference across the treatment groups in the proportion of people failing to complete the study, with the exception of withdrawal because of an AE			
AEs, *n* (%)	0	1 (3)	0	3 (12)
Lost to follow-up, *n* (%)	24 (21.8%) across the four groups; data for each group not reported separately			
Treatment regimen	It is stated that patients were given detailed instructions on how to apply the imiquimod 5% cream; further details not available. Men were assigned to apply imiquimod 5% cream three times a week, once daily, twice daily or three times a day for a maximum of 16 weeks or until complete clearance, whichever occurred earlier			
Duration/number of administered treatment	Not reported			

TABLE 78 Fife *et al.*[129] (*continued*)

Item	Details				
Baseline patient characteristics	*Imiquimod 5% three times per week*	*Imiquimod 5% once daily*	*Imiquimod 5% twice daily*	*Imiquimod 5% three times a day*	p-*value*
Age (years), mean (range)	32 (19–53)	32 (18–50)	31 (20–47)	32 (19–67)	Not reported
Duration of disease (months), median (range)	25.9 (1.5–182)	35.6 (1.1–423)	32.9 (0.8–225)	21.6 (0.3–117)	Not reported
Site of AGWs, *n* (%)	Not reported				
Type of AGWs, *n* (%)	Not reported				
Number of AGWs, median (range)	10 (3–29)	9 (2–41)	12 (2–34)	11(2–39)	Not reported
Area of AGWs (mm^2), median (range)	83 (31–1830)	225 (12–1699)	122 (31–3656)	88 (31–1886)	Not reported
Sex (M/F), *n* (%)	All men				
Any previous treatment, *n* (%)	19 (73)	22 (76)	20 (69)	16 (62)	Not reported
Ethnicity: white, *n* (%)	25 (96)	25 (86)	24 (83)	22 (85)	Not reported
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Patients were assessed at the end of weeks 1, 2, 3 and 4 then every other week through to week 16 (maximum duration of treatment) or until they experienced complete clinical clearance of AGWs				
AGW clearance at other time points	Complete clearance at 4 weeks after the end of treatment (16 weeks) in people whose lesions had not cleared by week 16				
Time to complete clearance	Median time until complete AGW clearance during the 16-week treatment period or 4-week observation period				
Appearance of new warts during treatment	Development of new lesions				
AEs	Specific local reactions (erythema, oedema, induration, vesicles, erosion, ulceration, excoriation/flaking and scabbing), application site reactions (pain, burning and itching) and systemic AEs were assessed at each visit. Local skin reactions were clinician assessed using a scale from 0 (none) to 3 (severe). Patient-assessed severity of each local skin reaction was based on three categorisations: mild = reaction with little or no discomfort and no effect on normal activities; moderate = causing considerable discomfort, but not disrupting normal activities; severe = sufficient discomfort to interfere with normal activities				

continued

TABLE 78 Fife *et al.*[129] (*continued*)

Item	Details						
Section 4: Data extraction form							
Outcome	*Time frame*	*Imiquimod 5% three times per week,* n/N	*Imiquimod 5% once daily,* n/N	*Imiquimod 5% twice daily,* n/N	*Imiquimod 5% three times a day,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes							
AGW clearance at completion of treatment	16 weeks	9/26	8/29	7/29	7/26		Difference among groups reported to be not significant
AGW clearance at other time points	4 weeks after end of treatment	10/26	10/29	8/29	7/26		
Appearance of new warts during treatment	16 weeks	39 men developed new AGWs during treatment; data not reported separately for each group					
AEs							
Application site reactions	16 weeks	15/26	18/29	21/29	20/26		$p = 0.43$
Systemic AEs attributed to interferon	16 weeks	Reported to be 3.4–26.9% of men in the different treatment groups; data not reported separately for the individual treatment groups					Not reported
Continuous outcomes							
Time to complete clearance (weeks), median	Up to 20 weeks	10 ($n = 26$)	9 ($n = 29$)	7 ($n = 29$)	10 ($n = 26$)		Not reported

Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	✓	It is stated that 'Eligible patients were assigned consecutive study numbers according to order of enrolment. A randomisation table assigning each study number to one of the four treatments was generated before study initiation' (p. 227)
	Allocation concealment	?	It is stated that 'treatment assignments were kept in sealed envelopes until each study number was assigned' (p. 227). It is unclear whether the envelopes were opaque
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	It is stated that 'No attempt was made to blind the assigned treatment regimens, but patients were told about the uncertainty of the optimal treatment regimen' (p. 227). It is unclear whether the statement about masking also applies to clinical personnel or outcome assessors
	Blinding of outcomes assessment	?	

TABLE 78 Fife *et al.*[129] (*continued*)

Item	Details		
	Incomplete outcome data	?	Number of people withdrawing from the study is reported, with data by treatment group available for those withdrawing because of an AE. It is unclear whether there is an imbalance across the groups in the proportion of people withdrawing from treatment
Time to complete clearance	Blinding (participants and personnel)	?	It is stated that 'No attempt was made to blind the assigned treatment regimens, but patients were told about the uncertainty of the optimal treatment regimen' (p. 227). It is unclear whether the statement about masking also applies to clinical personnel or outcome assessors
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Number of people withdrawing from the study is reported, with data by treatment group available for those withdrawing because of an AE. It is unclear whether there is an imbalance across the groups in the proportion of people withdrawing from treatment
Appearance of new warts during treatment	Blinding (participants and personnel)	?	It is stated that 'No attempt was made to blind the assigned treatment regimens, but patients were told about the uncertainty of the optimal treatment regimen' (p. 227). It is unclear whether the statement about masking also applies to clinical personnel or outcome assessors
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Number of people withdrawing from the study is reported, with data by treatment group available for those withdrawing because of an AE. It is unclear whether there is an imbalance across the groups in the proportion of people withdrawing from treatment
AEs	Blinding (participants and personnel)	?	It is stated that 'No attempt was made to blind the assigned treatment regimens, but patients were told about the uncertainty of the optimal treatment regimen' (p. 227). It is unclear whether the statement about masking also applies to clinical personnel or outcome assessors
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Number of people withdrawing from the study is reported, with data by treatment group available for those withdrawing because of an AE. It is unclear whether there is an imbalance across the groups in the proportion of people withdrawing from treatment
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	• Reduction in AGW volume is also reported but data are presented graphically. It is stated that 'most patients had a significant reduction in extent of disease, as determined by the median reduction in total wart area during the treatment period' (p. 228). Although the difference from baseline was reported to be statistically significant in each group, there was no statistically significant difference in reduction in AGW area among the four treatment groups • Men were allowed rest periods from treatment to allow local skin reactions to diminish. Of men with documented dosing information, a smaller proportion in the group applying imiquimod 5% three times a week took a rest period than in the other groups [three times a week: 9/24 (38%); once daily: 18/29 (62%); twice daily: 24/27 (89%); three times a day: 20/24 (83%)]		

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 79 Gabriel and Thin[145]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Fatima Salih and Sam Barton	
Study ID	Gabriel 1983	
Study details	*Br J Vener Dis* 1983;**9**:124–6	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Department of Genital Medicine at St Bartholomew's Hospital, London, UK	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Men attending the Department of Genital Medicine were considered for entry into the trial	
Trial design	RCT	
Trial duration	Treatment was administered over 6 weeks. Follow-up occurred for a minimum period of 3 months from the beginning of treatment	
Line of therapy	Unclear	
Inclusion criteria	Male gender and presence of AGWs	
Exclusion criterion	Receipt of treatment for AGWs in the 3 months before the initial visit	
All outcomes reported in paper	Complete clearance of AGWs; recurrence; AEs	
Subgroups evaluated	Not reported	
Stratification	Not reported	
Baseline measurement of disease	Not reported	
Treatment	*TCAA 50% plus podophyllin 25%*	*Podophyllin 25%*
Randomised, *n*	35	38
Withdrawals, *n* (%)	4 (11.4); reasons for withdrawal not reported	9 (23.7); reasons for withdrawal not reported
Treatment regimen	Men were treated weekly for up to 6 weeks with TCAA 50% plus podophyllin 25% in industrial methylated spirits saturated with a brown inert dye	Men were treated weekly for up to 6 weeks with podophyllin 25% in industrial methylated spirits
	In both groups, treatment was carried out by one clinician. Treatment was applied with an orange stick and care was taken to ensure that the application was strictly limited to AGWs and that surrounding skin was avoided. Each application was allowed to air dry for 5 minutes out of sight of the treating clinician, who also assessed clearance of AGWs. If AGWs persisted after 6 weeks, treatment was changed to TCAA 100% or cryocautery on a non-trial basis	
Duration/number of administered treatment	Number of treatments to clear AGWs at 6 weeks, mean (SD): 2.9 (1.1)	Number of treatments to clear AGWs at 6 weeks, mean (SD): 4.0 (1.6)
	Difference between groups in mean number of treatments required to clear AGWs is statistically significant ($0.02 > p > 0.01$)	

TABLE 79 Gabriel and Thin[145] (*continued*)

Item	Details			
Baseline patient characteristics	*TCAA 50% plus podophyllin 25%*		*Podophyllin 25%*	p-*value*
Age (years), mean (with SD/SE if given)	Not reported			
Duration of disease	Not reported			
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean (with SD/SE if given)	Not reported			
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	All men			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	AGW clearance at completion of treatment (6 weeks)			
Recurrence of AGWs	Recurrence is not defined within the study. Data are reported for the proportion of men who 'remained clear' at 3 months after the initiation of treatment. The number of men not remaining clear has been assumed to be the number of men who experience recurrence of AGWs			
AEs	Not defined			
Section 4: Data extraction form				
Outcome	*Time frame*	*TCAA 50% plus podophyllin 25%,* n/N	*Podophyllin 25%,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	6 weeks	21/35	20/38		$p > 0.5$
Recurrence of AGW	3 months	11/21	11/20		$p > 0.5$
AEs					
Superficial ulceration at site of treatment	6 weeks	3/35	0/38		Not reported
Excessive soreness a day or two after treatment	6 weeks	2/35	0/38		Not reported

continued

TABLE 79 Gabriel and Thin[145] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	It is stated that 'patients were allocated by means of a random numbers table' (p. 124), but additional information on method of randomisation is not available
	Allocation concealment	✓	Both treatment solutions were prepared by one pharmacy and dispensed in stock 10-ml bottles labelled A and B. The pharmacy alone held the code key, which was not revealed until the end of the trial
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment	Blinding (participants and personnel)	✓	It is reported that the study was double blind. The key difficulty encountered with maintaining masking in this study was described as the characteristic white appearance of AGWs after treatment with TCAA. In the study, the pharmacy preparing the solutions added an inert brown dye to the TCAA plus podophyllin solution, which masked the white appearance of AGWs after treatment with TCAA and made the solution the same colour as podophyllin solution
	Blinding of outcomes assessment	✓	The treating clinician also assessed clinical outcomes. The treating clinician was masked to treatment allocation
	Incomplete outcome data	?	The number of people withdrawing from each group is reported, but reasons for withdrawal are not provided. There is an imbalance in withdrawal between the groups (11.4% with TCAA plus podophyllin vs. 23.4% with podophyllin). As reasons for withdrawal are not reported, the potential impact of the imbalance on the relative treatment effect is unclear

TABLE 79 Gabriel and Thin[145] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	✓	It is reported that the study was double blind. The key difficulty encountered with maintaining masking in this study was described as the characteristic white appearance of AGWs after treatment with TCAA. In the study, the pharmacy preparing the solutions added an inert brown dye to the TCAA plus podophyllin solution, which masked the white appearance of AGWs after treatment with TCAA and made the solution the same colour as podophyllin solution
	Blinding of outcomes assessment	✓	The treating clinician also assessed clinical outcomes. The treating clinician was masked to treatment allocation
	Incomplete outcome data	✓	Analysis of recurrence is based on all people with complete clearance at the end of treatment
AEs	Blinding (participants and personnel)	✓	It is reported that the study was double blind. The key difficulty encountered with maintaining masking in this study was described as the characteristic white appearance of AGWs after treatment with TCAA. In the study, the pharmacy preparing the solutions added an inert brown dye to the TCAA plus podophyllin solution, which masked the white appearance of AGWs after treatment with TCAA and made the solution the same colour as podophyllin solution
	Blinding of outcomes assessment	✓	The treating clinician also assessed clinical outcomes. The treating clinician was masked to treatment allocation
	Incomplete outcome data	?	The number of people withdrawing from each group is reported, but reasons for withdrawal are not provided. There is an imbalance in withdrawal between the groups (11.4% with TCAA plus podophyllin vs. 23.4% with podophyllin). As reasons for withdrawal are not reported, the potential impact of the imbalance on AEs is unclear
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	Baseline characteristics were not reported in the full publication but it is stated that 'the two groups of patients were statistically comparable in age range, country of origin, sexual preference, and sites of warts present' (p. 125)		

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 80 Garland *et al.*[130]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Victoria Wakefield and Sam Barton
Study ID	Garland 2006
Study details	*Int J STD AIDS* 2006;**17**:448–52
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at nine public sexual health clinics in Australia
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Only women enrolled; no details provided on methods used to identify and recruit women or dates of enrolment
Trial design	Four-arm RCT
Trial duration	Initial treatment period of 4–16 weeks, dependent on treatment allocation. All women were followed up until the end of the study at 16 weeks. Women could stop treatment earlier than the allocated treatment period if AGWs had completely cleared
Line of therapy	Mixed: 88/120 (73.3%) women had received previous treatment for their AGWs (cryotherapy in 73 women and podophyllotoxin in 49 women)
Inclusion criteria	Female gender; aged $\geq$ 16 years; presence of 1–50 visible external genital and/or perianal AGWs with an area of 10–2000 mm^2
Exclusion criteria	Pregnant or lactating; HIV-positive status; internal vaginal or anal lesions requiring treatment; presence of psoriasis or other skin disease (e.g. herpes) that may confound examination; moderate or severe dysplasia [cervical intraepithelial neoplasia (CIN) 2 or 3]; carcinoma in situ; presence of squamous cell carcinoma; receipt of organ transplant; use of other therapies for AGWs or topical immunomodulators (including imiquimod) in the 4 weeks preceding entry to the study or corticosteroids within 2 weeks of study entry
All outcomes reported in paper	Complete clearance of AGWs at 4, 8, 12 and 16 weeks; AEs
Subgroups evaluated	None reported
Stratification	None reported
Baseline measurement of disease	The size, number and location of AGWs were recorded and AGWs were photographed twice

TABLE 80 Garland *et al.*[130] (*continued*)

Item	Details				
Treatment	*Imiquimod 5% cream for 4 weeks (patient applied)*	*Imiquimod 5% cream for 8 weeks (patient applied)*	*Imiquimod 5% cream for 12 weeks (patient applied)*	*Imiquimod 5% cream for 16 weeks (patient applied)*	
Randomised, *n*	30	31	28	31	
Withdrawals, *n* (%)	13 (43) 6 (19)		8 (29)	8 (26)	
	It is stated that the main reasons for discontinuation were non-compliance and loss to follow-up. Two women withdrew because of the severity of local skin reactions and one woman withdrew because of nausea, fatigue and vagueness. The number of women excluded because of non-compliance and the number lost to follow-up not reported for overall trial population or individual treatment groups				
Treatment regimen	Imiquimod 5% cream was applied by women three times a week (every other night followed by 2 days without treatment) for the allocated period of time (4, 8, 12 or 16 weeks) or until complete clearance of AGWs, whichever occurred earlier. No additional treatment was allowed				
Duration/number of administered treatment	Not reported				
Baseline patient characteristics	*Imiquimod 5% cream for 4 weeks (patient applied)*	*Imiquimod 5% cream for 8 weeks (patient applied)*	*Imiquimod 5% cream for 12 weeks (patient applied)*	*Imiquimod 5% cream for 16 weeks (patient applied)*	p-*value*
Age (years), mean (range)	Overall trial population: 26.5 (17–67); not reported separately by treatment group				Not reported
Duration of disease (months), median (range)	3.2 (0.6–93.3)	3.3 (0.2–25.0)	3.8 (0.8–24.3)	3.1 (0.4–89.7)	$p = 0.889$
Site of AGWs (%)	Overall trial population: 69.2% vulvar; 59.2% labial; 45.8% perianal; 34.2% perineal; not reported separately by treatment group				Not reported
Type of AGWs, *n* (%)	Not reported				Not reported
Number of AGWs, median (range)	12.5 (1–43)	13.0 (1–43)	18.0 (3–43)	12.0 (2–52)	$p = 0.336$
Area of AGWs (mm^2), median (range)	168.5 (10–1706)	86.0 (18–577)	153.0 (41–1983)	109.0 (38–860)	$p = 0.403$
Sex (M/F), *n* (%)	All women				
Any previous treatment, *n* (%)	19 (63.3)	24 (77.4)	23 (82.1)	22 (71.0)	$p > 0.15$
Ethnicity, *n* (%)	Trial population was reported to be 117 (97.5%) white: ethnicity not reported separately by treatment group and no further details reported on ethnicity of remaining 2.5% of study population				Not reported

continued

TABLE 80 Garland *et al.*[130] (*continued*)

Item	Details						
Section 3: Outcomes							
Outcome	*Definition*						
AGW clearance at completion of treatment	Complete clearance of AGWs at 16 weeks: additional details not available						
AGW clearance at other time points	Complete clearance of AGWs at 4, 8 and 12 weeks; additional details not available. Absolute numbers not reported (results presented graphically in the full publication)						
AEs	Assessed by spontaneous reporting of application site reactions (symptoms at treatment site) and other AEs, in addition to local skin reactions (the most common signs at the treatment site)						
Section 4: Data extraction form							
Outcome	*Time frame*	*Imiquimod 5% cream for 4 weeks (patient applied),* n/N	*Imiquimod 5% cream for 8 weeks (patient applied),* n/N	*Imiquimod 5% cream for 12 weeks (patient applied),* n/N	*Imiquimod 5% cream for 16 weeks (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes							
AGW clearance at completion of treatment	16 weeks	12/30	15/31	11/28	16/31		$p = 0.724$
AGW clearance at completion at other time points	4, 8 and 12 weeks	Absolute numbers not reported; results presented graphically in the full publication					
AEs (%)							
Pain	16 weeks	0	19	4	13		$p = 0.026$
Local skin reactions	16 weeks	67	87	96	87		$p = 0.021$
Section 5: Clinical trial quality							
Outcome	*Risk of bias*		*Risk assessment*[a]		*Comments*		
	Random sequence generation		?		It is stated that the study was randomised but details on the method of randomisation are not available		
	Allocation concealment		?		Information on method of allocation concealment not provided		
	Selective reporting		✗		Complete clearance at various time points is presented graphically, with no absolute numbers reported. In addition, results for AEs are not reported separately for each treatment group. Data reported for key outcomes cannot be entered in a meta-analysis		
	'Other bias'		?		Insufficient information provided to determine presence of additional sources of bias		

TABLE 80 Garland *et al.*[130] (*continued*)

Item	Details		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence by lack of masking
	Blinding of outcomes assessment	✗	Study is described as 'open label'. Assessment of AGW clearance is likely to be subjective and open to influence by lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	Although number of withdrawals and loss to follow-up are reported for each treatment group, accompanying reasons are not available. In addition, there is an imbalance across the groups in the proportion of women withdrawing or lost to follow-up (19–43%). The effect of this imbalance on estimates of effect is unclear
AEs	Blinding (participants and personnel)	✗	Study is described as 'open label'. Assessment of AEs is likely to be subjective and open to influence by lack of masking
	Blinding of outcomes assessment	✗	Study is described as 'open label'. Assessment of AEs is likely to be subjective and open to influence by lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	Although number of withdrawals and loss to follow-up are reported for each treatment group, accompanying reasons are not available. In addition, there is an imbalance across the groups in the proportion of women withdrawing or lost to follow-up (19–43%). The effect of this imbalance on estimates of effect is unclear
Overall rating of bias		✗	Reflects open-label nature of trial and limited reporting on key clinical outcomes (complete clearance at various time points and occurrence of AEs)

continued

TABLE 80 Garland *et al.*[130] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	• Reported as a pilot study, which was not powered to show statistically significant differences or statistical equivalence between treatment groups or study time points • Patients who discontinued prematurely were considered to be treatment failures. Patients discontinuing before 16 weeks were analysed using the last observation carried forward method for the 4-, 8- and 12-week and AEs analyses • Per-protocol analysis for complete clearance at 16 weeks: 52.4%, 50.0%, 52.4% and 60.9% for the 4-, 8-, 12- and 16-week groups respectively • It is reported that most women who cleared their AGWs did so by the end of week 8. The authors comment that the results of the study suggest that the efficacy of imiquimod 5% cream is maximal at 8 weeks, irrespective of whether the treatment duration was 4 or 8 weeks • AEs – It was reported that 84.2% of the trial population experienced application site reactions, although they were generally mild to moderate. Most frequent application site reactions were itching (39%), soreness (23%), tenderness (19%) and burning (13%). Local skin reactions were also mild to moderate. The most frequent local signs were erythema (81%), erosion (30%), scaling (30%), oedema (24%) and ulceration (24%). None was statistically different between treatment groups

M/F, male/female; SD, standard deviation.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 81 Gilson *et al.*[119]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Sjokvist Garcia-Stewart and Sam Barton
Study ID	Gilson 1999
Study details	*AIDS* 1999;**13**:2397–404
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out in the UK (eight sites) and USA (five sites)
Trial sponsor	3M Healthcare Ltd, UK, and 3M Pharmaceuticals, USA
Conflicts of interest	None reported
Patient enrolment	Information on recruitment of patients and dates of enrolment not available
Trial design	RCT
Trial duration	Treatment duration of 16 weeks. People experiencing > 80% but < 100% clearance of baseline AGWs continued on blinded treatment for an additional 8 weeks
Line of therapy	Mixed; proportion of people receiving previous treatment unclear
Inclusion criteria	Aged ≥ 18 years; clinical diagnosis of external AGWs; laboratory-confirmed diagnosis of HIV infection (patients with AIDS were eligible if they had been clinically stable for 4 weeks before enrolment); minimum of two AGWs with an area totalling at least 10 mm^2; CD4 T-lymphocyte count of ≥ 100×10^6 cells/l; haemoglobin ≥ 10 g/dl; granulocytes ≥ 1.5×10^9 cells/l; platelet count ≥ 75×10^9 cells/l; total bilirubin ≤ 26 µmol/l; aspartate aminotransferase and alanine transaminase less than three times the upper limit of normal; creatinine ≤ 130 µmol/l; minimum Karnofsky score of 70

TABLE 81 Gilson *et al.*[119] (*continued*)

Item	Details	
Exclusion criteria	Previous treatment with imiquimod; sexual or household partner currently being treated with imiquimod; pregnancy; lactating or < 3 months post partum or post abortion; presence of class 2 or greater vaginal, vulvar or cervical intraepithelial neoplasia; presence of psoriasis or other dermatological disease at the AGW site; experience of more than six outbreaks per year of herpes genitalis; receipt of interferon (IFN), IFN inducers, cytotoxic or investigational drugs, immunomodulators or topical acyclovir; receipt of chemical or surgical AGW therapy in the 4 weeks preceding study initiation	
All outcomes reported in paper	Safety [primary objective was to evaluate safety of imiquimod (local skin reactions, other AEs, vital signs, laboratory tests (including CD4 T lymphocyte counts) and serum pregnancy tests]; complete clearance; reduction in AGW area; appearance of new AGWs during treatment	
Subgroups evaluated	None reported	
Stratification	Gender	
Baseline measurement of disease	Not reported	
Treatment	*Imiquimod 5% cream (patient applied)*	*Placebo (vehicle) cream (patient applied)*
Randomised, *n*	65	35
Withdrawals, *n* (%)	27 (42)	20 (57)
Local skin reaction	1 (2)[a]	1 (3)
Lack of therapeutic effect	5 (8)	8 (23)
Intercurrent disease	4 (6)	0 (0)
Personal	6 (9)	2 (6)
Non-compliance	2 (3)	0 (0)
Lost to follow-up	5 (8)	7 (20)
Other	4 (6)	2 (6)
Treatment regimen	Imiquimod 5% cream or placebo cream was self-applied for 8 ± 2 hours three times per week (prior to normal sleeping hours) every other day, followed by two consecutive days without treatment. The treatment cycle was repeated until complete AGW clearance was achieved or for a maximum of 16 weeks, whichever occurred earlier. New AGWs that appeared during treatment were eligible for treatment but were analysed separately. Extended blinded treatment for 8 weeks was allowed for those people experiencing > 80% but < 100% clearance of their baseline AGWs. Lamivudine, saquinavir, ritonavir and indinavir were approved during the conduct of the study and were permitted as pre-study or concomitant medication	
Duration/number of administered treatment	Median amount of imiquimod 5% cream applied during treatment period (16 weeks): 2476 mg (containing 123.8 mg of imiquimod)	Median amount of vehicle cream applied during treatment period (16 weeks): 2450 mg

continued

TABLE 81 Gilson *et al.*[119] (*continued*)

Item	Details		
Baseline patient characteristics	*Imiquimod 5% cream (patient applied)*	*Placebo (vehicle) cream (patient applied)*	p-*value*
Age (years), mean (SD) (range)	35 (6.9) (20–52)	33 (8.3) (21–58)	$p = 0.023$ (not considered to be a clinically meaningful difference)
Duration of disease since onset (months), median (range)	12.0 (0.3–173.9)	12.3 (0.5–195.8)	$p = 0.715$
Site of AGWs, *n* (%)	Not reported		
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, median (range)	5 (1–28)	5 (1–14)	$p = 0.558$
Area of AGWs (mm^2), median (range)	48.0 (11–3612)	60.5 (10–2304)	$p = 0.299$
Sex, *n* (%)	Men: 62 (95); women: 3 (5%)	Men: 35 (100)	$p = 0.550$
Any previous treatment, *n* (%)			
Podophyllin	40 (62)	16 (46)	Difference between groups reported to be non-significant
Cryotherapy	35 (54)	19 (54)	
Electrocautery	18 (28)	5 (14)	
Ethnicity, *n* (%)			
White	59 (91)	31 (89)	$p = 0.737$
Black	3 (5)	3 (9)	
Asian	3 (5)	1 (3)	
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Not defined. Total clearance was reported, based on a maximum of 16 weeks' treatment		
Volume of wart clearance (proportion of patients with > 50% clearance in wart area)	Proportion of people experiencing a > 50% reduction in total AGW area		
Appearance of new warts during treatment	Appearance of AGWs during the treatment period that were not present at the initiation visit		
AEs	Safety was evaluated through the incidence and severity of local skin reactions: erythema, erosion and ulceration at the AGW site and at remote sites (non-treated areas near the AGW site where study cream may have come into contact with the skin). AEs were graded as mild, moderate or severe (definitions of mild, moderate and severe not available)		

TABLE 81 Gilson *et al.*[119] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Imiquimod 5% cream (patient applied)*, n/N	*Placebo (vehicle) cream (patient applied)*, n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	16 weeks				
	ITT	7/65	2/35		$p = 0.488$
	PP	7/53	2/25		$p = 0.710$
Volume of wart clearance (> 50% reduction in total wart area)	16 weeks				
	ITT	25/65	5/35		$p = 0.013$
	PP	25/53	5/25		$p = 0.026$
Appearance of new warts during treatment	16 weeks	12/62	7/30		$p = 0.784$
AEs					
Mild skin reaction at AGW site	16 weeks				
Erythema		16/62	8/30	Differences between groups reported to be non-significant	
Erosion		6/62	3/30		
Ulceration		4/62	1/30		
Any[b]		16/62	11/30		
Moderate skin reaction at AGW site	16 weeks				
Erythema		9/62	0/30	Differences between groups reported to be non-significant	
Erosion		3/62	0/30		
Ulceration		0/62	0/30		
Any[b]		10/62	0/30		
Severe skin reaction at AGW site	16 weeks				
Erythema		1/62	0/30	Differences between groups reported to be non-significant	
Erosion		1/62	0/30		
Ulceration		1/62	0/30		
Any[b]		2/62	0/30		
Application site reaction[c]	16 weeks	10/65	7/35	Difference between groups reported to be non-significant	
Diarrhoea[c]	16 weeks	12/65	2/35		
Herpes simplex[c]	16 weeks	8/65	3/35		
Number of people reporting at least one event	16 weeks	45/65	23/35		
Number of people reporting at least one moderate or severe event	16 weeks	34/65	23/35		

continued

TABLE 81 Gilson *et al.*[119] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[d]	*Comments*
	Random sequence generation	?	It is stated that eligible people were randomised to treatment group. Additional details on random number sequence generation not available
	Allocation concealment	?	Information on method of allocation concealment not available
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	The study is described as double blind but information on who was masked or how masking was achieved is not available
	Blinding of outcomes assessment	?	Although an independent safety review board, not otherwise involved in the study, reviewed AE data, it is unclear whether the clinician assessing clearance was masked to treatment
	Incomplete outcome data	?	Number of withdrawals and reasons for withdrawals reported. There is an imbalance between the groups in the number of withdrawals, with a larger proportion of people not available for evaluation in the placebo group. A larger proportion of people withdrew from the placebo group as a result of lack of therapeutic effect and a larger proportion of this group was also lost to follow-up. The greater loss to follow-up observed for the placebo group may also be attributed to the lack of therapeutic effect, but this cannot be stated with certainty. This difference is likely to influence the effect estimate

TABLE 81 Gilson *et al.*[119] (*continued*)

Item	Details		
Volume of wart clearance	Blinding (participants and personnel)	?	The study is described as double blind but information on who was masked or how masking was achieved is not available
	Blinding of outcomes assessment	?	Although an independent safety review board, not otherwise involved in the study, reviewed AE data, it is unclear whether the clinician assessing clearance was masked to treatment
	Incomplete outcome data	✗	Number of withdrawals and reasons for withdrawals reported. There is an imbalance between the groups in the number of withdrawals, with a larger proportion of people not available for evaluation in the placebo group. A larger proportion of people withdrew from the placebo group as a result of lack of therapeutic effect and a larger proportion of this group was also lost to follow-up. The greater loss to follow-up observed for the placebo group may also be attributed to the lack of therapeutic effect, but this cannot be stated with certainty. The impact of the imbalance on the effect estimate is unclear
Appearance of new warts during treatment	Blinding (participants and personnel)	?	The study is described as double blind but information on who was masked or how masking was achieved is not available
	Blinding of outcomes assessment	?	Although an independent safety review board, not otherwise involved in the study, reviewed AE data, it is unclear whether the clinician assessing AGW appearance was masked to treatment
	Incomplete outcome data	✗	Number of withdrawals and reasons for withdrawals reported. There is an imbalance between the groups in the number of withdrawals, with a larger proportion of people not available for evaluation in the placebo group. A larger proportion of people withdrew from the placebo group as a result of lack of therapeutic effect and a larger proportion of this group was also lost to follow-up. The greater loss to follow-up observed for the placebo group may also be attributed to the lack of therapeutic effect, but this cannot be stated with certainty

continued

TABLE 81 Gilson *et al.*[119] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	?	The study is described as double blind but information on who was masked or how masking was achieved is not available
	Blinding of outcomes assessment	✓	It is stated that an independent safety review board, not otherwise involved in the study, reviewed individual patient data in a blinded manner to assess the relationship of AEs to study drug, underlying HIV disease or associated treatment
	Incomplete outcome data	✗	Number of withdrawals and reasons for withdrawals reported. There is an imbalance between the groups in the number of withdrawals, with a larger proportion of people not available for evaluation in the placebo group. A larger proportion of people withdrew from the placebo group as a result of lack of therapeutic effect and a larger proportion of this group was also lost to follow-up. The greater loss to follow-up observed for the placebo group may also be attributed to the lack of therapeutic effect, but this cannot be stated with certainty
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	Study was not powered to show statistically significant differences between treatment groups in defined safety and efficacy outcomes		

SD, standard deviation.
a Discontinued during extended treatment period.
b Includes any one of erythema, oedema, induration, vesicles, erosion, ulceration, excoriation/flaking or scabbing.
c Occurrence expressed as a percentage in full publication. Absolute event rate calculated by review authors.
d ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 82 Gilson *et al.*[159]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Shannon Amoils and Sam Barton	
Study ID	Gilson 2009	
Study details	*Sex Trans Infect* 2009;**85**:514–19	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	United Kingdom, five sexual health clinics: Camden Primary Care Trust, London; Whittall Street Clinic, Birmingham; Royal Victoria Hospital, Belfast; Royal South Hants Hospital, Southampton; and Addenbrooke's Hospital, Cambridge	
Trial sponsor	Investigator-led study funded by Stiefel International R&D	
Conflicts of interest	None declared	
Patient enrolment	Information on methods used to identify and recruit patients not available. Patients enrolled 2005–6	
Trial design	RCT	
Trial duration	Initial 12-week treatment period. After 12 weeks, treatment was given at the discretion of the clinician. Participants were followed up until 24 weeks after commencement of treatment	
Line of therapy	Mixed population; 70% of people enrolled were experiencing their first episode of AGW	
Inclusion criteria	Aged 18–70 years; at least two (maximum 30) external AGWs with a combined area of at least 10 mm^2; AGWs could be appropriately treated with cryotherapy with or without podophyllotoxin cream, based on opinion of the investigator; previously untreated AGW or AGWs that had not been treated for at least 4 months	
Exclusion criteria	AGW treated in the past 4 months before enrolment; known to be HIV positive (HIV testing not required); concurrent internal AGWs; individual AGWs with an area > 4 cm^2	
All outcomes reported in paper	Primary end points: clearance of all AGWs at 4 and 12 weeks. Secondary endpoints: complete clearance at 24 weeks; recurrence at 12 weeks in those cleared at 4 weeks; recurrence at 24 weeks in those cleared at 12 weeks	
Subgroups evaluated	It is noted that the subgroup analyses (gender, history of AGWs and type of AGW) are only exploratory and interaction effects would not be investigated	
Stratification	Randomisation stratified by gender and history of AGWs (blocks of four)	
Baseline measurement of disease	Baseline evaluation included documentation of number, size (area judged against a calibration template), location and type (hyperkeratotic, non-keratotic, mixed) of AGWs	
Treatment	*Cryotherapy plus podophyllotoxin 0.15% cream*	*Cryotherapy plus placebo*
Randomised, *n*	74	75
	All results and baseline characteristics are based on 140 people (70 people per group). Data were reported for people who received at least one treatment with cryotherapy and who attended at least one follow-up assessment	
Total withdrawals, *n* (%)[a]	19 (27)	24 (34)
Perceived condition cured	3 (4)	2 (3)
Personal reasons	0	2 (3)
Lost to follow-up	14 (20)	16 (23)
Withdrew consent	1 (1.4)	2 (3)
Other	1 (1.4)	2 (3)

continued

TABLE 82 Gilson *et al.*[159] (*continued*)

Item	Details		
Treatment regimen	Cryotherapy was applied using a liquid nitrogen spray (Cry-Ac; Brymill Cryogenic Systems, Basingsstoke, UK) to obtain a minimum of a 45-s freeze (from start of application), which was repeated after a thaw in a standardised manner. Cryotherapy was repeated weekly for up to 12 weeks. Starting the day after cryotherapy, podophyllotoxin 0.15% cream was applied twice daily for 3 consecutive days and repeated weekly for up to 4 weeks or until all AGWs had cleared, whichever occurred first. If further treatment after week 4 was required, only cryotherapy was used and this was repeated weekly between week 4 and week 12. From weeks 12–24, treatment was at the discretion of the clinician (who remained blinded to the earlier treatment allocation)	Cryotherapy was applied using a liquid nitrogen spray (Cry-Ac; Brymill Cryogenic Systems, Basingsstoke, UK) to obtain a minimum of a 45-s freeze (from start of application), which was repeated after a thaw in a standardised manner. Cryotherapy was repeated weekly for up to 12 weeks. Starting the day after cryotherapy, placebo cream was applied twice daily for 3 consecutive days and repeated weekly for up to 4 weeks or until all AGW had cleared, whichever occurred first. If further treatment was required after week 4, only cryotherapy was used and this was repeated weekly between week 4 and week 12 if required. From weeks 12–24, treatment was at the discretion of the clinician (who remained blinded to the earlier treatment allocation)	
Duration/number of administered treatment	Not reported. Use of podophyllotoxin cream declined over the masked phase of the treatment protocol (first 4 weeks) to 31.1%	Not reported. Use of the placebo cream declined over the masked phase of the treatment protocol (first 4 weeks) to 54.8%	
Baseline patient characteristics	*Cryotherapy plus podophyllotoxin 0.15% cream*	*Cryotherapy plus placebo*	p-*value*
Note: Baseline characteristics are based on 70 people in each group (those who were randomised, received at least one cryotherapy treatment and attended at least one follow-up assessment)			
Age (years), median (range)	26 (18–58)	24.5 (18–43)	Not reported
Duration of disease	Not reported		
Site of AGWs, *n* (%)			
Anal only	7 (10.0)	4 (5.7)	Not reported
Non-anal only	52 (74.3)	55 (78.6)	Not reported
Both anal and non-anal	11 (15.7)	11 (15.7)	Not reported
Type of AGWs, *n* (%)			
Keratotic	25 (35.7)	12 (17.1)	Not reported[b]
Non-keratotic	29 (41.4)	38 (54.3)	Not reported
Mixed	16 (22.9)	20 (28.6)	Not reported
Number of AGWs, median (range)	7 (2–30)	6.5 (2–34)	Not reported
Total area of AGWs (mm^2), median (range)	49.5 (10–400)	38.0 (12–464)	Not reported[b]

TABLE 82 Gilson *et al.*[159] (*continued*)

Item	Details		
Sex: male, *n* (%)	47 (67.1)	44 (62.9)	Not reported
Any previous treatment, *n* (%)			
First episode	49 (70.0)	52 (74.3)	Not reported
Previous history	21 (30.0)	18 (25.7)	Not reported
Ethnicity, *n* (%)			
White	61 (87.1)	63 (90.0)	Not reported
Black	5 (7.1)	6 (8.6)	Not reported
Other	4 (5.7)	1 (1.4)	Not reported
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Complete clearance of AGWs at weeks 4 (end of podophyllotoxin treatment) and 12 (end of cryotherapy), including AGWs that had been present at baseline and any AGWs that may have appeared, or recurred, during follow-up. Analysis based on last observation carried forward. Also, if patients did not attend but were contactable, self-assessed clearance was recorded. Self-assessment was documented on a proforma returned by the patient to the clinic or by the investigator after a telephone interview		
AGW clearance at other time points	Complete clearance of AGWs at 24 weeks		
Recurrence of AGWs	Recurrence or new AGWs at 12 weeks in those with complete clearance at 4 weeks and recurrence or new AGWs at 24 weeks in those with complete clearance at 12 weeks		
Volume of wart clearance	It is stated that more patients receiving cryotherapy in combination with podophyllotoxin had at least a 50% reduction in AGW area by weeks 4 and 12, but the difference was not statistically significant (no other details reported)		
AEs	Not defined		
Section 4: Data extraction form			

Outcome	*Time frame*	*Cryotherapy plus podophyllotoxin 0.15% cream,* n/N	*Cryotherapy plus placebo,* n/N	*Estimate of effect*	*CI and* p*-value*
Dichotomous outcomes					
AGW clearance at completion of treatment	4 weeks	42/70	32/70	RR 1.31	0.95 to 1.81
				Unadjusted OR 1.78	0.91 to 3.48
				Adjusted OR 1.99[c]	0.91 to 4.36
	12 weeks	42/70	32/70	RR 1.31	0.95 to 1.81
				Unadjusted OR 1.78	0.91 to 3.48
				Adjusted OR 1.94[c]	0.95 to 3.97
AGW clearance at other time points	24 weeks	48/70	45/70	RR 1.07	0.84 to 1.35
				Unadjusted OR 1.21	0.60 to 2.45
				Adjusted OR 1.18[c]	0.56 to 2.49
Recurrence of AGWs	12 weeks	12/42	11/32		$p = 0.67$
Recurrence of AGWs	12–24 weeks	7/42	6/32		Not reported

continued

TABLE 82 Gilson *et al.*[159] (*continued*)

Item	Details			
AEs				
Any AE	Unclear	51/70	49/70	$p = 0.85$
Application site events (all)	Unclear	45/70	31/70	$p = 0.027$
Type of application site event: pain	Unclear	24/70	13/70	$p = 0.055$

Section 5: Clinical trial quality

Outcome	*Risk of bias*	*Risk assessment*[d]	*Comments*
	Random sequence generation	?	It is stated that people were 'randomly assigned in equal numbers to each group' (p. 515). Additional details on random number sequence generation not available
	Allocation concealment	✓	It is stated that 'treatment packs were supplied prelabelled by the clinical trials unit at the manufacturer (Stiefel). Study numbers and corresponding treatment packs were then allocated in sequence by site investigators, against a local register. Blocks were reallocated between centres if required by the rate of recruitment' (p. 515)
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	Information on level of masking is not available. For all outcomes, the authors relied on self-report for those people not attending follow-up clinics, which, if masking had not been maintained, could introduce bias in favour of the combination therapy
	Blinding of outcomes assessment	?	The outcome assessors were masked to treatment groups. However, for patients who could not attend follow-up clinics, self-report from patients was used to determine AGW clearance. As the authors note, self-report is unreliable and may overestimate AGW clearance. At week 4, more people in the combination group self-reported than in the cryotherapy alone group [9 (13%) vs. 4 (6%)]. Self-report was also more frequent in the combination group than in the cryotherapy alone group at 12 weeks (14% vs. 10%). The results of self-report might also be influenced by the person's assessment of whether they have received active treatment. It was unclear how closely the placebo matches the active treatment in physical appearance. Self-report may be more favourable to the combination group

TABLE 82 Gilson *et al.*[159] (*continued*)

Item	Details		
	Incomplete outcome data	?	The number of people withdrawing from each group is reported, together with reasons for withdrawal. However, the numbers include people with more than one reason for withdrawal and it is unclear how many people had multiple reasons for withdrawal. In addition, reported analyses are not based on all those randomised. Imputed data are based on last observation carried forward
Recurrence of AGWs	Blinding (participants and personnel)	?	Information on level of masking is not available. For all outcomes, the authors rely on self-report for those people not attending follow-up clinics, which, if masking had not been maintained, could introduce bias in favour of the combination therapy
	Blinding of outcomes assessment	?	The outcomes assessors were masked to treatment groups. However, for patients who could not attend follow-up clinics, self-report from patients was used. As the authors note, self-report is unreliable and may overestimate AGW clearance. At week 4, more people in the combination group self-reported than in the cryotherapy alone group [9 (13%) vs. 4 (6%)]. Self-report was also more frequent in the combination group than in the cryotherapy alone group at 12 weeks (14% vs. 10%). The results of self-report might also be influenced by the person's assessment of whether they have received active treatment. It was unclear how closely the placebo matches the active treatment in physical appearance. Self-report may be more favourable to the combination group
	Incomplete outcome data	✓	Analysis of recurrence is based on all those with complete clearance
AEs	Blinding (participants and personnel)	?	Information on level of masking is not available. For all outcomes, the authors rely on self-report for those people not attending follow-up clinics, which, if masking had not been maintained, could introduce bias in favour of the combination therapy

continued

TABLE 82 Gilson *et al.*[159] (*continued*)

Item	Details		
	Blinding of outcomes assessment	?	The outcome assessors were masked to treatment groups. However, for patients who could not attend follow-up clinics, self-report from patients was used. As the authors note, self-report is unreliable and may overestimate AGW clearance. At week 4, more people in the combination group self-reported than in the cryotherapy alone group [9 (13%) vs. 4 (6%)]. Self-report was also more frequent in the combination group than in the cryotherapy alone group at 12 weeks (14% vs. 10%). The results of self-report might also be influenced by the person's assessment of whether they have received active treatment. It was unclear how closely the placebo matches the active treatment in physical appearance. Self-report may be more favourable to the combination group
	Incomplete outcome data	?	Number of people withdrawing from each group is reported, together with reasons for withdrawal. However, the numbers include people with more than one reason for withdrawal and it is unclear how many people had multiple reasons for withdrawal. In addition, reported analyses are not based on all those randomised. Imputed data are based on last observation carried forward
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	If patients did not attend for follow-up assessments they were contacted by letter and telephone and encouraged to reattend. If this failed, self-assessed clearance was recorded, together with information on any treatment received outside of the trial. Self-assessment was documented on a proforma returned by the patient to the clinic or by the investigator after a telephone interview Sample size calculation – the sample size for the study was based on an estimate of a 45% response rate in the cryotherapy alone arm and a 70% response in the podophyllotoxin combination arm. Sixty-eight patients in each group would have provided 80% power to detect such a difference, or 85 patients after allowing for a 20% loss to follow-up (170 patients in total) Analysis – in the event of an observation being missing (because of non-attendance), the analysis was based on the last observation carried forward process to impute the status at relevant time points In a multivariate analysis of factors associated with clearance of AGWs, there were associations with history of AGWs and gender		

SD, standard deviation.
a People might have had more than one reason for withdrawal from the study.
b Authors noted that the group receiving podophyllotoxin plus cryotherapy had a higher proportion of keratotic AGWs and a larger median area of AGWs than the group given cryotherapy alone. *p*-values not recorded and not noted whether the differences between the two groups were significant.
c OR adjusted for baseline number and area of AGWs, history and treatment centre.
d ✓, low risk of bias; ?, unclear risk of bias.

TABLE 83 Godley *et al.*[154]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Shannon Amoils and Sam Barton	
Study ID	Godley 1987	
Study details	*Genitourin Med* 1987;**63**:390–2	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Single site: St Thomas' Hospital, London, UK	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Heterosexual men with penile AGWs attending the Department of Genitourinary Medicine at St Thomas' Hospital from May 1983 to July 1985 were invited to join the study	
Trial design	RCT	
Trial duration	Weekly treatment until disappearance of AGWs for up to a maximum of 10 treatments. If complete AGW clearance was achieved, men were followed up for 2 months after the end of treatment	
Line of therapy	Of 106 men who completed the study, the authors noted that the study interventions were first-line therapy for 61 men (data for individual groups not reported separately) and recurrent therapy for 45 men (data for individual groups not reported separately). Data on previous lines of treatment not available for 24 men who failed to complete the trial	
Inclusion criteria	Heterosexual men with penile AGWs	
Exclusion criteria	Men were excluded if they had received treatment for AGWs in the previous 8 weeks; had AGWs at sites other than the penile shaft, prepuce or glans; had intrameatal AGWs	
All outcomes reported in paper	Complete regression of AGWs; number of treatments until complete regression of AGWs; recurrence within 2 months of treatment; AEs	
Subgroups evaluated	First episode of AGWs; unclear whether this analysis was prespecified	
Stratification	Not reported	
Baseline measurement of disease	Presence and site of AGWs were examined at baseline	
Treatment	*TCAA*	*Cryotherapy*
Randomised, *n*	69	61
Withdrawals, *n* (%)		
Withdrawn from the trial after randomisation because of 'failure to attend regularly'	12 (17.4)	11 (18.0)
AEs, *n* (%)	0 (0)	1 (1.6)
Treatment regimen	TCAA was applied to the AGW with an orange stick followed by starch talc application to protect adjacent skin	Liquid nitrogen was applied to the AGW using a fine nozzle spray gun (Cryak Unit, Alcon Laboratories, Camberley, UK). Each AGW was frozen for 15 seconds, allowed to thaw out and refrozen for 15 seconds, if tolerated. No local anaesthetic or lubricant was used
Duration/number of administered treatment	Mean (SD) number of treatments to complete resolution of AGWs: 4.0 (2.3)	Mean (SD) number of treatments to complete resolution of AGWs: 3.0 (2.2)

continued

TABLE 83 Godley *et al.*[154] (*continued*)

Item	Details		
Baseline patient characteristics	*TCAA*	*Cryotherapy*	p-*value*
Note: Baseline characteristics were recorded for only the 106 (57 in the TCAA group and 49 in the cryotherapy group) men of the 130 randomised who completed the study			
Age (years), median (range)	24 (18–64)	24 (19–44)	Difference reported to be non-significant
Duration of disease (weeks), median (range)	6 (1–300)	5 (1–125)	Difference reported to be non-significant
Site of AGWs, *n* (%)			
Prepuce	35 (61)	26 (53)	Differences reported to be non-significant
Glans	1 (2)	0 (0)	
Shaft	14 (25)	9 (18)	
Prepuce and glans	3 (5)	10 (20)	
Prepuce and shaft	4 (7)	3 (6)	
Shaft and glans	0 (0)	1 (2)	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, median (range)	6 (1–32)	6 (1–60)	Difference reported to be non-significant
Area of AGWs (mm^2), mean	Not reported		
Sex (M/F), *n* (%)	All men		
Any previous treatment, *n* (%)	23 (40%) had previous history of AGWs, but previous treatment received not reported	22 (45%) had previous history of AGWs, but previous treatment received not reported	Difference reported to be non-significant
Ethnicity, *n* (%)			
White	51 (89)	40 (82)	Differences reported to be non-significant
Black	5 (9)	8 (16)	
Asian	1 (2)	1 (2)	
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Defined as complete resolution of warts at end of treatment (up to 10 treatments)		
Recurrence of AGWs	For those with complete clearance during treatment, presence of AGWs at 2 months after the end of treatment		
AEs	AEs reported were local discomfort, ulceration and scab formation		

TABLE 83 Godley *et al.*[154] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*TCAA, n/N*	*Cryotherapy, n/N*	*Estimate of effect*	*p-value*
Dichotomous outcomes					
AGW clearance at completion of treatment	Up to 10 weeks	46/57	43/49		Difference reported to be non-significant
Recurrence of AGWs	2 months after the end of treatment	14/39	15/38		Not reported
AEs					
Mild		3/57	9/49		Not reported
Moderate (ulceration/ scabbing)		26/57	10/49		Not reported
Severe (withdrawn from trial)		0/57	1/49		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	It is stated that people were 'randomly allocated to treatment with either TCAA or cryotherapy' (p. 390). Additional details on method of randomisation not available	
	Allocation concealment		?	Detail on method used to conceal allocation not available	
	Selective reporting		?	Insufficient information provided to determine risk of selective reporting	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is stated that 'the patients were reviewed at weekly intervals by an independent observer who had no knowledge of the treatment given' (p. 390). It is unclear whether masking could have been broken (e.g. participants might have inadvertently revealed treatment allocated)	
	Blinding of outcomes assessment		?		
	Incomplete outcome data		?	The number of people not included in the analysis is reported and a similar proportion of people was withdrawn from each group. Reason for withdrawal given as failure to attend regularly. Unclear how many people were lost to follow-up rather than withdrew from treatment and whether there is an imbalance between the groups with regard to irregular attendance	

continued

TABLE 83 Godley *et al.*[154] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is stated that 'the patients were reviewed at weekly intervals by an independent observer who had no knowledge of the treatment given' (p. 390). It is unclear whether masking could have been broken (e.g. participants might have inadvertently revealed treatment allocated)
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✓	All people with complete clearance were evaluated for recurrence
AEs	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is stated that 'the patients were reviewed at weekly intervals by an independent observer who had no knowledge of the treatment given' (p. 390). It is unclear whether masking could have been broken (e.g. participants might have inadvertently revealed treatment allocated)
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The number of people not included in the analysis is reported and a similar proportion of people was withdrawn from each group. Reason for withdrawal given as failure to attend regularly. Unclear how many people were lost to follow-up rather than withdrew from treatment and whether there is an imbalance between the groups with regard to irregular attendance
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	Baseline characteristics for men with a first episode of AGWs are reported separately		

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 84 Goh *et al.*[66]

Item	Details		
Section 1: Reviewer and study information			
Reviewers' names	Jacoby Patterson and Sam Barton		
Study ID	Goh 1998		
Study details	*Singapore Med J* 1998;**39**:17–19		
Language of publication	English		
Type of report	Full publication		
Section 2: Study information			
Location and number of sites	One site (clinic situated within the Department of STD Control) in Singapore		
Trial sponsor	Not reported		
Conflicts of interest	Not reported		
Patient enrolment	All consecutive male patients presenting with penile AGWs to the Department of STD Control clinic were eligible for entry into the trial; dates of enrolment not reported		
Trial design	RCT (three arm)		
Trial duration	Treatment groups were reviewed weekly for up to 6 weeks		
Line of therapy	15% of men had a past history of penile AGWs		
Inclusion criteria	Male gender; age > 16 years; presence of penile AGWs		
Exclusion criteria	More than five penile AGWs; receipt of treatment in the 2 weeks before trial entry; keratinised penile AGWs; HIV-positive status or immunocompromised		
All outcomes reported in paper	Complete clearance; AEs		
Subgroups evaluated	None		
Stratification	None		
Baseline measurement of disease	On the first visit, demographic data were collected and the number and size of AGWs were carefully described and recorded		
Treatment	*Podophyllin 25% solution (in tincture benzoin) (clinician applied)*	*Podophyllin 0.5% in ethanol (patient applied)*	*Podophyllin 0.25% in ethanol (patient applied)*
Randomised, *n*	It is stated that 45 men were recruited into the study. The number of men randomised into each treatment group was not reported. Of the 35 men for whom data were available, it is stated that 11 men were treated with podophyllin 0.5%, six with podophyllin 0.25% and 18 with podophyllin 25%		
Withdrawals	Overall, 10/45 (22%) men were lost to follow-up. Withdrawals and loss to follow-up were not reported separately by treatment group		
Treatment regimen	Podophyllin 25% solution in tincture benzoin was applied by a doctor or nurse at the STD clinic twice weekly. The solution was washed off 4 hours after application	Podophyllin 0.5% or 0.25% in ethanol was applied by the patient at home twice a day for 3 consecutive days. If AGWs persisted, patients were instructed to repeat the application 1 week later	
Duration/number of administered treatment	Not reported		

continued

TABLE 84 Goh *et al.*[66] (*continued*)

Item	Details			
Baseline patient characteristics	*Podophyllin 25% solution (in tincture benzoin) (clinician applied)*	*Podophyllin 0.5% in ethanol (patient applied)*	*Podophyllin 0.25% in ethanol (patient applied)*	p-*value*
Age (years), mean (with SD/SE if given)	The age range of men in the study was 20–71 years. It is stated that most men were aged from 20 to 39 years (93.3% in the podophyllin 25% group and 100% in the podophyllin 0.5% and 0.25% groups). Age range not reported separately for the individual treatment groups. Mean or median age not reported			It is stated that 'there were no significant differences between treatment groups in terms of age or racial composition' (p. 18)
Duration of disease	It is reported that 68% of men had AGWs of < 1 months' duration. The duration of disease was not reported separately for the individual treatment groups			Not reported
Site of AGWs, *n* (%)	Sites of AGWs in the groups receiving podophyllin 0.5% and 0.25% in ethanol were reported to be the corona (43.5%) and the glans (26.1%). The remainder were located on the frenulum, prepuce, meatus and shaft (decreasing order of frequency; proportions not given). Men in the group receiving podophyllin 25% in tincture benzoin had a similar distribution, with the exception that AGWs were found more commonly on the prepuce than the frenulum. The site of AGWs was not reported separately for the individual treatment groups			Not reported
Type of AGWs, *n* (%)	100% non-keratinised (keratinised AGWs excluded)			
Number of AGWs, mean (with SD/SE if given)	Not reported			
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% male			
Any previous treatment, *n* (%)	15% of men had a past history of penile AGWs; previous history not reported separately for the individual treatment groups. Type of previous treatment not reported			Not reported
Ethnicity, *n* (%)	The racial distribution of the trial was Chinese 29/35 (82.9%); Indian 5/35 (14.3%); and other 1/35 (2.9%). Breakdown by treatment group not reported			It is stated that 'there were no significant differences between treatment groups in terms of age or racial composition' (p. 18)
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Clearance at 6 weeks; no further details on 'clearance' provided			
AGW clearance at other time points	Clearance at 1 week; no further details on 'clearance' provided			
AEs	Skin irritation			

TABLE 84 Goh *et al.*[66] (*continued*)

Item	Details					
Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllin 25% solution (in tincture benzoin) (clinician applied)*, n/N	*Podophyllin 0.5% in ethanol (patient applied)*, n/N	*Podophyllin 0.25% in ethanol (patient applied)*, n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	6 weeks	15/17	9/11	6/6		Reported to be not significant
AGW clearance at other time points	1 week	6/18	4/11	4/6		Reported to be not significant
AEs: skin irritation	6 weeks	7/18	8/11	0/6		Reported to be not significant
Section 5: Clinical trial quality						
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*		
	Random sequence generation		?	It is stated that men were randomly assigned. Details on method of randomisation not available		
	Allocation concealment		?	Details not provided		
	Selective reporting		?	Insufficient information provided to determine risk of selective reporting		
	'Other bias'		?	Baseline characteristics not reported separately for treatment groups; thus, it is unclear whether the groups are comparable at baseline		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		?	Details on whether the authors made attempts to mask patients and personnel not provided. Given the two different settings in which treatments were administered (clinic vs. home), it might be impractical to mask patients and key personnel to treatment. In addition, it is unclear whether the clinician assessing clearance was masked to treatment allocation. If the assessor was not masked to treatment, assessment of complete clearance could be considered to be a subjective assessment and at risk of bias		
	Blinding of outcomes assessment		?			
	Incomplete outcome data		?	Overall, 10/45 (22%) men were lost to follow-up. It is unclear how many men were randomised to each group. Withdrawals and loss to follow-up were not reported separately by treatment group and so it is unclear whether there is an imbalance among groups in the proportion of men lost to follow-up or who withdrew		

continued

TABLE 84 Goh *et al.*[66] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	?	It might not be feasible to mask treatment between patient-applied and physician-applied treatment. Details on whether the authors attempted to mask patients and personnel are not provided. Also, it is unclear whether the clinician assessing clearance was masked to treatment allocation. If the assessor was not masked to treatment, assessment of AEs could be considered to be a subjective assessment and at risk of bias
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Overall, 10/45 (22%) men were lost to follow-up. It is unclear how many men were randomised to each group. Withdrawals and loss to follow-up were not reported separately by treatment group and so it is unclear whether there is an imbalance among groups in the proportion of men lost to follow-up or who withdrew
Overall rating of bias		?	Reflects limited details reported in full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ?, unclear risk of bias.

TABLE 85 Greenberg *et al.*[62]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Orla Ní Ógáin and Sam Barton	
Study ID	Greenberg 1991	
Study details	*Obstet Gynecol* 1991;**77**:735–9	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Single-centre study; location not specified, but all authors based in USA	
Trial sponsor	It is stated that the trial was supported by Oclassen Pharmaceuticals, San Rafael, CA, USA	
Conflicts of interest	Not reported	
Patient enrolment	Details on patient recruitment and dates of enrolment not available	
Trial design	RCT	
Trial duration	Treatment given for a maximum of 4 weeks, with patients followed up until week 10 after the start of treatment	
Line of therapy	Not reported	
Inclusion criteria	Women with a clinical diagnosis of exophytic vulvar condyloma; ≤ 25 lesions to be treated; total area of involvement of < 10 cm^2 and occupying $< 30\%$ of the vulva	
Exclusion criteria	Women were excluded if they had received treatment for AGWs within 1 month of study entry or might have been immunocompromised. The study does not explicitly state that pregnancy was an exclusion criterion but it is stated that 'all women were given a serologic test for pregnancy before starting drug therapy, and all were cautioned to use a reliable method of contraception during the 10-week study period' (p. 736). Concurrent use of topical or systemic medication for condylomata was not permitted during the study	
All outcomes reported in paper	Treatment response (two analyses, with the first analysis evaluating clearance by patient and the second evaluating clearance based on individual AGWs); recurrence; appearance of new AGWs during treatment; AEs (local and systemic complications)	
Subgroups evaluated	None	
Stratification	None	
Baseline measurement of disease	At the baseline visit, clinicians performed a general health history and physical, concentrating on any known previous genital AGW infections. Sites of clinically overt condylomata were mapped out on a diagram and a total AGW count recorded	
Treatment	*Podophyllotoxin 0.5% (solution and cream formulations; patient applied)*	*Placebo (patient applied)*
Randomised, *n*	48; women were allocated to podophyllotoxin 0.5% solution ($n = 24$) and podophyllotoxin 0.5% cream ($n = 24$)	24; women were allocated to placebo solution and placebo cream; the numbers allocated to the different formulations of placebo were not reported
Withdrawals, *n* (%)	Not reported	Three (12.5%) women did not return after their baseline visit. The reasons for withdrawal were not reported, but authors propose that withdrawals are likely to be because of an inadequate response
	Analyses are based on 69 women; they exclude the three women who did not return after their baseline visit	

continued

TABLE 85 Greenberg *et al.*[62] (*continued*)

Item	Details		
Treatment regimen	Patients applied their allocated treatment (either podophyllotoxin 0.5% or placebo) twice daily for 3 days followed by a 4-day rest period. Patients were required to undergo a minimum of two treatment cycles, with up to two more cycles if baseline AGWs were not totally cleared after two treatments. Patients were instructed on the correct method of application, treating only external lesions and avoiding application to adjacent normal skin or areas of skin that were bleeding, inflamed or ulcerated		
Duration/number of administered treatment	Not specified	Not specified	
Baseline patient characteristics	*Podophyllotoxin 0.5% (solution and cream formulations; patient applied)*	*Placebo (patient applied)*	p-*value*
Age (years), mean (range)	Not reported		
Duration of disease	Not reported		
Site of AGWs, *n* (%)	Not reported. It is stated that 'over one-third of the warts in 60% of the patients were located in the perianal area' (p. 737)		
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	9.29	9.62	$p = 0.8485$
Area of AGWs (mm^2), mean	Not reported		
Sex (M/F), *n* (%)	Women 100%		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at other time points	Number/percentage of people completely healed at any time during the study. Investigator clinical assessment was based on a 5-point rating scale: progression of disease; no change; some improvement; marked improvement; and complete cure. Complete clearance was reported separately		
Recurrence of AGWs	No definition reported		
Appearance of new warts during treatment	New AGWs were defined as condylomata developing in sites that were anatomically remote from the baseline AGWs		
AEs	Reported as local and systemic complications. AEs were graded on 4-point scale ranging from none to severe. Local AEs were patient report of pain, burning or itching and clinician assessment of inflammation and erosion. Systemic complications were identified through haematological and biochemical testing (further details on tests not available) and from patient reports		

TABLE 85 Greenberg *et al.*[62] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% (solution and cream formulations; patient applied),* n/N	*Placebo (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at other time points	Unclear; assumed 10 weeks	24/48	5/21		Not reported
	Analysis by individual AGWs	332/446	37/202		$p < 0.05$
Recurrence of AGWs	Unclear; assumed 10 weeks	Recurrence not reported by group. Reported that, of people who responded completely, relapse rate was 33% (8/24)			
Appearance of new warts during treatment	Unclear; assumed 10 weeks	19 people (77 new AGWs)/not reported	8 people (23 new AGWs)/not reported		
AEs					
Inflammation	Unclear; assumed 10 weeks	Podophyllotoxin 0.5% solution: 12/24	Placebo solution: 1/10		Not reported
		Podophyllotoxin 0.5% cream: 10/24	Placebo cream: 0/11		
Erosion	Unclear; assumed 10 weeks	Podophyllotoxin 0.5% solution: 11/24	Placebo solution: 3/10		Not reported
		Podophyllotoxin 0.5% cream: 8/24	Placebo cream: 10/11		
Pain	Unclear; assumed 10 weeks	Podophyllotoxin 0.5% solution: 15/24	Placebo solution: 4/10		Not reported
		Podophyllotoxin 0.5% cream: 13/24	Placebo cream: 10/11		
Burning	Unclear; assumed 10 weeks	Podophyllotoxin 0.5% solution: 19/24	Placebo solution: 7/10		Not reported
		Podophyllotoxin 0.5% cream: 18/24	Placebo cream: 0/11		
Itching	Unclear; assumed 10 weeks	Podophyllotoxin 0.5% solution: 15/24	Placebo solution: 5/10		Not reported
		Podophyllotoxin 0.5% cream: 17/24	Placebo cream: 5/11		

continued

TABLE 85 Greenberg *et al.*[62] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	✓	It is stated that 'patients were sequentially assigned by a random code to either an active (solution or cream) or placebo (solution or cream) preparation in an active-to-placebo ratio of 2 : 1' (p. 736). It is stated that the randomised list was computer generated
	Allocation concealment	?	Details on allocation concealment not available
	Selective reporting	✗	It is stated that complete clearance at various time points was measured, as was recurrence. However, the reported event rates are incompletely reported and cannot be entered in a meta-analysis. In addition, the time frame over which the reported events have been reported is unclear
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at other time points	Blinding (participants and personnel)	?	It is stated that the study is a double-blinded study and a placebo has been implemented. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	Unclear whether the clinician assessing clinical outcomes was masked to treatment allocation
	Incomplete outcome data	?	The number of people not included in the analysis is reported. Reasons for withdrawal not reported. Unclear how many people were lost to follow-up rather than withdrew from treatment and whether there is an imbalance between the groups
Recurrence of AGW	Blinding (participants and personnel)	?	It is stated that study is a double-blinded study and a placebo has been implemented. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	Unclear whether the clinician assessing clinical outcomes was masked to treatment allocation

TABLE 85 Greenberg *et al.*[62] (*continued*)

Item	Details		
	Incomplete outcome data	✗	Data not presented separately by treatment group. The number of people not included in the analysis is reported. Reasons for withdrawal not reported. Unclear how many people were lost to follow-up rather than withdrew from treatment and whether there is an imbalance between the groups
Appearance of new warts during treatment	Blinding (participants and personnel)	?	It is stated that study is a double-blinded study and a placebo has been implemented. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	Unclear whether the clinician assessing clinical outcomes was masked to treatment allocation
	Incomplete outcome data	✗	Data not presented separately by treatment group. The number of people not included in the analysis is reported. Reasons for withdrawal not reported. Unclear how many people were lost to follow-up rather than withdrew from treatment and whether there is an imbalance between the groups
AEs	Blinding (participants and personnel)	?	It is stated that study is a double-blinded study and a placebo has been implemented. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	Unclear whether the clinician assessing clinical outcomes was masked to treatment allocation
	Incomplete outcome data	?	The number of people not included in the analysis is reported. Reasons for withdrawal not reported. Unclear how many people were lost to follow-up rather than withdrew from treatment and whether there is an imbalance between the groups
Overall rating of bias		✗	A key domain has been determined to be at a high risk of bias
Section 6: Additional comments			
Additional comments	AGWs developing on internal mucosal surfaces treated with ablative or destructive methods. By contrast, new lesions developing on cutaneous surfaces could be treated with podophyllotoxin, provided that the person was still enrolled in the active phase of the study. Missing data were imputed based on the last observation carried forward method		

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 86 Handley *et al.*[67]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Orla Ní Ógáin and Sam Barton	
Study ID	Handley 1992	
Study details	*Irish J Med Sci* 1992;**161**:56	
Language of publication	English	
Type of report	Conference abstract	
Section 2: Study information		
Location and number of sites	Not specified; author affiliation listed as Department of Genitourinary Medicine, Royal Victoria Hospital, Belfast, Northern Ireland	
Trial sponsor	Not specified	
Conflicts of interest	Not specified	
Patient enrolment	Not reported	
Trial design	RCT	
Trial duration	Initial treatment period of up to 5 weeks, with follow-up review at 3 months (unclear whether this was final follow-up)	
Line of therapy	Not specified	
Inclusion criteria	Men with primary AGWs: no other details provided in conference abstract	
Exclusion criteria	Not reported	
All outcomes reported in paper	Complete clearance at 5 weeks and 3 months; recurrence at 3 months in men who were AGW free at 5 weeks; systemic AEs	
Subgroups evaluated	Men with perianal AGWs. It is stated that 'multiple warts at diagnosis were associated with an adverse prognosis' (p. 56); further details not reported in abstract	
Stratification	None reported	
Baseline measurement of disease	Not reported	
Treatment	*Podophyllin 0.5% solution (patient applied)*	*Podophyllotoxin 0.5% solution (patient applied)*
Randomised, *n*	Number randomised not reported	
	29 treated	28 treated
Withdrawals, *n* (%)	Not reported. Analysis at 3 months included 21 men, which infers that eight men withdrew or were lost to follow-up	Not reported. Analysis at 3 months included 20 men, which infers that eight men withdrew or were lost to follow-up
Treatment regimen	Men self-applied allocated treatment (podophyllin 0.5% or podophyllotoxin 0.5% solution) twice daily for the same 3 consecutive days per week for 5 weeks	
Duration/number of administered treatment	Not reported	

TABLE 86 Handley *et al.*[67] (*continued*)

Item	Details			
Baseline patient characteristics	*Podophyllin 0.5% solution (patient applied)*	*Podophyllotoxin 0.5% solution (patient applied)*	p-*value*	
Age (years), mean	Not reported			
Duration of disease	Not reported			
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	Not reported			
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% male			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Data reported for number of men 'clinically wart free' at 5 weeks (end of treatment). No further details available			
AGW clearance at other time points	Data reported for number of men 'clinically wart free' at 3 months' follow-up. No further details available			
Recurrence of AGWs	Data reported for 'recurrence in patients wart free'. No further details available			
AEs	Number of events reported for systemic side effects and local irritation (moderate to severe). No further details available			
Section 4: Data extraction form				
Outcome	*Time frame*	*Podophyllin 0.5% solution (patient applied),* n/N	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	5 weeks	5/22[a]	6/23[a]		Difference reported to be not significant
AGW clearance at other time points	3 months	1/21	3/20		Difference reported to be not significant
Recurrence of AGWs	3 months	3/4	0/3		Difference reported to be not significant
AEs					
Systemic side effects		0/29	0/28		Not reported
Local irritation (moderate to severe)		2/29	2/28		Not reported

continued

TABLE 86 Handley *et al.*[67] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*
	Random sequence generation	?	Title of abstract describes the study as randomised. Details on method used to generate random sequence not available
	Allocation concealment	?	Details on method used to conceal allocation not available
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	Title describes study as double blind. Details on masking not available and it is unclear who was masked to treatment
	Blinding of outcomes assessment	?	Title describes study as double blind. Details on masking not available and it is unclear whether the outcomes assessor was masked to treatment
	Incomplete outcome data	?	Number of men randomised to each group not reported. Number of withdrawals and loss to follow-up not reported. It is unclear whether there was an imbalance between the groups in the proportion of men withdrawing or lost to follow-up
Recurrence of AGWs	Blinding (participants and personnel)	?	Title describes study as double blind. Details on masking not available and it is unclear who was masked to treatment
	Blinding of outcomes assessment	?	Title describes study as double blind. Details on masking not available and it is unclear whether the outcomes assessor was masked to treatment
	Incomplete outcome data	?	Number of men randomised to each group not reported. Number of withdrawals and loss to follow-up not reported. It is unclear whether there was an imbalance between the groups in the proportion of men withdrawing or lost to follow-up
AEs	Blinding (participants and personnel)	?	Title describes study as double blind. Details on masking not available and it is unclear who was masked to treatment
	Blinding of outcomes assessment	?	Title describes study as double blind. Details on masking not available and it is unclear whether the outcomes assessor was masked to treatment
	Incomplete outcome data	?	Number of men randomised to each group not reported. Number of withdrawals and loss to follow-up not reported. It is unclear whether there was an imbalance between the groups in the proportion of men withdrawing or lost to follow-up
Overall rating of bias		?	Reflects limited reporting in conference abstract

TABLE 86 Handley *et al.*[67] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	None

M/F, male/female; SD, standard deviation.
a Denominator calculated by authors of review based on reporting in abstract. It is stated that five men (22.7%) in the podophyllin 0.5% group and six men (26%) in the podophyllotoxin 0.5% group were clinically wart free at 5 weeks.
b ?, unclear risk of bias.

TABLE 87 Hellberg *et al.*[137]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Shannon Amoils and Sam Barton
Study ID	Hellberg 1995
Study details	*Int J STD AIDS* 1995;**6**:257–61
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Sweden; number of sites not stated
Trial sponsor	Yamanouchi Europe BV
Conflicts of interest	None declared
Patient enrolment	No details available on how people were recruited or the dates of enrolment
Trial design	RCT
Trial duration	Maximum duration of treatment time 4 weeks. Women with complete clearance were followed up at 3 months (unclear whether 3 months after the end of treatment or 3 months from initiation of trial)
Line of therapy	Unclear. It is stated that 24 women (40.6%) had a history of AGWs but details of any previous treatments received not available
Inclusion criteria	Women with overt AGWs
Exclusion criteria	Current pregnancy; not using adequate contraception; immunosuppressive disease; vaginal, cervical or rectal AGWs; AGW exceeding 5 mm in size; treatment for AGWs in the previous month
All outcomes reported in paper	Primary clearance (complete clearance at end of treatment); final clearance (complete clearance at 3 months' follow-up); reduction in the total number of AGWs after each treatment cycle; recurrence; AEs (special attention paid to local tenderness, burning, pain, erythema, erosion and oedema) graded as slight, moderate or severe
Subgroups evaluated	Performed a subgroup analysis comparing treatment effects between the groups based on site of AGWs (analysis based on reduction in number of AGWs rather than the proportion of women with complete clearance)
Stratification	None reported
Baseline measurement of disease	At baseline, size of AGWs was estimated and the location (labiae, vulva or perianal) and number affecting each area were recorded

continued

TABLE 87 Hellberg *et al.*[137] (*continued*)

Item	Details		
Treatment	*Podophyllotoxin 0.5% cream (patient applied)*	*Podophyllin 20% solution (clinician applied)*	
Randomised, *n*	30	30	
Withdrawals, *n* (%)	2 (6.7%). Women failed to return to one or more check-ups and were considered dropouts. No reasons given for failure to return to check-ups	3 (10%). Women failed to return to one or more check-ups and were considered dro outs. No reasons given for failure to return to check-ups	
Treatment regimen	Self-treatment with podophyllotoxin 0.5% cream twice daily for 3 consecutive days in weekly intervals, for a maximum of 4 weeks. Women were instructed how to locate individual AGWs with one finger and apply cream with another finger	Weekly application of podophyllin 20% by a health-care professional for a maximum of 4 weeks. Women were instructed to wash off the solution 4 hours after application	
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Podophyllotoxin 0.5% cream (patient applied)*	*Podophyllin 20% solution (clinician applied)*	p-*value*
Age (years), mean (range)	24.5 (17–45)	24.8 (17–58)	Not reported
Duration of disease	Not recorded separately for the different treatment groups. Noted that mean duration of AGWs was 9.3 months overall		Difference between groups reported to be not significant (*p*-value not reported)
Site of AGWs	Reported as number of AGWs at various sites (not number of women)		
Vulva	11	16	Not reported
Labia	24	17	Not reported
Perianal	9	9	Not reported
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	9.0 (total 251 AGWs)	11.3 (total 305 AGWs)	Not reported
Area of AGWs (mm^2), mean	Not reported		
Sex (M/F), *n* (%)	All women		
Any previous treatment, *n* (%)	Not recorded separately for the different treatment groups. Noted that 24 women (40.6%) had a history of AGWs		Difference between groups reported to be not significant (*p*-value not reported)
Ethnicity, *n* (%)	Not reported		

TABLE 87 Hellberg *et al.*[137] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Referred to as 'primary clearance' in the full publication. Defined as complete clearance at a maximum of four cycles of treatment				
AGW clearance at other time points	Referred to as 'final clearance' in the full publication. Defined as no relapse at 3 months' follow-up				
Recurrence of AGWs	Not defined but can be calculated at 3 months based on AGW clearance at 3 months				
AEs	Focused on occurrence of local tenderness, burning, pain, erythema, erosion and oedema. AEs graded as slight, moderate or severe: slight = symptoms have no impact on the woman's daily life; moderate = symptoms that have prevented some actions of the woman's daily life; severe = symptoms that led to absence from work				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% cream (patient applied),* n/N	*Podophyllin 20% solution (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomess					
AGW clearance at completion of treatment	4 weeks	23/28	16/27		$p < 0.05$
AGW clearance at other time points					
One treatment cycle	1 week	7/28	2/27		Not reported
Two treatment cycles	2 weeks	18/28	12/27		Not reported
Three treatment cycles	3 weeks	21/28	15/27		Not reported
Recurrence of AGWs	3 months	3/23	3/16		Not reported
AEs					
Tenderness					
Mild	4 weeks	6/28	11/27		Difference between groups reported to be not significant for all comparisons
Moderate	4 weeks	11/28	9/27		
Severe	4 weeks	1/28	0/27		
Burning					
Mild	4 weeks	8/28	9/27		
Moderate	4 weeks	14/28	10/27		
Severe	4 weeks	0/28	0/27		

continued

TABLE 87 Hellberg *et al.*[137] (*continued*)

Item	Details		
Pain			
Mild	4 weeks	7/28	7/27
Moderate	4 weeks	11/28	10/27
Severe	4 weeks	0/28	0/27
Erythema/erosion			
Mild	4 weeks	2/28	1/27
Moderate	4 weeks	5/28	0/27
Severe	4 weeks	0/28	0/27

Section 5: Clinical trial quality

Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	It is stated that 'The women were randomly allocated' (p. 258). Information on the method used to generate the random sequence is not available
	Allocation concealment	?	Information on method of allocation concealment not provided
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	✓	Although the reasons for loss to follow-up are not specified, few people have been lost to follow-up and missing outcome data are balanced between the groups

TABLE 87 Hellberg *et al.*[137] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of recurrence of AGWs is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of recurrence of AGWs is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	✓	Although the reasons for loss to follow-up are not specified, few people have been lost to follow-up and missing outcome data are balanced between the groups
AEs	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	✓	Although the reasons for loss to follow-up are not specified, few people have been lost to follow-up and missing outcome data are balanced between the groups
Overall rating of bias		✗	Reflects open-label nature of trial

continued

TABLE 87 Hellberg *et al.*[137] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	It is noted that 7/60 (11.7%) women had cellular atypias at baseline

Outcome	Podophyllotoxin 0.5% cream		Podophyllin 20% solution		*p*-value
	Number of AGWs	Number of AGWs at baseline	Number of AGWs	Number of AGWs at baseline	
Mean number of AGWs					
One treatment cycle	151	251	144	305	
Two treatment cycles	45	251	84	305	
Three treatment cycles	27	251	66	305	
Four treatment cycles	14	251	78	305	$p < 0.001$
	n	***N***	***n***	***N***	
Mean number of AGWs by location[a,b]					
One treatment cycle					
Vulva	5	11	15	16	
Labiae	17	24	13	17	
Perianal	7	9	6	9	
Two treatment cycles					
Vulva	1	11	8	16	
Labiae	7	24	9	17	
Perianal	5	9	3	9	
Three treatment cycles					
Vulva	2	11	7	16	
Labiae	3	24	8	17	
Perianal	2	9	2	9	
Four treatment cycles					
Vulva	2	11	7	16	
Labiae	2	24	7	17	
Perianal	1	9	2	9	
Primary cure rate by number of AGWs					
> 8	9	12	6	13	
< 8	14	16	10	14	

a Sum of denominators is larger than the trial population as some women had AGWs at more than one site.
b Differences between groups stated to be non-significant for vulval and perianal AGWs. Podophyllotoxin 0.5% was found to be significantly more efficient than podophyllin 20% in eliminating labial AGWs ($p = 0.03$).

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 88 Jensen[146]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Orla Ní Ógáin and Sam Barton
Study ID	Jensen 1985
Study details	*Lancet* 1985;**2**:1146–8
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Not specified; it is inferred that the trial was carried out at one site in Denmark
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Patients were enrolled from June 1979 to December 1983. Details on method of recruitment not available
Trial design	RCT
Trial duration	Initial assessment was 1 week after the final treatment. People were followed up at 3, 6, 9 and 12 months;12 months was the final follow-up
Line of therapy	First (first episode)
Inclusion criteria	People were included if they were experiencing their first episode of AGWs and had perianal AGWs and the clinical appearance of lesions made the diagnosis obvious. The perianal region was defined as a circle of diameter 6 cm centring on the anus
Exclusion criteria	Not explicit; patients were examined at baseline to exclude the presence of other sexually transmitted diseases
All outcomes reported in paper	Complete clearance; recurrence; median number of visits required to achieve complete clearance; AEs
Subgroups evaluated	None
Stratification	Not reported
Baseline measurement of disease	At the initial visit, the clinical appearance of AGWs was documented and a full proctological examination carried out to determine the extent of AGWs. Patients with genital warts also underwent urethroscopy

continued

TABLE 88 Jensen[146] (*continued*)

Item	Details		
Treatment	*Podophyllin 25% (clinician applied)*	*Surgical excision*	
Randomised, *n*	30	30	
Withdrawals, *n* (%)	0 (0)	0 (0)	
Treatment regimen	Local application of a podophyllin 25% tincture of benzoin by a health-care professional. Lesions were painted, avoiding the adjacent skin and mucosa. Participants were instructed to wash the lesions 6 hours after each application. Treatment was repeated weekly for up to 6 weeks if required	Participants underwent simple surgical excisions, under local anaesthetic (lidocaine with noradrenaline). If there were too many AGWs to be removed in one procedure, AGWs were removed in two procedures, with an interval of 2 weeks. Participants were allowed home within 30 minutes, with aspirin tablets and a dry dressing on the wounds	
Duration/number of administered treatment	Median number of visits to complete clearance: 5 (range 1–6)	Median number of visits to complete clearance: 1 (range 1–4)	
	Difference between groups in the median number of visits required to achieve complete clearance was statistically significant, favouring surgical excision ($p < 0.01$)		
Baseline patient characteristics	*Podophyllin 25% (clinician applied)*	*Surgical excision*	p-*value*
Age (years), median (range)	24 (19–38)	26 (17–44)	Differences between groups reported to be non-significant
Duration of disease (weeks), median (range)	8 (2–20)	7 (3–24)	
Site of AGWs, *n* (%)			
Perianal alone	4 (13)	6 (20)	
Perianal plus			
Anal canal	12 (40)	10 (33)	
Anal canal, genitalia	5 (17)	6 (20)	
Anal canal, genitalia, rectum	1 (3)	0 (0)	
Genitalia	6 (20)	5 (17)	
Rectum	2 (7)	3 (10)	
	Two people were identified as having urethral AGWs, which were removed by a urologist		
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, median (range)	7 (3–31)	9 (3–27)	Difference reported to be non-significant
Area of AGWs (mm^2), mean	Not reported		
Sex, *n* (%)			
Men	24 (80)	21 (70)	Difference reported to be non-significant
Women	6 (20)	9 (30)	
Any previous treatment, *n* (%)	All first episode		
Ethnicity, *n* (%)	Not reported		

TABLE 88 Jensen[146] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	It is stated that the 'short-term effect of both regimens was evaluated 1 week after the final treatment' (p. 1146). No further details reported. The publication includes data on recurrence in people with complete clearance. Based on the numbers reported, it has been assumed that data for short-term effect are complete clearance at 1 week after treatment				
Recurrence of AGWs	Not defined. Data on recurrent AGWs requiring further treatment are reported				
AEs	Not defined. Data on pain, bleeding, burns and soiling are reported				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllin 25% (clinician applied),* n/N	*Surgical excision,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	1 week after treatment	23/30	28/30		Not reported
Recurrence of AGWs	12 months	17/23	8/28		$p < 0.01$
AEs	During treatment				
Skin burns		3/30	0/30		
Minor bleeding		4/30	0/30		
Bleeding		0/30	11/30		
Soiling		4/30	0/30		
Pain					
Requiring analgesics		3/30	12/30		
Slight		4/30	9/30		
Severe		0/30	4/30		
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	The study is described as a randomised controlled study but further details on method of randomisation not available	
	Allocation concealment		?	No details provided	
	Selective reporting		?	Insufficient information provided to determine risk of selective reporting	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	

continued

TABLE 88 Jensen[146] (*continued*)

Item	Details		
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	Level of masking is not described. Given that one of the treatments is surgical excision, it is likely not to have been feasible to mask participants and key study personnel to treatment. It is stated that follow-up was carried out by an independent observer who was masked to treatment. It is unclear whether the independent observer also evaluated short-term effect (reporting suggests not, but does not state that this is the case). If the outcome assessor was masked to treatment, the probability of masking being broken is unclear
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✓	No missing outcome data
Recurrence of AGWs	Blinding (participants and personnel)	?	Level of masking is not described. Given that one of the treatments is surgical excision, it is likely not to have been feasible to mask participants and key study personnel to treatment. It is stated that follow-up was carried out by an independent observer who was masked to treatment. It is unclear whether the independent observer also evaluated short-term effect (reporting suggests not, but does not state that this is the case). If the outcome assessor was masked to treatment, the probability of masking being broken is unclear
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✓	No missing outcome data
AEs	Blinding (participants and personnel)	?	Level of masking is not described. Given that one of the treatments is surgical excision, it is likely not to have been feasible to mask participants and key study personnel to treatment. It is stated that follow-up was carried out by an independent observer who was masked to treatment. It is unclear whether the independent observer also evaluated short-term effect (reporting suggests not, but does not state that this is the case). If the outcome assessor was masked to treatment, the probability of masking being broken is unclear
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✓	No missing outcome data
Overall rating of bias		?	Reflects the limited reporting in the trial
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 89 Kar *et al.*[138]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Orla Ní Ógáin and Sam Barton	
Study ID	Kar 2003	
Study details	*Indian J Dermatol* 2003;**48**:146–50	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Location was STD treatment centres located in hospitals for military, serving personnel; although not explicitly stated, authors' affiliation suggests trial carried out in India. Number of sites not reported	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Men attending STD treatment centres in hospitals for military, serving personnel were enrolled between January 1995 and December 2001	
Trial design	RCT	
Trial duration	Initial treatment period of 6 weeks with a subsequent follow-up period of 6 months (unclear whether this is 6 months after the end of treatment or 6 months from start of treatment)	
Line of therapy	Not reported	
Inclusion criterion	Presence of AGWs as determined by visual inspection (without biopsy confirmation)	
Exclusion criteria	Presence of untreated syphilis; frequent genital herpes; presence of bowenoid papulosis; allergy to podophyllin 20% in 1% benzoin tincture; received treatment for AGWs within a month of study entry; immunocompromised (by history or clinical examination)	
All outcomes reported in paper	Treatment response/cure; recurrence of AGWs or formation of new lesions; occurrence of local adverse reactions	
Subgroups evaluated	None reported	
Stratification	None reported	
Baseline measurement of disease	Presence of AGWs at baseline was determined by visual inspection. The site, number, and size of AGWs were recorded at baseline and at subsequent follow-up visits	
Treatment	*Podophyllin 20% (in 1% tincture of benzoin; clinician applied)*	*Podophyllotoxin 0.5% solution (patient applied)*
Randomised, *n*	35	37
Withdrawals, *n* (%)	Not reported. It is stated that 'no patient withdrew from any treatment because of the side effects' (p. 148). Analyses are based on ITT population	

continued

TABLE 89 Kar *et al.*[138] (*continued*)

Item	Details		
Treatment regimen	Podophyllin 20% in 1% tincture of benzoin was applied with a cotton swab once a week by a health-care professional in a clinic. The surrounding skin was covered with Vaseline to avoid chemical injury to normal skin. Men were instructed to keep the area open for 30 minutes to allow the treatment to dry and to wash the area with soap and water 4 hours after application. Treatment was repeated weekly for up to 6 weeks or until there was no visible AGW tissue. If there was an incomplete response after 6 weeks, treatment was discontinued	The men were instructed to apply podophyllotoxin 0.5% solution twice a day (every 12 hours) for 3 consecutive days and then to withhold application for 4 consecutive days. Treatment was repeated weekly for up to 6 weeks or until there was no visible AGW tissue. If there was an incomplete response after 6 weeks, treatment was discontinued	
Duration/number of administered treatment	Mean number of treatments (presumed to be to complete clearance): 4.8 (SD/SE not reported)	Mean number of treatments (presumed to be to complete clearance): 4.6 (SD/SE not reported)	
Baseline patient characteristics	*Podophyllin 20% (in 1% tincture of benzoin; clinician applied)*	*Podophyllotoxin 0.5% solution (patient-applied)*	p-*value*
Age (years)	Mean and median age not reported for either the full trial population or by treatment group. Overall age distribution in study: < 20 years: 7 (9.7%), 21–25 years: 15 (20.8%), 26–30 years: 18 (25%), 31–35 years: 16 (22.2%), 36–40 years: 9 (12.5%), 41–50 years: 5 (6.9%), > 50 years: 2 (2.7%)		Not reported
Duration of disease (months)	4.8 (unclear whether this is mean or median)	5.7 (unclear whether this is mean or median)	Not reported
Site of AGWs, *n* (%)			
Glans penis	7 (20)	8 (21.6)	Not reported
Coronal sulcus	27 (77.1)	29 (78.3)	Not reported
Urethral meatus	2 (5.7)	1 (2.7)	Not reported
Prepuce	7 (20)	5 (13.5)	Not reported
Shaft of penis	2 (5.7)	3 (8.1)	Not reported
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	4	5	Not reported
Size of AGWs (mm), mean [size given in mm not area (mm^2)]	4.8	3.5	Not reported
Sex (M/F), *n* (%)	100% male		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		

TABLE 89 Kar *et al.*[138] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	It is reported that complete resolution was recorded at the end of treatment (6 weeks)				
AGW clearance at other time points	It is reported that complete resolution was also recorded at the end of weeks 1, 2, 3, 4 and 5 during treatment and at weeks 4, 8, 12 and 24 of follow-up. Men were categorised as clinically 'cured' at the end of 24 weeks' follow-up				
Recurrence of AGWs	Recurrence of AGWs was recorded by the investigator. It is unclear whether data for recurrence include new lesions appearing during or after treatment				
Appearance of new warts during treatment	It is stated that formation of new AGWs was recorded by the investigator. A new AGW was defined as one that arose at a site distant from that of the original AGWs. Data for the appearance of new AGWs either during treatment or during the post-treatment follow-up period are not reported separately. It is unclear whether data for recurrence include new lesions appearing during or after treatment				
AEs	Local adverse reactions (pain, burning, inflammation and erosion) were reported and categorised as none, mild, moderate or severe (definitions of the individual categories not available)				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllin 20% (in 1% tincture of benzoin; clinician applied),* n/N	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	6 weeks	29/35	33/37		Not reported
AGW clearance at other time points[a]	1 week	0/35	0/37		Not reported
	2 weeks	0/35	0/37		Not reported
	3 weeks	0/35	0/37		Not reported
	4 weeks	16/35	18/37		Not reported
	5 weeks	22/35	27/37		Not reported
Recurrence of AGWs	6 months	8/29	11/33		Not reported
Appearance of new warts during treatment		Not reported separately; unclear whether data have been recorded with 'recurrence of warts'			
AEs					
Pain					
None	6 weeks	25/35	23/37		Not reported
Mild	6 weeks	6/35	7/37		
Moderate	6 weeks	3/35	6/37		
Severe	6 weeks	1/35	1/37		
Burning					
None	6 weeks	22/35	22/37		Not reported
Mild	6 weeks	9/35	8/37		
Moderate	6 weeks	4/35	6/37		
Severe	6 weeks	0/35	1/37		

continued

TABLE 89 Kar *et al.*[138] (*continued*)

Item	Details			
Erosion				
None	6 weeks	23/35	21/37	Not reported
Mild	6 weeks	7/35	10/37	
Moderate	6 weeks	4/35	4/37	
Severe	6 weeks	1/35	1/37	
Inflammation				
None	6 weeks	21/35	21/37	Not reported
Mild	6 weeks	10/35	9/37	
Moderate	6 weeks	3/35	5/37	
Severe	6 weeks	1/35	2/37	

Section 5: Clinical trial quality

Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*
	Random sequence generation	?	It is stated that men were randomly divided into groups but details on method of randomisation not available
	Allocation concealment	?	No details provided
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting. In the paper, there is a description of the assessment of the formation of new AGWs, but data are not presented. Unclear whether formation of new AGWs is captured within recurrence
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	Details on whether the authors made attempts to mask patients and personnel not provided. Given the two different settings in which treatments were administered (clinic vs. home), it might be impractical to mask patients and key personnel to treatment. Also, it is unclear whether the clinician assessing clearance was masked to treatment allocation. If assessor not masked to treatment, assessment of complete clearance could be considered to be a subjective assessment and at risk of bias
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Although the analysis is based on the ITT population, the number of people lost to follow-up or withdrawing from the trial is not reported. There might be an imbalance between the groups in the number of people for whom data are not available

TABLE 89 Kar *et al.*[138] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	?	Details on whether the authors made attempts to mask patients and personnel not provided. Given the two different settings in which treatments were administered (clinic vs. home), it might be impractical to mask patients and key personnel to treatment. Also, it is unclear whether the clinician assessing clearance was masked to treatment allocation. If assessor not masked to treatment, assessment of complete clearance could be considered to be a subjective assessment and at risk of bias
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Although the analysis is based on all people with complete clearance, the number of people lost to follow-up or withdrawing from the trial during the observation period is not reported. There might be an imbalance between the groups in the number of people for whom data are not available
AEs	Blinding (participants and personnel)	?	Details on whether the authors made attempts to mask patients and personnel not provided. Given the two different settings in which treatments were administered (clinic vs. home), it might be impractical to mask patients and key personnel to treatment. Also, it is unclear whether the clinician assessing clearance was masked to treatment allocation. If assessor not masked to treatment, assessment of complete clearance could be considered to be a subjective assessment and at risk of bias
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Although the analysis is based on the ITT population, the number of people lost to follow-up or withdrawing from the trial is not reported. There might be an imbalance between the groups in the number of people for whom data are not available
Overall rating of bias		?	Reflects limited reporting in full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a During treatment period, number of men achieving complete clearance is cumulative.
b ?, unclear risk of bias.

TABLE 90 Kinghorn *et al.*[63]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Sam Barton	
Study ID	Kinghorn 1993	
Study details	*Int J STD AIDS* 1993;**4**:194–9	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Carried out at six clinics in the UK and Eire: Royal Hallamshire Hospital, Sheffield; St James's Hospital, Dublin; Royal Infirmary, Edinburgh; Coventry and Warwickshire Hospital, Coventry; Middlesex Hospital, London; and General Infirmary, Leeds	
Trial sponsor	Brocades Pharma supplied the study treatments	
Conflicts of interest	Not reported	
Patient enrolment	Patients were recruited from people presenting to the six genitourinary clinics listed above; dates of enrolment not reported	
Trial design	RCT	
Trial duration	Treatment period of a maximum of 5 weeks followed by a final assessment at week 13 from the start of the study	
Line of therapy	31% of people had received previous treatment for AGWs	
Inclusion criteria	Presence of external AGWs (condylomata acuminata); aged ≥ 16 years	
Exclusion criteria	People were not eligible if they had or were at high risk of having HIV infection; had any other immunosuppressive disorder; had other untreated STD; had received any AGW treatment within 1 month of study entry; had condylomata of the vagina, cervix or anus; were a pregnant or lactating woman	
All outcomes reported in paper	Complete clearance; recurrence; AEs	
Subgroups evaluated	Gender; location of lesion (presented by lesions rather than patients)	
Stratification	Unclear. Baseline characteristics and results are presented by gender, but it is unclear whether randomisation was stratified by gender	
Baseline measurement of disease	At the initial visit, the number and sites of AGWs were described and recorded. Details on the morphological types of AGW were not routinely collected	
Treatment	*Podophyllotoxin 0.5% cream (patient applied)*	*Podophyllin 25% solution (clinician applied)*
Randomised, *n*	Number of people randomised unclear; 138 available for follow-up	Number of people randomised unclear; 62 available for follow-up
Withdrawals, *n* (%)	Overall, 52/252 (21%) people were lost to follow-up by the 5-week assessment (number of people lost to follow-up not reported separately for each treatment group). At the 13-week follow-up, of men and women with complete clearance, 75 out of 157 (47.8%) returned for assessment of relapse	

TABLE 90 Kinghorn *et al.*[63] (*continued*)

Item	Details		
Treatment regimen	Podophyllotoxin 0.5% cream was self-applied twice daily for 3 consecutive days each week, followed by a 4-day treatment-free period. The treatment cycle was repeated until AGWs were eradicated or for a maximum of 5 weeks, whichever occurred first	Podophyllin 25% solution was applied by a physician or nurse twice weekly. The patient was instructed to wash the area 4 hours after application. The treatment cycle was repeated until AGWs were eradicated or for a maximum of 5 weeks, whichever occurred first	
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Podophyllotoxin 0.5% cream (patient applied)*	*Podophyllin 25% solution (clinician applied)*	p-*value*
	All baseline characteristics were reported by gender within each treatment group rather than for the full group		
Age (years), mean (range)	Men 25 (16–46); women 22 (18–30)	Men 25 years (18–46); women 23 years (17–37)	Difference between groups reported to be not significant
Duration of disease (weeks), mean	Men 16; women 9	Men 24; women 14	Difference between groups reported to be not significant
Site of AGWs, *n*			
Men[a]			
Prepuce	29	13	Not reported
Glans	14	7	
Shaft	21	8	
Other	51	21	
Women[a]			
Labia majora	18	11	Not reported
Labia minora	15	8	
Introitus	14	16	
Other	18	11	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean (range)	Men 8.8 (1–35); women 9.3 (1–40)	Men 8.8 (1–26); women 13.4 (range 2–48)	Difference between groups reported to be not significant
Area of AGWs (mm^2), mean	Not reported		
Sex, *n* (%)			
Men	97 (70.3)	36 (58.1)	Not significant
Women	41 (29.7)	26 (41.9)	Not significant
Any previous treatment, *n* (%)			
Men	34 (35.1)	14 (38.9)	Difference between groups reported to be statistically significant for women
Women	13 (31.7)	1 (3.8)	
Ethnicity, *n* (%)	Not reported		

continued

TABLE 90 Kinghorn *et al.*[63] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Clearance of all AGWs				
AGW clearance at other time points	Clearance of all AGWs at 1 week after start of treatment				
Recurrence of AGWs	Referred to as relapse in the full publication; not further defined				
AEs	Subjective effects defined as tenderness, burning and pain. Objective effects defined as erythema, oedema and erosions				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% cream (patient applied),* n/N	*Podophyllin 25% solution (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment					
Men	5 weeks	83/97	26/36		$p = 0.08$
Women		32/41	16/26		$p = 0.14$
Total		115/138	42/62		
AGW clearance at other time points					
Men	1 week	51/97	7/36		
Women		15/41	5/26		
Total		66/138	12/62		
Recurrence of AGWs					
Men	13 weeks	7/37	5/10		$p = 0.015$
Women		5/21	3/7		$p = 0.35$
Total		12/58	8/17		
AEs					
Subjective: tenderness, burning and pain					
Men	1 week	57/97	1/36		Not reported
Women		18/41	3/26		
Total		75/138	4/62		
Objective: erythema, oedema and erosions					
Men	1 week	48/97	4/36		Not reported
Women		10/41	2/26		
Total		58/138	6/62		

TABLE 90 Kinghorn *et al.*[63] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*
	Random sequence generation	?	It is stated that patients were randomly allocated in strict sequence. Additional information on method used to generate random sequence not available
	Allocation concealment	?	It is stated that patients were randomly allocated in strict sequence by numbered sealed envelopes. It is unclear whether the envelopes were opaque
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Imbalance between treatment groups in the proportion of women who had received previous treatment for AGWs. The group with a higher proportion of women who had received previous treatment could be more resistant to treatment
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✗	Described as an open, unblinded trial. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	The personnel assessing the outcomes were not independent observers. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Incomplete outcome data	?	Number of people randomised to each group not reported. Loss to follow-up at 5 weeks not reported by treatment group but for the overall population. As number of people randomised to each group was not reported, unclear whether there is an imbalance between groups in number of people lost to follow-up
Recurrence of AGWs	Blinding (participants and personnel)	✗	Described as an open, unblinded trial. Assessment of AGW relapse is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	The personnel assessing the outcomes were not independent observers. Assessment of AGW relapse is likely to be subjective and open to influence from lack of masking
	Incomplete outcome data	?	Number of people randomised to each group not reported. A large proportion of people was lost to follow-up during the observation phase. The proportion returning for assessment was similar for the two groups. It is unclear what effect the large loss to follow-up will have on the effect estimate

continued

TABLE 90 Kinghorn *et al.*[63] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	✗	Described as an open, unblinded trial. Assessment of AEs is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	The personnel assessing the outcomes were not independent observers. Assessment of AEs is likely to be subjective and open to influence from lack of masking
	Incomplete outcome data	?	Number of people randomised to each group not reported. Loss to follow-up at 5 weeks not reported by treatment group but for the overall population. As the number of people randomised to each group was not reported, unclear whether there is an imbalance between groups in number of people lost to follow-up
Overall rating of bias		✗	Reflects open-label nature of trial
Section 6: Additional comments			

Additional comments

Site	Podophyllotoxin 0.5% cream		Podophyllin 25% solution	
	Number of sites cleared, *n* (%)	Number of sites treated, *n*	Number of sites cleared, *n* (%)	Number of sites treated, *n*
Men				
Prepuce	27 (93.1)	29	12 (92.3)	13
Glans	11 (78.6)	14	5 (71.4)	7
Shaft	16 (76.2)	21	1 (12.5)	8
Other	44 (86.3)	51	13 (61.9)	21
Total[a]	98 (85.2)	115	31 (63.3)	49
Women				
Labia majora	12 (66.7)	18	5 (45.5)	11
Labia minora	11 (73.3)	15	5 (62.5)	8
Introitus	10 (71.4)	14	10 (62.5)	16
Other	14 (77.8)	18	7 (63.6)	11
Total[a]	47 (72.3)	65	27 (58.7)	46

a *p*-values for the difference between treatments in healing at 5 weeks for all sites treated were < 0.002 and 0.10 for men and women respectively.

SD, standard deviation; STD, sexually transmitted disease.
a Total number of sites of AGWs is greater than the number of participants in each group as participants could have AGWs at more than one site.
b ?, unclear risk of bias; ✗, high risk of bias.

TABLE 91 Kirby *et al.*[61]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Sam Barton	
Study ID	Kirby 1990	
Study details	*Am J Med* 1990;**88**:465–9	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Study carried out in Washington, USA. Number of sites not specified; study possibly carried out a single site	
Trial sponsor	It is stated that the study was part funded by grants from Oclassen Pharmaceuticals, Inc. and the National Institutes of Health	
Conflicts of interest	Not reported	
Patient enrolment	Details not available	
Trial design	RCT	
Trial duration	Initial treatment period of 4 weeks with subsequent follow-up at 12 and 16 weeks for those categorised as cured at week 6	
Line of therapy	25/38 (65.8%) men had received previous treatment for AGWs	
Inclusion criteria	Male gender; aged $\geq$ 18 years; presence of 2–20 external AGWs, excluding anal AGWs; total AGW surface area of $< 10\,cm^2$	
Exclusion criteria	Presence of untreated syphilis; previous AGW therapy within 1 month of enrolment; possible immunocompromise; active genital herpes simplex infection; history of bowenoid papulosis; unreliable history	
All outcomes reported in paper	Complete clearance; proportion of men with AGWs resistant to treatment; volume reduction in area of AGWs; recurrence; AEs	
Subgroups evaluated	None reported	
Stratification	Stratified based on duration of AGWs: $\leq$ 12 months vs. $>$ 12 months	
Baseline measurement of disease	Examination of AGWs included recording of size, location and number together with circumcision status. At baseline, AGWs were characterised as keratotic or non-keratotic. Each lesion was assigned a number and a diagram was made to facilitate monitoring	
Treatment	*Podophyllotoxin 0.5% solution (patient applied)*	*Placebo solution (patient applied)*
Randomised, *n*	19	19
Withdrawals, *n* (%)	1 (5.3%). Patient withdrew because of AEs and was subsequently lost to follow-up	0
Treatment regimen	Men applied podophyllotoxin 0.5% solution or placebo solution twice daily for 3 consecutive days a week, for a minimum of 2 weeks and a maximum of 4 weeks. Solutions were applied using a swab. Men were instructed not to treat inflamed or bleeding lesions	
Duration/number of administered treatment	Not reported	

continued

TABLE 91 Kirby *et al.*[61] (*continued*)

Item	Details		
Baseline patient characteristics	*Podophyllotoxin 0.5% solution (patient applied)*	*Placebo solution (patient applied)*	*p-value*
Age (years), mean (SE)	28.8 (1.66)	29.8 (1.71)	Not significant
Duration of disease, *n* (%)	Mean duration not reported		
≤ 12 months	9 (47.4)	10 (52.6)	Not significant
> 12 months	10 (52.6)	9 (47.4)	Not significant
Site of AGWs, *n* (%)	Not reported		Not significant
Type of AGWs, *n* (%)	100% non-keratinised	100% non-keratinised	Not significant
Number of AGWs, mean (SE) (range)	8.1 (1.09) (1–20)	9.5 (1.34) (2–20)	Not significant
Area of AGWs (mm^2), mean (SE) (range)	86.2 (19.43) (7–331)	118.2 (47.97) (8–942)	Not significant
Sex (M/F), *n* (%)	100% male	100% male	Not significant
Any previous treatment, *n* (%)			
Podophyllin	10 (52.6)	7 (36.8)	Not significant
Liquid nitrogen	11 (57.9)	9 (47.4)	Not significant
Electrocautery	2 (10.5)	2 (10.5)	Not significant
Laser	0 (0)	0 (0)	
5-Fluoruracil	0 (0)	0 (0)	
Any previous genital wart therapy	15 (78.9)	10 (52.6)	Not significant
Ethnicity, *n* (%)			
Caucasian	16 (84.2)	18 (94.7)	Not significant
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Free of visible genital AGWs at 4 weeks		
Recurrence of AGWs	Men judged to have resolution of genital AGWs at the week 6 visit returned at weeks 12 and 16 for evaluation of recurrence		
Volume of wart clearance	Various measures of reduction in volume of AGWs were used: at least 50% reduction in original AGW area; percentage of original AGW area visible; and percentage of original AGW count present		
Appearance of new warts during treatment	New lesions that appeared during 4 weeks of treatment		
AEs	Men were questioned about the presence of AEs and the investigator examined the men for the presence of erosion, inflammation and other findings. The investigator graded AEs as mild, moderate or severe; severity not further defined. Effects evaluated were burning, erosions, pain, inflammation, itching, dryness, erythema, irritation and nausea		

TABLE 91 Kirby *et al.*[61] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Placebo solution (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	4 weeks	11/19	0/19		$p < 0.01$
Recurrence of AGWs	16 weeks	10/11	0/0		–
Volume of wart clearance (at least 50% reduction in original wart area)	2 weeks	19/19	1/19		Not reported
	4 weeks	19/19	1/19		
	6 weeks	17/19	1/19		
Appearance of new warts during treatment	4 weeks	8/19	9/19		Not reported
AEs					
Burning	4 weeks	14/19	1/19		$p < 0.01$
Erosions		11/19	0/19		Not reported
Pain		11/19	1/19		Not reported
Inflammation		9/19	0/19		Not reported
Itching		6/19	3/19		Not reported
Dryness		2/19	1/19		Not reported
Erythema		1/19	0/19		Not reported
Irritation		1/19	0/19		Not reported
Nausea		1/19	0/19		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	It is stated that men were randomly assigned to treatment. Details on method of randomisation not available	
	Allocation concealment		✓	Men were given coded vials that were identical in appearance. The code for the double-blind portion of the trial was not broken until the conclusion of the placebo-controlled and open phases of the study	
	Selective reporting		?	Insufficient information reported to assess level of selective reporting	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	

continued

TABLE 91 Kirby *et al.*[61] (*continued*)

Item	Details		
AGW clearance at completion of treatment	Blinding (participants and personnel)	✓	Described as a double-blind study. Given that identical vials were used and the randomisation code was not broken until after conclusion of the open phase of the trial, it is likely that masking has been maintained
	Blinding of outcomes assessment	?	It is stated that a single investigator performed all assessments. Although the study is described as double blinded and it is likely that the investigator was masked to treatment and masking has been maintained, which personnel have been masked to treatment is not explicitly stated
	Incomplete outcome data	✓	Number of people lost to follow-up reported. Only one person lost to follow-up from the study during the treatment phase. An additional person lost to follow-up from the phase evaluating recurrence
Recurrence of AGWs	Blinding (participants and personnel)	✓	Described as a double-blind study. Given that identical vials were used and the randomisation code was not broken until after conclusion of the open phase of the trial, it is likely that masking has been maintained
	Blinding of outcomes assessment	?	It is stated that a single investigator performed all assessments. Although the study is described as double blinded and it is likely that the investigator was masked to treatment and masking has been maintained, which personnel have been masked to treatment is not explicitly stated
	Incomplete outcome data	✓	Number of people lost to follow-up reported. Only one person lost to follow-up from the study during the treatment phase. An additional person lost to follow-up from the phase evaluating recurrence
Volume of wart clearance (proportion of patients with at least 50% clearance)	Blinding (participants and personnel)	✓	Described as a double-blind study. Given that identical vials were used and the randomisation code was not broken until after conclusion of the open phase of the trial, it is likely that masking has been maintained
	Blinding of outcomes assessment	?	It is stated that a single investigator performed all assessments. Although the study is described as double blinded and it is likely that the investigator was masked to treatment and masking has been maintained, which personnel have been masked to treatment is not explicitly stated
	Incomplete outcome data	✓	Number of people lost to follow-up reported. Only one person lost to follow-up from the study during the treatment phase. An additional person lost to follow-up from the phase evaluating recurrence

TABLE 91 Kirby *et al.*[61] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	✓	Described as a double-blind study. Given that identical vials were used and the randomisation code was not broken until after conclusion of the open phase of the trial, it is likely that masking has been maintained
	Blinding of outcomes assessment	?	It is stated that a single investigator performed all assessments. Although the study is described as double blinded and it is likely that the investigator was masked to treatment and masking has been maintained, which personnel have been masked to treatment is not explicitly stated
	Incomplete outcome data	✓	Number of people lost to follow-up reported. Only one person lost to follow-up from the study during the treatment phase. An additional person lost to follow-up from the phase evaluating recurrence
Overall rating of bias		?	
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 92 Komericki *et al.*[131]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Sam Barton
Study ID	Komericki 2011
Study details	*Sex Trans Dis* 2011;**38**:216–18
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at the Medical University of Graz, Austria. Number of sites not specified; study likely to have been carried out a single site
Trial sponsor	It is stated that the study was not funded by any drug manufacturer
Conflicts of interest	Not reported
Patient enrolment	Consecutive patients presenting with untreated AGWs over a 2-year period (date not stated) were eligible. Further details not available
Trial design	RCT
Trial duration	Study focused on the treatment period: 4 weeks of treatment with podophyllotoxin 0.5% solution vs. 16 weeks of treatment with imiquimod 5% cream
Line of therapy	First line

continued

TABLE 92 Komericki *et al.*[131] (*continued*)

Item	Details		
Inclusion criterion	Untreated AGWs		
Exclusion criteria	Age < 18 years; lack of informed consent; known immunosuppression; pregnancy; breastfeeding; involvement of the anal canal; severe disease requiring surgery		
All outcomes reported in paper	Complete clearance; AEs		
Subgroups evaluated	None reported		
Stratification	None reported		
Baseline measurement of disease	Initial evaluation of AGWs included recording of location of AGWs (anal, genital or anogenital) together with an assessment of severity, which was graded as mild (area of involvement 0–100 mm^2), moderate (area of involvement 100–200 mm^2) or severe (area of involvement > 200 mm^2)		
Treatment	*Podophyllotoxin 0.5% solution (patient applied)*	*Imiquimod 5% cream (patient applied)*	
Randomised, *n*	26	25	
Withdrawals, *n* (%)	1 (3.8%) lost to follow-up (reason not reported)	5 (20%) lost to follow-up (reasons not reported)	
Treatment regimen	Podophyllotoxin 0.5% solution was applied by the patient twice daily for 3 consecutive days per week either until complete clearance of AGWs or for a maximum of 4 weeks, whichever occurred first	Imiquimod 5% cream was applied by the patient three times a week either until complete clearance of AGW or for a maximum of 16 weeks, whichever occurred first	
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Podophyllotoxin 0.5% solution (patient applied)*	*Imiquimod 5% cream (patient applied)*	p-*value*
	Note: Baseline characteristics are reported for the people completing the study rather than all people randomised		
Age (years), mean	30.0	30.8	Not reported
Duration of disease	Not reported		
Site of AGWs, *n* (%)			
Genital	14 (56.0)	13 (65.0)	Differences between groups reported to be not significant
Anal	5 (20.0)	4 (20.0)	
Anogenital	6 (24.0)	3 (15.0)	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean (with SD/SE if given)	Not reported		
Mean area of AGWs, *n* (%)			
Mild (0–100 mm^2)	9 (36.0)	8 (40.0)	Differences between groups reported to be not significant
Moderate (100–200 mm^2)	9 (36.0)	7 (35.0)	
Severe (> 200 mm^2)	7 (28.0)	5 (25.0)	

TABLE 92 Komericki *et al.*[131] (*continued*)

Item	Details			
Sex, *n* (%)				
Men	22 (88.0)	16 (80.0)	Differences between groups reported to be not significant	
Women	3 (12.0)	4 (20.0)		
Any previous treatment, *n* (%)	None; all AGWs were untreated			
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Complete clearance of AGWs at 5 weeks after start of podophyllotoxin 0.5% or 16 weeks after start of imiquimod 5%			
AEs	At the individual assessments, for AEs, patients were assigned to one of no side effects; erythema/inflammation; erosions; or erythema/inflammation plus erosions			
Section 4: Data extraction form				
Outcome	*Time frame*	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Imiquimod 5% cream (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	Treatment dependent	18/25	15/20		$p = 1$
AEs					
Erythema/ inflammation	Treatment dependent	10/25	7/20		Differences between groups reported to be not significant
Erosion	Treatment dependent	5/25	5/20		
Erythema/ inflammation plus erosion	Treatment dependent	6/25	8/20		
Section 5: Clinical trial quality				
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*
	Random sequence generation		?	It is stated that 'Allocation to treatment groups was done according to a ranking, which was created by block randomisation. Each block contained 4 items (2 × imiquimod and 2 × podophyllotoxin) to assure a balanced design with equal group sizes' (p. 216). Details on method of sequence generation not available
	Allocation concealment		?	Information on allocation concealment not reported
	Selective reporting		?	Insufficient information provided to determine risk of selective reporting
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias

continued

TABLE 92 Komericki *et al.*[131] (*continued*)

Item	Details		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	✗	The number of people lost to follow-up from each group is reported, but reasons for loss to follow-up are not available. There is an imbalance between the groups in the proportion of people randomised and subsequently lost to follow-up (3.8% podophyllotoxin vs. 20.0% imiquimod). This imbalance is likely to influence the effect estimate
AEs	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking
	Incomplete outcome data	✗	The number of people lost to follow-up from each group is reported, but reasons for loss to follow-up are not available. There is an imbalance between the groups in the proportion of people randomised and subsequently lost to follow-up (3.8% podophyllotoxin vs. 20.0% imiquimod). Unclear what impact this imbalance could have on analysis of AEs. This imbalance is likely to influence the effect estimate
Overall rating of bias		✗	Reflects open-label nature of the study
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 93 Lacey *et al.*[64]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Sam Barton
Study ID	Lacey 2003
Study details	*Sex Transm Infect* 2003;**79**:270–5
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Carried out at 11 STD clinics in the UK
Trial sponsor	Perstorp Pharma, Lund, Sweden
Conflicts of interest	Dr Lacey has acted as a consultant to 3M Pharmaceuticals, GlaxoSmithKline, Merck and Xenova. Dr Maw has acted as an adviser to Perstorp Pharma, 3M Pharmaceuticals and Stiefel. None of the other authors has acted as a consultant for Stiefel and none has a financial interest in Stiefel or podophyllotoxin
Patient enrolment	Details not available
Trial design	RCT
Trial duration	Initial treatment period of a maximum of 4 weeks. Those with complete clearance at any time point during treatment were followed up at 12 weeks after trial entry
Line of therapy	Not reported
Inclusion criteria	Aged 18–65 years; current AGWs with a history of ≤ 3 months and no therapy in that time
Exclusion criteria	Known HIV infection or immunosuppression; homosexual male with perianal AGWs; total lesional area $> 400\ mm^2$; any individual lesion with an area of $> 100\ mm^2$; presence of intrameatal or vaginal AGWs or ulcerative or inflammatory STDs of the anogenital region; pregnancy
All outcomes reported in paper	Complete clearance at end of treatment; recurrence; AEs; cost-effectiveness
Subgroups evaluated	None reported
Stratification	Gender and number of AGWs at baseline (< 10 AGWs vs. ≥ 10 AGWs)
Baseline measurement of disease	The number and location of AGWs were recorded

continued

TABLE 93 Lacey *et al.*[64] (*continued*)

Item	Details			
Treatment	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllotoxin 0.15% cream (patient applied)*	*Podophyllin 25% (clinician applied)*	
Randomised, *n*	120	118	116	
Withdrawals, *n* (%)	24 (20.0)	36 (30.5)	18 (15.5)	
	Data reported for withdrawals are the number of people reported not to have completed the trial as per the trial protocol. Reasons for non-completion of the trial are not available. Number of people lost to follow-up during treatment not reported. It should be noted that a large proportion of people with complete clearance after treatment failed to attend follow-up at 12 weeks [103/177 (58.2%)]			
Treatment regimen	Podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream were self-applied twice daily for 3 consecutive days, followed by 4 treatment-free days. Treatment was applied for a maximum of 4 weeks or until complete clearance of AGWs, whichever occurred earlier		Podophyllin 25% in tincture of compound benzoin was applied twice weekly by a health-care professional. Treatment was applied for a maximum of 4 weeks or until complete clearance of AGWs, whichever occurred earlier	
Duration/number of administered treatment	Not reported			
Baseline patient characteristics	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllotoxin 0.15% cream (patient applied)*	*Podophyllin 25% (clinician applied)*	p-*value*
Age (years), mean (range)	Not reported			
Duration of disease	Not reported			
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	Not reported			
Number of people with < 10 AGWs, *n* (%)	79 (66)	84 (71)	82 (71)	
Number of people with ≥ 10 AGWs, *n* (%)	41 (34)	34 (29)	34 (29)	
Area of AGWs (mm^2), mean	Not reported			
Sex, *n* (%)				
Men	62 (52)	60 (51)	60 (52)	
Women	58 (48)	58 (49)	56 (48)	
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)				
White	114 (95)	111 (94)	110 (95)	

TABLE 93 Lacey *et al.*[64] (*continued*)

Item	Details					
Section 3: Outcomes						
Outcome	*Definition*					
AGW clearance at completion of treatment	Complete clearance of original AGWs (those identified at baseline) during treatment up to a maximum of four cycles of treatment. Authors based primary analysis on the per-protocol population but also carried out 'best case' and 'worst case' analyses in which missing data were imputed as all excluded people being cured or not cured respectively. Separate analysis of all AGWs (including new AGWs appearing during treatment) was also reported					
Recurrence of AGWs	For those with complete clearance after treatment, recurrence at 12 weeks after study entry					
AEs	AEs were not defined. Data were reported for occurrence of local side effects and ulceration. Unclear whether analysis is based on per-protocol population, people receiving at least one dose of treatment or ITT population					
Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Podophyllotoxin 0.15% cream (patient applied),* n/N	*Podophyllin 25% (clinician applied),* n/N	*Estimate of effect*	*CI and p-value*
Dichotomous outcomes						
AGW clearance at completion of treatment	4 weeks	72/96	53/82	52/98	Podophyllotoxin solution significantly better than the other interventions (*p*-value not reported)	
Recurrence of AGWs	12 weeks	15/33	12/22	5/19		
AEs						
Local side effects	4 weeks	32/96	20/82	17/98		Not reported
Ulceration		17/96	10/82	10/98		Not reported
Section 5: Clinical trial quality						
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*		
	Random sequence generation		?	It is stated that men were randomly allocated to treatment. Details on method used to generate random sequence not available		
	Allocation concealment		?	Details on method used to conceal allocation not available		
	Selective reporting		?	Insufficient information available to assess potential bias in selective reporting		
	'Other bias'		?	Insufficient information available to evaluate other potential sources of bias		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		✗	Described as an open-label trial. Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. AGW clearance is a subjective outcome that could potentially be influenced by patients and key study personnel		
	Blinding of outcomes assessment		✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken		

continued

TABLE 93 Lacey *et al.*[64] (*continued*)

Item	Details		
	Incomplete outcome data	?	The analyses reported are based on the per-protocol population. The number of people who withdrew from the trial, together with reasons for withdrawal, are not reported. There might be an imbalance across the groups in reasons for withdrawal that could influence the effect estimate
Recurrence of AGWs	Blinding (participants and personnel)	✗	Described as an open-label trial. Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. AGW recurrence is a subjective outcome that could potentially be influenced by patients and key study personnel
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AGW recurrence is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	A large proportion of people with complete clearance during the treatment phase of the study failed to return for subsequent assessment. Reasons for loss to follow-up are not reported. There might be an imbalance across the groups in reasons for withdrawal that could influence the effect estimate
AEs	Blinding (participants and personnel)	✗	Described as an open-label trial. Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. Interpretation of subjective AEs (such as pain) could potentially be influenced by patients and key study personnel
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	It is unclear whether the results reported are based on the per-protocol population, those receiving one dose of allocated treatment or the ITT population
Overall rating of bias		✗	Reflects the open-label nature of the study
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation; STD, sexually transmitted disease.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 94 Landthaler and Frosschl[139]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Sam Barton and Charlotta Karner
Study ID	Landthaler 1987
Study details	*Dt Dermatol* 1987;**11**:1223–5
Language of publication	German
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Unclear
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	People were enrolled from October 1985 to August 1986. Further details on how people were recruited are not available
Trial design	RCT
Trial duration	It was initially planned that people would receive treatment over a period of 6 weeks and would then be followed up 4 weeks after the end of treatment. However, the authors decided that this schedule was impractical. Instead, AGWs were treated until clearance and people were followed up at 4 weeks (or longer) after clearance. All patients were treated for a minimum of 2 weeks. It is noted that treatment was stopped early in those not responding to treatment; the criteria used to determine non-response to treatment are unclear
Line of therapy	Not reported
Inclusion criteria	Not reported
Exclusion criteria	Not reported
All outcomes reported in paper	Complete clearance; recurrence; AEs
Subgroups evaluated	Not reported
Stratification	Not reported
Baseline measurement of disease	Not reported

continued

TABLE 94 Landthaler and Frosschl[139] (*continued*)

Item	Details		
Treatment	*Podophyllotoxin 0.5% (patient applied)*	*Podophyllin 20% (clinician applied)*	
Randomised, *n*	22	17	
Withdrawals	5 (22.7%) people were classified as dropouts, with 3 people lost to follow-up	6 (35.3%) people were classified as dropouts, with 4 people lost to follow-up	
Treatment regimen	People self-applied podophyllotoxin 0.5% in the morning and again in the evening for 3 consecutive days (Monday, Tuesday and Wednesday) each week until complete clearance or classification of non-response, whichever occurred earlier. Of the 22 people receiving podophyllotoxin 0.5%, 19 men applied the treatment as a solution and three women as a cream	People receiving podophyllin 20% were treated once a week by a clinician in the outpatient clinic. Treatment continued until complete clearance or classification of non-response, whichever occurred earlier	
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Podophyllotoxin 0.5% (patient applied)*	*Podophyllin 20% (clinician applied)*	p-*value*
Age (years), mean (SD) (range)	30 (9) (20–45)	26 (6) 19–43	Difference reported to be not significant
Duration of disease (months), mean (SD) (range)	6.8 (6.2) (1–14)	5.3 (4.9) (1–18)	Difference reported to be not significant
Site of AGWs, *n* (%)[a]	Not reported		
Genital	17	14	Difference reported to be not significant
Perianal	5	4	Difference reported to be not significant
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean (SD) (range)	9.3 (5.2) (2–20)	9.5 (5.7) (2–17)	Difference reported to be not significant
Area of AGWs (mm^2), mean	Not reported		
Sex, *n* (%)			
Male	19 (86.4)	17 (100)	Difference reported to be not significant
Female	3 (13.6)	0	
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		

TABLE 94 Landthaler and Frosschl[139] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Complete clearance of AGWs				
Recurrence of AGWs	Not defined				
Time to complete clearance	Mean time to complete clearance of AGWs				
AEs	AEs not defined. Limited data reported on occurrence of AEs				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% (patient applied),* n/N	*Podophyllin 20% (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	At least 2 weeks	13/17	6/11		Difference reported to be not significant
Recurrence of AGWs[b]	At least 4 weeks after complete clearance	2/13	3/11		Difference reported to be not significant
AEs: 'toxic dermatitis with erythema, swelling, blistering, and subsequent scaly crusts'	At least 2 weeks	4/17 All patients experienced a moderate reddening of the treated areas of the skin and a slight burning sensation	3/11		
Continuous outcomes					
Time to complete clearance (weeks), mean (SD/SE)	At least 2 weeks	2.6 (1.1) ($n = 17$)	3.4 (3.2) ($n = 11$)		Difference reported to be not significant
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[c]	*Comments*	
	Random sequence generation		?	Described as a randomised study but details on method of randomisation not available	
	Allocation concealment		?	Details on method used to conceal allocation not available	
	Selective reporting		✗	Clear definitions of duration of treatment regimens, outcome assessment and time at which outcomes were reported are not available. Lack of reporting of duration of treatment and time points for key clinical outcomes makes it difficult to compare the study with other trials in a meta-analysis	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	

continued

TABLE 94 Landthaler and Frosschl[139] (*continued*)

Item	Details		
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The numbers of people withdrawing and lost to follow-up are reported. There is a slight imbalance across the groups in the proportion of people withdrawing. The impact on the estimate of effect is unclear
Recurrence of AGWs	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The numbers of people withdrawing and lost to follow-up are reported. There is a slight imbalance across the groups in the proportion of people withdrawing. The impact on the estimate of effect is unclear
Time to complete clearance	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The numbers of people withdrawing and lost to follow-up are reported. There is a slight imbalance across the groups in the proportion of people withdrawing. The impact on the estimate of effect is unclear
AEs	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The numbers of people withdrawing and lost to follow-up are reported. There is a slight imbalance across the groups in the proportion of people withdrawing. The impact on the estimate of effect is unclear
Overall rating of bias		✗	Reflects the limited reporting in the study around the duration of treatment and clinical outcomes evaluated

TABLE 94 Landthaler and Frosschl[139] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	• Eight of 36 men recruited were positive for HIV infection at baseline, five men in the podophyllotoxin 0.5% group and three in the podophyllin 20% group • Keratotic AGWs treated with podophyllotoxin 0.5% solution healed more quickly than those treated with podophyllin 20% (2.6 weeks with podophyllotoxin 0.5% vs. 3.4 weeks with podophyllin 20%)

SD, standard deviation.
a One man had both genital and perianal AGWs.
b The authors comment that it was not possible to distinguish between recurrence of AGWs present at baseline and new AGWs.
c ?, unclear risk of bias; ✗, high risk of bias.

TABLE 95 Lassus *et al.*[140]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Sam Barton
Study ID	Lassus 1984
Study details	*Eur J Sex Transm Dis* 1984;**2**:31–3
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at the University Central Hospital, Helsinki, Finland
Trial sponsor	Study podophyllotoxin 0.5% solution was donated by Produktkontroll AB, Sweden
Conflicts of interest	Not reported
Patient enrolment	Men attending the Outpatient Department for Venereal Diseases at the University Central Hospital were enrolled between January 1981 and February 1982
Trial design	RCT
Trial duration	Initial treatment period of a maximum of 4 weeks. Those with complete clearance at the end of treatment were followed up for up to 6 months after the start of treatment
Line of therapy	Not reported
Inclusion criteria	Men with condylomata acuminata in the preputial cavity
Exclusion criteria	Not reported
All outcomes reported in paper	Complete clearance; recurrence; AEs
Subgroups evaluated	None reported
Stratification	Not reported
Baseline measurement of disease	Not reported. Based on presented baseline characteristics, number of AGWs and number of sites affected in the preputial cavity were recorded

continued

TABLE 95 Lassus *et al.*[140] (*continued*)

Item	Details		
Treatment	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllin 20% solution (clinician applied)*	
Randomised, *n*	48	52	
Withdrawals, *n* (%)	Not reported		
Treatment regimen	Podophyllotoxin 0.5% solution was self-applied twice daily for 3 days for up to four weekly treatments or until complete clearance, whichever occurred earlier	Podophyllin 20% solution was applied in clinic by a clinician or a nurse. Men were instructed to wash off the solution 6 hours after application. Treatment was repeated weekly for up to 4 weeks or until complete clearance, whichever occurred earlier	
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllin 20% solution (clinician applied)*	p-*value*
Age (years), *n* (%)	Mean age not reported; data reported based on two age groups		
18–30	39 (81.3)	46 (88.5)	Difference between groups reported to be not significant
≥ 31	9 (18.7)	6 (11.5)	
Duration of disease (months), *n* (%)	Mean duration of disease not reported		
< 1 month	5 (10.4)	4 (7.7)	Difference between groups reported to be not significant
1–2 months	24 (50.0)	26 (50.0)	
> 2 months	19 (39.6)	22 (42.3)	
Site of AGWs, *n* (%)	All AGWs located in the preputial cavity. Data reported for number of sites affected		
One site	19 (39.6)	21 (40.4)	Difference between groups reported to be not significant
Two sites	8 (16.7)	13 (25.0)	
Three or four sites	21 (43.8)	18 (34.6)	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, *n* (%)	Mean number of AGWs not reported. Data reported based on three categories of number of AGWs at baseline		
< 5	12 (25.0)	13 (25.0)	Difference between groups reported to be not significant
5–15	27 (56.3)	24 (46.2)	
> 15	9 (18.8)	15 (28.8)	
Area of AGWs (mm^2)	Mean area of AGWs not reported. It was stated that all AGWs were 1–6 mm in size		
Sex (M/F), *n* (%)	100% men		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		

TABLE 95 Lassus *et al.*[140] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Not defined. Treatment failure was defined as follows: 'if the patient still had warts after four treatments, he was transferred to other therapy, mainly surgery' (p. 32). For this review, data on complete clearance after three or four cycles of treatment have been used for complete clearance at the end of treatment; data not reported separately for three and four treatments				
AGW clearance at other time points	Not defined. Data on complete clearance after one and two cycles of treatment are reported in the full publication				
Recurrence of AGWs	Recurrence at 3 months' follow-up from initiation of treatment				
AEs	AEs were not defined. Data are reported on occurrence of local reactions, categorised as mild, moderate or severe; definition of mild, moderate and severe not available				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Podophyllin 20% solution (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	Three to four treatments	48/48	37/52		$p < 0.001$
AGW clearance at other time points	One treatment	45/48	15/52		Not reported
	Two treatments	47/48	24/52		
Recurrence of AGWs	3 months	11/48	14/37		Not reported
AEs: local reactions (mild, moderate and severe)	4 weeks	8/48	13/52		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	It is stated that men were randomly allocated to treatment. Details on method used to generate random sequence not available	
	Allocation concealment		?	Details on method used to conceal allocation not available	
	Selective reporting		?	Insufficient information available to assess potential bias in selective reporting	
	'Other bias'		?	Insufficient information available to evaluate other potential sources of bias	
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		?	Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. AGW clearance is a subjective outcome that could potentially be influenced by patients and key study personnel. However, it is not explicitly stated that the trial is open label and it is unclear whether attempts were made to mask patients and personnel	

continued

TABLE 95 Lassus *et al.*[140] (*continued*)

Item	Details		
	Blinding of outcomes assessment	?	It is unclear whether attempts were made to mask the outcome assessor to treatment allocation
	Incomplete outcome data	?	Analysis of complete clearance is based on all men randomised. However, it is not stated that no men were lost to follow-up or withdrew from the trial
Recurrence of AGWs	Blinding (participants and personnel)	?	Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. AGW recurrence is a subjective outcome that could potentially be influenced by patients and key study personnel. However, it is not explicitly stated that the trial is open label and it is unclear whether attempts were made to mask patients and personnel
	Blinding of outcomes assessment	?	It is unclear whether attempts were made to mask the outcome assessor to treatment allocation
	Incomplete outcome data	?	Analysis of recurrence is based on all men randomised. However, it is not stated that no men were lost to follow-up or withdrew from the trial
AEs	Blinding (participants and personnel)	?	Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. AGW clearance is a subjective outcome that could potentially be influenced by patients and key study personnel. However, it is not explicitly stated that the trial is open label and it is unclear whether attempts were made to mask patients and personnel
	Blinding of outcomes assessment	?	It is unclear whether attempts were made to mask the outcome assessor to treatment allocation
	Incomplete outcome data	?	Analysis of AEs is based on all men randomised. However, it is not stated that no men was lost to follow-up or withdrew from the trial
Overall rating of bias		?	Reflects limited reporting on methods in the full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation.
a ?, unclear risk of bias.

TABLE 96 Maiti and Haye[147]

Item	Details		
Section 1: Reviewer and study information			
Reviewers' names	Jacoby Patterson and Sam Barton		
Study ID	Maiti 1985		
Study details	*Practitioner* 1985;**229**:37–9		
Language of publication	English		
Type of report	Full publication		
Section 2: Study information			
Location and number of sites	Study carried out at St Luke's Clinic, Manchester, UK		
Trial sponsor	Not reported		
Conflicts of interest	Not reported		
Patient enrolment	Men were recruited from those attending St Luke's Clinic. Dates of enrolment not reported		
Trial design	Blind controlled study		
Trial duration	Initial treatment period of 1 week. Those who had complete clearance after 1 week were followed up at 3 weeks and 3 months		
Line of therapy	Unclear; inclusion criterion of no treatment in preceding 6 months		
Inclusion criteria	Men with penile AGWs who had not received treatment for their AGWs in the 6 months before enrolment		
Exclusion criteria	Not reported		
All outcomes reported in paper	Complete clearance; recurrence; AEs		
Subgroups evaluated	None reported		
Stratification	None reported		
Baseline measurement of disease	Not reported		
Treatment	*Podophyllin 0.5% solution (patient applied)*	*Podophyllin 1.0% solution (patient applied)*	*Podophyllin 2.0% solution (patient applied)*
Randomised, *n*	It is stated that 100 men were allocated to treatment but number of men randomised to each group not reported. Results are reported for those men attending the 3-month follow-up visit (84 men)		
Attended 3-month follow-up	28	27	29
Withdrawals	16 men in total did not attend the 3-month follow-up. Reasons for withdrawal and number of men withdrawing from each treatment group not reported		
Treatment regimen	All solutions were applied by the patient twice daily for 3 consecutive days using sticks supplied by the investigators. Men were instructed to wash the afflicted area before application of the solution and to not wash the site after application. Treatment regimen was not repeated		
Duration/number of administered treatment	Not applicable; treatments were evaluated over only 1 week		

continued

TABLE 96 Maiti and Haye[147] (*continued*)

Item	Details				
Baseline patient characteristics	*Podophyllin 0.5% solution (patient applied)*	*Podophyllin 1.0% solution (patient applied)*	*Podophyllin 2.0% solution (patient applied)*		p-*value*
Age (years), mean (range)	Not reported				
Duration of disease	Not reported				
Site of AGWs, *n* (%)	Not reported				
Type of AGWs, *n* (%)	Not reported				
Number of AGWs, mean	Not reported				
Area of AGWs (mm^2), mean	Not reported				
Sex (M/F), *n* (%)	100% male				
Any previous treatment, *n* (%)	Not reported				
Ethnicity, *n* (%)	Not reported				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Free of AGWs at 1 week				
Recurrence of AGWs	Recurrence of AGWs at 3 months in those who were AGW free at 1 week				
AEs	Not defined. Data on general AEs reported				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllin 0.5% solution (patient applied),* n/N	*Podophyllin 1.0% solution (patient applied),* n/N	*Podophyllin 2.0% solution (patient applied),* n/N	*Estimate of effect*	*p-value*
Dichotomous outcomes						
AGW clearance at completion of treatment	1 week	23/28	24/27	27/29		Not reported
Recurrence of AGWs	3 months	6/23	6/24	8/27		Not reported
AEs: any[a]	1 week	0/28	5/27	10/29		Not reported

TABLE 96 Maiti and Haye[147] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[b]	*Comments*
	Random sequence generation	?	It is stated that men were allocated to treatment. Unclear whether a random sequence has been used to allocate treatment
	Allocation concealment	?	It is stated that the podophyllin solutions were stored in numbered bottles as prepared by the pharmacy. It is unclear whether treatment allocation could have been broken
	Selective reporting	?	Insufficient information available to assess potential bias in selective reporting
	'Other bias'	?	Insufficient information available to evaluate other potential sources of bias. Baseline characteristics have not been reported; unclear whether there is an imbalance across groups in patient characteristics
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✓	The podophyllin solutions were prepared by the pharmacy in a hospital. Solutions (2 ml) were stored in numbered bottles. The solution concentration in the bottle was known only to the pharmacist and was not revealed until completion of the study
	Blinding of outcomes assessment	✓	It is not stated that the clinician assessing AGW clearance was masked to treatment but the reviewers consider it likely that the assessor was masked to treatment as only the pharmacist was aware of the solution concentrations
	Incomplete outcome data	?	Number of men randomised to each group is not reported. In total, 16 men did not attend the 3-month follow-up. It is unclear whether the 100 men randomised were treated or whether the 16 men withdrew before treatment and whether there is an imbalance between groups in the number of men withdrawing. Reasons for withdrawal are not reported. The impact of withdrawal on the effect estimate is unclear
Recurrence of AGWs	Blinding (participants and personnel)	✓	The podophyllin solutions were prepared by the pharmacy in a hospital. Solutions (2 ml) were stored in numbered bottles. The solution concentration in the bottle was known only to the pharmacist and was not revealed until completion of the study

continued

TABLE 96 Maiti and Haye[147] (*continued*)

Item	Details		
	Blinding of outcomes assessment	✓	It is not stated that the clinician assessing AGW recurrence was masked to treatment but the reviewers consider it likely that the assessor was masked to treatment as only the pharmacist was aware of the solution concentrations
	Incomplete outcome data	?	Number of men randomised to each group is not reported. It is unclear whether there were any additional losses to follow-up during the follow-up period. The analysis is based on all people with complete clearance
AEs	Blinding (participants and personnel)	✓	The solutions of podophyllin were prepared by the pharmacy in a hospital. Solutions (2 ml) were stored in numbered bottles. The solution concentration in the bottle was known only to the pharmacist and was not revealed until completion of the study
	Blinding of outcomes assessment	✓	It is not stated that the clinician assessing AEs was masked to treatment but the reviewers consider it likely that the assessor was masked to treatment as only the pharmacist was aware of the solution concentrations
	Incomplete outcome data	?	Number of men randomised to each group is not reported. In total, 16 men did not attend the 3-month follow-up. It is unclear whether the 100 men randomised were treated or whether the 16 men withdrew before treatment and whether there is an imbalance between groups in the number of men withdrawing. Reasons for withdrawal are not reported. The impact of withdrawal on the effect estimate is unclear
Overall rating of bias		?	Reflects limited reporting in the full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation.

a The five men in the group receiving podophyllin 1% solution experienced minor inflammation that was treated with salt baths. By contrast, in the podophyllin 2% solution group, men experienced moderate chemical burns and soreness that required medication (hydrocortisone 0.5% cream).

b ✓, low risk of bias; ?, unclear risk of bias.

TABLE 97 Matteelli *et al.*[120]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Sam Barton	
Study ID	Matteelli 2001	
Study details	*Sex Transm Dis* 2001;**28**:343–6	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Study carried out at one site in Italy	
Trial sponsor	Study drug provided complementarily by Pharmacia & Upjohn	
Conflicts of interest	Not reported	
Patient enrolment	Not reported	
Trial design	Crossover RCT. People initially receiving placebo were crossed over to cidofovir at 4 weeks in an open-label extension phase. Pre- and post-crossover data are reported in the publication. Only pre-crossover data have been extracted	
Trial duration	Initial treatment period of 2 weeks followed by 2 weeks of observation	
Line of therapy	Most people enrolled were experiencing recurrence of AGWs after surgery	
Inclusion criteria	Men and women were eligible for enrolment if they aged ≥ 18 years; had a laboratory-confirmed diagnosis of HIV infection; had a clinical diagnosis of external AGWs established by physical examination; were able to give signed, informed consent; were able to use condoms during the treatment and follow-up period; were free of signs and symptoms associated with other HIV-related opportunistic infections and neoplasms at the time of enrolment	
Exclusion criteria	Men and women were ineligible if they had impaired renal function; were pregnant; had received chemical or surgical therapy for their AGWs in the preceding 2 months	
All outcomes reported in paper	Volume of AGW clearance; AEs	
Subgroups evaluated	By gender (pre- and post-crossover results combined for cidofovir) and by AGW location	
Stratification	None reported	
Baseline measurement of disease	A clinical examination was performed at baseline, but, because most patients had very extensive lesions, the total AGW area and total number of AGWs were not recorded	
Treatment	*Cidofovir 1% cream*	*Placebo*
Randomised, *n*	6	6
Withdrawals, *n* (%)	Not reported. It is stated that 4 out of 12 (33%) people discontinued cidofovir 1% after the first week of therapy because of severe mucosal erosions. It is unclear how many of the four people discontinuing were included among the six people allocated to cidofovir 1% in the blinded treatment phase and how many were from the open-label phase	
Treatment regimen	Cidofovir 1% cream or placebo was applied once daily on all external AGWs at bedtime 5 days a week for 2 weeks	
Duration/number of administered treatment	Not reported	

continued

TABLE 97 Matteelli *et al.*[120] (*continued*)

Item	Details		
Baseline patient characteristics	*Cidofovir 1% cream*	*Placebo*	p-*value*
Age (years), mean	33.8	31.8	Difference between groups reported to be not significant
Duration of disease	Not reported		
Site of AGWs, *n* (%)			
Perianal	5 (83.3)	3 (50.0)	Difference between groups reported to be not significant
Vulvar	3 (50.0)	2 (33.3)	
Perineal	1 (16.7)	3 (50.0)	
Penile	1 (16.7)	2 (33.3)	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	Not reported		
Area of AGWs (mm^2), mean	Not reported		
Sex, *n* (%)			
Male	3 (50.0)	3 (50.0)	Difference between groups reported to be not significant
Female	3 (50.0)	3 (50.0)	
Any previous treatment, *n* (%)	5 (83.3)	4 (66.7)	Difference between groups reported to be not significant
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
Volume of wart clearance	AGW clearance at 4 weeks was assessed by comparison between baseline and post-treatment (day 28) photographic documentation of the lesions by three independent clinicians who were masked to treatment. Treatment outcome was categorised as no modification or worsening of the total AGW area between baseline and end of the follow-up period; a reduction in volume of < 25%; a reduction in volume between 25% and 50%; a reduction in volume of ≥ 50%. Data for complete clearance were not reported separately		
AEs	Signs (oedema, erythema and erosion) and symptoms (itching, pain and burning) of local reactions were recorded		
Section 4: Data extraction form			

Outcome	*Time frame*	*Cidofovir 1% cream,* n/N	*Placebo,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
Volume of wart clearance					
No reduction	4 weeks	1/6	4/6		$p = 0.02$
Reduction < 25%	4 weeks	1/6	2/6		
Reduction 25–50%	4 weeks	1/6	0/6		
Reduction > 50%	4 weeks	3/6	0/6		

TABLE 97 Matteelli *et al.*[120] (*continued*)

Item	Details			
AEs				
Itching	2 weeks	0/6	0/6	Not reported
Pain	2 weeks	1/6	0/6	
Burning	2 weeks	3/6	0/6	
Oedema	2 weeks	1/6	0/6	
Erythema	2 weeks	3/6	0/6	
Erosion	2 weeks	2/6	0/6	
Any	2 weeks	5/6	0/6	$p < 0.001$

Section 5: Clinical trial quality

Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	It is stated that people were randomly allocated to treatment. Details on method used to generate random sequence not available
	Allocation concealment	?	Details on method used to conceal allocation not available
	Selective reporting	✗	Given that volume of AGW clearance has been evaluated, it could be expected that the number of people with complete clearance would have been reported
	'Other bias'	?	Insufficient information available to evaluate other potential sources of bias
Volume of wart clearance	Blinding (participants and personnel)	✗	Described as a single-blind study (independent clinicians assessing outcomes are masked to treatment). Lack of masking of study personnel and patients could introduce bias and potentially risk breaking of masking of outcome assessors
	Blinding of outcomes assessment	✓	AGW clearance was assessed by three independent clinicians who were masked to treatment. Although patients and study personnel were aware of treatment allocation, which could influence assessment of AGW clearance, it is thought that assessment by three independent clinicians minimises the risk of bias
	Incomplete outcome data	?	The number of people withdrawing from the study is not reported. It is stated that four people withdrew from cidofovir treatment because of AEs, but results are combined from the treatment and open-label phase. It is unclear how many people withdrew from each group during the treatment phase

continued

TABLE 97 Matteelli *et al.*[120] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	✗	Described as a single-blind study (independent clinicians assessing outcomes are masked to treatment). Lack of masking of study personnel and patients could introduce bias and potentially risk breaking of masking of outcome assessors
	Blinding of outcomes assessment	✗	AGW clearance was assessed by three independent clinicians who were masked to treatment. Unclear whether same clinicians evaluated AEs. Patients were aware of treatment allocation, which could influence reporting of symptoms associated with treatment
	Incomplete outcome data	?	The number of people withdrawing from the study is not reported. It is stated that four people withdrew from cidofovir treatment because of AEs, but results are combined from the treatment and open-label phase. It is unclear how many people withdrew from each group during the treatment phase
Overall rating of bias		✗	Reflects the single-blind nature of the trial and limited reporting on clinical outcomes
Section 6: Additional comments			
Additional comments	• Baseline CD4 cell counts were 408 mm^3 and 136 mm^3 in the cidofovir 1% and placebo groups respectively • It is stated that men had a significantly higher probability of clearance after treatment with cidofovir than women [6/6 (100%) men with clearance vs. 1/6 (16.7%) women with clearance; $p = 0.003$]. Clearance rate was also significantly higher for penile than for vulvar AGWs [3/3 (100%) for penile AGWs vs. 0/3 (0%) for vulvar AGWs; $p = 0.01$]. Unclear whether clearance refers to > 50% reduction in volume of baseline AGW area		

SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 98 Mazurkiewicz and Jablonska[60]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Sam Barton
Study ID	Mazurkiewicz 1990
Study details	*J Dermatol Treat* 1990;**1**:123–5
Language of publication	English
Type of report	Full publication

TABLE 98 Mazurkiewicz and Jablonska[60] (*continued*)

Item	Details		
Section 2: Study information			
Location and number of sites	Study was carried out at the Department of Dermatology and Venereology, Warsaw School of Medicine, Poland		
Trial sponsor	Not reported		
Conflicts of interest	Not reported		
Patient enrolment	Not reported		
Trial design	RCT		
Trial duration	Initial treatment period of up to 6 weeks followed by an observation period of 4 weeks after the end of treatment for those whose AGWs had completely cleared		
Line of therapy	Mixed; patients who had received previous treatment for AGWs were included		
Inclusion criteria	Males or females with condylomata acuminata		
Exclusion criteria	People were ineligible for enrolment if they were aged < 12 years; were female and pregnant, lactating or not taking adequate contraception; had a total AGW surface area of > 10 cm^2; had received treatment for their AGWs within the 2 weeks preceding study entry		
All outcomes reported in paper	Complete clearance at various time points; appearance of new AGW during treatment; relapse; AEs		
Subgroups evaluated	None reported		
Stratification	None reported		
Baseline measurement of disease	At baseline, an investigator counted the number of AGWs and recorded AGW diameter		
Treatment	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllotoxin 0.5% cream (patient applied)*	*Podophyllin 20% solution (clinician applied)*
Randomised, *n*	16	22	16
Withdrawals, *n* (%)	2 (12.5)	6 (27.3)	3 (18.8)
Lost to follow-up	0	4 (18.2)	2 (12.5)
Other	2 (12.5%) (one dropped out because of a head injury and one because of marked pruritus)	2 (9.1%) (dropped out because of swelling of foreskin)	1 (6.3%) (withdrawn because of enlargement of papule on prepuce)
Treatment regimen	Podophyllotoxin 0.5% solution or 0.5% cream was self-applied twice daily for 3 consecutive days per week for up to 6 weeks or until complete clearance, whichever occurred earlier		Podophyllin 20% solution was applied once a week by a physician. Podophyllin solution was washed off after 2 hours after the first application, after 4 hours for the second application and after 6 hours for subsequent applications. Treatment was repeated for up to 6 weeks or until complete clearance, whichever occurred earlier
Duration/number of administered treatment	Mean number of treatments not reported		

continued

TABLE 98 Mazurkiewicz and Jablonska[60] (*continued*)

Item	Details			
Baseline patient characteristics	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllotoxin 0.5% cream (patient applied)*	*Podophyllin 20% solution (clinician applied)*	p-*value*
Age (years), mean (SD) (range)	29.2 (4.9) (21–38)	26.6 (5.4) (18–36)	31.8 (11.6) (17–54)	Difference across groups reported to be not significant
Duration of disease (months), *n* (%)	Mean duration of disease not reported. Data presented based on categories of duration			
< 2	4 (25.0)	5 (22.7)	6 (37.5)	Difference across groups reported to be not significant
2–4	10 (62.5)	7 (31.8)	7 (43.8)	
> 4	2 (12.5)	10 (45.5)	3 (18.8)	
Site of AGWs, *n* (%)				
Males				
Glans	0 (0)	0 (0)	1 (6.3)	Difference across groups reported to be not significant
Prepuce	4 (25.0)	6 (27.3)	5 (31.2)	
Shaft	1 (6.3)	0 (0)	0 (0)	
Perianal	0 (0)	0 (0)	1 (6.3)	
Other	0 (0)	0 (0)	1 (6.3)	
More than one site	9 (56.3)	13 (59.1)	6 (37.5)	
Females				
Labia majora	0 (0)	1 (4.5)	0 (0)	
Introitus	0 (0)	0 (0)	1 (6.3)	
More than one site	2 (12.5)	2 (9.1)	1 (6.3)	
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, *n* (%)	Mean number of AGWs at baseline not reported. Data presented based on categories of number of AGWs			
< 15	6 (37.5)	7 (31.8)	10 (62.5)	Difference across groups reported to be not significant
16–30	6 (37.5)	7 (31.8)	3 (18.8)	
> 30	4 (25.0)	8 (36.4)	3 (18.8)	
Area of AGWs (mm^3), mean	Mean area of AGWs at baseline not reported. Data presented based on categories of area of AGWs			
< 40	7 (43.8)	4 (18.2)	10 (62.5)	$p = 0.01$
41–80	4 (25.0)	8 (36.4)	1 (6.3)	
> 80	5 (31.2)	10 (45.5)	5 (31.2)	
Sex, *n* (%)				
Male	14 (87.5)	19 (86.4)	14 (87.5)	Difference across groups reported to be not significant
Female	2 (12.5)	3 (13.6)	2 (12.5)	
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	Not reported			

TABLE 98 Mazurkiewicz and Jablonska[60] (*continued*)

Item	Details					
Section 3: Outcomes						
Outcome	*Definition*					
AGW clearance at completion of treatment	Complete clearance at end of treatment not defined. Data on complete clearance are reported at various time points. End of treatment has been taken to be 6 weeks, which is the maximum number of treatments permitted					
AGW clearance at other time points	Complete clearance reported at 1–5 weeks of treatment					
Recurrence of AGWs	Not defined. It is stated that people with complete clearance were followed up for a further 4 weeks after the end of treatment. Data on recurrence have been presumed to be reported after 4 weeks of observation					
AEs	Local AEs were reported: oedema or swelling, pain, burning, erythema, erosion, enlarging of papule and marked pruritus					
Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Podophyllotoxin 0.5% cream (patient applied),* n/N	*Podophyllin 20% solution (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	6 weeks	11/14	9/16	5/13		Not reported
AGW clearance at other time points (cumulative on a weekly basis)	1 week	1/14	2/16	0/13		Not reported
	2 weeks	3/14	3/16	1/13		Not reported
	3 weeks	7/14	7/16	1/13		Not reported
	4 weeks	8/14	7/16	2/13		Not reported
	5 weeks	8/14	8/16	3/13		Not reported
Recurrence of AGWs	4 weeks after end of treatment	2/11	0/9	0/5	Note: it is stated that one person experiencing relapse had new lesions in a different location. Unclear whether lesions also developed in same location	
AEs						
Oedema/ swelling	6 weeks	1/16	6/22	0/16	AEs reported as occurring more frequently in podophyllotoxin group (especially cream) but *p*-values not reported	
Pain	6 weeks	1/16	5/22	0/16		
Burning	6 weeks	0/16	4/22	1/16		
Erythema	6 weeks	7/16	6/22	4/16		
Erosion	6 weeks	9/16	14/22	4/16		
Enlarging of papule	6 weeks	0/16	0/22	1/16		
Marked pruritus	6 weeks	1/16	0/22	0/16		

continued

TABLE 98 Mazurkiewicz and Jablonska[60] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	It is stated that people were randomly allocated to treatment. Details on method used to generate random sequence not available
	Allocation concealment	?	Details on method used to conceal allocation not available
	Selective reporting	?	Insufficient information available to determine risk of selective reporting
	'Other bias'	?	Insufficient information available to evaluate other potential sources of bias. It is noted that there was a significant difference in total size of AGW at baseline, with the difference potentially favouring the podophyllin 20% group. The extent of influence on the estimate of effect is unclear
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	It is stated that the study is single blind. Information on who is masked is not reported. Given the different settings for application of treatment (home vs. clinic), it could be considered impractical to mask patients and key personnel to treatment
	Blinding of outcomes assessment	?	It is unclear whether the investigator assessing clinical outcomes was masked to treatment
	Incomplete outcome data	?	The number of people withdrawing (with accompanying reasons) and lost to follow-up is reported. There is an imbalance across the groups in the proportion of people withdrawing. The impact on the estimate of effect size for complete clearance is unclear
Recurrence of AGWs	Blinding (participants and personnel)	?	It is stated that the study is single blind. Information on who is masked is not reported. Given the different settings for application of treatment (home vs. clinic), it could be considered impractical to mask patients and key personnel to treatment
	Blinding of outcomes assessment	?	It is unclear whether the investigator assessing clinical outcomes was masked to treatment
	Incomplete outcome data	?	The number of people withdrawing (with accompanying reasons) and lost to follow-up is reported. There is a slight imbalance across the groups in the proportion of people withdrawing. The impact on the estimate of effect size for recurrence is unclear
AEs	Blinding (participants and personnel)	?	It is stated that the study is single blind. Information on who is masked is not reported. Given the different settings for application of treatment (home vs. clinic), it could be considered impractical to mask patients and key personnel to treatment
	Blinding of outcomes assessment	?	It is unclear whether the investigator assessing clinical outcomes was masked to treatment

TABLE 98 Mazurkiewicz and Jablonska[60] (*continued*)

Item	Details		
	Incomplete outcome data	✓	The number of people withdrawing (with accompanying reasons) and lost to follow-up is reported. There is a slight imbalance across the groups in the proportion of people withdrawing but all but one person has been included in the analysis of AEs
Overall rating of bias		?	Reflects limited reporting in the full publication
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 99 Nath *et al.*[148]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Sam Barton
Study ID	Nath 1990
Study details	*Indian J Dermatol Venereol Leprol* 1990;**56**:22–4
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Authors based at the Departments of Dermatology and Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, India; number of sites involved not reported
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Patients were recruited from people with AGWs attending the STD clinic between 1986 and 1988
Trial design	RCT, with the exception that pregnant women were allocated to TCAA
Trial duration	Initial treatment period of 12 weeks. People who achieved a 'cure' were followed up for an additional 3 months
Line of therapy	Not reported
Inclusion criterion	Presence of AGWs
Exclusion criterion	Receipt of any treatment for AGWs in the preceding 2 months
All outcomes reported in paper	Complete clearance; recurrence
Subgroups evaluated	Duration of AGWs (< 6 months vs. > 6 months); number of lesions at baseline (< 5 vs. ≥ 5); location (moist vs. dry and keratotic areas)
Stratification	None reported
Baseline measurement of disease	Initial evaluation involved recording site and morphology of AGWs

continued

TABLE 99 Nath *et al.*[148] (*continued*)

Item	Details		
Treatment	*Podophyllin 25% solution (clinician applied)*	*TCAA 50% solution (clinician applied)*	
Randomised, *n*	It is stated that 100 people were randomised to treatment. Number randomised to each group not reported. Clinical results based on the 95 people who were followed up during the treatment period		
	47	48	
Withdrawals	Overall, five people 'defaulted' and were lost to follow-up from the initial 100 people randomised. Reasons for loss to follow-up not reported		
Treatment regimen	Podophyllin 25% solution was applied weekly with a swab stick and allowed to dry in air for 2–3 minutes. People washed off the solution with tap water 2 hours after application. Treatment was repeated weekly for up to a maximum of 12 weeks or until complete clearance, whichever occurred earlier	TCAA 50% was applied weekly with a swab stick and allowed to dry in air for 2–3 minutes. Treatment was repeated weekly for up to a maximum of 12 weeks or until complete clearance, whichever occurred earlier	
Duration/number of administered treatment	Mean number of treatments required to achieve complete clearance: 3	Mean number of treatments required to achieve complete clearance: 3.8	
	Difference between groups not statistically significant ($p > 0.05$)		
Baseline patient characteristics	*Podophyllin 25% solution (clinician applied)*	*TCAA 50% solution (clinician applied)*	p-*value*
Age (years), mean (range	Overall trial population: 25.9 (17–43); mean age for individual treatment groups not reported		Reported to be 'statistically comparable'
Duration of disease	Not reported		Not reported
Site of AGWs, *n* (%)	Not reported		Reported to be 'statistically comparable'
Type of AGWs, *n* (%)			
Hyperplastic	35 (74.5)	34 (70.8)	Not reported
Flat	4 (8.5)	4 (8.3)	
Verruca vulgaris	3 (6.4)	6 (12.5)	
Pigmented	3 (6.4)	4 (8.3)	
Giant	2 (4.3)	0 (0)	
Number of AGWs, mean	Not reported		
Area of AGWs (mm^2), mean	Not reported		
Sex, *n* (%)			
Male	44 (93.6)	44 (91.7)	Not reported
Female	3 (6.4) (no women were pregnant)	4 (8.3) (all women were pregnant)	Not reported
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		

TABLE 99 Nath *et al.*[148] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Free of AGWs at 3 months (end of maximum number of permitted treatments)				
Recurrence of AGWs	Recurrence of AGWs within 3 months of clearance				
AEs	Absolute numbers not reported. It is stated that 'Local soreness was experienced by 8.5% cases. There was no systemic toxicity' (p. 23)				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllin 25% solution (clinician applied),* n/N	*TCAA 50% solution (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	3 months	38/47	39/48		Not reported
Recurrence of AGWs	3 months after clearance	14/38	6/39		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	It is stated that people were randomly allocated to treatment. However, women were allocated by pregnancy status, not randomly. The rationale for this decision is not reported. Only seven women (7% of full trial population) were included. The impact of this decision on the estimate of effect is unclear. Details on method used to generate random sequence not available	
	Allocation concealment		?	Details on method used to conceal allocation not available	
	Selective reporting		?	Insufficient information available to determine risk of selective reporting. Limited information reported on AEs (no absolute numbers) but authors of the paper acknowledge that both treatments are associated with recognised AEs; unclear whether this is selective reporting or whether presence of AEs was not a prespecified outcome	
	'Other bias'		?	Insufficient information available to evaluate other potential sources of bias	
AGW clearance at completion of treatment	Blinding (participants and personnel)		?	Level of masking of study personnel and patients is not reported. It is stated that the treatments were applied by the same observer. It is unclear whether the observer was masked to treatment	
	Blinding of outcomes assessment		?	It is unclear whether the investigator assessing clinical outcomes was masked to treatment	

continued

TABLE 99 Nath *et al.*[148] (*continued*)

Item	Details		
	Incomplete outcome data	?	The number of people randomised to each group is not reported. The number of people lost to follow-up during the treatment period is reported, but it is unclear whether these were the only people withdrawing from treatment and whether there is a potential imbalance across the groups
Recurrence of AGWs	Blinding (participants and personnel)	?	Level of masking of study personnel and patients is not reported. It is stated that the treatments were applied by the same observer. It is unclear whether the observer was masked to treatment
	Blinding of outcomes assessment	?	It is unclear whether the investigator assessing clinical outcomes was masked to treatment
	Incomplete outcome data	?	The number of people randomised to each group is not reported. The number of people lost to follow-up during treatment is reported, but it is unclear whether these were the only people withdrawing from treatment and whether other people withdrew during the follow-up phase
Overall rating of bias		?	Reflects limited reporting of methods in full publication
Section 6: Additional comments			
Additional comments	• It is stated that recent AGWs (< 6 months' duration) responded earlier than older lesions. Recent AGWs required a mean of 3.4 applications to achieve clearance compared with a mean of 4.1 applications for older lesions (≥ 6 months' duration); results not reported separately by treatment group • Patients with fewer than five lesions achieved complete clearance much faster than those with five or more lesions (no data reported) • Lesions in moist areas (glans, inner prepuce, interlabial) required a mean of 3.4 applications for complete clearance compared with a mean of 4.3 applications for dry and keratotic lesions; data not reported separately by treatment group		

	Number (%) of people cleared of AGW at 3 months		Mean (SD) number of treatments required to clear AGW at 3 months	
Type of AGW	Podophyllin 25%	TCAA 50%	Podophyllin 25%	TCAA 50%
Hyperplastic	31/35 (88)	30/34 (88)	3.4 (1.88)	3.7 (1.9)
Flat	3/4 (75)	3/4 (75)	4.0 (1.84)	5.0 (2.1)
Verruca vulgaris	2/3 (67)	4/6 (67)	4.0 (1.76)	5.0 (2.12)
Pigmented	2/3 (67)	2/4 (50)	4.2 (1.67)	4.4 (1.82)
Giant	0/2	–	–	–

SD, standard deviation; STD, sexually transmited disease.
a ?, unclear risk of bias.

TABLE 100 Orlando *et al.*[128]

Item	Details		
Section 1: Reviewer and study information			
Reviewers' names	Jacoby Patterson and Sam Barton		
Study ID	Orlando 2002		
Study details	*AIDS* 2002;**16**:447–50		
Language of publication	English		
Type of report	Full publication		
Section 2: Study information			
Location and number of sites	Study carried out at the Department of Infectious Diseases, STD Service, L Sacco Hospital, Milan, Italy		
Trial sponsor	Not reported		
Conflicts of interest	Not reported		
Patient enrolment	Patients were enrolled from people referred to the Department of Infectious Diseases, STD Service, L Sacco Hospital, from January 2000 to March 2001		
Trial design	RCT (three arms)		
Trial duration	Initial assessment at the end of treatment (varies with allocated treatment) followed by 6 months' follow-up for those who achieved complete clearance with treatment		
Line of therapy	Not reported		
Inclusion criteria	HIV-positive people with genital AGWs were eligible for enrolment		
Exclusion criteria	Not reported		
All outcomes reported in paper	Complete clearance; recurrence		
Subgroups evaluated	None reported		
Stratification	None reported		
Baseline measurement of disease	At baseline, lesion size, number and location were recorded, the sum of which was defined as the 'lesion score'. For the full trial population, at baseline, the mean lesion score was 76.57 (range 5–292). Difference between groups reported to be not significant		
Treatment	*Electrocauterisation*	*Cidofovir 1% (patient applied)*	*Electrocauterisation plus cidofovir 1%*
Randomised, *n*	29	26	19
Withdrawals, *n* (%)	Not reported	Not reported It is stated that three people definitively stopped application of cidofovir 1%. It is unclear from which treatment group or groups people withdrew	Not reported

continued

TABLE 100 Orlando *et al.*[128] (*continued*)

Item	Details			
Treatment regimen	Surgical excision by electrocautery; further details not reported	Topical cidofovir 1% gel was self-applied for 1–2 hours for 5 days per week. Treatment was repeated weekly for a maximum of 6 weeks or until complete clearance, whichever occurred earlier	After initial electrocauterisation, cidofovir 1% gel was self-applied for 1–2 hours for 5 days per week for 2 weeks. Application of cidofovir 1% commenced within 1 month of surgical treatment	
Duration/ number of administered treatment	Not applicable	Not reported		
Baseline patient characteristics	*Electrocauterisation*	*Cidofovir 1% (patient applied)*	*Electrocauterisation plus cidofovir 1%*	p-*value*
Age (years), mean (range)	Full trial population 33.4 (24–41); mean age not reported for individual treatment groups			Difference between groups reported to be not significant
Duration of disease	Not reported			
Site of AGWs, *n* (%)	It is stated that 'warts lesions were located in the perianal area (15 patients), the vulval area (15 patients), on the perineum (three patients) and on the penis (42 patients)' (p. 448). Site of AGWs not reported by treatment group			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	Not reported. Mean lesion score for full trial population was 76.57 (range 5–292)			Difference between groups reported to be not significant
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	Full trial population consisted of 53 men (71.6%) and 21 (28.4%) women; proportions not reported for individual treatment groups			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Complete response was defined as an end of treatment lesion score of 0% of the baseline score. Lesion score was calculated by summing the size (mm), number and anatomic localisation of lesions			
Recurrence of AGWs	Recurrence was defined as the reappearance of lesions in the same anatomical area after a complete response			
AEs	Not defined. Occurrence of mild local erosion was reported			

TABLE 100 Orlando *et al.*[128] (*continued*)

Item	Details					
Section 4: Data extraction form						
Outcome	*Time frame*	*Electrocauterisation*, n/N	*Cidofovir 1% (patient applied)*, n/N	*Electrocauterisation plus cidofovir 1%*, n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	Treatment dependent	27/29	20/26	19/19		$p = 0.033$
Recurrence of AGWs	6 months after end of treatment	14/19	6/17	3/11		$p = 0.018$
AEs: mild local erosions	End of treatment	–	11/26	6/19		
Section 5: Clinical trial quality						
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*		
	Random sequence generation		?	It is stated that men were randomly allocated to treatment. Details on method used to generate random sequence not available		
	Allocation concealment		?	Details on method used to conceal allocation not available		
	Selective reporting		✗	It is stated that partial response (defined as an end of treatment score of < 50% of baseline score) was recorded but data on this outcome are not reported		
	'Other bias'		?	Insufficient information available to evaluate other potential sources of bias. Unclear whether any imbalances in baseline characteristics are present as few details reported		
AGW clearance at completion of treatment	Blinding (participants and personnel)		✗	Described as an open-label trial. Given that two of the treatment groups involve a surgical intervention, it might be impractical to mask to treatment allocation. Assessment of AGW clearance is typically subjective and could potentially be influenced by patients and key study personnel		
	Blinding of outcomes assessment		✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence by lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken		
	Incomplete outcome data		?	The number of people withdrawing during the treatment period because of an AE of cidofovir is reported, but it is unclear whether these were the only people withdrawing during treatment and whether there is a potential imbalance across the groups		

continued

TABLE 100 Orlando *et al.*[128] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	✗	Described as an open-label trial. Given that two of the treatment groups involve a surgical intervention, it might be impractical to mask to treatment allocation. Assessment of AGW recurrence is typically subjective and could potentially be influenced by patients and key study personnel
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AGW recurrence is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	✗	The number of people with complete clearance returning for assessment at 6 months is reported. There is an imbalance across groups in the proportion of people lost to follow-up for this assessment. The large variation in proportion of missing outcomes could introduce clinically relevant bias in the evaluation of the effect estimate
AEs	Blinding (participants and personnel)	✗	Described as an open-label trial. Given that two of the treatment groups involve a surgical intervention, it might be impractical to mask to treatment allocation. Assessment of AEs could be subjective and potentially influenced by patients and key study personnel
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	The number of people withdrawing during the treatment period because of an AE of cidofovir is reported, but it is unclear whether these were the only people withdrawing during treatment and whether there is a potential imbalance across the groups
Overall rating of bias		✗	Reflects limited reporting on clinical outcomes and the open-label nature of the trial
Section 6: Additional comments			
Additional comments	Mean CD4 count at baseline was 264.9 mm^3; not reported by treatment group		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 101 Padhiar *et al.*[132]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Vicky Wakefield and Sam Barton	
Study ID	Padhiar 2006	
Study details	*Indian J Sex Transmit Dis* 2006;**27**:67–9	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	STD clinic at the Civil Hospital, Ahmedabad, India	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	People enrolled from the STD clinic at the Civil Hospital, Ahmedabad, India. Additional details not provided	
Trial design	RCT	
Trial duration	Initial treatment period (16 weeks with imiquimod 5% vs. 6 weeks with podophyllin 20%) followed by a 6-month follow-up period after clearance of AGWs	
Line of therapy	Not reported	
Inclusion criteria	Aged 12–65 years; clinically diagnosed external AGWs with at least two but no more than 50 AGWs at baseline; HIV-negative status	
Exclusion criteria	Not reported	
All outcomes reported in paper	Clearance of AGWs at end of treatment; recurrence; time to complete clearance; volume of AGW clearance; AEs	
Subgroups evaluated	None	
Stratification	Not reported	
Baseline measurement of disease	At baseline, a detailed assessment of AGWs was carried out, including evaluation of number, area and location of AGWs	
Treatment	*Imiquimod 5%*	*Podophyllin 20%*
Randomised, *n*	30	30
Withdrawals, *n* (%)	Not reported	
Treatment regimen	After cleaning and drying the skin, participants applied the cream before going to bed to all external lesions in an amount that could be rubbed into the skin until the cream disappeared. The skin was cleaned 6–10 hours after application. Imiquimod 5% was applied three times a week until all baseline AGWs had disappeared or for a maximum of 16 weeks, whichever occurred first	Perilesional skin was covered with petroleum jelly. After cleaning and drying the AGWs, podophyllin 20% was applied with a swab stick. The skin was cleaned 4–6 hours after application. Podophyllin 20% was applied once a week until all baseline AGWs had disappeared or for a maximum of 6 weeks, whichever occurred first. Not reported whether podophyllin was applied by the patient or clinician; assumed to be the clinician
Duration/number of administered treatment	Not reported	

continued

TABLE 101 Padhiar *et al.*[132] (*continued*)

Item	Details				
Baseline patient characteristics	*Imiquimod 5%*		*Podophyllin 20%*	p-*value*	
Age (years), mean (with SD/SE if given) (range)	Not reported [reports that largest proportion of people were in the age range 26–35 years: 27 (45%) people]				
Duration of disease (months), median	5				
Site of AGWs, *n* (%)	Not reported				
Type of AGWs, *n* (%)	Not reported				
Total number of AGWs (mean number not reported)	105		90	Not reported	
Total area of AGWs (mm^2) (mean area not reported)	2100		2500	Not reported	
Sex (M/F), *n* (%)	54 males and 6 females randomised				
Any previous treatment, *n* (%)	Not reported				
Ethnicity, *n* (%)	Not reported				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Complete clearance by the end of the treatment period (16 weeks with imiquimod 5% vs. 6 weeks with podophyllin 20%)				
Recurrence of AGWs	Recurrence at 6 months' follow-up				
Time to complete clearance	Median duration in weeks until complete clearance				
Volume of wart clearance	Proportion of people with a decrease in area of lesions corresponding to < 50% or 50–99% of baseline lesion area at end of treatment				
AEs	Not defined. Data presented for erythema, oedema, scabbing, itching, systemic signs and symptoms, headache, flu-like symptoms, diarrhoea and tingling				
Section 4: Data extraction form					
Outcome	*Time frame*	*Imiquimod 5%,* n/N	*Podophyllin 20%,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at end of treatment	Treatment dependent	16/30	14/30		Not reported
Recurrence of AGWs	6 months after end of treatment	5/16	9/14		Not reported
Volume of wart clearance (%)					
< 50	End of treatment	4/30	3/30		Not reported
50–99	End of treatment	10/30	13/30		Not reported

TABLE 101 Padhiar *et al.*[132] (*continued*)

Item	Details			
AEs				
Erythema	End of treatment	21/30	16/30	Not reported
Oedema	End of treatment	4/30	17/30	Not reported
Scabbing, induration, ulceration, and vesiculation	End of treatment	6/30	20/30	Not reported
Itching	End of treatment	9/30	15/30	Not reported
Systemic signs and symptoms (not further defined)	End of treatment	3/30	10/30	Not reported
Headache	End of treatment	2/30	4/30	Not reported
Flu-like symptoms	End of treatment	1/30	0/30	Not reported
Diarrhoea	End of treatment	0/30	3/30	Not reported
Tingling	End of treatment	0/30	3/30	Not reported
Continuous outcomes				
Time to complete clearance (weeks), median		8 ($n = 16$)	4.85 ($n = 14$)	Not reported

Section 5: Clinical trial quality

Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	Described as a randomised study but details on method of randomisation not available
	Allocation concealment	?	No details provided
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	Information on masking not available
	Blinding of outcomes assessment	?	Unclear whether clinician assessing clearance was masked to treatment
	Incomplete outcome data	?	Withdrawals and loss to follow-up were not disclosed. Although analysis of AGW clearance at end of treatment is based on an ITT analysis, unclear whether there is an imbalance in withdrawals between the groups

continued

TABLE 101 Padhiar *et al.*[132] (*continued*)

Item	Details		
Recurrence of AGW	Blinding (participants and personnel)	?	Information on masking not available
	Blinding of outcomes assessment	?	Unclear whether clinician assessing recurrence was masked to treatment
	Incomplete outcome data	?	Withdrawals and loss to follow-up were not disclosed. Unclear whether there is an imbalance in withdrawals between the groups
Time to complete clearance	Blinding (participants and personnel)	?	Information on masking not available
	Blinding of outcomes assessment	?	Unclear whether clinician assessing clearance was masked to treatment
	Incomplete outcome data	?	Withdrawals and loss to follow-up were not disclosed. Unclear whether there is an imbalance in withdrawals between the groups
Volume of wart clearance (e.g., proportion of patients with 50% clearance)	Blinding (participants and personnel)	?	Information on masking not available
	Blinding of outcomes assessment	?	Unclear whether clinician assessing clearance was masked to treatment
	Incomplete outcome data	?	Withdrawals and loss to follow-up were not disclosed. Unclear whether there is an imbalance in withdrawals between the groups
AEs	Blinding (participants and personnel)	?	Information on masking not available
	Blinding of outcomes assessment	?	Unclear whether clinician assessing AEs was masked to treatment
	Incomplete outcome data	?	Withdrawals and loss to follow-up were not disclosed. Unclear whether there is an imbalance in withdrawals between the groups
Overall rating of bias		?	Reflects limited reporting in full publication
Section 6: Additional comments			
Additional comments	Reports that the most common location of AGWs was the penis in men and the vulva in women (50%)		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ?, unclear risk of bias.

TABLE 102 Petersen *et al.*[141]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Fatima Salih and Sam Barton
Study ID	Petersen 1995
Study details	*Genitourin Med* 1995;**71**:391–2
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at three dermato-venereological centres at the University of Copenhagen: Bispebjerg Hospital, Rigshospitalet and Gentofte Hospital
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Not reported
Trial design	RCT
Trial duration	Initial treatment duration of 2–4 weeks, with final follow-up at 12 weeks
Line of therapy	Not reported
Inclusion criteria	Diagnosis of condyloma acuminatum; general good health; no topical or systemic antiviral or AGW treatment in the 4 weeks preceding the study
Exclusion criteria	No additional exclusion criteria reported
All outcomes reported in paper	Complete clearance; AEs
Subgroups evaluated	None reported
Stratification	None reported
Baseline measurement of disease	Not reported. It is stated that 'clinical efficacy was determined by quantitative assessment of the treated AGWs. The two larger perpendicular dimensions of the AGWs were measured and the AGW area was defined as the product of these two measurements' (p. 391). It is inferred that this measurement was also carried out at baseline

continued

TABLE 102 Petersen *et al.*[141] (*continued*)

Item	Details		
Treatment	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllotoxin 0.5% cream (patient applied)*	
Randomised, *n*	Number of people randomised to each group not reported. It is reported that 36 people were enrolled (in batches of 14, 12 and 10 at the three individual sites)		
Number of lesions randomised	133	136	
Withdrawals, *n* (%)	Not reported. It is stated that 'Only one patient treated with podophyllotoxin cream 0.5% did not complete the trial for reasons not associated with therapy' (p. 392); no further details available		
Treatment regimen	Podophyllotoxin 0.5% in alcoholic solution or podophyllotoxin 0.5% cream was self-applied twice daily for 3 days and the cycle repeated after a 4-day interval for a minimum of two and a maximum of four cycles		
Duration/ number of administered treatment	Not reported. It is stated that the number of applications of podophyllotoxin cream or solution was not statistically significantly different between the two treatment groups		
Baseline patient characteristics	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllotoxin 0.5% cream (patient applied)*	p-*value*
Age (years), mean	24	22	Not reported
Duration of disease (months), mean	2.5	3.5	Not reported
Site of AGWs, *n* (number of AGWs at sites)			
Penile	122	126	Not reported
Perianal	5	7	Not reported
Urethral	4	3	Not reported
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, median	7	8	Not reported
Area of AGWs (mm^2), mean (SD)	92.3 (7.5)	87.7 (8.4)	Not reported
Sex (M/F), *n* (%)	100% men		
Any previous treatment (%)	30 (absolute numbers not reported)	28 (absolute numbers not reported)	Not reported
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at other time points	Not defined. Results for number of AGWs remaining are presented at various time points (extracted into additional comments); no data specified as results at 'end of treatment'. Proportion of men with complete clearance (expressed as a percentage) is reported for 2 weeks after the end of treatment and for week 12		
AEs	Safety was assessed by questioning and examining patients for local reactions indicating intolerance of the treatment. It is stated that tenderness, burning, pain, erythema, erosions and oedema were noticed and recorded as mild, moderate or severe (definitions not available)		

TABLE 102 Petersen *et al.*[141] (*continued*)

Item	Details						
Section 4: Data extraction form							
Outcome	*Time frame*	*Podophyllotoxin 0.5% solution (patient applied),* n/N		*Podophyllotoxin 0.5% cream (patient applied),* n/N		*Estimate of effect*	p-*value*
Dichotomous outcomes							
AGW clearance at other time points	2 weeks after end of treatment	95%	Not reported	63%	Not reported		Not reported
	12 weeks (end of study)	63%	Not reported	63%	Not reported		Not reported
AEs: mild to moderate	During treatment	35%	Not reported	40%	Not reported	Separate analyses of individual AEs identified no statistically significant differences between treatment groups	
Section 5: Clinical trial quality							
Outcome	*Risk of bias*				*Risk assessment*[a]	*Comments*	
	Random sequence generation				?	It is stated that men were randomly allocated to treatment. Details on method used to generate random sequence not available	
	Allocation concealment				?	Details on method used to conceal allocation not available	
	Selective reporting				✗	Complete clearance at various time points is reported by number of AGWs cleared and percentage of men with complete clearance, with no absolute numbers reported. Data reported cannot be entered in a meta-analysis. In addition, data for clearance at end of treatment are not reported	
	'Other bias'				?	Insufficient information available to evaluate other potential sources of bias	
AGW clearance at various time points	Blinding (participants and personnel)				?	Study is described as single blind. It is unclear who was masked to treatment (men participating, key study personnel or outcome assessor). Given the difference in the formulations of podophyllotoxin 0.5% (cream vs. solution), it is likely not to have been feasible to mask participants and key study personnel to treatment. It is unclear whether the outcome assessor was masked to treatment. If the outcome assessor was masked to treatment, the probability of masking been broken is unclear	
	Blinding of outcomes assessment				?		

continued

TABLE 102 Petersen *et al.*[141] (*continued*)

Item	Details		
	Incomplete outcome data	?	Number of people randomised to each group and number of people evaluated in each group not reported. It is stated that only one person withdrew for a non-treatment-related reason; not reported from which group the person withdrew. Number of people withdrawing for treatment-related reasons or lost to follow-up not reported. Unclear whether there is an imbalance between groups in those excluded from analysis
AEs	Blinding (participants and personnel)	?	Study is described as single blind. It is unclear who was masked to treatment (men participating, key study personnel or outcome assessor). Given the difference in the formulations of podophyllotoxin 0.5% (cream vs. solution), it might be difficult to mask participants to treatment, which could jeopardise masking of study personnel or outcome assessor
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Number of people randomised to each group and number of people evaluated in each group not reported. It is stated that only one person withdrew for a non-treatment-related reason; not reported from which group the person withdrew. Number of people withdrawing for treatment-related reasons or lost to follow-up not reported. Unclear whether there is an imbalance between groups in those excluded from analysis
Overall rating of bias		✗	Reflects limited reporting of clinical effectiveness results in full publication

Section 6: Additional comments

Additional comments

	Podophyllotoxin 0.5% solution		Podophyllotoxin 0.5% cream	
Week of study	Number of lesions	Mean (SD) AGW area (mm²)	Number of lesions	Mean (SD) AGW area (mm²)
0	133	92.3 (7.5)	136	87.7 (8.4)
1	85	59.7 (6.7)[a]	122	76.0 (5.6)
2	72	47.0 (4.8)[a]	102	66.4 (8.7)
3	38	25.2 (3.2)[b]	80	52.2 (7.2)[a]
5	12	9.2 (0.8)[b]	51	33.6 (4.2)[a]
6	5	4.5 (0.5)[b]	44	29.2 (3.2)[b]
12	29	21.5 (2.8)[b]	32	20.6 (2.7)[b]

a $p < 0.05$ (significant reduction from baseline).
b $p < 0.01$ (significant reduction from baseline).

M/F, male/female; SD, standard deviation.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 103 Sherrard and Riddell[149]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Sam Barton
Study ID	Sherrard 2007
Study details	*Int J STD AIDS* 2007;**18**:365–8
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out in UK; number of sites involved is unclear
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	People presenting with new or recurrent AGWs were eligible for enrolment; dates of enrolment not reported
Trial design	RCT (five treatment groups)
Trial duration	8 weeks (maximum treatment period); no follow-up observation period
Line of therapy	Mixed
Inclusion criteria	People with new or recurrent AGWs that had not been treated in the preceding 3 months
Exclusion criteria	People were excluded if they were aged < 16 years; were pregnant women or women not using effective contraception; had atypical lesions where malignancy suspected; were unable to complete 8 weeks' treatment at the department; refused a specific treatment modality; were immunosuppressed, including HIV infevtion
All outcomes reported in paper	Complete clearance
Subgroups evaluated	By number of AGWs (< 4 vs. 5–9 vs. ≥ 10)
Stratification	None reported
Baseline measurement of disease	Number and surface area of AGWs were assessed at baseline

Treatment	*Podophyllin 25% (clinician applied)*	*TCAA*	*Cryotherapy*	*TCAA plus podophyllin 25%*	*Cryotherapy plus podophyllin 25%*
Randomised, *n*	79	88	81	85	76
Withdrawals, *n* (%)	23 (29.1)	30 (34.1)	15 (18.5)	20 (23.5)	17 (22.4)
Withdrawals for various reasons, *n* (%)	4 (5.1)	3 (3.4)	4 (4.9)	4 (4.7)	4 (5.3)
	Reasons for withdrawal were reported to be difficulty attending for follow up (seven people); wanting to try to conceive (two women); fear of cryotherapy machine (three people); reaction to podophyllin (one person); cryotherapy too painful to tolerate (one person); cryotherapy machine out of order (one person). Other reasons not reported. Reasons for withdrawal not reported by treatment group				

continued

TABLE 103 Sherrard and Riddell[149] (*continued*)

Item	Details					
Loss to follow-up (defined as 'did not attend'), *n* (%)	19 (24.1)	27 (30.7)	11 (12.5)	16 (18.8)	13 (17.1)	
Treatment regimen	Podophyllin 25%	TCAA (concentration not reported)	Cryotherapy	TCAA followed by podophyllin 25%	Cryotherapy followed by podophyllin 25%	
	Treatment regimens were applied on a weekly basis until AGW clearance or for a maximum of eight treatments, whichever occurred earlier. It is stated that a standard assessment and treatment proforma was used and that all doctors and nurses in the department were formally instructed in the use of each modality. When combined treatments were given, treatments were applied together to each wart, with initial application of the destructive method (i.e. cryotherapy or TCAA) followed by podophyllin 25%					
Median number of treatments to wart clearance (based on 'on-treatment' population)	2.6	2.6	1.7	1.5	1.3	
Baseline patient characteristics	*Podophyllin 25% (clinician applied)*	*TCAA*	*Cryotherapy*	*TCAA plus podophyllin 25%*	*Cryotherapy plus podophyllin 25%*	p-*value*
Age (years), mean	25.4	25.4	26.8	26.0	25.7	Not reported
Duration of disease	Not reported					
Site of AGWs, *n* (%)	Not reported					
Type of AGWs, *n* (%)	Not reported					
Number of AGWs, median	4.2	4.8	4.1	4.7	4.4	Not reported
Area of AGWs (mm^2), mean	Not reported					
Sex, *n* (%)	*n* calculated by review authors; proportion of men and women in each group presented as ratios in full publication					
Male	41 (51.9)	46 (52.3)	42 (51.8)	46 (54.1)	41 (53.9)	Not reported
Female	38 (49.1)	42 (47.7)	39 (49.2)	39 (45.9)	35 (46.1)	Not reported
Any previous treatment, *n* (%)	Not reported					
Ethnicity, *n* (%)	Not reported					

TABLE 103 Sherrard and Riddell[149] (*continued*)

Item	Details							
Section 3: Outcomes								
Outcome	*Definition*							
AGW clearance at completion of treatment	AGW clearance after a maximum of eight treatments. Analysis based on ITT population, in which defaulters were counted as treatment failures							
AGW clearance at other time points	Percentage of AGWs cleared after two treatments (stated to represent 'clinical situation')							
Section 4: Data extraction form								
Outcome	*Time frame*	*Podophyllin 25% (clinician applied),* n/N	*TCAA,* n/N	*Cryotherapy,* n/N	*TCAA plus podophyllin 25%,* n/N	*Cryotherapy plus podophyllin 25%,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes								
AGW clearance at completion of treatment	Up to 8 weeks	46/79	49/88	61/81	63/85	59/76		
AGW clearance at other time points (number of events calculated by review authors)	After two treatments	22/79	22/88	41/81	42/85	42/76	Based on Figure 1; assumed reported percentages were based on proportion of people with complete clearance rather than percentage of AGWs cleared. *p*-value not reported	
Section 5: Clinical trial quality								
Outcome	*Risk of bias*			*Risk assessment*[a]			*Comments*	
	Random sequence generation			?			It is stated that people were randomly allocated to treatment. Details on method used to generate random sequence not available	
	Allocation concealment			?			Details on method used to conceal allocation not available	
	Selective reporting			?			Results are presented only for complete clearance. No information is reported for AEs. It is stated that the objective of the study was 'to assess effectiveness of the five most commonly used clinic-based wart treatments' (p. 365). Protocol is not available. Unclear whether there are prespecified outcomes that have not been reported	

continued

TABLE 103 Sherrard and Riddell[149] (*continued*)

Item	Details		
	'Other bias'	?	Insufficient information available to evaluate other potential sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	Level of masking is not described. Given the variation in the treatment types (topical vs. surgical vs. combination), it is likely not to have been feasible to mask participants and key study personnel to treatment. It is unclear whether the outcome assessor was masked to treatment. If the outcome assessor was masked to treatment, the probability of masking been broken is unclear
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Number of withdrawals and loss to follow-up is reported. Reasons for withdrawal are not reported for all withdrawals. There is a slight variation across groups in the proportion of people who withdrew or were lost from each group (from 18.5% to 34.1%) and the impact of this variation on the effect estimate is unclear
Overall rating of bias		?	Reflects limited reporting on methods in full publication
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 104 Simmons *et al.*[160]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Sam Barton	
Study ID	Simmons 1981a	
Study details	*Br J Vener Dis* 1981;**57**:273–4	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Study was carried out in the UK; number of sites and location unclear	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Not reported	
Trial design	RCT	
Trial duration	Up to two treatments at a 2-week interval plus a minimum follow-up for 3 months from start of the trial	
Line of therapy	Not reported	
Inclusion criteria	Men with AGWs who had given informed consent	
Exclusion criteria	Not reported	
All outcomes reported in paper	Complete clearance	
Subgroups evaluated	None reported	
Stratification	None reported	
Baseline measurement of disease	Not reported	
Treatment	*Cryotherapy*	*Electrocautery*
Randomised, *n*	24	18
Withdrawals, *n* (%)	8 (33.3%) (at 3 months' follow-up); reasons for withdrawal not reported	7 (38.9%) (at 3 months' follow-up); reasons for withdrawal not reported
Treatment regimen	Cryotherapy with nitrous oxide (no local anaesthetic). The cryoprobe produced ice balls 1–2 mm larger than the diameter of the AGW to be treated (no electrolyte or lubricant applied). Treatment could be repeated once, 2 weeks later (based on assessment by a clinician who was masked to treatment)	Electrocautery with 2% lidocaine as a local anaesthetic. No further details reported. Treatment could be repeated once, 2 weeks later (based on assessment by a clinician who was masked to treatment)
Duration/number of administered treatment	Mean number of treatments required for 'cure': 2.6	Mean number of treatments required for 'cure': 1.4

continued

TABLE 104 Simmons *et al.*[160] (*continued*)

Item	Details			
Baseline patient characteristics	*Cryotherapy*		*Electrocautery*	p-*value*
Age (years), mean	Not reported			Reported to be comparable between treatment groups
Duration of disease	Not reported			
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	Not reported			Reported to be comparable between treatment groups
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% men			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	Not reported			Reported to be comparable between treatment groups
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at other time points	Complete clearance at 3 months' follow-up			
AEs	Reporting of AEs was minimal. It was stated that 'No ulceration occurred after cryotherapy and no patient required local anaesthesia' (p. 274). It is also reported that no patient complained of pain			
Section 4: Data extraction form				
Outcome	*Time frame*	*Cryotherapy,* n/N	*Electrocautery,* n/N	*Estimate of effect* p-*value*
Dichotomous outcomes				
AGW clearance at other time points	3 months	10/16	10/11	$p > 0.05$
Section 5: Clinical trial quality				
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*
	Random sequence generation		✓	It is stated that men were randomly allocated to treatment using a random number table
	Allocation concealment		?	Details on method used to conceal allocation not available
	Selective reporting		✗	Complete clearance at end of treatment is not reported, although results are reported for clearance at 3 months' follow-up. Limited information available on AEs
	'Other bias'		?	It is stated that treatment groups were comparable in terms of age, country of origin, marital state, sexual orientation, previous STDs and number of warts present at baseline, but no baseline characteristics are reported. Insufficient information reported to evaluate presence of other sources of bias

TABLE 104 Simmons *et al.*[160] (*continued*)

Item	Details		
AGW clearance	Blinding (participants and personnel)	✗	The trial is described as single blind and it is reported that the clinician assessing clearance was masked to treatment. Given that the treatments evaluated are both surgical, it is likely that masking of personnel and participants was not feasible, but this could introduce bias. It is stated that the assessor evaluated participants after the first round of treatment. It is unclear whether the same assessor evaluated clearance at 3 months and also whether masking could have been broken
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The number of people not evaluated at 3 months is reported, but reasons for withdrawal are not available. It is unclear whether there is an imbalance between the groups in reasons for not returning for evaluation at 3 months
Overall rating of bias		✗	Reflects limited reporting of outcomes and lack of masking of participants and study personnel
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 105 Simmons[150]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Sam Barton
Study ID	Simmons 1981b
Study details	*Br J Vener Dis* 1981;**57**:208–9
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out in the UK at two clinical sites (Departments of Genital Medicine at St Bartholomew's Hospital and the Prince of Wales Hospital, London)
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Men were recruited from those with AGWs attending the Departments of Genital Medicine at the study sites
Trial design	RCT

continued

TABLE 105 Simmons[150] (*continued*)

Item	Details		
Trial duration	Initial treatment period of 6 weeks with subsequent follow-up to 3 months after the start of treatment		
Line of therapy	Not reported		
Inclusion criteria	Men with AGWs who had not received treatment for AGWs in the preceding 3 months		
Exclusion criteria	No additional criteria reported		
All outcomes reported in paper	Complete clearance		
Subgroups evaluated	None reported		
Stratification	None reported		
Baseline measurement of disease	Not reported		
Treatment	*Podophyllin 25% (clinician applied)*	*Podophyllin 10% (clinician applied)*	
Randomised, *n*	140 men were randomised; number of men randomised to each group not reported. Results are based on the men attending for assessment at 3 months' follow-up (55 in the podophyllin 25% group vs. 54 in the podophyllin 10% group)		
Withdrawals, *n* (%)	31 (22.1%) men withdrew before follow-up at 3 months. Reasons for withdrawal and number of withdrawals from individual treatment groups not reported		
Treatment regimen	Podophyllin 25% and 10% solutions were applied with cotton-wool swabs by one doctor once weekly for 6 weeks. External AGWs were washed 4, 6, 8, 12 and 24 hours after application at the first through to fifth attendance for treatment		
Duration/number of administered treatment	Number of mean treatments required for complete clearance: 3.7	Number of mean treatments required for complete clearance: 4.3	
Baseline patient characteristics	*Podophyllin 25% (clinician applied)*	*Podophyllin 10% (clinician applied)*	p-*value*
Age (years), mean	Not reported		Reported to be statistically comparable between treatment groups
Duration of disease	Not reported		
Site of AGWs, *n* (%)	Not reported		
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	Not reported		Reported to be statistically comparable between treatment groups
Area of AGWs (mm^2), mean	Not reported		
Sex (M/F), *n* (%)	100% men		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		Reported to be statistically comparable between treatment groups

TABLE 105 Simmons[150] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at other time points	Complete clearance at 3 months' follow-up				
Volume of wart clearance	Number of patients with ≤ 10% of original AGW volume at 6 weeks				
AEs	Reporting of AEs was minimal. It was stated that 'neither hypersensitivity nor chemical ulceration occurred with either concentration of podophyllin' (p. 209)				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllin 25% (clinician applied),* n/N	*Podophyllin 10% (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at other time points	3 months	12/55	12/54		Not reported
Volume of wart clearance (proportion of people with ≤ 10% of original AGW volume remaining, i.e. ≥ 90% reduction in AGW volume)	6 weeks	17/55	16/54		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		✓	It is stated that men were randomly allocated to treatment using a random number table	
	Allocation concealment		?	Podophyllin solutions were prepared in one pharmacy and dispensed in stock bottles labelled A and B. The pharmacy alone held the code key, which was broken only on completion of the trial. It is unclear whether the bottles were sequentially numbered or of identical appearance	
	Selective reporting		✗	Complete clearance at end of treatment is not reported, although results are reported for clearance at 3 months' follow-up. Limited information available on AEs	
	'Other bias'		?	It is stated that treatment groups were comparable in terms of age, country of origin, marital state, sexual orientation, previous STDs and number of warts present at baseline, but no baseline characteristics are reported. Insufficient information reported to evaluate presence of other sources of bias	

continued

TABLE 105 Simmons[150] (*continued*)

Item	Details		
AGW clearance	Blinding (participants and personnel)	?	The study is described as double blind but it is unclear who was masked to treatment. From the full publication it could be inferred that the patients and treating clinician are masked. Only one doctor applied the podophyllin solution in both groups. It is unclear whether the treating clinician also evaluated clinical outcomes and, if not, whether the outcome assessor was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The number of people randomised to each group is not reported. The number of people not evaluated at 3 months is reported, but reasons for withdrawal are not available. It is unclear whether there is an imbalance between the groups in reasons for not returning for evaluation at 3 months
Volume of wart clearance (e.g. proportion of patients with 50% clearance)	Blinding (participants and personnel)	?	The study is described as double blind but it is unclear who was masked to treatment. From the full publication it could be inferred that the patients and treating clinician are masked. Only one doctor applied the podophyllin solution in both groups. It is unclear whether the treating clinician also evaluated clinical outcomes and, if not, whether the outcome assessor was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The number of people randomised to each group is not reported. The number of people included in the analysis of volume of wart clearance at 6 weeks is not reported. It is unclear whether there is an imbalance between the groups in the number of people withdrawn or lost to follow-up at 6 weeks
Overall rating of bias		✗	Reflects the limited reporting of clinical outcomes in the full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 106 Snoeck *et al.*[121]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Sam Barton
Study ID	Snoeck 2001
Study details	*Clin Infect Dis* 2001;**33**:597–602
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at four centres in Belgium: Erasme Hospital, Brussels; Saint-Luc Hospital, Brussels; St Rafael Hospital, Leuven; and Etterbeek-Ixelles Hospital Centre
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Participants were enrolled from people attending the listed centres. Dates of enrolment not reported
Trial design	RCT
Trial duration	Up to 12 weeks' treatment with subsequent follow-up for 4 weeks after completion of treatment or removal from the study. Those with a complete response were followed up for 6 months (unclear whether this is additional to the 4-week observation period or whether those with a complete response were followed up for a further 5 months to give a total of 6 months)
Line of therapy	Mixed
Inclusion criteria	External biopsy-proven genital AGWs, perianal AGWs or both; use of an adequate means of birth control during the study (partners were asked to use barrier contraception)
Exclusion criteria	Any AGW > 10 mm in height or > 20 AGWs; presence of any other dermatological condition in the anogenital area; history of significant renal, hepatic or hematological abnormalities or of substance abuse within the previous 12 months; serum creatinine level > 2 mg/dl; women with current evidence of vulvar or cervical intraepithelial neoplasia grade II or III; presence of internal warts requiring immediate treatment; seropositive for HIV or a history of underlying immunodeficiency; treatment within the previous 4 weeks with any drug of known or potential anti-HPV activity; treatment within the previous 8 weeks with interferon; women who were pregnant, lactating or planning to become pregnant
All outcomes reported in paper	Complete clearance (defined as complete response); volume of AGW clearance [partial response (≥ 50% decrease in total surface area) and no change (< 50% decrease or < 25% increase in total surface area)]; AEs
Subgroups evaluated	Total lesion surface area (< 50 mm^2 vs. ≥ 50 mm^2)
Stratification	Stratified by total lesion surface area at screening (< 50 mm^2 vs. ≥ 50 mm^2)
Baseline measurement of disease	Baseline evaluation not described. Based on reporting, it can be inferred that the area and number of AGWs were recorded at baseline

continued

TABLE 106 Snoeck *et al.*[121] (*continued*)

Item	Details		
Treatment	*Cidofovir 1%*	*Placebo*	
Randomised, *n*	19	11	
	It is reported that a total of 31 adult patients were included in the study. One person was determined to be ineligible for the study after 1 week of treatment because of a lack of biopsy confirmation of condylomata. Data from this person were excluded from further analysis and the patient was replaced by a newly randomised patient. However, presented results are based on a total of 30 people rather than 31		
Withdrawals, *n* (%)	4 (21.1)	Not reported	
Lost to follow-up	2 (10.5)	–	
Treatment discontinuation	2 (10.5)	–	
Treatment regimen	Cidofovir 1% gel or placebo was applied once daily at bedtime for 5 consecutive days every other week for a maximum of six cycles (a cycle was defined as 1 week of gel application followed by 1 week of observation). All external AGWs, including new AGWs that developed after the baseline assessment, were treated. The treated areas, particularly those occluded by skin folds or foreskin, were washed the next morning to remove residual gel. The first administration was made under the supervision of a doctor. Later applications were self-administered on an outpatient basis. The gel was applied with a cotton-tipped swab or a rubber glove in a thin layer sufficient to cover the wart area and to extend beyond the edge of each AGW by a margin of 5 mm. If a complete response was achieved any time during the 12 weeks of treatment, the patient continued treatment through one additional 2-week cycle and then proceeded to follow-up		
Duration/number of administered treatment	For people with a complete response in the cidofovir group, the median duration of therapy was 43 days		
Baseline patient characteristics	*Cidofovir 1%*	*Placebo*	p-*value*
Age (years), median (range)	27 (20–51)	27 (21–41)	Reported to be similar in each group
Duration of disease	Not reported		
Site of AGWs, *n* (%)	Not reported		
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, median (range)	9 (1–18)	7 (2–20)	Reported to be similar in each group
Area of AGWs (mm^2), median (range)	56.4 (8.4–1259.2)	55.7 (15.3–1756.1)	Reported to be similar in each group
Sex, *n* (%)			
Male	8 (42.1)	5 (45.4)	Not reported
Female	11 (57.9)	6 (54.5)	Not reported
Any previous treatment, *n* (%)	8 (42.1)	5 (45.4)	Reported to be similar in each group
Ethnicity, *n* (%)			
White	15 (78.9)	10 (90.9)	Not reported
African	1 (5.3)	1 (9.1)	
Asian	1 (5.3)	0 (0)	
Other	2 (10.5)	0 (0)	

TABLE 106 Snoeck *et al.*[121] (*continued*)

Item	Details
Section 3: Outcomes	
Outcome	*Definition*
AGW clearance at completion of treatment	Complete response by 12 weeks, where 'complete response' was defined as total healing. New lesions appearing after the baseline assessment were treated and quantified but were not included as part of the evaluation of complete response
Recurrence of AGWs	Recurrence not defined; assessed in those achieving a complete response
Volume of wart clearance	Definitions of response, other than complete response, were as follows: partial response: ≥ 50% decrease in total surface area; no change: < 50% decrease or < 25% increase in total surface area; progression: > 25% increase in total surface area
Appearance of new warts during treatment	It is stated that new lesions appearing after the baseline assessment were treated and quantified. The number of new lesions appearing during treatment in each group was not reported
AEs	AEs were not defined. Data were reported for pain, pruritus and rash at the application site and for erosion or ulceration

Section 4: Data extraction form					
Outcome	*Time frame*	*Cidofovir 1%,* n/N	*Placebo,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	12 weeks	9/19	0/11		$p = 0.006$
Recurrence of AGWs	Median follow-up period of 168 days (range 77–217 days)	1/9	0/0		Not reported
Volume of wart clearance					
≥ 50% decrease in total surface area	12 weeks	7/19	2/11		$p = 0.001$
< 50% decrease or < 25% increase in total surface area	12 weeks	3/19	4/11		Not reported
AEs					
Pain, pruritus and rash at the application site	12 weeks	13/19	7/11		$p = 1.0$
Erosion or ulceration	12 weeks	6/19	5/11		Not reported

continued

TABLE 106 Snoeck *et al.*[121] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	It is stated that 'randomisation was performed by permuted blocks of size 3 within strata. Each investigator was assigned blocks' (p. 598). Methods used to generate sequence not available
	Allocation concealment	?	Details on method used to conceal allocation not available
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information to assess whether an important risk of bias exists
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	The study is described as double blind but it is unclear who was masked to treatment. From the full publication, it could be inferred that the patients and treating clinician are masked. It is unclear whether the treating clinician also evaluated clinical outcomes and, if not, whether the outcome assessor was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Analysis is based on 30 people. A total of 31 people were randomised. One person withdrew and was replaced by a newly randomised person. Withdrawals from the cidofovir group with accompanying reasons are reported but it is unclear whether anyone was lost to follow-up or withdrew from the placebo group
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blind but it is unclear who was masked to treatment. From the full publication, it could be inferred that the patients and treating clinician are masked. It is unclear whether the treating clinician also evaluated clinical outcomes and, if not, whether the outcome assessor was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Analysis of recurrence is based on all people with complete clearance but it is unclear whether anyone was lost to follow-up during the observation period
Volume of wart clearance (e.g. proportion of patients with 50% clearance)	Blinding (participants and personnel)	?	The study is described as double blind but it is unclear who was masked to treatment. From the full publication, it could be inferred that the patients and treating clinician are masked. It is unclear whether the treating clinician also evaluated clinical outcomes and, if not, whether the outcome assessor was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Analysis is based on 30 people. A total of 31 people were randomised. One person withdrew and was replaced by a newly randomised person. Withdrawals from the cidofovir group with accompanying reasons are reported but is unclear whether anyone was lost to follow-up or withdrew from the placebo group

TABLE 106 Snoeck *et al.*[121] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	?	The study is described as double blind but it is unclear who was masked to treatment. From the full publication, it could be inferred that the patients and treating clinician are masked. It is unclear whether the treating clinician also evaluated clinical outcomes and, if not, whether the outcome assessor was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Analysis is based on 30 people. A total of 31 people were randomised. One person withdrew and was replaced by a newly randomised person. Withdrawals from the cidofovir group with accompanying reasons are reported but is unclear whether anyone was lost to follow-up or withdrew from the placebo group
Overall rating of bias		?	Reflects limited reporting on methods in full publication
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a ?, unclear risk of bias.

TABLE 107 Stefanaki *et al.*[133]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Fatima Salih and Sam Barton
Study ID	Stefanaki 2008
Study details	*Int J STD AIDS* 2008;**19**:441–4
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at one centre in Greece (the Sexually Transmitted Disease Unit of Andreas Sygros University Hospital for Skin and Sexually Transmitted Diseases)
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Not reported
Trial design	RCT
Trial duration	Initial treatment period of 3 months with subsequent follow-up at 6 and 12 months
Line of therapy	First
Inclusion criteria	Male gender; immunocompetency; diagnosis of external genital or perianal AGWs; no previous treatment for AGWs

continued

TABLE 107 Stefanaki *et al.*[133] (*continued*)

Item	Details		
Exclusion criteria	Presence of Bowenoid papulosis; presence of a severe medical condition [haematological, hepatic (hepatitis B or C), neurological, renal, endocrine, collagen and gastrointestinal]; drug or alcohol dependency; HIV infection or syphilis; recent treatment with corticosteroids, cytotoxic drugs and interferon		
All outcomes reported in paper	Complete clearance; recurrence; AEs		
Subgroups evaluated	Time to cure was evaluated by baseline number of lesions and total AGW area but results were not presented separately by treatment group		
Stratification	None reported		
Baseline measurement of disease	At the initial visit prior to treatment, AGWs were photographed and measured in cm^2 and the exact number of AGWs and their location, morphology, colour and duration were recorded		
Treatment	*Cryotherapy (liquid nitrogen)*	*Imiquimod 5% (patient applied)*	
Randomised, *n*	70	50	
	Number of men randomised calculated by review authors based on number of men evaluated and number of withdrawals reported for each group		
Withdrawals, *n* (%)	25 (35.7)	15 (30.0)	
	Reasons for withdrawal not reported. It is stated that men were 'either lost from follow-up or did not provide analysable data' (p. 442); no further details available		
Treatment regimen	Cryotherapy with liquid nitrogen was applied once every 3 weeks for three consecutive sessions or until complete clearance of AGWs, whichever occurred earlier. Using a spray gun, AGWs were frozen for 10–20 seconds or until the AGWs and a small margin of surrounding normal skin were frozen. Larger lesions underwent two freeze cycles	Men applied imiquimod 5% cream '3 times a week for 6–10 hours' (p. 441). Treatment was repeated weekly for 3 months or until complete clearance of AGWs, whichever occurred earlier. Men were allowed to take a rest period of 7–10 days if they developed severe local reactions	
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Cryotherapy (liquid nitrogen)*	*Imiquimod 5% (patient applied)*	p-*value*
	Note: Baseline characteristics are based on the 80 men evaluated (45 in the cryotherapy group vs. 35 in the imiquimod 5% group) not the 120 men randomised		
Age (years), mean (unclear whether SD or SE)	30.7 (12.2)	31.8 (10.8)	$p = 0.859$
Duration of disease (months), *n* (%)			
< 3	26 (57.8)	28 (79.5)	$p = 0.03$
3–6	3 (6.6)	5 (14.3)	
7–12	9 (20)	1 (2.9)	
> 12	6 (13.3)	1 (2.9)	

TABLE 107 Stefanaki *et al.*[133] (*continued*)

Item	Details		
Site of AGWs, *n* (%)[a]			
1	8 (17.8)	7 (20)	$p = 0.101$
2	11 (24.4)	13 (37.1)	
3	3 (6.6)	7 (20)	
1 + 2	20 (44.4)	6 (17.1)	
1 + 3	1 (2.2)	0 (0)	
2 + 3	0 (0)	1 (2.9)	
1 + 2 + 3	2 (4.4)	1 (2.9)	
Type of AGWs, *n* (%)			
Pedunculated	9 (20)	20 (57.1)	$p = 0.001$
Papular	18 (40)	3 (8.6)	
Flat	0 (0)	1 (2.9)	
Pedunculated and papular	18 (40)	11 (31.4)	
Number of AGWs, *n* (%)			
1	4 (8.9)	5 (14.3)	$p = 0.533$
2–5	13 (28.9)	6 (17.1)	
6–10	12 (26.7)	9 (25.7)	
11–20	8 (17.8)	5 (14.3)	
> 20	8 (17.8)	10 (28.6)	
Total area of AGWs (mm^2)			
< 0.5	1 (2.2)	6 (17.1)	$p = 0.067$
0.6–1	9 (20)	11 (31.4)	
1.1–2	9 (20)	4 (11.4)	
2.1–3	8 (17.8)	4 (11.4)	
3.1–4	4 (8.9)	5 (14.3)	
> 4	14 (31.1)	5 (14.3)	
Sex (M/F), *n* (%)	100% men		
Any previous treatment (%)	0 (men who had received previous treatment were excluded)		
Ethnicity, *n* (%)	Not reported		

continued

TABLE 107 Stefanaki *et al.*[133] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Not defined. Results are presented for complete clearance at 3 months, which is the end of treatment				
AGW clearance at other time points	Complete clearance at 1 and 2 months during treatment and at 6 months after treatment				
Recurrence of AGWs	Results for recurrence reported at 12 months. Absolute numbers are not reported and it is unclear whether results are based on all men evaluated (80 men) or just those with complete clearance at any point (i.e. more men had complete clearance at 6 months)				
AEs	Not defined. Local or adverse systemic reactions were recorded (erythema, oedema, erosions, ulceration, fever and pain). AEs were graded as mild, moderate or severe; definitions of mild, moderate and severe not available				
Section 4: Data extraction form					
Outcome	*Time frame*	*Cryotherapy (liquid nitrogen),* n/N	*Imiquimod 5% (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	12 weeks	29/45	24/35		Not reported
AGW clearance at other time points (cumulative)	4 weeks	9/45	10/35		Not reported
	8 weeks	19/45	20/35		
	6 months	39/45	24/35		
Recurrence of AGWs (%)	12 months	59	41		$p = 0.138$
AEs					
Number of men experiencing at least one AE	12 weeks	45/45	19/35		$p = 0.034$
Pain	12 weeks	38/45	9/35		$p < 0.0001$
Painful ulcerations	12 weeks	7/45	8/35		Not reported
Fever	12 weeks	0/45	1/35		
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[b]	*Comments*	
	Random sequence generation		?	It is stated that men were randomly allocated to treatment. Details on method used to generate random sequence not available	
	Allocation concealment		?	Details on method used to conceal allocation not available	
	Selective reporting		✗	Insufficient information is reported on recurrence to facilitate entry into a meta-analysis	
	'Other bias'		?	Insufficient information available to evaluate other potential sources of bias	

TABLE 107 Stefanaki *et al.*[133] (*continued*)

Item	Details		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✗	Described as an open-label trial. Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. AGW clearance is a subjective outcome that could potentially be influenced by patients and key study personnel. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	?	The number of men randomised to each group is not reported. The analyses reported are based on men for whom evaluable data were available. The number of men excluded from the analysis is reported, but reasons for withdrawal are not reported. There might be an imbalance across the groups in reasons for withdrawal that could influence the effect estimate
Recurrence of AGWs	Blinding (participants and personnel)	✗	Described as an open-label trial. Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. AGW recurrence is a subjective outcome that could potentially be influenced by patients and key study personnel. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	✗	Data are presented as percentages and it is unclear whether the analysis is based on all men randomised or those with complete clearance of AGWs at some point during the study
AEs	Blinding (participants and personnel)	✗	Described as an open-label trial. Given the variation in settings in which the treatments were applied (home vs. clinic), it might be impractical to mask to treatment allocation. Evaluation of pain and local AEs is subjective and could potentially be influenced by patients and key study personnel. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Blinding of outcomes assessment	✗	

continued

TABLE 107 Stefanaki *et al.*[133] (*continued*)

Item	Details		
	Incomplete outcome data	?	The number of men randomised to each group is not reported. The analyses reported are based on men for whom evaluable data were available. The number of men excluded from the analysis is reported, but reasons for withdrawal are not reported. There might be an imbalance across the groups in reasons for withdrawal that could influence the effect estimate
Overall rating of bias		✗	Reflects open-label nature of trial and lack of reporting of number of men experiencing recurrence
Section 6: Additional comments			
Additional comments	• Men with a total wart area $< 2\ cm^2$ were found to respond better to imiquimod 5% cream than cryotherapy ($p = 0.018$) • Penduculated lesions responded better to imiquimod 5% cream whereas papular lesions responded better to cryotherapy ($p < 0.001$) • It is stated that, although there was no significant difference between imiquimod and cryotherapy in the rate of recurrence at 12 months, significantly more men in the cryotherapy group experienced more than one recurrence during follow-up (33% with cryotherapy vs. 8% with imiquimod; $p = 0.03$)		

M/F, male/female; SD, standard deviation.
a 1, mons pubis, scrotum, genital crurae, shaft of penis; 2, prepuce, bridle, foreskin, glans penis, urethra, coronal sulcus; 3, anus.
b ?, unclear risk of bias; ✗, high risk of bias.

TABLE 108 Stone *et al.*[151]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Victoria Wakefield
Study ID	Stone 1990
Study details	*Genitourin Med* 1990;**66**:16–19
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at one centre (number of sites not reported) in the USA
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	People were recruited between September 1984 and May 1986. Anyone with external AGWs not treated in the month before recruitment was eligible for the trial
Trial design	RCT
Trial duration	Initial treatment period of up to 6 weeks with follow-up after 3 months for those achieving complete clearance. People were asked to return sooner if AGWs reappeared
Line of therapy	Not reported

TABLE 108 Stone *et al.*[151] (*continued*)

Item	Details		
Inclusion criteria	People with external AGWs that had not been treated in the month preceding trial entry		
Exclusion criteria	Pregnancy; age < 18 years; allergy to podophyllin, tincture of benzoin compound or lidocaine; presence of obvious internal (cervical, vaginal or anal) warts or Buschke–Lowenstein lesions; contraindications for electrosurgical procedures (such as presence of a cardiac pacemaker)		
All outcomes reported in paper	Complete clearance at various time points; recurrence; post-treatment pain; local infection		
Subgroups evaluated	Gender, male sexual preference (heterosexual vs. gay/bisexual), volume of AGWs ($\leq 50\,mm^3$ vs. $> 50\,mm^3$), duration of AGWs (≤ 30 days vs. > 30 days) and site (anal vs. genital)		
Stratification	None reported		
Baseline measurement of disease	Not reported		
Treatment	*Podophyllin 25% (clinician applied)*	*Cryotherapy*	*Electrofulguration*
Randomised, *n*	144	154	152
Withdrawals, *n* (%)	Total number of withdrawals for individual treatment groups and for the overall trial population not reported. Information is available on the number of patients lost to follow-up and the number not completing the therapy as per the protocol. It is unclear whether there were any other withdrawals		
Did not complete therapy (non-compliant)	81 (56.3)	68 (44.2)	64 (42.1)
Lost to follow-up (defined as non-compliant patients)	10 (6.9)	26 (16.9)	37 (24.3)
Treatment regimen	Podophyllin 25% in tincture of benzoin compound was applied using a cotton swab. Patients were instructed to wash off the podophyllin 25% 2 hours after the first treatment. If the preceding application did not produce excessive irritation, the interval between application and washing was extended by 2 hours with each successive treatment to a maximum of 12 hours. A maximum surface area of $4\,cm^2$ was treated in any visit	Cryotherapy was administered using liquid nitrogen applied with a tapered cotton pledget on the end of a wooden applicator stick. The pledget was applied long enough to freeze the AGW and a 1-mm margin of surrounding skin, with each AGW being frozen once. A maximum surface area of $4\,cm^2$ was treated in any visit	Electrofulguration is a modification of electrodessication in which the electrode does not touch the tissue. After anaesthetising the area to be treated with subcutaneous 1% lidocaine, electrofulguration was performed with an electrosurgical apparatus using a point electrode and standard settings for electrodessication. A maximum surface area of $4\,cm^2$ was treated in any visit
	All treatments were administered weekly until complete clearance of AGWs or for a maximum of 6 weeks, whichever occurred earlier		
Duration/number of administered treatment	Mean number of treatments required to achieve complete clearance: 3.4	Mean number of treatments required to achieve complete clearance: 3.2	Mean number of treatments required to achieve complete clearance: 1.3

continued

TABLE 108 Stone *et al.*[151] (*continued*)

Item	Details			
Baseline patient characteristics	*Podophyllin 25% (clinician applied)*	*Cryotherapy*	*Electrofulguration*	p-*value*
	Note: Baseline characteristics are based on those patients who were classed as 'compliant', that is, those who completed treatment and were followed up at the end of treatment			
n	53	60	51	
Age (years), mean	26.7	27.3	26.9	Difference across groups reported to be not significant
Duration of disease	Not reported			Reported to be similar across groups
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	Not reported			
Area of AGWs (mm^2), mean	Not reported			Reported to be similar across groups
Sex, *n* (%)				
Male	38 (72)	43 (72)	38 (75)	Difference across groups reported to be not significant
Female	15 (28)	17 (28)	13 (25)	
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)				
White	33 (62)	31 (52)	29 (57)	Difference across groups reported to be not significant
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	AGW free within six treatments			
Recurrence of AGWs	Recurrence at 3 months			
AEs	AEs were not defined. Occurrence of local infection and post-treatment pain were reported. It is stated that similar proportions (17%) of people in each treatment group experienced post-treatment pain (absolute event numbers not reported)			

TABLE 108 Stone *et al.*[151] (*continued*)

Item	Details					
Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllin 25% (clinician applied),* n/N	*Cryotherapy,* n/N	*Electrofulguration,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	6 weeks	26/63	68/86	83/88	Electrotherapy was more effective than cryotherapy ($p = 0.003$), which in turn was more effective than podophyllin 25% ($p < 0.0001$)	
Recurrence of AGWs	3 months	7/16	9/42	10/46		$p = 0.17$
AEs: local infection	6 weeks	0/63	1/86	0/88	Note: denominator not reported in publication; assumed to be same as that used in the efficacy analyses	
Section 5: Clinical trial quality						
Outcome	*Risk of bias*		*Risk assessment*[a]		*Comments*	
	Random sequence generation		✓		It is stated that randomisation was carried out using a computer-generated randomisation schedule	
	Allocation concealment		?		Details on method used to conceal allocation not available	
	Selective reporting		?		Insufficient information provided to determine risk of selective reporting	
	'Other bias'		?		Insufficient information provided to determine presence of additional sources of bias	
AGW clearance at completion of treatment	Blinding (participants and personnel)		?		Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is unclear whether the clinician assessing clinical outcomes was masked to treatment	
	Blinding of outcomes assessment		?			
	Incomplete outcome data		✗		The total number of withdrawals is not reported. The numbers of people lost to follow-up (7–24%) and withdrawing from treatment are reported (42–56%). The high number of people withdrawing from treatment and the noted imbalance across the groups in loss to follow-up and withdrawal is likely to introduce clinically relevant bias in the estimate of effect	

continued

TABLE 108 Stone *et al.*[151] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✗	The total number of withdrawals is not reported. The numbers of people lost to follow-up (7–24%) and withdrawing from treatment are reported (42–56%). Follow-up of those who achieved complete clearance was also low (55–62%). The high number of people withdrawing from treatment and the noted imbalance across the groups in loss to follow-up and withdrawal is likely to introduce clinically relevant bias in the estimate of effect
AEs	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible. It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	✗	The total number of withdrawals is not reported. The numbers of people lost to follow-up (7–24%) and withdrawing from treatment are reported (42–56%). The high number of people withdrawing from treatment and the noted imbalance across the groups in loss to follow-up and withdrawal is likely to introduce clinically relevant bias in the estimate of effect
Overall rating of bias		✗	Reflects the imbalance across the groups in the combined high rate of withdrawal and loss to follow-up
Section 6: Additional comments			
Additional comments	• Patients who failed to complete the treatment regimen or who did not return for a 3-month follow-up visit after AGW clearance were considered non-compliant and were excluded from analysis. Although patients were clearly instructed and reminded to return in 3 months, many patients reported late. AGW-free patients who reported for follow-up later than 3 months but within 5 months after therapy were assumed to have been AGW free 3 months after therapy and their visits have been considered as '3-month' follow-up visits • Despite frequent attempts at follow-up by telephone, all treatment groups had high rates of non-compliance. Compliance rates were higher for female, white and older patients. Patients in the podophyllin group were less likely to complete the regimen than those receiving cryotherapy or electrodessication (44%, 56% and 58% respectively; $p = 0.03$)		

SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 109 Strand *et al.*[142]

Item	Details		
Section 1: Reviewer and study information			
Reviewers' names	Jacoby Patterson and Victoria Wakefield		
Study ID	Strand 1995		
Study details	*Genitourin Med* 1995;**71**:387–90		
Language of publication	English		
Type of report	Full publication		
Section 2: Study information			
Location and number of sites	Study carried out at three sites (two in Sweden and one in France)		
Trial sponsor	Not reported		
Conflicts of interest	Not reported		
Patient enrolment	Enrolment occurred at the STD clinics of the Akademiska Hospital, Uppsala and the Military Hospital, Enköping, Sweden, and the Institut Alfred Fournier, Paris, France. Men were enrolled between January 1990 and January 1991. No further details on recruitment reported		
Trial design	RCT (three arms)		
Trial duration	Initial treatment period of up to 4 weeks with subsequent follow-up at 16 weeks after entry into the study		
Line of therapy	Mixed; proportion of men having received previous treatment not reported		
Inclusion criteria	Men with genital AGWs (acuminata or papular)		
Exclusion criteria	HIV-positive status; age < 18 years; duration of present lesion > 3 months; presence of intra-anal or anal warts; receipt of treatment within the 3 months preceding the study		
All outcomes reported in paper	Complete clearance at end of treatment and other time points; relapse; AEs		
Subgroups evaluated	Site of lesion		
Stratification	None reported		
Baseline measurement of disease	Location and number of warts		
Treatment	*Podophyllotoxin 0.15% cream (patient applied)*	*Podophyllotoxin 0.3% cream (patient applied)*	*Podophyllotoxin 0.5% solution (patient applied)*
Randomised, *n*	30	31	29
Withdrawals, *n* (%)	Overall, 11 men were lost to follow up at 16 weeks; loss to follow-up not reported by individual treatment group		
Treatment regimen	Men self-applied podophyllotoxin 0.15% or 0.3% cream using a finger and podophyllotoxin 0.5% solution using an applicator. All treatments were applied twice a day for 3 consecutive days followed by a 4-day no treatment period (defined as a treatment cycle). The cream preparations of podophyllotoxin consisted of an oil phase blended into a purified water phase. The podophyllotoxin 0.5% solution contained 5.0 mg of podophyllotoxin. Men were treated until complete clearance or for a maximum of 4 weeks (four treatment cycles), whichever occurred earlier. Non-achievement of complete clearance after 4 treatment cycles was regarded as a treatment failure		
Duration/number of administered	Not reported		

continued

TABLE 109 Strand *et al.*[142] (*continued*)

Item	Details			
Baseline patient characteristics	*Podophyllotoxin 0.15% cream (patient applied)*	*Podophyllotoxin 0.3% cream (patient applied)*	*Podophyllotoxin 0.5% solution (patient applied)*	p-*value*
Age (years), mean (range)	25.7 (18–44)	27.2 (20–48)	27.5 (20–43)	Not reported
Duration of disease (months), mean (range)	2.5 (0.4–5.5)	2.5 (0.7–5.6)	2.6 (0.6–4.9)	Not reported
Site of AGWs, number of lesions				
Prepuce	129	137	139	Not reported
Glans	43	61	73	Not reported
Shaft	34	22	8	Not reported
Other	11	0	9	Not reported
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean (range)	6.9 (1–23)	7.0 (1–32)	7.9 (1–27)	Not reported
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% male			
Any previous treatment, *n* (%)	5 (16.6)	5 (16.1)	6 (20.7)	Not reported
Ethnicity	Overall, the study included 88 white and two black men; numbers not reported for individual treatment groups			Not reported
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Complete clearance at 4 weeks			
AGW clearance at other time points	Complete clearance at 1, 2 or 3 weeks			
Recurrence of AGWs	Recurrence at 16 weeks			
AEs	AEs were recorded as itching, burning sensation, tenderness, pruritus, erythema, erosion and others. It is reported that most AEs were mild to moderate, with 59 men experiencing an AE (number of events in each treatment group not reported separately); definitions for mild, moderate and severe not available			

TABLE 109 Strand *et al.*[142] (*continued*)

Item	Details					
Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllotoxin 0.15% cream (patient applied),* n/N	*Podophyllotoxin 0.3% cream (patient applied),* n/N	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	4 weeks	21/30	25/31	24/29		Not significant
AGW clearance at other time points	1 week	11/30	14/31	15/29		Not significant
	2 weeks	15/30	23/31	23/29	Reported to be significantly lower in the 0.15% cream group	
	3 weeks	20/30	24/31	23/29		Not significant
Recurrence of AGWs (recurrence in areas similar to those of original AGWs)	16 weeks	4/21	4/25	4/24		Not reported
Recurrence of AGWs (includes recurrence in locations other than those of original AGWs)	16 weeks	4/21	6/25	5/24		Not significant
Severe AEs	16 weeks	2/30	5/31	5/29		Not significant
Section 5: Clinical trial quality						
Outcome	*Risk of bias*		*Risk assessment*[a]		*Comments*	
	Random sequence generation		?		Study is described as randomised. Details on method used to generate random sequence not provided	
	Allocation concealment		?		Details on method used to conceal allocation not provided	
	Selective reporting		?		Insufficient information provided to determine risk of selective reporting	
	'Other bias'		?		Insufficient information provided to determine presence of additional sources of bias	
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		✗		Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking	
	Blinding of outcomes assessment		✗		Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken	

continued

TABLE 109 Strand *et al.*[142] (*continued*)

Item	Details		
	Incomplete outcome data	?	Absolute numbers for loss to follow-up and withdrawal are not reported for individual treatment groups. Reasons for loss to follow-up not reported. It is unclear whether there is an imbalance across treatment groups in numbers lost to follow-up or withdrawing
Recurrence of AGWs	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of recurrence is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of recurrence is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	Absolute numbers for loss to follow-up and withdrawal are not reported for individual treatment groups. Reasons for loss to follow-up not reported. It is unclear whether there is an imbalance across treatment groups in numbers lost to follow-up or withdrawing
AEs	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	Absolute numbers for loss to follow-up and withdrawal are not reported for individual treatment groups. Reasons for loss to follow-up not reported. It is unclear whether there is an imbalance across treatment groups in numbers lost to follow-up or withdrawing
Overall rating of bias		✗	Reflects open-label nature of trial

TABLE 109 Strand *et al.*[142] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	• It was reported that 571 of 666 lesions were successfully eradicated by the end of the study. Results for each treatment group were as follows: 0.15% cream 83.4%; 0.3% cream 91.4%; 0.5% solution 82.5%. The differences between groups were reported to be not significant • It was reported that the best result was observed for treatment of lesions on the glans penis and the prepuce, followed by the shaft and other sites

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 110 Syed and Lundin[143]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Sjokvist Garcia-Stewart and Sam Barton
Study ID	Syed 1993
Study details	*Dermatology* 1993;**187**:30–3
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	The study was carried out at three clinics in Pakistan (clinics located in Karachi, Lahore and Peshawar)
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Not reported
Trial design	RCT (three arms)
Trial duration	Initial treatment period of a maximum of 4 weeks with subsequent follow-up at 16 weeks after treatment for those classed as achieving cure during treatment
Line of therapy	Unclear
Inclusion criteria	Male gender; age between 15 and 40 years; clinical diagnosis of AGWs
Exclusion criteria	Not reported
All outcomes reported in paper	Complete clearance; partial response or no response (based on percentage regression of baseline AGWs); response rate after 1, 2, 3 and 4 weeks of treatment; relapse; AEs
Subgroups evaluated	None reported
Stratification	Not reported
Baseline measurement of disease	Diagnosis based on clinical examination with androscopy and painting with 5% acetic acid at the initial visit. At baseline, the location, number, type and size in diameter of each AGW were evaluated and recorded. A representative biopsy specimen was taken from each patient for the detection of HPV lesions

continued

TABLE 110 Syed and Lundin[143] (*continued*)

Item	Details			
Treatment	*Podophyllotoxin 0.3% cream (patient applied)*	*Podophyllotoxin 0.15% cream (patient applied)*	*Podophyllotoxin 0.3% solution (patient applied)*	
Randomised, *n*	20	20	20	
Withdrawals, *n* (%)	0 (0)	0 (0)	0 (0)	
Treatment regimen	Men applied podophyllotoxin 0.3% cream, podophyllotoxin 0.15% cream or podophyllotoxin 0.3% solution at home, twice daily, for 3 consecutive days. If complete clearance was not achieved, the treatment cycle was repeated after 4 treatment-free days. The cycle was repeated until complete clearance was achieved or for a maximum of four treatments, whichever occurred earlier. A maximum of 24 applications was permitted. Men were taught the basic steps and precautions to be observed, including how to wash, dry and carefully paint the affected area with the provided cotton swab, avoiding excess spreading to adjacent tissue. The painted area was to be left to dry for at least 1 minute. Trial preparations were dispensed in identical test tubes containing 5 ml of active preparation per period of 3-day treatment			
Duration/number of administered treatment	Not reported			
Baseline patient characteristics	*Podophyllotoxin 0.3% cream (patient applied)*	*Podophyllotoxin 0.15% cream (patient applied)*	*Podophyllotoxin 0.3% solution (patient applied)*	p-*value*
Age (years), mean (range)	Overall population 19.5 (15–40). Mean age for individual treatment groups not reported			
Duration of disease	Not reported			
Site of AGWs, *n* (%)	For overall population, 39 (65.0%) men had lesions of the penile shaft and perianal area and 21 (35.0%) men had lesions on the penile shaft alone. Sites for individual treatment groups not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean (with SD/SE if given)	For overall population, 6.5 at baseline; not reported for individual treatment groups. Of the overall trial population, five (8.3%) men had one to two AGWs, 30 (50.0%) men had three to five AGWs and the remainder [25 men (41.7%)] had > 10 AGWs			
area of AGWs (mm^2), mean	Mean area of baseline AGWs not reported. Range of diameter of AGWs for overall trial population reported to be between 1 and 8 mm, with a mean diameter of 1.9 mm (not reported for individual treatment groups)			
Sex (M/F), *n* (%)	100% male			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	100% Asian			

TABLE 110 Syed and Lundin[143] (*continued*)

Item	Details					
Section 3: Outcomes						
Outcome	*Definition*					
AGW clearance at completion of treatment	Complete eradication of venereal AGWs. Achievement of complete cure was recorded as 100% regression of baseline AGWs. Complete clearance at various time points is reported. For the purposes of this review, end of treatment has been taken as 4 weeks (maximum number of permitted treatments)					
AGW clearance at other time points	Complete clearance after 1, 2 and 3 weeks					
Recurrence of AGWs	For those achieving complete clearance, reappearance of AGWs at a previously treated site at 16 weeks' follow-up					
Volume of wart clearance	Men with ≥ 50% regression of baseline AGWs were classified as partially cured and those with < 50% regression were categorised as having 'no response'					
AEs	It is stated that AEs were graded as mild, moderate or severe or none; definitions of mild, moderate and severe not available. Duration of AEs was noted. AEs monitored were pain, pruritus, burning sensation, tenderness, erythema and erosion					
Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllotoxin 0.3% cream (patient applied),* n/N	*Podophyllotoxin 0.15% cream (patient applied),* n/N	*Podophyllotoxin 0.3% solution (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	4 weeks	20/20	14/20	20/20		Not reported
AGW clearance at other time points	1 week	0/20	0/20	0/20	NR; inferred to be zero	Not reported
	2 weeks	NR/20	NR/20	16/20		
	3 weeks	15/20	NR/20	20/20		
Recurrence of AGWs	16 weeks after treatment	Of the 54 men with complete clearance, three experienced recurrence; recurrence by treatment group not reported				
Volume of wart clearance (≥ 50% regression from baseline)	4 weeks	0/20	6/20	0/20		Not reported
AEs		AEs not reported separately by treatment group. It is reported that six (30.0%) men in the podophyllotoxin 0.3% solution group experienced localised mild erythema and burning sensation. In the groups receiving the cream preparations, 18 men (45.0%), predominantly in the 0.3% cream group, reported mild to moderate erythema, pruritus and burning sensation				Not reported

continued

TABLE 110 Syed and Lundin[143] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	Trial described as a randomised trial. Details on methods used to generate random sequence not available
	Allocation concealment	?	Methods implemented to conceal allocation not reported
	Selective reporting	✗	Data for key clinical outcomes (recurrence and AEs) are not reported as absolute events rates by treatment group. Results presented cannot be used in a meta-analysis
	'Other bias'	?	Insufficient information reported to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✗	Participants and personnel are not masked to treatment. Given that the techniques evaluated are topical applications, it is feasible to mask key study personnel and participants to treatment. AGW clearance is a subjective outcome and is liable to bias because of lack of masking
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	✓	All people randomised were reported to be followed up
Recurrence of AGWs	Blinding (participants and personnel)	✗	Participants and personnel are not masked to treatment. Given that the techniques evaluated are topical applications, it is feasible to mask key study personnel and participants to treatment. AGW recurrence is a subjective outcome and is liable to bias because of lack of masking
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	✓	All people randomised were reported to be followed up
Volume of wart clearance (≥ 50% regression)	Blinding (participants and personnel)	✗	Participants and personnel are not masked to treatment. Given that the techniques evaluated are topical applications, it is feasible to mask key study personnel and participants to treatment. AGW clearance is subjective and liable to bias from lack of masking
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	✓	All people randomised were reported to be followed up

TABLE 110 Syed and Lundin[143] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	✗	Participants and personnel are not masked to treatment. Given that the techniques evaluated are topical applications, it is feasible to mask key study personnel and participants to treatment. AE outcomes are subjective outcomes and are liable to bias because of lack of masking
	Blinding of outcomes assessment	✗	
	Incomplete outcome data	✓	All people randomised were reported to be followed up
Overall rating of bias		✗	Reflects the limited reporting of results for outcomes of interest and the open-label nature of the trial
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 111 Syed *et al.*[122]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Victoria Wakefield
Study ID	Syed 1994
Study details	*Dermatology* 1994;**189**:142–5
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Multiple centres (number of sites not reported) in Pakistan
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Participants were recruited from Asian women attending clinics in Pakistan during the summer of 1991
Trial design	RCT
Trial duration	Initial treatment period of up to 4 weeks with subsequent follow-up for 12 weeks (i.e. total study duration of 16 weeks) for those achieving complete clearance during treatment
Line of therapy	Not reported
Inclusion criteria	Asian women between the ages of 16 and 40 years with extravaginal condylomata
Exclusion criteria	Heart, renal or liver insufficiency; untreated classical STDs; pregnancy or lactation; duration of condylomata > 6 months; receipt of medication for AGWs in the 3 months preceding study entry
All outcomes reported in paper	Complete clearance; relapse; AEs

continued

TABLE 111 Syed *et al.*[122] (*continued*)

Item	Details			
Subgroups evaluated	None reported			
Stratification	None reported			
Baseline measurement of disease	Location and number of warts recorded at baseline visit			
Treatment	*Podophyllotoxin 0.3% cream (patient applied)*	*Podophyllotoxin 0.5% cream (patient applied)*	*Placebo cream (patient applied)*	
Randomised, *n*	30	30	20	
Withdrawals, *n* (%)	0	0	0	
Treatment regimen	Women self-applied their allocated treatment (podophyllotoxin 0.3% cream, podophyllotoxin 0.5% cream or placebo) twice daily for 3 consecutive days per week. Treatment cycle was repeated until complete clearance was achieved or for a maximum of 4 weeks (24 topical applications), whichever occurred earlier. Women were instructed to avoid excessive spreading to surrounding tissue and to allow the cream to dry for at least 1 minute without washing the treated area			
Duration/number of administered treatment	Not reported			
Baseline patient characteristics	*Podophyllotoxin 0.3% cream (patient applied)*	*Podophyllotoxin 0.5% cream (patient applied)*	*Placebo cream (patient applied)*	p-*value*
Age (years), mean	22.4	24.0	24.8	Not reported
Duration of disease	Not reported			
Site of AGWs, number of lesions				
Total number of lesions	206	214	124	
Labia majora	41	45	33	Not reported
Labia minora	39	48	31	Not reported
Introitus	44	53	28	Not reported
Clitoris	10	12	5	Not reported
Perineum	29	27	9	Not reported
Perianal area	31	16	10	Not reported
Anal	12	13	8	Not reported
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	6.86	7.13	6.2	Not reported
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% women			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	100% Asian			

TABLE 111 Syed *et al.*[122] (*continued*)

Item	Details					
Section 3: Outcomes						
Outcome	*Definition*					
AGW clearance at completion of treatment	Women achieving complete clearance at 4 weeks. Number of AGWs cleared at 4 weeks also reported					
Recurrence of AGWs	Relapse at 16 weeks (i.e. 12 weeks after end of treatment) in those achieving complete clearance of AGWs					
AEs	AEs recorded were pruritus, burning sensation, tenderness, erythema, erosion and any other symptoms					
Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllotoxin 0.3% cream (patient applied),* n/N	*Podophyllotoxin 0.5% cream (patient applied),* n/N	*Placebo cream (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment (analysis based on number of women)	4 weeks	16/30	25/30	0/20	Podophyllotoxin 0.3% or 0.5% cream vs. placebo: $p < 0.001$; podophyllotoxin 0.3% vs. 0.5% cream: $p < 0.01$	
AGW clearance at completion of treatment (analysis based on number of AGWs)	4 weeks	144/206	205/214	0/124		Not reported
Recurrence of AGWs	16 weeks	3/16	1/25	0/0		Not reported
AEs						
Any	4 weeks	9/30	22/30	6/20		Not reported
Tenderness	4 weeks	5/30	12/30	6/20		Not reported
Burning	4 weeks	4/30	10/30	0/20		Not reported
Section 5: Clinical trial quality						
Outcome	*Risk of bias*		*Risk assessment*[a]		*Comments*	
	Random sequence generation		?		It is stated that people were randomly allocated to treatment. Additional details on method of randomisation not available	
	Allocation concealment		?		Detail on method used to conceal allocation not available	
	Selective reporting		?		Insufficient information provided to determine risk of selective reporting	
	'Other bias'		?		Insufficient information provided to determine presence of additional sources of bias	

continued

TABLE 111 Syed *et al.*[122] (*continued*)

Item	Details		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication test tube preparations were similar. However, it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication test tube preparations were similar. However, it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
AEs	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication test tube preparations were similar. However, it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
Overall rating of bias		?	Reflects limited reporting on methods in full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 112 Syed *et al.*[123]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Victoria Wakefield	
Study ID	Syed 1995a	
Study details	*Dermatology* 1995;**191**:129–32	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Multiple sites (number not stated) in the Punjab region of Pakistan	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Study was carried out between March 1992 and February 1993; details on patient recruitment not available	
Trial design	RCT (three arms; third arm evaluated interferon, which is not an intervention of interest for this review)	
Trial duration	Initial treatment period of up to 4 weeks with follow-up at 16 weeks for those achieving complete clearance during treatment. Final follow-up was 1 year after the first day of treatment	
Line of therapy	Not reported	
Inclusion criteria	Men aged 18–40 years with genital AGWs (on the glans, shaft, corona sulcus or perianal area) and who were HIV negative at baseline	
Exclusion criteria	Untreated classical STDs; duration of genital AGWs > 6 months; intake of immunosuppressive drugs or use of any topical antiviral medication or any type of therapy for genital AGWs in the 4 weeks preceding study entry	
All outcomes reported in paper	Complete clearance; relapse; AEs	
Subgroups evaluated	None reported	
Stratification	None reported	
Baseline measurement of disease	Location, size and number of AGWs recorded at the baseline visit	
Treatment	*Podophyllotoxin 0.5% cream (patient applied)*	*Placebo*
Randomised, *n*	20	20
Withdrawals, *n* (%)	0	0
Treatment regimen	Podophyllotoxin 0.5% in a hydrophilic cream or matching placebo cream was self-applied three times daily for 3 consecutive days (maximum of nine applications per week) until either complete clearance was achieved or for 4 weeks, whichever occurred earlier	
Duration/number of administered treatment	Not reported	

continued

TABLE 112 Syed *et al.*[123] (*continued*)

Item	Details				
Baseline patient characteristics	*Podophyllotoxin 0.5% cream (patient applied)*	*Placebo*	p-*value*		
Age (years), mean	24.4	25.0	Groups reported to be 'comparable'		
Duration of disease	Not reported				
Site of AGWs, initial number of lesions					
Corona sulcus	30	27	Groups reported to be 'comparable'		
Glans and shaft	62	59			
Perianal	39	43			
Type of AGWs, *n* (%)	Not reported				
Number of AGWs, mean	6.5	6.4	Groups reported to be 'comparable'		
Area of AGWs (mm^2), mean	Not reported				
Sex (M/F), *n* (%)	100% male				
Any previous treatment, *n* (%)	Not reported				
Ethnicity, *n* (%)	100% Asian				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Complete elimination of lesions defined as disappearance of all visible lesions by colposcopy and absence of HPV DNA and cellular atypia confirmed by Southern dot blot at 4 weeks. Analysis based on number of AGWs cured at 4 weeks also reported				
Recurrence of AGWs	Relapse after 10 months				
AEs	Data were reported on occurrence of erythema, burning sensation, itching (pruritus) and fever plus headache plus itching				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% cream (patient applied),* n/N	*Placebo,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment (patients)	4 weeks	11/20	3/20		$p < 0.0098$
AGW clearance at completion of treatment (number of warts)	4 weeks	83/131	15/129		Not reported
Recurrence of AGWs	10 months	2/11	0/3		Not reported

TABLE 112 Syed *et al.*[123] (*continued*)

Item	Details			
AEs				
Erythema	4 weeks	4/20	1/20	Not reported
Burning	4 weeks	3/20	1/20	Not reported
Itching	4 weeks	1/20	0/20	Not reported
Fever plus headache plus itching	4 weeks	0/20	0/20	Not reported
Any	4 weeks	8/20	2/20	Not reported
Section 5: Clinical trial quality				
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*
	Random sequence generation		?	It is stated that people were randomly assigned to treatment. Additional details on method of randomisation not available
	Allocation concealment		?	Detail on method used to conceal allocation not available
	Selective reporting		?	Insufficient information provided to determine risk of selective reporting
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		?	The study is described as double blind and it is reported that the study medication test tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment		?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data		✓	No withdrawals or missing outcome data
Recurrence of AGWs	Blinding (participants and personnel)		?	The study is described as double blind and it is reported that the study medication test tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken

continued

TABLE 112 Syed *et al.*[123] (*continued*)

Item	Details		
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
AEs	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication test tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
Overall rating of bias		?	Reflects limited reporting in full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 113 Syed *et al.*[124]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Victoria Wakefield
Study ID	Syed 1995b
Study details	*J Mol Med (Berl)* 1995;**73**:255–8
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Multiple sites (number not stated) in the Punjab region of Pakistan
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Participants enrolled from March 1992 to February 1993; details on how patients were recruited not available
Trial design	RCT [three arms; only two arms of interest to this review (third arm evaluated interferon)]

TABLE 113 Syed *et al.*[124] (*continued*)

Item	Details		
Trial duration	Initial treatment period of 4 weeks with subsequent follow-up at 16 weeks from the start of the trial for those achieving complete clearance during treatment. Final follow-up was 1 year after the initial visit		
Line of therapy	Not reported		
Inclusion criteria	Women aged 18–40 years with AGWs and who were HIV negative		
Exclusion criteria	Pregnancy; breastfeeding; receipt of any therapy for AGWs in the 4 weeks preceding trial entry; concurrent cardiac, renal, hepatic, pulmonary, gastrointestinal or haematological disorder or untreated classical STD; AGWs with a duration > 6 months; receiving any immunosuppressive or topical antiviral drugs		
All outcomes reported in paper	Clearance (complete, partial and no response); relapse		
Subgroups evaluated	None reported		
Stratification	None reported		
Baseline measurement of disease	Location, size and number of AGWs were recorded at the baseline visit		
Treatment	*Podophyllotoxin 0.5% cream (patient applied)*	*Placebo cream (patient applied)*	
Randomised, *n*	20	20	
Withdrawals, *n* (%)	0	0	
Treatment regimen	Women self-applied podophyllotoxin 0.5% cream or placebo cream three times daily for 3 consecutive days per week until complete AGW clearance or for up to 4 weeks, whichever occurred earlier. Maximum number of treatments allowed (as per the protocol) was 36 applications		
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Podophyllotoxin 0.5% cream (patient applied)*	*Placebo cream (patient applied)*	p-*value*
Age (years), mean	22.9 years for full trial population (three treatment groups); not reported separately by treatment group		Not reported
Duration of disease	Not reported		
Site of AGWs	Overall for full trial population (three treatment groups; locations not reported by treatment group): 26 women had 138 lesions on the labia majora or minora; 13 women had 66 lesions on the introitus; 10 women had 51 lesions on the perianal area; seven women had 40 lesions on the perineum; four women had 25 lesions on the clitoris		Not reported
Type of AGWs, *n* (%)	Not reported		
Baseline number of AGWs	Overall for full trial population (three treatment groups; number of AGWs not reported by treatment group): one to five AGWs: 33 women; six to eight AGWs: 27 women		Not reported
Area of AGWs (mm^2), mean	Not reported		
Sex (M/F), *n* (%)	100% women		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	100% Asian		

continued

TABLE 113 Syed *et al.*[124] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Biopsy-confirmed total elimination of lesion; analysed by number of patients with complete clearance and number of AGWs cleared				
AGW clearance at other time points	Biopsy-confirmed total elimination of lesions at 1 week				
Recurrence of AGWs	Relapse after 9 months. It is reported that two out of 34 cured women achieving complete clearance of AGWs across the three treatment groups experienced relapse. However, data are not reported by treatment group				
Volume of wart clearance (proportion of women with ≥ 50% clearance)	Proportion of women with ≥ 50% reduction in the surface area of baseline lesions (referred to as partial response)				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% cream (patient applied),* n/N	*Placebo cream (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment (number of women; note, includes women with partial clearance)	4 weeks	12/20	4/20		Not reported
AGW clearance (number of lesions)	4 weeks	87/108	16/104		Not reported
AGW clearance (number of women)	1 week	0/20	0/20		
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	It is stated that people were randomly allocated to treatment. Additional details on method of randomisation not available	
	Allocation concealment		?	Detail on method used to conceal allocation not available	
	Selective reporting		✗	It is stated that partial response was recorded but data are not reported separately from data for complete clearance. Recurrence is not reported separately for each treatment group and thus data reported cannot be entered in a meta-analysis	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	

TABLE 113 Syed *et al.*[124] (*continued*)

Item	Details		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication test tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication test tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	?	It is unclear whether there were any additional losses to follow-up during the follow-up period. The analysis is based on all people with complete clearance
Overall rating of bias		✗	Reflects limited reporting of clinical effectiveness results in full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 114 Syed *et al.*[161]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Victoria Wakefield
Study ID	Syed 1998
Study details	*J Dermatol* 1998;**25**:429–33
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Multiple centres (number not stated) in the Punjab region of Pakistan
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	Participants enrolled from February 1994 to July 1995; details on how patients were recruited not available

continued

TABLE 114 Syed *et al.*[161] (*continued*)

Item	Details		
Trial design	RCT		
Trial duration	Initial treatment period of 6 weeks with subsequent follow-up at 16 weeks from the start of the trial for those achieving complete clearance during treatment. Final follow-up was 11 months after the initial visit		
Line of therapy	Not reported		
Inclusion criteria	Women aged 18–45 years		
Exclusion criteria	History or presence of malignancy; Papanicolaou smear cervical intraepithelial neoplasia positivity; HIV-positive status; abnormal cardiac, hepatic, pulmonary, gastrointestinal or renal function; concomitant STD; pregnant or breastfeeding; using immunosuppressive or topical antiviral drugs; receipt of any therapy for AGWs in the 8 weeks preceding trial entry		
All outcomes reported in paper	Clearance (complete, partial or no response); recurrence; AEs (nausea, tenderness, erythema and burning sensation)		
Subgroups evaluated	None reported		
Stratification	None reported		
Baseline measurement of disease	Location, size and number of AGWs were recorded at the baseline visit		
Treatment	*Imiquimod 2% cream (self-applied)*	*Placebo cream (self-applied)*	
Randomised, *n*	30	30	
Withdrawals, *n* (%)	0	0	
Treatment regimen	Women self-applied imiquimod 2% cream or placebo cream twice daily for 5 consecutive days per week until complete clearance or for up to 6 weeks, whichever occurred earlier. Maximum number of treatments allowed (as per the protocol) was 60 applications		
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Imiquimod 2% cream (self-applied)*	*Placebo cream (self-applied)*	p-*value*
Age (years), mean	24.2	24.4	Not reported
Duration of disease	Not reported		
Site of AGWs, initial number of AGWs			
Labia majora	62	55	Not reported
Labia minora	54	65	
Introitus	31	34	
Clitoris	10	11	
Perineum	21	19	
Perianal area	23	26	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	6.8	6.9	Not reported
Area of AGWs (mm^2), mean	Not reported		Not reported
Sex (M/F), *n* (%)	100% female		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		

TABLE 114 Syed *et al.*[161] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Total elimination of AGWs, as confirmed by colposcopy; analysed by number of patients with complete clearance and number of AGWs cleared				
Recurrence of AGWs	Relapse after 11 months				
Volume of wart clearance (proportion of women with ≥ 50% clearance)	Proportion of women with ≥ 50% reduction in the surface area of baseline lesions (referred to as partial response)				
AEs	Data reported on occurrence of nausea, burning, tenderness and erythema				
Section 4: Data extraction form					
Outcome	*Time frame*	*Imiquimod 2% cream (self-applied), n/N*	*Placebo cream (self-applied)*	*Estimate of effect*	*p-value*
Dichotomous outcomes					
AGW clearance at completion of treatment (number of women)	6 weeks	22/30	1/30		Not reported
AGW complete or partial clearance (number of AGWs)	6 weeks	172/204	4/207		Reported as significant
Recurrence of AGWs	11 months	4/25[a]	1/1		Not reported
Volume of wart clearance (proportion of women with ≥ 50% clearance)	6 weeks	3/30	0/30		Not reported
AEs					
Nausea	6 weeks	2/30	0/30		Not reported
Burning	6 weeks	1/30	0/30		Not reported
Tenderness	6 weeks	3/30	0/30		Not reported
Erythema	6 weeks	2/30	0/30		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[b]	*Comments*	
	Random sequence generation		?	It is stated that people were randomly assigned to treatment. Additional details on method of randomisation not available	
	Allocation concealment		?	Detail on method used to conceal allocation not available	
	Selective reporting		?	Insufficient information provided to determine risk of selective reporting	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	

continued

TABLE 114 Syed *et al.*[161] (*continued*)

Item	Details		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
Volume of wart clearance (proportion of women with ≥ 50% clearance)	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
AEs	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medication tube preparations were similar. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	No withdrawals or missing outcome data
Overall rating of bias		?	Reflects limited reporting in full publication
Section 6: Additional comments			
Additional comments	• Reported that cure and response to trial medication were unrelated to location or AGW type • In most cases the AEs of treatment resolved within 24 hours		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.

a In the full publication, analysis of complete clearance at the end of treatment included three women in the imiquimod 2% group who were identified as having partial clearance. The authors of the review excluded these women from the analysis of complete clearance. It is not clear whether women with partial clearance experienced recurrence and so they have been included in the denominator for recurrence.

b ✓, low risk of bias; ?, unclear risk of bias.

TABLE 115 Syed *et al.*[162]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Victoria Wakefield	
Study ID	Syed 2000	
Study details	*J Infect* 2000;**41**:148–51	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Multiple sites (number not stated) in the Punjab region of Pakistan	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Participants were selected from those attending family planning clinics, public health centres and government-affiliated municipal dispensaries as well as from those referred by physicians who were aware of the study. The trial was carried out between February 1995 and July 1996; it is unclear over what time period people were recruited	
Trial design	RCT	
Trial duration	Initial treatment period of up to 4 weeks, with follow-up at 16 weeks after trial initiation for those achieving complete clearance during treatment. Final follow-up took place at 18 months after the first day of treatment	
Line of therapy	17/60 men had previously used podophyllotoxin cream 0.5% and had experienced resistance or treatment failure	
Inclusion criteria	Men aged 18–50 years	
Exclusion criteria	Concurrent STD; past or current malignancy; HIV-positive status; allergy to imidazoquinoline; abnormal cardiac, renal, pulmonary, gastrointestinal or hepatic function; use of immunosuppressive drugs or any topical antiviral compound for external AGWs in the 8 weeks preceding trial entry	
All outcomes reported in paper	Clearance (complete, partial or no response); recurrence; AEs	
Subgroups evaluated	None reported	
Stratification	None reported	
Baseline measurement of disease	Location, size and number of AGWs were recorded at the baseline visit	
Treatment	*Imiquimod 2% cream (patient applied)*	*Placebo cream (patient applied)*
Randomised, *n*	30	30
Withdrawals, *n* (%)	0	0
Treatment regimen	Men self-applied imiquimod 2% or placebo cream once daily at bedtime for 3 consecutive days per week until complete clearance or for up to 4 weeks, whichever occurred earlier. Maximum number of treatments allowed (as per the protocol) was 12 applications	
Duration/number of administered treatment	Not reported	

continued

TABLE 115 Syed *et al.*[162] (*continued*)

Item	Details			
Baseline patient characteristics	*Imiquimod 2% cream (patient applied)*	*Placebo cream (patient applied)*	p-*value*	
Age (years), mean	24.7	23.7	Not reported	
Duration of disease	Not reported			
Site of AGWs	Of the overall trial population, 45 men (75%) had lesions on the penile shaft and corona sulcus and 15 men (25%) had lesions confined to the perianal area. Site of AGWs not reported separately by treatment group		Not reported	
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	9.6	9.0	Not reported	
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% male			
Any previous treatment	17/60 (28.3%) men had previously used podophyllotoxin 0.5% cream and had encountered resistance or treatment failure; number of men in each treatment group undergoing previous treatment with podophyllotoxin 0.5% not reported		Not reported	
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Total elimination of AGWs, as confirmed by colposcopy; analysed by number of patients with complete clearance and number of AGWs cleared			
Recurrence of AGWs	Recurrence after 14 months			
Volume of wart clearance	Proportion of men with ≥ 50% reduction in the surface area of baseline lesions (referred to as partial response). Number of men achieving a partial response in each treatment group not reported. Data on number of AGWs partially eliminated by treatment are available			
AEs	AEs were scored as mild, moderate, severe or none with respect to duration in days; further definitions of mild, moderate or severe not available. Data reported on occurrence of burning sensation, itching, pain, erythema, erosion and oedema			
Section 4: Data extraction form				
Outcome	*Time frame*	*Imiquimod 2% cream (patient applied),* n/N	*Placebo (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment (number of men)	4 weeks	21/30	3/30		$p < 0.0001$
AGW clearance (number of AGWs)	4 weeks	250/288	28/270		$p < 0.0001$
Recurrence of AGWs	14–18 months	1/21	2/3		Not reported
Volume of wart clearance (proportion of women with ≥ 50% clearance)	4 weeks	It is reported that seven men experienced partial regression of 18 lesions. Results not reported by treatment group			

TABLE 115 Syed *et al.*[162] (*continued*)

Item	Details			
AEs				
Erythema	4 weeks	4/30	0/30	Not reported
Erosion[a]	4 weeks	4/30	1/30	Not reported
Oedema	4 weeks	2/30	0/30	Not reported
Section 5: Clinical trial quality				
Outcome	*Risk of bias*		*Risk assessment*[b]	*Comments*
	Random sequence generation		?	It is reported that people were randomly allocated to treatment. Additional details on method of randomisation not available
	Allocation concealment		?	Detail on method used to conceal allocation not available
	Selective reporting		?	It is stated that partial response was recorded but data are not reported in a way that they can be entered in a meta-analysis. Volume of AGW clearance has not been defined as a primary outcome for this review. Although data for this outcome cannot be entered into a meta-analysis, data on the primary outcomes of interest are available
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		?	The study is described as double blind and it is reported that the study medications were packed in identical precoded tubes. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment		?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data		✓	No withdrawals or missing outcome data
Recurrence of AGWs	Blinding (participants and personnel)		?	The study is described as double blind and it is reported that the study medications were packed in identical precoded tubes. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment		?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data		✓	No withdrawals or missing outcome data

continued

TABLE 115 Syed *et al.*[162] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	?	The study is described as double blind and it is reported that the study medications were packed in identical precoded tubes. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	?	Minor discrepancy in the numbers reported in the text and results table for the outcome of erosion
Overall rating of bias		?	Reflects limited reporting in full publication
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation; STD, sexually transmitted disease.
a Results reported in main body of text differ from those presented in a table (in the text it is stated that five out of 30 men in the group receiving imiquimod 2% cream experienced erosion).
b ✓, low risk of bias; ?, unclear risk of bias.

TABLE 116 Tabari *et al.*[152]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Shannon Amoils and Sam Barton
Study ID	Tabari 2010
Study details	*Casp J Intern Med* 2010;**1**:16–19
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at a single site in Iran (Babol University of Medical Sciences)
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	It is stated that people were recruited from 'outpatient genital wart cases' (p. 17) attending the outpatient dermatology clinic from June 2005 to June 2008
Trial design	RCT
Trial duration	Total duration including follow-up is 6 months. Duration of treatment is unclear. Participants were followed up at 1 month, 2 months and 6 months
Line of therapy	Not reported
Inclusion criteria	People with a diagnosis of genital AGWs as evaluated by physical examination of the lesions were eligible

TABLE 116 Tabari *et al.*[152] (*continued*)

Item	Details		
Exclusion criteria	Pregnant women were excluded		
All outcomes reported in paper	Complete clearance; recurrence after treatment; complications		
Subgroups evaluated	None reported		
Stratification	None reported		
Baseline measurement of disease	Not reported. Participants were included on the basis of a 'clinical examination of the lesions' (p. 17) to confirm diagnosis of genital warts. The presence of multiple lesions was noted. No other baseline measurements on the lesions were carried out		
Treatment	*Podophyllin 20% (clinician applied)*	*TCAA 30% (clinician applied)*	
Randomised, *n*	60	60	
Withdrawals, *n*	0	0	
	It is stated that no patient interrupted treatment because of complications		
Treatment regimen	Podophyllin 20% was 'applied on the affected area topically twice a week and was washed after 20 minutes of application' (p. 17)	TCAA 30% was applied 'with topical cotton soap' every other day and was washed off 1 minute after application' (p. 17)	
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Podophyllin 20% (clinician applied)*	*TCAA 30% (clinician applied)*	p-*value*
Age (years), mean (SD)	32.0 (17.0)	31.8 (16.2)	Not reported
Duration of disease	Not reported		
Site of AGWs, *n* (%)	Not reported		
Type of AGWs, *n* (%)	Not reported		
Presence of multiple lesions, *n* (%)	42 (70.0)	45 (75.0)	Reported as no significant difference between treatment groups; *p*-value not reported
Area of AGWs (mm^2), mean	Not reported		
Sex (M/F), *n* (%)	Not reported		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance	Proportion of people who had complete clearance is reported. However, description of assessment of complete clearance is not available and it is unclear for which follow-up time point the data are reported (i.e. 1, 2 or 6 months). In addition, duration of treatment is unclear; thus, it is unclear whether reported data are for end of treatment or some other time point		
Recurrence of AGWs	Not defined. It is unclear how recurrence was determined. It is stated that recurrence was observed 'three months later' (p. 17). It is unclear whether this is 3 months after study initiation, after the end of treatment or after diagnosis of complete clearance of AGWs		
AEs	Not defined. Data are reported for the number of people reporting a burning sensation		

continued

TABLE 116 Tabari *et al.*[152] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllin 20% (clinician applied),* n/N	*TCAA 30% (clinician applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance (referred to as 'completely treated')	Unclear	56/60	56/60		Not reported
Recurrence of AGWs	Unclear	4/56	0/56		Not reported
AEs; burning sensation	Not reported	35/60	28/60		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		✓	It is stated that 'For the selection of patients in each arm, we prepared 120 cards and wrote the regimen podophyllin (60 cards) and regimen trichloroacetic acid (60 cards) on it. For every patient, a card was drawn and the regimen therapy noted on it was administered' (p. 17)	
	Allocation concealment		?	Insufficient information to determine risk of bias. It is stated that 'For every patient, a card was drawn and the regimen therapy noted on it was administered' (p. 17). It is unclear whether the cards were concealed in any way. It could be inferred that the personnel randomising participants were aware of allocation concealment	
	Selective reporting		✗	Clear definitions of duration of treatment regimens, outcome assessment and time at which outcomes were reported are not available. Lack of reporting of duration of treatment and time points for key clinical outcomes makes it difficult to compare the study with other trials in a meta-analysis	
	'Other bias'		?	Insufficient information reported to evaluate presence of other potential sources of bias	
AGW clearance	Blinding (participants and personnel)		?	Level of masking of participants and key study personnel not reported. It is unclear whether the person evaluating AGW clearance was masked to treatment	
	Blinding of outcomes assessment		?		
	Incomplete outcome data		✓	It is stated that 'all cases were followed' (p. 17) at 1 month, 2 months and 6 months	

TABLE 116 Tabari *et al.*[152] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	?	Level of masking of participants and key study personnel not reported. It is unclear whether the person evaluating AGW clearance was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Rate of recurrence is reported for people receiving podophyllin 20%. The reported text infers that no person receiving TCAA experienced recurrence, but this is not explicitly stated
AEs	Blinding (participants and personnel)	?	Level of masking of participants and key study personnel not reported. It is unclear whether the person evaluating AGW clearance was masked to treatment
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	Number of people evaluated for AEs unclear. Reporting suggests that all people randomised have been included but denominator has not been reported
Overall rating of bias		✗	Reflects unclear reporting as to duration of treatment and time point for reported clinical data
Section 6: Additional comments			
Additional comments	None		

M/F, male/female; SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 117 Trofatter *et al.*[134]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Shannon Amoils and Sam Barton
Study ID	Trofatter 2002
Study details	*Int J Gynaecol Obstet* 2002;**76**:191–3
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Not reported
Trial sponsor	Study supported by a research grant from 3M Pharmaceuticals
Conflicts of interest	Not reported
Patient enrolment	Not reported
Trial design	RCT (Phase II, dose-ranging study)
Trial duration	Initial treatment period of up to 16 weeks with a subsequent 4-week observational period
Line of therapy	Not reported

continued

TABLE 117 Trofatter *et al.*[134] (*continued*)

Item	Details			
Inclusion criteria	Women with histologically confirmed external AGWs			
Exclusion criteria	Not reported			
All outcomes reported in paper	Complete clearance; proportion of women with > 50% reduction in baseline AGW area; median time to clearance; AEs: application site reactions			
Subgroups evaluated	None reported			
Stratification	None reported			
Baseline measurement of disease	Not reported			
Treatment	*Imiquimod 5% cream twice daily (patient applied)*	*Imiquimod 5% cream once daily (patient applied)*	*Imiquimod 5% cream three times weekly (patient applied)*	
Randomised, *n*	32	32	26	
Withdrawals, *n* (%)	Not reported			
Treatment regimen	Women self-applied imiquimod 5% cream twice daily, once daily or three times weekly until complete resolution of baseline AGWs was confirmed or up to a maximum of 16 weeks, whichever occurred earlier. Women who developed an intolerable reaction were given the option to either discontinue treatment or take a rest period, during which treatment was deferred (for up to 14 consecutive days) until the reaction had subsided			
Duration/number of administered treatment	Not reported			
Baseline patient characteristics	*Imiquimod 5% cream twice daily (patient applied)*	*Imiquimod 5% cream once daily (patient applied)*	*Imiquimod 5% cream three times weekly (patient applied)*	p-*value*
Age (years), mean (SD	29 (9.1)	30 (12.3)	30 (13.0)	$p = 0.928$
Duration of disease (months), median (range)				
Time since onset	11.0 (2.0–248)	7.3 (1.1–368)	10.5 (0.1–361)	$p = 0.438$
Duration of current outbreak	4.1 (0.3–248)	2.6 (0.7–368)	3.7 (0.2–361)	$p = 0.306$
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, median (range)	10 (2–50)	11 (2–50)	13 (2–49)	$p = 0.801$
Area of AGWs (mm^2), median (range)	260 (34–1995)	138 (13–1975)	121 (31–1231)	$p = 0.211$
Sex (M/F), *n* (%)	100% female			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)				
Caucasian	29 (90.6)	28 (87.5)	23 (88.5)	$p = 1.000$
African American	3 (9.4)	4 (12.5)	3 (11.5)	

TABLE 117 Trofatter *et al.*[134] (*continued*)

Item	Details
Section 3: Outcomes	
Outcome	*Definition*
AGW clearance at completion of treatment	Not defined. Results are presented for the proportion of women with a 100% reduction in AGW area during the treatment and observation periods. Number of women achieving 100% reduction during the observation period noted. Number of women achieving clearance at end of treatment calculated by review authors
AGW clearance at other time points	Not defined. Results are presented for the proportion of women with a 100% reduction in AGW area during the treatment and observation periods (4 weeks after the end of treatment)
Time to complete clearance	Reported as 'median time to clearance' (p. 192)
Volume of wart clearance (> 50% clearance)	Number of women with a > 50% reduction in AGW area during the treatment and observation periods is reported. Presented results include those with 100% clearance. Proportion achieving > 50% but < 100% reduction in AGW area calculated by review authors
AEs	AEs not defined. Data reported for occurrence of application site reactions and patient-reported AEs of burning, itching and pain at the AGW site. Occurrence of investigator-observed local skin reactions (erythema, ulceration and erosion) presented graphically

Section 4: Data extraction form						
Outcome	*Time frame*	*Imiquimod 5% cream twice daily (patient applied),* n/N	*Imiquimod 5% cream once daily (patient applied),* n/N	*Imiquimod 5% cream three times weekly (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	Up to 16 weeks	18/32	23/32	16/26		Not reported
AGW clearance at other time points (cumulative)	4 weeks after end of treatment	20/32	23/32	16/26		$p = 0.3$
Volume of wart clearance (> 50% clearance)	Up to 20 weeks	9/32	7/32	6/26		$p = 0.61$
AEs						
Burning	Up to 16 weeks	7/31	10/31	6/28		$p > 0.50$
Itching	Up to 16 weeks	11/31	9/31	12/28		$p = 0.40$
Pain	Up to 16 weeks	8/31	7/31	3/28		$p = 0.48$
Severe erythema	Up to 16 weeks	Numerator and denominator not reported for severe erythema; number of women evaluated unclear				$p = 0.01$
		25%	10%	4%		
Erythema or erosion or ulceration	Up to 16 weeks	Results presented graphically; unable to report numbers accurately				Not reported
Continuous outcomes						
Time to complete clearance (weeks), median		8 (*n* not reported)	6 (*n* not reported)	12 (*n* not reported)		Not reported

continued

TABLE 117 Trofatter *et al.*[134] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	It is stated that women were randomised to treatment but details on method of randomisation not available
	Allocation concealment	?	Details on method used to conceal allocation not available
	Selective reporting	?	Insufficient information provided to determine risk of selective reporting
	'Other bias'	?	Insufficient information to determine risk of bias from other potential sources
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	The number of people withdrawing or lost to follow-up is not reported. Data are reported for the ITT population but it is unclear whether there is an imbalance across the groups in the number of people withdrawing or lost to follow-up
Time to complete clearance	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	The number of people withdrawing or lost to follow-up is not reported. Data are reported for the ITT population but it is unclear whether there is an imbalance across the groups in the number of people withdrawing or lost to follow-up

TABLE 117 Trofatter *et al.*[134] (*continued*)

Item	Details		
Volume of wart clearance (> 50% clearance)	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	The number of people withdrawing or lost to follow-up is not reported. Data are reported for the ITT population but it is unclear whether there is an imbalance across the groups in the number of people withdrawing or lost to follow-up
AEs	Blinding (participants and personnel)	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	The number of people withdrawing or lost to follow-up is not reported. It is unclear whether there is an imbalance across the groups in the number of people withdrawing or lost to follow-up. Data reported for AEs are not based on the same number of women in each group as reported for clinical outcomes. Reasons for the difference in number of women evaluated not discussed
Overall rating of bias		✗	Reflects open-label nature of the study
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 118 Tuncel *et al.*[135]

Item	Details		
Section 1: Reviewer and study information			
Reviewers' names	Victoria Wakefield and Sam Barton		
Study ID	Tuncel 2005		
Study details	*Eur Acad Dermatol Venereol* 2005;**19**(Suppl. 2):361		
Language of publication	English		
Type of report	Conference abstract		
Section 2: Study information			
Location and number of sites	Study carried out in Turkey; number of sites not reported		
Trial sponsor	Not reported		
Conflicts of interest	Not reported		
Patient enrolment	Not reported		
Trial design	Three-arm RCT		
Trial duration	Initial treatment period of up to 16 weeks; unclear whether there was an additional follow-up period		
Line of therapy	At least second line: inclusion criterion of persistent AGWs that were refractory to at least one conventional therapy		
Inclusion criteria	Presence of recalcitrant AGWs (perianal and/or genital) that were refractory to at least one conventional therapy		
Exclusion criteria	None reported		
All outcomes reported in paper	Results at end of study (presumed to be complete clearance); recurrence; AEs		
Subgroups evaluated	Gender (male vs. female)		
Stratification	None reported		
Baseline measurement of disease	Not reported		
Treatment	*Imiquimod 5% cream (self-applied)*	*Cryotherapy plus imiquimod 5% cream (self-applied)*	*Cryotherapy*
Randomised, *n*	20	20	20
Withdrawals, *n* (%)	Not reported		
Treatment regimen	Imiquimod 5% cream was self-applied to all external AGWs overnight three times a week until AGW clearance or for up to 16 weeks, whichever occurred earlier	Cryotherapy was administered at 3-week intervals until AGW clearance or for up to 16 weeks. Concomitantly, imiquimod 5% cream was self-applied to all external AGWs overnight three times a week until AGW clearance or for up to 16 weeks, whichever occurred earlier	Cryotherapy was administered at 3-week intervals until AGW clearance or for up to 16 weeks, whichever occurred earlier
Duration/number of administered treatment	Not reported		

TABLE 118 Tuncel *et al.*[135] (*continued*)

Item	Details			
Baseline patient characteristics	*Imiquimod 5% cream (self-applied)*	*Cryotherapy plus imiquimod 5% cream (self-applied)*	*Cryotherapy*	p-*value*
Age (years), mean	Not reported			
Duration of disease	Not reported			
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	Not reported			
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	Not reported			
Any previous treatment, *n* (%)	Not reported			
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Results at end of study are discussed in the abstract; no further details available			
Recurrence of AGWs	Recurrence rates are discussed in the abstract; no further details available			
AEs	Local and systemic AEs are discussed in the abstract. AEs were graded as mild, moderate or severe; no further details available			
Section 4: Data extraction form				
Outcome	*Time frame*	*Imiquimod 5% cream (self-applied),* n/N	*Cryotherapy plus imiquimod 5% cream (self-applied),* n/N	*Cryotherapy,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	16 weeks	Absolute numbers not reported. It is stated that 'statistically significant differences were found among the results in the groups at the end of the study' (p. 361) ($p < 0.05$). In addition, it is stated that better results were seen with imiquimod 5% cream plus cryotherapy than with imiquimod 5% cream monotherapy, but the difference did not reach statistical significance ($p > 0.05$)				
Recurrence of AGWs	16 weeks	Absolute numbers not reported. It is stated that recurrence rates were lower with both imiquimod 5% cream ($p < 0.05$) and imiquimod 5% cream ($p < 0.01$) plus cryotherapy than with cryotherapy alone				
AEs	16 weeks	Absolute numbers not reported. It is stated that 'home application of imiquimod was better tolerated and associated with fewer side effects than combination therapy' (p. 361)				

continued

TABLE 118 Tuncel *et al.*[135] (*continued*)

Item	Details		
Section 5: Clinical trial quality			
Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	?	The study is described as randomised but details on the method of randomisation are not reported
	Allocation concealment	?	Insufficient information available to assess whether allocation concealment has been implemented and, if so, the risk of bias associated with the method
	Selective reporting	✗	Absolute numbers are not reported for any outcome assessed and thus data cannot be evaluated in a meta-analysis
	'Other bias'	?	Insufficient information available to assess presence of other potential sources of bias
AGW clearance at completion of treatment	Blinding (participants and personnel)	✗	Study is described as open label. Given the difference in the types of treatment administered (topical vs. ablative), it might be impractical to mask personnel and patients to treatment. AGW clearance is a subjective outcome and at risk of bias
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	Number of withdrawals not reported

TABLE 118 Tuncel *et al.*[135] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	✗	Study is described as open label. Given the difference in the types of treatment administered (topical vs. ablative), it might be impractical to mask personnel and patients to treatment. Recurrence of AGWs is a subjective outcome and at risk of bias
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of recurrence is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	Number of withdrawals not reported
AEs	Blinding (participants and personnel)	✗	Study is described as open label. Given the difference in the types of treatment administered (topical vs. ablative), it might be impractical to mask personnel and patients to treatment. AEs associated with the treatments under evaluation are likely to be subjective and thus at risk of bias
	Blinding of outcomes assessment	✗	Study is described as open label. Assessment of AEs is likely to be subjective and open to influence from lack of masking. Although it is unclear whether the outcome assessor was masked to treatment, given that patients and other key study personnel were not, it is likely that masking would be broken
	Incomplete outcome data	?	Number of withdrawals not reported
Overall rating of bias		✗	Reflects open-label nature of study and lack of numerical data for use in a meta-analysis
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 119 Tyring *et al.*[125]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Shannon Amoils and Sam Barton
Study ID	Tyring 1998a. Related publications: Arany *et al.*[249]
Study details	*J Infect Dis* 1998;**178**:551–5
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Not reported
Trial sponsor	Not reported
Conflicts of interest	Not reported
Patient enrolment	It is stated that 'patients were enrolled after study procedures were explained, and they signed formal written consent' (p. 57).[249] Date of enrolment not reported
Trial design	RCT
Trial duration	Up to 16 weeks (treatment was administered until complete clearance or for a maximum of 16 weeks, whichever occurred earlier)
Line of therapy	Unclear. It is stated that people entering the trial were receiving treatment with imiquimod for the first time
Inclusion criteria	Aged ≥ 18 years; histologically confirmed diagnosis of condylomata acuminata; presence of at least 10 but no more than 50 AGWs prior to prestudy biopsy
Exclusion criteria	Known positive status for HIV infection; presence of high-grade cervical intraepithelial lesions; previous treatment with imiquimod; receipt of interferon, an interferon inducer, an immunomodulator, oral or topical antiviral drugs, cytotoxic or investigational drugs or chemical and/or surgical AGW treatment within the 4 weeks preceding study entry; receipt of topical non-AGW treatment to the AGW site or oral or inhaled corticosteroids (1000 µg/day) within the 2 weeks preceding study entry
All outcomes reported in paper	Complete clearance of AGWs (reported in Tyring *et al.*[126]); volume of AGW clearance (proportion of people with ≥ 75% clearance in AGW area from baseline); cytokine mRNA expression (changes from baseline); immune cell surface marker mRNA expression (changes from baseline); markers of viral infection (changes from baseline); keratinocyte markers (changes from baseline); cell cycle markers (changes from baseline)
Subgroups evaluated	None reported
Stratification	Study drug was randomised at a ratio of 4 : 1 for each gender such that, for every four patients who received imiquimod 5% cream, one received vehicle
Baseline measurement of disease	A biopsy of the target AGW area was obtained at baseline for confirmation of diagnosis and to establish a baseline for biological markers

TABLE 119 Tyring *et al.*[125] (*continued*)

Item	Details		
Treatment	*Imiquimod 5% cream (patient applied)*	*Vehicle (placebo) cream (patient applied)*	
Randomised, *n*	Number randomised to each group not reported. It is stated that 22 people were randomised and three people were lost to follow-up. Loss to follow-up not reported by treatment group		
	16 included in analysis	Three included in analysis	
Withdrawals	In total, three (13.6%) people were lost to follow-up. Reasons for withdrawal and loss by treatment group not reported		
Treatment regimen	People self-applied either imiquimod 5% cream or vehicle cream to AGWs overnight (for 8 ± 2 hours) three times per week on non-consecutive days. Treatment was repeated weekly until clearance of AGWs or for a maximum of 16 weeks, whichever occurred earlier		
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Imiquimod 5% cream (patient applied)*	*Vehicle (placebo) cream (patient applied)*	p-*value*
Age (years), mean	Not reported		
Time since onset of disease (months), median (range) (reported in Tyring *et al.*[126])	60 (3.5–204)	19.7 (6.6–100.3)	Not reported
Site of AGWs, *n* (%)	Not reported		
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean (with SD/SE if given)	Not reported		
Area of AGWs (mm^2), mean	Not reported		
Sex (M/F), *n* (%)	In total, 12 men and 10 women were randomised. Ratio of genders in each treatment group not reported separately		
Any previous treatment, *n* (%)	Not reported		
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Data reported on complete clearance of baseline AGWs at any point during the 16-week treatment period (Tyring *et al.*[126]). Clinical evaluation of clearance not described		
Volume of wart clearance (proportion of patients with ≥ 75% clearance)	Data reported on proportion of people with ≥ 75% clearance in total AGW area from baseline (Tyring *et al.*[126] and Arany *et al.*[249]); data reported include those with 100% clearance. Number of people with clearance between ≥ 75% and < 100% calculated by review authors		

continued

TABLE 119 Tyring *et al.*[125] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Imiquimod 5% cream (patient applied),* n/N	*Vehicle (placebo) cream (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	Up to 16 weeks	7/16	1/3		Not reported
Volume of wart clearance (proportion of people with ≥ 75% clearance)	Up to 16 weeks	9/16	0/3		Not reported
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[a]	*Comments*	
	Random sequence generation		?	It is stated that people were randomly allocated to treatment. Details on method used to generate random sequence not available	
	Allocation concealment		?	Details on method used to conceal allocation not available	
	Selective reporting		?	The objectives of the study seem to be to assess cellular response to imiquimod 5% cream by measuring viral load and the molecular immune response to treatment. The outcomes reported do not pertain to a clinical outcomes study and appropriate molecular and immunological outcomes are reported. Protocol is not available and it is unclear whether clinical outcomes were prespecified	
	'Other bias'		✗	In this small study of 22 people, the authors randomised participants in a ratio of 4 : 1 (study drug : placebo). Reasons for unequal randomisation were not available. Unequal randomisation reduces the power of the study to detect a true difference between treatment groups. Based on the 22 participants randomised, at most, five people would receive placebo, which is likely to be too small a number to provide clinically meaningful results. In addition, although limited details on baseline characteristics are reported, there is a marked difference between groups in the time since onset of disease, with a median time since onset of 60 months in the group treated with imiquimod and 19.7 months in the group treated with placebo	

TABLE 119 Tyring *et al.*[125] (*continued*)

Item	Details		
AGW clearance at completion of treatment	Blinding (participants and personnel)	?	Described as a double-blinded trial. Details on who was masked to treatment are not available. In addition, it is unclear whether attempts were made to mask the outcome assessor to treatment allocation
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The number of people randomised to each group is not reported. The analyses reported are based on those for whom evaluable data were available. The number of people excluded from the analysis is reported, but reasons for withdrawal are not. Although the number of people withdrawing is low, because of the small size of the trial the proportion of people withdrawing is high
Volume of wart clearance	Blinding (participants and personnel)	?	Described as a double-blinded trial. Details on who was masked to treatment are not available. In addition, it is unclear whether attempts were made to mask the outcome assessor to treatment allocation
	Blinding of outcomes assessment	?	
	Incomplete outcome data	?	The number of people randomised to each group is not reported. The analyses reported are based on those for whom evaluable data were available. The number of people excluded from the analysis is reported, but reasons for withdrawal are not. Although the number of people withdrawing is low, because of the small size of the trial, the proportion of people withdrawing is high
Overall rating of bias		✗	Reflects the considerable imbalance in the randomisation ratio between groups in a small study and imbalance in available baseline characteristics
Section 6: Additional comments			
Additional comments	None		

SD, standard deviation.
a ?, unclear risk of bias; ✗, high risk of bias.

TABLE 120 Tyring *et al.*[68]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Vicky Wakefield	
Study ID	Tyring 1998b	
Study details	*Arch Dermatol* 1998;**134**:33–8	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Study carried out at multiple sites (number not reported) in the USA	
Trial sponsor	Supported by a grant from Oclassen Pharmaceuticals Inc., San Rafael	
Conflicts of interest	Not reported	
Patient enrolment	People were recruited from private dermatology practices, university clinics (dermatology, gynaecology and infectious diseases) and contract research organisations and were enrolled between December 1992 and March 1994	
Trial design	RCT	
Trial duration	Initial treatment period of up to 8 weeks followed by assessment after a further 8 weeks to evaluate recurrence (depending on number of treatment cycles, total study time ranged from 9 to 16 weeks)	
Line of therapy	It is reported that approximately 20% of patients had received previous treatment for their current AGWs; no further details available	
Inclusion criteria	Age > 18 years; immunocompetent; at least two distinct external AGWs (genital and/or perianal); negative pregnancy test for women of child-bearing potential; women who were not breastfeeding and used an approved method of birth control during the study	
Exclusion criteria	People were excluded if they had received treatment for AGWs within the month preceding trial entry	
All outcomes reported in paper	Complete clearance; number of AGWs remaining each week; change in AGW surface area; change in individual AGW assessment scores; physician assessment of overall response; recurrence; AEs (including pain, burning, inflammation, itching, erosion and bleeding)	
Subgroups evaluated	Location (external AGWs vs. perianal AGWs) and gender (male vs. female)	
Stratification	None reported	
Baseline measurement of disease	Location, number, size, morphology and total area of AGWs were recorded at the baseline visit	
Treatment	*Podophyllotoxin 0.5% gel (self-applied)*	*Placebo gel (self-applied)*
Randomised, *n*	219	107
Withdrawals, *n* (%)	40 (18.3)	66 (61.7)
Not compliant with protocol (excluded from efficacy analysis)	16	8
Discontinuation because of inadequate response	17 (8.6) (three people had discontinued by week 4)	58 (61.1) (35 people had discontinued by week 4)
Discontinuation because of drug-related reactions	7 (3.2)	0 (0)

TABLE 120 Tyring *et al.*[68] (*continued*)

Item	Details		
Treatment regimen	Podophyllotoxin 0.5% gel or placebo gel were self-applied using a finger or applicator twice daily for 3 consecutive days, followed by 4 treatment-free days. The treatment cycle was repeated until complete clearance or for a maximum of eight cycles, whichever occurred earlier. People underwent a minimum of two cycles. If a local reaction was experienced, treatment was postponed for up to 1 week		
Duration/number of administered treatment	Not reported		
Baseline patient characteristics	*Podophyllotoxin 0.5% gel (self-applied)*	*Placebo gel (self-applied)*	p-*value*
n	Note: baseline characteristics are based on those patients who returned after the first visit		
	213	103	
Age (years), mean	31.5	30.6	Difference between groups reported to be not significant
Duration of disease (months), mean	27.3	24.0	Difference between groups reported to be not significant
Site of AGWs, *n/N* (%)	Note: characteristics reported for those included in the efficacy analysis		
External genital only	158/197 (80.2)	79/95 (83.2)	Differences between groups reported to be not significant
Perianal only	12/197 (6.1)	11/95 (11.6)	
Both	27/197 (13.7)	5/95 (5.3)	
Type of AGWs, *n* (%)	Not reported		Difference between groups reported as not significant for AGW morphology; further details not available
Number of AGWs, mean	5.5	5.4	Difference between groups reported to be not significant
Area of AGWs (mm^2), mean	159.2	141.8	Difference between groups reported to be not significant
Sex, *n* (%)			
Male	127 (59.6)	62 (60.2)	Difference between groups reported to be not significant
Female	86 (40.4)	41 (39.8)	
Any previous treatment	It is reported that about 20% of people had received previous treatment; number of people receiving previous treatment not reported by treatment group. The most frequent previous therapies administered for AGWs, in both treatment groups, were podophyllum resin (10–12%) and cryotherapy (9–10%)		Difference between groups reported to be not significant
Ethnicity	For the overall population, 80% white, 12% black. Ethnicity not reported by treatment group		Difference between groups reported to be not significant

continued

TABLE 120 Tyring *et al.*[68] (*continued*)

Item	Details				
Section 3: Outcomes					
Outcome	*Definition*				
AGW clearance at completion of treatment	Total disappearance of all treated AGWs at week 8 (last observation carried forward)				
AGW clearance at other time points	Total disappearance of all treated AGWs at week 4 (last observation carried forward)				
Recurrence of AGWs	Recurrence of at least one AGW within 12 weeks of successful treatment of all AGWs				
AEs	Severity of local AEs in the treated area (including pain, burning, inflammation, itching, erosion and bleeding) was assessed and categorised as mild, moderate or severe; definitions of mild, moderate and severe not available				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% gel (self-applied),* n/N	*Placebo gel (self-applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment[a]	8 weeks	81/181	4/93		$p < 0.001$
AGW clearance at other time points[a]	4 weeks	62/167	2/86		$p < 0.001$
Recurrence of AGWs	12 weeks	25/81	Not assessed/ 4		Not reported
AEs (%)[b]					
Burning	8 weeks	76.1	45.6		Not reported
Inflammation	8 weeks	71.4	11.7		
Itching	8 weeks	58.7	25.2		
Erosion	8 weeks	54.0	2.9		
Pain	8 weeks	54.0	5.8		
Bleeding	8 weeks	29.1	1.9		
Headache	8 weeks	9.4	5.8		
Any non-local AE	8 weeks	38	24		$p = 0.02$
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[c]	*Comments*	
	Random sequence generation		?	It is reported that people were randomised 2 : 1 to treatment groups. Additional details on method of randomisation not available	
	Allocation concealment		?	Detail on method used to conceal allocation not available	
	Selective reporting		✗	Number of people included in analysis of AGW clearance differs from that specified in the statistical analysis. Number of people experiencing recurrence in the placebo group is not reported. AEs are reported as percentages, with no indication of how many people were included in the analysis. As presented, data for recurrence and AEs cannot be entered in a meta-analysis	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	

TABLE 120 Tyring *et al.*[68] (*continued*)

Item	Details		
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	The study is described as double blind. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✗	It is unclear why the number of people included in the analysis of AGW clearance differs from that specified in the statistical analysis. In addition, the number of people analysed at week 4 differs from the number analysed at week 8. This potential discrepancy is not discussed. The number of people withdrawing from treatment and lost to follow-up is reported. A significantly larger proportion of people in the placebo group withdrew from treatment as a result of treatment inefficacy than in the podophyllotoxin 0.5% gel group. Although the analysis is based on last observation carried forward, and as such people withdrawing from treatment will be considered treatment failures, the imbalance in withdrawals is likely to induce clinically relevant bias in intervention effect estimates
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blind. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	?	All people achieving complete clearance were reported to have been followed up. However, it is unclear what influence the high rate of withdrawal from treatment will have on the estimate of effect for recurrence
AEs	Blinding (participants and personnel)	?	The study is described as double blind. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	?	It is unclear how many people are included in the analysis and therefore unclear whether a large proportion of people have been excluded and whether there is an imbalance in the number of people analysed in each group
Overall rating of bias		✗	Reflects limited reporting of some key outcomes and high rate of withdrawal from the study

continued

TABLE 120 Tyring *et al.*[68] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	• ITT analysis with last observation carried forward for missing data • Most AGWs were located on the penile shaft in men (66.8% in both groups) and on the labia in women (60.1% in placebo group and 55.2% in podophyllotoxin 0.5% gel group) • Patients with only perianal AGWs and receiving podophyllotoxin 0.5% gel were significantly older than those with perianal AGWs and receiving placebo gel (34.1 vs. 28.8 years; $p < 0.04$) • It was reported that the majority of recurrences occurred within the first 4 weeks after treatment cessation • Local AEs that occurred in < 7% of patients included stinging, erythema and scabbing. Almost all local AEs were resolved within 4 weeks of cessation of treatment, with the exception of one patient with burning and six with itching • Absolute change in mean surface area of AGWs was presented graphically and was reported to represent a statistically significant reduction at weeks 4 and 8 in the podophyllotoxin 0.5% gel group ($p = 0.001$; absolute numbers not reported). It is presumed that the statement describing the statistically significant reduction in AGW area is referring to the difference between the podophyllotoxin 0.5% group and the placebo group and not the reduction from baseline AGW wart area in the podophyllotoxin 0.5% group *Subgroup analyses* Complete clearance by location of AGW (external vs. perianal) is presented in the following table

	External AGWs, *n*/*N*		Perianal AGWs, *n*/*N*	
Treatment week	Podophyllotoxin 0.5%	Placebo	Podophyllotoxin 0.5%	Placebo
4	60/157[a]	0/75[a]	11/36	2/15
8	77/170[a]	1/82[a]	16/38	3/16

a $p < 0.001$.

SD, standard deviation.
a It is stated that the efficacy analysis would be based on all people returning for at least the first visit, which is reported to be 197 and 95 people in the podophyllin 0.5% gel group and placebo group respectively. However, analysis of AGW clearance is based on 181 and 93 people in the podophyllin 0.5% gel group and placebo group respectively. It is unclear how the number of people included in the analysis of AGW clearance has been reached.
b Number of people included in safety analysis not reported.
c ?, unclear risk of bias; ✗, high risk of bias.

TABLE 121 Viazis *et al.*[155]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Victoria Wakefield	
Study ID	Viazis 2007	
Study details	*Dis Colon Rectum* 2007;**50**:2173–9	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Study carried out at one centre in Greece	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Patients with intra-anal AGWs who were referred to the gastroenterology unit for treatment of AGWs between October 2002 and March 2005 were offered entry into the study	
Trial design	RCT	
Trial duration	Argon laser treatment was repeated every 4 weeks until complete clearance of AGWs was achieved. After elimination of AGWs, participants were followed up for a mean of 12 months (range 3–21 months)	
Line of therapy	First line of treatment for intra-anal AGWs; people were excluded if they had received previous treatment for intra-anal warts or had a history of any warts on the penis, groin, cervix, urethral meatus, vagina or pubis	
Inclusion criteria	No previous treatment of intra-anal AGWs with any modality; absence of AGWs or previous elimination of AGWs on the penis, groin, cervix, urethral meatus, vagina or pubis. People with simultaneous perianal AGWs were included	
Exclusion criteria	People were excluded if they had AGWs in sites other than the anal area	
All outcomes reported in paper	Time to elimination of all intra-anal AGWs; recurrence of intra-anal AGWs; AEs	
Subgroups evaluated	HIV status (positive vs. negative)	
Stratification	None reported	
Baseline measurement of disease	Not reported	
Treatment	*Argon plasma coagulation plus imiquimod 5% cream (self-applied)*	*Argon plasma coagulation*
Randomised, *n*	24	25
Withdrawals, *n* (%)	2 (8.3) (lost to follow-up)	2 (8.0) (lost to follow-up)
Treatment regimen	Argon plasma coagulation was repeated every 4 weeks until elimination of intra-anal AGWs. Using a finger, imiquimod 5% cream was self-applied to intra-anal AGWs at bedtime three times a week. Perianal AGWs, if present, were treated with imiquimod 5% cream at bedtime three times a week. Treatment with imiquimod 5% cream commenced just after the first treatment with argon laser and continued until the elimination of intra-anal AGWs	Argon plasma coagulation was repeated every 4 weeks until elimination of intra-anal AGWs. Perianal AGWs, if present, were treated with imiquimod 5% cream at bedtime three times a week

continued

TABLE 121 Viazis *et al.*[155] (*continued*)

Item	Details		
Duration/number of administered treatment	Mean number of sessions of argon plasma coagulation required to achieve complete clearance: 2.1 ± 0.2	Mean number of sessions of argon plasma coagulation required to achieve complete clearance: 3 ± 0.2	
	Difference between groups reported to be statistically significant, favouring the combination treatment ($p = 0.0016$)		
Baseline patient characteristics	*Argon plasma coagulation plus imiquimod 5% cream (self-applied)*	*Argon plasma coagulation*	p-*value*
Age (years), mean (unclear whether SD or SE)	32.3 (11.5)	30.4 (12.4)	Not reported
Duration of disease	Not reported		
Site of AGWs	100% intra-anal. Note: two people also had perianal warts	100% intra-anal. Note: three people also had perianal warts	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	Not reported		
Area of AGWs (mm^2), mean	Not reported		
Sex, *n* (%)			
Male	20 (83.3)	22 (88)	Not reported
Female	4 (16.7)	3 (12)	Not reported
Any previous treatment, *n*	0 for intra-anal AGWs	0 for intra-anal AGWs	
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Treatments were administered until all intra-anal AGWs in each person had been eliminated. Maximum number of treatments not specified and so time frame for completion of treatment not specified		
Recurrence of AGWs	Recurrence of intra-anal AGWs during the follow-up period after complete clearance (mean follow-up was 12 months)		
Time to complete clearance	Time to complete elimination of intra-anal AGWs in all people		
AEs	Occurrence of AEs of argon plasma coagulation and imiquimod 5% cream reported for itching/burning, erythema in anal canal and pain/bleeding		

TABLE 121 Viazis *et al.*[155] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Argon plasma coagulation plus imiquimod 5% cream (self-applied),* n/N	*Argon plasma coagulation,* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
Complete clearance of AGWs at end of treatment	End of treatment	22/22	23/23		–
Recurrence of AGWs	Mean follow-up of 12 months	5/22	8/23		Not significant
AEs					
Itching/burning[a]	Unclear	16/24	0/25		Not reported
Mild erythema in anal canal	Unclear	10/24	0/25		Not reported
Pain/bleeding	Unclear	0/24	0/25		Not reported
Continuous outcomes					
Time to complete clearance (days), mean (SE)		62.5 (5.4) ($n = 24$)	91.2 (6.4) ($n = 25$)		$p = 0.0016$
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[b]	*Comments*	
	Random sequence generation		✓	It is stated that randomisation was based on a table of random numbers	
	Allocation concealment		✓	It is stated that opaque, serially numbered envelopes were used to allocate treatment	
	Selective reporting		?	Insufficient information provided to determine risk of selective reporting	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	
Recurrence of AGWs	Blinding (participants and personnel)		?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible	
	Blinding of outcomes assessment		✗	The endoscopist assessing the outcomes was not an independent observer. Assessment of AGW recurrence is likely to be subjective and open to influence from lack of masking	
	Incomplete outcome data		✓	Few people were lost to follow-up and missing outcome data are balanced in numbers between the groups	

continued

TABLE 121 Viazis *et al.*[155] (*continued*)

Item	Details		
Time to complete clearance	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible
	Blinding of outcomes assessment	✗	The endoscopist assessing the outcomes was not an independent observer. Assessment of AGW clearance is likely to be subjective and open to influence from lack of masking
	Incomplete outcome data	✓	Few people were lost to follow-up and missing outcome data are balanced in numbers between the groups
AEs	Blinding (participants and personnel)	?	Details on level of masking of patients and personnel not provided. Given the difference in the treatments administered, it could be envisaged that masking of patients and personnel might not be feasible
	Blinding of outcomes assessment	✗	The endoscopist assessing the outcomes was not an independent observer. Assessment of AEs is likely to be subjective and open to influence from lack of masking
	Incomplete outcome data	✓	Few people were lost to follow-up and missing outcome data are balanced in numbers between the groups
Overall rating of bias		✗	Reflects the potential bias associated with outcome assessment
Section 6: Additional comments			
Additional comments	• The operative time for each session was approximately 10 minutes. The number of sessions of argon plasma coagulation required for elimination of AGWs was significantly less in the group receiving argon plasma coagulation plus imiquimod 5% cream than in the group receiving APC alone (2.1 ± 0.2 vs. 3 ± 0.2 sessions; $p = 0.0016$) • In addition, the five patients with perianal AGWs achieved complete clearance of these AGWs using imiquimod 5% cream before complete resolution of their intra-anal AGWs • It is reported that no major complications occurred in the study population • Mean time to recurrence was reported as 11.4 (range 6–18) months for argon plasma coagulation plus imiquimod 5% cream compared with 10.5 (range 6–18) months for argon plasma coagulation alone. Difference reported as not statistically significant • *Results for HIV-positive subgroup:* • Time to complete clearance was significantly shorter with argon plasma coagulation plus imiquimod 5% cream than with argon plasma coagulation alone (95 ± 22.6 days for argon plasma coagulation plus imiquimod 5% cream vs. 124.3 ± 20.7 days for argon plasma coagulation alone; $p = 0.033$) • Recurrence occurred in three people in the argon plasma coagulation plus imiquimod 5% cream group compared with five in the argon plasma coagulation alone group ($p = 0.59$) • Note: imiquimod 5% cream is not licensed for intra-anal use		

SD, standard deviation.
a Reported as occurring after application of imiquimod 5% cream.
b ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

TABLE 122 von Krogh *et al.*[126]

Item	Details	
Section 1: Reviewer and study information		
Reviewers' names	Jacoby Patterson and Sam Barton	
Study ID	von Krogh 1992	
Study details	*Sex Transm Dis* 1992;**19**:170–4	
Language of publication	English	
Type of report	Full publication	
Section 2: Study information		
Location and number of sites	Study carried out at the Department of Obstetrics and Gynaecology, Falu Hospital, Sweden	
Trial sponsor	Not reported	
Conflicts of interest	Not reported	
Patient enrolment	Patients were enrolled at the Department of Obstetrics and Gynaecology, Falu Hospital. Details on methods used to recruit patients and dates of enrolment not available	
Trial design	RCT	
Trial duration	3 weeks of treatment with subsequent follow-up at 3 months for those categorised as cured at any point in the trial	
Line of therapy	Overall, 25/60 (41.7%) participants had received previous treatment for AGWs in the previous 6 months	
Inclusion criteria	Women with vulvoanal condylomata (acuminata, popular or sessile)	
Exclusion criteria	Age < 18 years; presence of AGWs in the vagina, cervix or anus (as evaluated through colposcopy and proctoscopy); pregnancy or no safe contraceptive method; receipt of treatment for AGWs within the preceding 4 weeks	
All outcomes reported in paper	Complete clearance; recurrence; AEs	
Subgroups evaluated	Number of lesions (< 10 vs. ≥ 10), mean size of lesion (< 3 mm vs. ≥ 3 mm), site (outer vulva, inner vulva or perianal)	
Stratification	None reported	
Baseline measurement of disease	Details of baseline assessment not reported. Based on subgroups reported, it is inferred that location, size and number of AGWs were recorded	
Treatment	*Podophyllotoxin 0.5% cream (patient applied)*	*Placebo (patient applied)*
Randomised, *n*	48	12
Withdrawals, *n* (%)	4 (8.3)	0 (0)
Ineligible	1 (2.1; intra-anal condylomata detected)	0 (0)
Lost to follow-up	2 (4.2)	0 (0)
AEs	1 (2.1)	0 (0)
Treatment regimen	Podophyllotoxin 0.5% cream or placebo cream was applied by the patient twice daily for 3 days per week for up to 3 weeks. Participants were instructed how to locate individual condyloma with one finger and how to apply the cream with another finger	
Duration/number of administered treatment	Not reported	

continued

TABLE 122 von Krogh *et al.*[126] (*continued*)

Item	Details		
Baseline patient characteristics	*Podophyllotoxin 0.5% cream (patient applied)*	*Placebo (patient applied)*	p-*value*
	Note: baseline characteristics in the podophyllotoxin 0.5% cream group are based on the 44 women for whom data were available rather than the 48 randomised to treatment		
Age (years), mean	26.3	25.5	Difference between groups reported to be not significant
Duration of disease (months), mean	6.9	6.0	Difference between groups reported to be not significant
Site of AGWs, *n* (%)[a]			
Outer vulva[b]	8	Not reported	Not reported
Inner vulva[b]	35	Not reported	
Perianal	20	Not reported	
Type of AGWs, *n* (%)	Not reported		
Number of AGWs, mean	11.7	Not reported	
Area of AGWs (mm^2), mean	Not reported		
Sex (M/F), *n* (%)	100% female		
Any previous treatment	Overall, 25/60 (41.7%) women had been treated for AGWs in the preceding 6 months; data not reported separately by treatment group		
Ethnicity, *n* (%)	Not reported		
Section 3: Outcomes			
Outcome	*Definition*		
AGW clearance at completion of treatment	Complete clearance of AGWs at 3 weeks		
AGW clearance at other time points	Complete clearance of AGWs also recorded after 1 week and 2 weeks		
Recurrence of AGWs	Recurrence of AGWs in treated location at 3 months' follow-up. Authors corrected for instances of 'reoccurrences', which were defined as development of AGWs during follow-up on locations other than those initially identified as afflicted by AGWs; three women in the podophyllotoxin 5% group were identified as having 'reoccurrence' at follow-up		
AEs	AEs were not defined. Local AEs, including burning, pain/tenderness and erosion, were evaluated		

TABLE 122 von Krogh *et al.*[126] (*continued*)

Item	Details				
Section 4: Data extraction form					
Outcome	*Time frame*	*Podophyllotoxin 0.5% cream (patient applied),* n/N	*Placebo (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes					
AGW clearance at completion of treatment	3 weeks	40/44	1/12		Not reported
AGW clearance at other time points	1 week	18/44	0/12		Not reported
	2 weeks	29/44	0/12		
Recurrence of AGWs (does not include reoccurrences)	3 months	3/40	0/0		Not reported
AEs					
Burning	3 weeks	33/44	4/12		Not reported
Pain/tenderness	3 weeks	24/44	0/12		
Erosion	3 weeks	21/44	0/12		
Section 5: Clinical trial quality					
Outcome	*Risk of bias*		*Risk assessment*[c]	*Comments*	
	Random sequence generation		?	It is stated that women were randomly selected for treatment. Additional details on the method of randomisation not reported	
	Allocation concealment		?	Details not provided	
	Selective reporting		?	Insufficient information reported to assess level of selective reporting	
	'Other bias'		?	Insufficient information provided to determine presence of additional sources of bias	
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		?	The study is described as double blind and it is stated that 'all test tube preparations had an identical appearance' (p. 171). Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken	
	Blinding of outcomes assessment		?	Unclear whether the clinician assessing clinical outcomes was masked to treatment allocation	
	Incomplete outcome data		?	Loss to follow-up and reasons for withdrawal reported. Not all women randomised evaluated in their allocated treatment group. Although loss to follow-up is low, there is an imbalance between the groups in the proportion of women withdrawing. The effect of this minor imbalance on the estimate of effect is unclear	

continued

TABLE 122 von Krogh *et al.*[126] (*continued*)

Item	Details		
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blind and it is stated that 'all test tube preparations had an identical appearance' (p. 171). Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	Unclear whether the clinician assessing clinical outcomes was masked to treatment allocation
	Incomplete outcome data	?	It is unclear whether there were any additional losses to follow-up during the follow-up period. The analysis is based on all people with complete clearance
AEs	Blinding (participants and personnel)	?	The study is described as double blind and it is stated that 'all test tube preparations had an identical appearance' (p. 171). Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	Unclear whether the clinician assessing clinical outcomes was masked to treatment allocation
	Incomplete outcome data	?	Loss to follow-up and reasons for withdrawal reported. Not all women randomised were evaluated in their allocated treatment group. Although loss to follow-up is low, there is an imbalance between the groups in the proportion of women withdrawing. The effect of this minor imbalance on the results is unclear
Overall rating of bias		?	Reflects limited reporting on methodology in the full publication
Section 6: Additional comments			
Additional comments	• Data for subgroup analysis based on number of AGWs at baseline (< 10 vs. ≥ 10), mean size of AGWs (< 3 mm vs. ≥ 3 mm) and location of AGWs (outer[b] vs. inner[b] vs. perianal) are presented. Data for the podophyllotoxin 0.5% group only are reported • Number of women in the podophyllotoxin 0.5% group who were completely cured after 3 weeks: by number of AGWs at baseline: 22/24 (91.7%) with < 10 AGWs vs. 18/20 (90.0%) with ≥ 10 AGWs; by mean size of individual AGWs: 24/24 (100%) with mean size < 3 mm vs. 17/20 (85.0%) with mean size ≥ 3 mm; by location of AGWs: 7/8 (87.5%) with outer AGWs vs. 33/35 (94.3%) with inner AGWs vs. 19/20 (95.0%) with perianal AGWs • The difference between subgroups based on mean size of individual AGWs was statistically significant ($p < 0.05$)		

SD, standard deviation.
a The number of sites of AGWs is greater than the number of women evaluated as women could have AGWs at more than one site simultaneously.
b The outer vulva was defined as the area lateral to the outer border between the labium minora and labium majora. The inner vulva was defined as the labium minora and the adjacent mucous membrane up to the introitus vaginae.
c ?, unclear risk of bias.

TABLE 123 von Krogh *et al.*[127]

Item	Details		
Section 1: Reviewer and study information			
Reviewers' names	Jacoby Patterson and Sam Barton		
Study ID	von Krogh 1994		
Study details	*Genitourin Med* 1994;**70**:105–9		
Language of publication	English		
Type of report	Full publication		
Section 2: Study information			
Location and number of sites	Study carried out at Department of Dermatovenereology, South Hospital, Stockholm, Sweden; study indicates that only one site involved		
Trial sponsor	Not reported		
Conflicts of interest	Not reported		
Patient enrolment	Patients were recruited from men attending STD outpatient department for previously untreated penile warts. Dates of enrolment not reported		
Trial design	RCT		
Trial duration	Initial treatment period of a maximum of 2 weeks with follow-up of up to 23 weeks for those considered to have complete clearance		
Line of therapy	First line		
Inclusion criteria	Men attending STD outpatient department who had previously untreated penile AGWs		
Exclusion criteria	It is stated that at the first visit 'concurrent syphilis was ruled out' (p. 106); it is not stated that men with concurrent syphilis were excluded		
All outcomes reported in paper	Complete clearance; recurrence; AEs		
Subgroups evaluated	Location of AGWs		
Stratification	None reported		
Baseline measurement of disease	Four categories of AGW were recorded and monitored based on anatomical location: urinary meatus, preputial cavity, transitional area between the inner and outer aspect of the foreskin and the penile shaft. Each site was monitored for the number of AGWs during the trial. No additional details on baseline assessment available		
Treatment	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllotoxin 0.25% solution (patient applied)*	*Placebo solution (patient applied)*
Randomised, *n*	19	19	19
Withdrawals, *n* (%)	3 (15.8) (lost to follow-up)	1 (5.3) (lost to follow-up)	2 (10.5) (lost to follow-up)
	Loss to follow-up reported for men lost during the treatment period. Two more men from the podophyllotoxin groups were lost to follow-up during the treatment-free period		
Treatment regimen	Using swabs, men applied their allocated treatment (podophyllotoxin 0.5% solution, podophyllotoxin 0.25% solution or placebo solution) at home twice daily for 3 days. If complete clearance was not achieved after the first round of treatment, men were instructed to repeat the treatment cycle against residual AGWs. The second cycle was to start at day 8–10 after the initiation of the first cycle but could be initiated 'when required within another week or so' (p. 106). It is stated that the mean number of days to start of the second round of treatment was 9.5 (SD 0.6; range 6–28)		
Duration/number of administered treatment	Not reported		

continued

TABLE 123 von Krogh *et al.*[127] (*continued*)

Item	Details			
Baseline patient characteristics	*Podophyllotoxin 0.5% solution (patient applied)*	*Podophyllotoxin 0.25% solution (patient applied)*	*Placebo solution (patient applied)*	p-*value*
Age (years), mean (with SD/SE if given) (range)	Full trial population 25.4 (17–48). Range of mean age across groups was 23.2–27.2 years; mean age not reported for individual treatment groups			It is stated that, across the groups, ages were 'fairly well matched' (p. 107)
Duration of disease (months), mean	Full trial population 4.1 (1–24). Range of mean duration of disease across groups was 3.7–4.6 months; mean duration of disease not reported for individual treatment groups			Difference across groups reported to be not significant
Site of AGWs, number of lesions				
Preputial cavity	74	109	39	Not reported
Transition inner/outer part of foreskin	58	104	94	
Other	3	4	0	
Type of AGWs, *n* (%)	Not reported			
Number of AGWs, mean	8.4	12.1	7.8	$p = 0.27$
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% male			
Any previous treatment, *n* (%)	No (100% previously untreated AGWs)			
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Not defined. Defined here as complete clearance after a maximum of two cycles of treatment			
AGW clearance at other time points	Not defined. Defined here as complete clearance after one cycle of treatment			
Recurrence of AGWs	Reappearance of AGWs in people considered to be AGW free after treatment. Recurrence also includes men who experienced a reoccurrence (defined as AGWs occurring on previously untreated sites)			
AEs	AEs were classified as mild, moderate and pronounced; definitions of the individual categories not available. AEs monitored included itching, stinging, burning, erythema, tenderness or erosion. Data on individual AEs not reported separately for the two podophyllotoxin groups			

TABLE 123 von Krogh *et al.*[127] (*continued*)

Item	Details					
Section 4: Data extraction form						
Outcome	*Time frame*	*Podophyllotoxin 0.5% solution (patient applied),* n/N	*Podophyllotoxin 0.25% solution (patient applied),* n/N	*Placebo solution (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment	Two treatment cycles	13/16	13/18	0/17		$p < 0.001$ for podophyllotoxin (combined) vs. placebo; no significant difference between 0.5% and 0.25% podophyllotoxin solutions
AGW clearance at other time points	One treatment cycle	9/16	9/18	0/17		
Recurrence of AGWs	20–23 weeks after treatment	1/8	3/5	0/0		Not reported
AEs						
Mild	Maximum of two cycles of treatment	9/16	9/18	3/17		Not reported
Moderate		2/16	2/18	1/17		
Pronounced		3/16	3/18	0/17		
Section 5: Clinical trial quality						
Outcome	*Risk of bias*		*Risk assessment*[a]		*Comments*	
	Random sequence generation		?		It is stated that men were randomly allocated to treatment. Details on method used to generate random sequence not available	
	Allocation concealment		?		Details on method used to conceal allocation not available	
	Selective reporting		?		Insufficient information available to assess potential bias in selective reporting	
	'Other bias'		?		Insufficient information available to evaluate other potential sources of bias	
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)		?		The study is described as double blind but, from the information available, it is unclear whether the patients and key study personnel were masked to treatment. It is stated that the test bottles given to patients were of identical appearance but it is unclear whether there was the potential for masking to be broken	

continued

TABLE 123 von Krogh *et al.*[127] (*continued*)

Item	Details		
	Blinding of outcomes assessment	?	It is stated that 'patients who considered themselves as cured after the first three-day cycle of home treatment were instructed to return for a follow-up visit two weeks after initiation of therapy' (p. 106). Although patients are likely to be masked to treatment, self-assessment could introduce bias. In addition, it is unclear whether the clinician assessing AGW clearance and recurrence was masked to treatment
	Incomplete outcome data	✓	A small number of participants were lost to follow-up and a similar proportion of participants were lost from the three treatment groups. It is unlikely that the exclusion of these participants from the analyses will have a clinically relevant impact on the effect estimate
Recurrence of AGWs	Blinding (participants and personnel)	?	The study is described as double blind but, from the information available, it is unclear whether the patients and key study personnel were masked to treatment. It is stated that the test bottles given to patients were of identical appearance but it is unclear whether there was the potential for masking to be broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing AGW recurrence was masked to treatment
	Incomplete outcome data	✓	The number of people lost to follow-up during the observation period is reported and is low
AEs	Blinding (participants and personnel)	?	The study is described as double blind but, from the information available, it is unclear whether the patients and key study personnel were masked to treatment. It is stated that the test bottles given to patients were of identical appearance but it is unclear whether there was the potential for masking to be broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✓	A small number of participants were lost to follow-up and a similar proportion of participants were lost from the three treatment groups. It is unlikely that the exclusion of these participants from the analyses will have a clinically relevant impact on the effect estimate
Overall rating of bias		?	Reflects limited reporting in the full publication

TABLE 123 von Krogh *et al.*[127] (*continued*)

Item	Details
Section 6: Additional comments	
Additional comments	• It is stated that serological tests for HIV were negative in all men • Results were reported by number of AGWs permanently eradicated in each group and by site:

Site	Number of AGWs remaining after treatment/number of AGWs identified at site prior to treatment		
	Podophyllotoxin 0.5% solution (patient applied)	Podophyllotoxin 0.25% solution (patient applied)	Placebo solution (patient applied)
Preputial cavity	0/74	10/109	36/39
Transition inner/outer part of foreskin	4/58	22/104	89/94
Other	1/3	1/4	0/0
Total number of warts eradicated	130/135	184/217	8/133

SD, standard deviation; STD, sexually transmitted disease.
a ✓, low risk of bias; ?, unclear risk of bias.

TABLE 124 White *et al.*[144]

Item	Details
Section 1: Reviewer and study information	
Reviewers' names	Jacoby Patterson and Victoria Wakefield
Study ID	White 1997
Study details	*Genitourin Med* 1997;**73**:184–7
Language of publication	English
Type of report	Full publication
Section 2: Study information	
Location and number of sites	Study carried out at two centres in the UK (Birmingham General Hospital and Coventry and Warwickshire Hospital)
Trial sponsor	Former United Birmingham Hospitals trust fund
Conflicts of interest	Not reported
Patient enrolment	Men presenting with a first episode of untreated penile AGWs at the Departments of Genitourinary Medicine at Birmingham General Hospital and the Coventry and Warwickshire Hospital were eligible for the study. Recruitment occurred between September 1991 and October 1992
Trial design	RCT (three arms)
Trial duration	Final follow-up occurred at 3 months (period of initial treatment unclear)
Line of therapy	First line
Inclusion criteria	Men with first-episode, untreated penile AGWs were eligible
Exclusion criteria	Age < 16 years; presence of non-penile AGWs requiring separate treatment; any substantial risk for HIV infection; another painful penile condition; presence of intrameatal AGWs; receipt of any treatment for AGWs in the 12 months preceding trial entry

continued

TABLE 124 White *et al.*[144] (*continued*)

Item	Details			
All outcomes reported in paper	Complete clearance; AEs; patient satisfaction with treatment			
Subgroups evaluated	None reported			
Stratification	None reported			
Baseline measurement of disease	At baseline visit, the duration of AGWs was recorded. In addition, the number, size and morphology of AGWs was assessed and recorded			
Treatment	*Podophyllin 0.5% (patient applied)*	*Podophyllin 2% (patient applied)*	*Podophyllotoxin 0.5% (patient applied)*	
Randomised, *n*	103	106	106	
Withdrawals	86 men were eligible for assessment according to the protocol. Total number of withdrawals not reported	81 men were eligible for assessment according to the protocol. Total number of withdrawals not reported	77 men were eligible for assessment according to the protocol. Total number of withdrawals not reported	
Side effects, *n*	0	4	0	
Excluded from analysis because of protocol violations/ not meeting entry criteria, *n*	17	25	29	
Number of protocol-eligible men failing to attend follow-up at 5 weeks, *n*	46	42	51	
Treatment regimen	Allocated treatment [podophyllin 0.5% or 2.0% or podophyllotoxin 0.5% (formulations not reported)] was self-applied twice daily for 3 consecutive days per week using 1.0 µl soft plastic microbiological loops. Men were instructed that, if soreness occurred, they should stop applying the medication but could recommence the following week. If soreness/side effects proved unacceptable, the men left the study. Number of treatment cycles permitted is unclear. Podophyllin was prepared in the Birmingham General Hospital pharmacy, from *Podophyllum hexandrum* (emodi)-derived podophyllin resin powder in 90% industrial methylated spirits			
Duration/number of administered treatment	Not reported			
Baseline patient characteristics	*Podophyllin 0.5% (patient applied)*	*Podophyllin 2% (patient applied)*	*Podophyllotoxin 0.5% (patient applied)*	p-*value*
Age (years), mean	Not reported			
Duration of disease, *n* (%)				
Unknown	11 (10.7)	19 (17.9)	22 (20.8)	Reported as not significant
< 1 month	27 (26.2)	31 (29.2)	24 (22.6)	
1–3 months	45 (43.7)	33 (31.1)	36 (34.0)	
> 3 months	20 (19.4)	23 (21.7)	24 (22.6)	

TABLE 124 White *et al.*[144] (*continued*)

Item	Details			
Site of AGWs, *n* (%)	Not reported			
Type of AGWs, *n* (%)				
Unknown	19 (18.4)	25 (23.6)	28 (26.4)	Reported as not significant
Acuminata	38 (36.9)	29 (27.4)	40 (37.7)	
Sessile	41 (39.8)	47 (44.3)	30 (28.3)	
Mixed	5 (4.9)	5 (4.7)	8 (7.5)	
Number of AGWs, *n* (%)				
Unknown	17 (16.5)	20 (18.9)	22 (20.8)	Reported as not significant
1–5	54 (52.4)	55 (51.9)	45 (42.5)	
5–10	20 (19.4)	24 (22.6)	28 (26.4)	
> 10	12 (11.7)	7 (6.6)	11 (10.4)	
Area of AGWs (mm^2), mean	Not reported			
Sex (M/F), *n* (%)	100% male			
Any previous treatment, *n* (%)	100% untreated			
Ethnicity, *n* (%)	Not reported			
Section 3: Outcomes				
Outcome	*Definition*			
AGW clearance at completion of treatment	Complete clearance. Follow-up was carried out at week 5 and at 3 months after commencing treatment. In the full publication, results are reported only for week 5			
AEs	AEs were categorised as mild/none, moderate or severe. Definitions not reported for mild, moderate and severe and type of AEs experienced not reported			
Section 4: Data extraction form				
Outcome	*Time frame*	*Podophyllin 0.5% (patient applied),* n/N	*Podophyllin 2% (patient applied),* n/N	*Podophyllotoxin 0.5% (patient applied),* n/N	*Estimate of effect*	p-*value*
Dichotomous outcomes						
AGW clearance at completion of treatment (healed completely on clinical examination)	Week 5	28/40	28/39	18/26		$p = 0.97$
AGW clearance at completion of treatment (healed completely on clinical examination or patient self-assessment via postal questionnaire)	Week 5	41/106	42/103	38/106		Not reported

continued

TABLE 124 White *et al.*[144] (*continued*)

Item	Details				
AEs					
Unevaluable	Week 5	7/103	3/106	5/106	Not reported
Mild/none	Week 5	33/103	32/106	22/106	Not reported
Moderate	Week 5	2/103	5/106	2/106	Not reported
Severe	Week 5	2/103	0/106	0/106	Not reported
Severe/ withdrawn	Week 5	0/103	4/106	0/106	Not reported

Section 5: Clinical trial quality

Outcome	*Risk of bias*	*Risk assessment*[a]	*Comments*
	Random sequence generation	✓	It is stated that a computer-generated random allocation list was used
	Allocation concealment	✓	Treatment was dispensed by the hospital pharmacy in sealed boxes with obscured contents labels
	Selective reporting	✗	Formulations of included interventions and duration of treatment are not reported, which precludes comparison with results from other studies
	'Other bias'	?	Insufficient information provided to determine presence of additional sources of bias
AGW clearance at completion of treatment and at other time points	Blinding (participants and personnel)	?	The study is described as double blind. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✗	High number of withdrawals with no reasons reported and an imbalance in number of withdrawals across treatment groups. The high withdrawal rate and imbalance in withdrawal rate is likely to influence the estimate of effect

TABLE 124 White *et al.*[144] (*continued*)

Item	Details		
AEs	Blinding (participants and personnel)	?	The study is described as double blind. Limited details on methods are reported and it is unclear who was masked to treatment and whether masking could have been broken
	Blinding of outcomes assessment	?	It is unclear whether the clinician assessing clinical outcomes was masked to treatment
	Incomplete outcome data	✗	High number of withdrawals with no reasons reported and imbalance in number of withdrawals between treatment groups. The high withdrawal rate and imbalance in withdrawal rate is likely to influence the estimate of effect
Overall rating of bias		✗	Reflects limited reporting in full publication and high loss to follow-up
Section 6: Additional comments			
Additional comments	A total of 19 patients who did not conform to the entry criteria and a further 52 classified as 'protocol violators' had follow-up entries set to 'unknown results'. Only 105 of 277 protocol-eligible patients attended for clinical examination at week 5. Only 76 patients attended at 3 months for review. As a consequence of the low numbers attending follow-up, analyses were not carried out		

SD, standard deviation.
a ✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.

Economic data abstraction

TABLE 125 Identified economic evaluations in people with AGWs

Author, year, country	Overview	Population	Intervention	Costs	Outcomes	ICER	Uncertainty
Langley 2010,[163] USA	Cost-effectiveness analysis. A one-stage decision model (first-line therapies only) estimating cost-effectiveness. The decision model developed was based on the model described in a previous analysis by the same author. The analysis was from a US health-care perspective with a time horizon of treatment duration of 16 weeks. In addition, a two-stage model was reported; this model considered costs associated with the addition of a second line of therapy	People with external genital warts	First-line: sinecatechins, imiquimod	Costs captured: drug costs, physician costs and procedure costs Source: average wholesale price data and for procedures 2009 Medicare fee schedule Costs were not discounted Average cost of first-line therapy $774 for sinecatechins and $930 for imiquimod	Percentage sustained clearance (estimated as initial clearance multiplied by one minus recurrence rate) obtained from the published literature. Sustained clearance for sinecatechins was estimated by pooling data from two clinical trials Sustained clearance: 51.9% sinecatechins, 40.6% imiquimod	Incremental cost-effectiveness was not reported. Cost per sustained clearance was estimated to be $1492 and $2289 for sinecatechins and imiquimod respectively	The authors found that use of sinecatechins first line was the dominant strategy. Scenario analysis was carried out; the results of the model were robust to the scenarios modelled
Walczak 2009,[164] Poland	A cost-effectiveness analysis conducted from a payer (patient and health-care provider) perspective. A decision model was built with a time horizon of 28 weeks (duration of imiquimod clinical trial)	Adults with genital/perianal warts	Imiquimod, podophyllotoxin	Costs of medications and clinic visits were included. Costs were not discounted. Total costs estimated to be 1121.34 PLN for imiquimod and 218.35 PLN for podophyllotoxin	Total clearing of warts based on published literature. Effects were not discounted. Probability of total clearing of warts 0.429 imiquimod, 0.196 podophyllotoxin	The ICER was incremental cost per total clearing of warts. The ICER for imiquimod vs. podophyllotoxin was PLN 3865	Authors concluded that imiquimod was more effective and more expensive compared with podophyllotoxin. No sensitivity analysis was reported

Author, year, country	Overview	Population	Intervention	Costs	Outcomes	ICER	Uncertainty
Lacey 2003,[64] UK	A UK trial-based cost-effectiveness analysis carried out from a societal perspective. Time horizon was 12 weeks	354 immunocompetent women and men, aged 18–65 years with current genital warts and receiving no therapy	Clinic-applied 25% podophyllin, patient-applied 0.15% podophyllotoxin cream, patient-applied 0.5% podophyllotoxin solution	Cost year 1998. Costs captured included treatment costs, cost of physician visits, costs of AEs, costs resulting from absence from work and travelling costs. Costs for physician visits were obtained from six units participating in the study. Costs resulting from absence from work were estimated using average incomes for women and men in the UK in 1998. Costs were not discounted. The estimated total cost at 12 weeks was £535 for clinic-applied podophyllin solution, £573 for patient-applied podophyllotoxin cream and £517 for podophyllotoxin solution	Measure of effectiveness was complete remission of all warts at 12 weeks; data were obtained from the clinical trial. The probability of an AE was taken from the clinical trial. Outcomes were not discounted. The estimated complete remission rate at 12 weeks was 46.9% for clinic-applied podophyllin solution, 62.2% for patient-applied podophyllotoxin cream and 70.2% for podophyllotoxin solution	The ICER was incremental cost per additional patient cured. The ICER reported for podophyllotoxin cream vs. podophyllin was £246.73. Podophyllin vs. podophyllotoxin solution was assessed to be dominated (more costly and less effective)	No sensitivity analysis was reported; CIs reflect the uncertainty around the effectiveness data

continued

TABLE 125 Identified economic evaluations in people with AGWs (*continued*)

Author, year, country	Overview	Population	Intervention	Costs	Outcomes	ICER	Uncertainty
Lafuma 2003,[165] France	A cost-effectiveness analysis carried out from the perspective of the French national health insurance scheme. A decision tree was developed, incorporating two lines of treatment. At first line, people had a probability of being cured or not. At second line, people who were cured had a probability of relapse; people who were not initially cured had a probability of being cured with second-line treatment. The time horizon of the model was the initial treatment duration (4–16 weeks) followed by 3 months' follow-up	People with external AGWs	Imiquimod 5% (16 weeks) followed by CO_2 laser therapy for people with treatment failure or recurrence following clearance; podophyllotoxin 0.5% (4 weeks) followed by CO_2 laser therapy for people with treatment failure or recurrence following clearance	Direct medical-related costs were included. Resource use was estimated from a survey of 21 French physicians with experience of treating sexually transmitted diseases. Costs were obtained from national sources	The proportion of patients cured and the probability of relapse for imiquimod and podophyllotoxin was obtained from reanalysis of data published in two clinical trials.[68,118] The proportion of patients cured with laser therapy was obtained through a review of the literature	The ICER calculated was incremental cost per patient cured at the end of all treatments. The estimated incremental cost per additional patient cured for imiquimod vs. podophyllotoxin was €603	Scenario analyses were carried out, varying the number of sessions of podophyllotoxin (to 8 weeks) and effectiveness (clearance and recurrence). The authors reported the ICER to be robust to changes

Author, year, country	Overview	Population	Intervention	Costs	Outcomes	ICER	Uncertainty
Williams 2003,[166] UK	A cost-effectiveness analysis carried out from a UK NHS perspective. A decision model was developed with a time horizon of between 16 and 28 weeks	People with AGWs who were HIV negative	Imiquimod, podophyllotoxin	Costs included were UK drug acquisition costs obtained from the BNF 42 (2002); GUM clinic costs were obtained from Lacey *et al.*[64] Costs were not discounted. Total cost was estimated to be £109.95 for treatment with podophyllotoxin and £245.83 for treatment with imiquimod	Sustained clearance percentage was estimated by combining estimates of clearance at the end of clinical trials and estimates of recurrence in a 12-week follow-up period. Clinical trial estimates of clearance were obtained from a simple search (for podophyllotoxin) and use of a recent quantitative review (for imiquimod). Estimates identified were pooled by summation between trials and 95% CIs were calculated. Sustained clearance was estimated as the multiple of the pooled clearance rate and the pooled complement of the recurrence rate. Sustained clearance was estimated to be 35.1% for podophyllotoxin and 40.6% for imiquimod	Incremental cost-effectiveness (incremental cost per sustained clearance) for imiquimod vs. podophyllotoxin was £2477 per additional sustained clearance	A series of one-way and probabilistic sensitivity analyses were carried out. In probabilistic analysis, the authors found that, in 9995 of the 10,000 iterations of the model, podophyllotoxin treatment was dominant compared with imiquimod (i.e. was less costly and more effective). This conclusion implies that only five out of 10,000 simulations resulted in imiquimod having higher efficacy, despite having a higher base-case efficacy (40.6% vs. 35.1%)

continued

TABLE 125 Identified economic evaluations in people with AGWs (*continued*)

Author, year, country	Overview	Population	Intervention	Costs	Outcomes	ICER	Uncertainty
Alam 2001,[167] USA	A cost-effectiveness analysis carried out from a health-care provider perspective	Adults with no presenting complaints other than condylomata acuminata	Surgical excision, loop electrosurgical excision, electrodesiccation, CO_2 laser therapy, podofilox, pulsed-dye laser therapy, cryotherapy, TCAA, imiquimod, podophyllum resin 25%, interferon-alpha-2b. All interventions were assessed as monotherapy	Costs of physician visits, procedures, medications and medical devices were included (direct medical costs). Office visits and physician-administered treatment costs were estimated from the November 1999 Medicare fee schedule; costs of medications and medical devices were estimated as average wholesale prices quoted in the 2000 *Red Book Drug Topics*. Drug usage was estimated from published guidelines or published empirical data if more recent	Short-term efficacy rates taken from a review of the literature were used to weight treatment costs	ICERs were not reported. Mean medical costs per complete clearance of simple and extensive condylomata were $285 surgical excision, $316 loop electrosurgical excision, $347 electrodesiccation, $416 CO_2 laser therapy, $424 podofilox, $479 pulsed-dye laser therapy, $951 cryotherapy, $986 TCAA, $1255 imiquimod, $1632 podophyllum resin and $6665 interferon-alpha-2b. Surgical excision was associated with the lowest cost per complete clearance	No sensitivity analysis was reported
Fagnani 2000,[168] France	A cost-effectiveness analysis from a French national health system perspective. A decision model was developed in which people had a maximum of two lines of therapy and were either cured or not cured at each line; people could relapse at either line of therapy	People with external AGWs	First-line treatment: imiquimod 5%, podophyllotoxin gel 0.5%; second-line treatment: CO_2 laser therapy	Treatment-related direct costs were included. Costs were not discounted. The average cost per patient was estimated to be 2733 francs for imiquimod followed by CO_2 laser therapy and 2120 francs for podophyllotoxin followed by CO_2 laser therapy	Patients cured and relapse rates, based on published literature. Percentage of disease cured after imiquimod strategy: 62.4%; percentage of disease cured after podophyllotoxin strategy: 46.9%	Incremental cost-effectiveness was not reported. Cost per patient cured was 4383 francs for the imiquimod strategy and 4519 francs for the podophyllotoxin strategy	A scenario analysis was reported in which fewer sessions with podophyllotoxin was assessed

Author, year, country	Overview	Population	Intervention	Costs	Outcomes	ICER	Uncertainty
Langley 1999,[169] USA	A description of three cost-effectiveness analyses carried out from a health-care payer perspective. Decision-analytical models were developed for the analyses. All models considered two lines of treatment, with second-line treatment a result of first-line treatment failure	People with external genital warts	Analysis 1: imiquimod 5% first line followed by podophyllin, cryotherapy or TCAA Analysis 2: podofilox (podophyllotoxin 0.5% solution) first line followed by podophyllin, cryotherapy or TCAA Analysis 3: cryotherapy first line followed by imiquimod 5%	Cost year 1998. Direct treatment-related costs were used. Provider-administered costs were based on published literature whereas patient-applied therapy costs were based on average wholesale price costs. No discounting was applied to costs	Sustained clearance based on published literature	ICERs were not reported Analysis 1: cost per sustained clearance for imiquimod followed by podophyllin $1456, cryotherapy $1367, TCAA, $1237 Analysis 2: cost per sustained clearance for podophyllotoxin followed by podophyllin $1737, cryotherapy $1508, TCAA $1239 Analysis 3: cost per sustained clearance for cryotherapy followed by imiquimod $1368	A scenario analysis was carried out using lower bounds of clearance for the following combinations: imiquimod followed by cryotherapy, podofilox followed by cryotherapy and cryotherapy followed by imiquimod. Cost per sustained clearance decreased such that podofilox followed by cryotherapy became the least favourable option. Imiquimod followed by cryotherapy and cryotherapy followed by imiquimod had nearly identical costs per sustained clearance

continued

TABLE 125 Identified economic evaluations in people with AGWs (*continued*)

Author, year, country	Overview	Population	Intervention	Costs	Outcomes	ICER	Uncertainty
Langley 1999,[170] USA	A description of three cost-effectiveness analyses carried out from a health-care payer perspective, using decision tree models. Analysis 1 evaluated patient-applied therapies (12-week time horizon); analysis 2 evaluated provider-administered ablative therapies (time horizon not stated); analysis 3 evaluated a two-stage approach in which patient-applied therapies were used initially followed by provider-administered therapies for failures (time horizon not stated)	People with external genital warts	Analysis 1 (patient-applied therapies): imiquimod, podofilox (podophyllotoxin 0.5% solution) Analysis 2 (provider-administered therapies): podophyllin, laser surgery, cryotherapy, TCAA Analysis 3 (two-stage model): patient-applied therapies followed by provider-administered therapies for treatment failures	Direct treatment costs were included (costs of physician visits and drug therapy). The cost estimates were based on a 1992 study by Strauss.[198] Costs were inflated to 1997 prices. Costs were not discounted	A literature search was carried out using MEDLINE. Studies containing sustained clearance data at or close to 12 weeks for monotherapy were reviewed by an expert panel. ITT clearance rates were extracted from the included papers. People who discontinued therapy were assumed to be non-responders	ICERs were not reported. Analysis 1: cost per sustained clearance was $1150 for imiquimod and $990 for podofilox Analysis 2: cost per sustained clearance was $2508 for podophyllin, $1120 for laser surgery, $1833 for cryotherapy and $1300 for TCAA Analysis 3: Cost per sustained clearance when assuming clearance rate for ablative treatment was 30% (the average sustained clearance rate for provider-administered therapies) was $1263 and $1304 for imiquimod and podofilox respectively	A scenario analysis was carried out using alternative sustained clearance rates for provider treatments (10% and 20%). The authors found that, regardless of the assumed sustained clearance rate for provider treatments, imiquimod had a lower cost per sustained clearance

Author, year, country	Overview	Population	Intervention	Costs	Outcomes	ICER	Uncertainty
Mohanty 1994,[171] UK	A retrospective cost-effectiveness analysis using GUM clinic data. The perspective of the analysis was a health-care perspective	683 people aged ≥ 16 years who attended St Luke's Hospital GUM clinic in 1991, were diagnosed with genital warts and who received and completed treatment with either podophyllin 25% resin or 0.5% podophyllotoxin solution first line	Podophyllin 25% vs. podophyllotoxin 0.5% solution as first-line therapy followed by cryotherapy, TCAA or electrocautery; the choice of second-line therapy was dependent on the size and number of warts	Direct costs of treatment were included (staff and drug costs). An average cost associated with a doctor was applied to reflect the varying grades of doctors present at the GUM clinic. The cost of a receptionist was included in the analysis. Costs were not discounted. The average cost per patient was £14.95 for podophyllin 25% and £20.75 for podophyllotoxin 0.5% solution	Patients cured (complete clearance of warts and no recurrence after 3 weeks of clearance). The proportion of patients cured was estimated based on retrospective analysis of clinic data. The percentage of patients cured was 34.6% for podophyllin 25% and 66% for podophyllotoxin 0.5% solution	Incremental cost-effectiveness not reported. Cost per patient cured was £27.15 for podophyllin 25% and £25.73 for podophyllotoxin 0.5% solution. The authors concluded that, although the cost per patient was higher for podophyllotoxin solution than for podophyllin, because the efficacy of podophyllotoxin was greater than that of podophyllin the cost per patient cured was lower for podophyllotoxin	No sensitivity analysis was reported

PLN, Polish zloty.

TABLE 126 Identified HRQoL data in people with AGWs

Author, year, country	Population	Methods	Health states	Instrument (valuation)	Utility results
Dominiak-Felden 2013,[237] UK	186 patients aged 18–64 years with a current episode of genital warts	Patients completed the EQ-5D along with 43 patients with vulval intraepithelial neoplasia. Patients were recruited at 15 centres across the UK between May 2008 and March 2009. Their scores were compared with the UK general population normal values	With genital warts, without genital warts	EQ-5D	With genital warts: women 0.84 (SD 0.16), unweighted; men 0.89 (SD 0.17), unweighted; all 0.90 (SD 0.13), weighted; all (aged 18–24 years) 0.86, weighted; all (aged 25–34 years) 0.93, weighted Without genital warts: all 0.89; all (aged 18–24 years) 0.94; all (aged 25–34 years) 0.93
Mennini 2013, Italy[222]	421 patients with HPV-related diseases in Italy; number of patients with AGWs specifically was not reported	Patients completed a QoL questionnaire	With AGWs	EQ-5D (time trade-off)	Mean utility value with AGWs 0.58 (SD 0.31)
Shi 2012, China[223]	A convenience sample of 1358 genital wart patients from 18 centres in seven geographical regions of China	Patients completed QoL and demographic questionnaires	EQ-5D scores for multiple covariates including gender, region, urban/rural, marital status, education, income, insurance coverage, smoking status, number of sexual partners and clinical status. In addition, overall EQ-5D score was available for Japanese, US and UK valuations	EQ-5D (time trade-off), using Japanese valuations	**Preference weights** / **Mean** / **SD** Japan / 0.843 / 0.129 UK / 0.826 / 0.201 USA / 0.859 / 0.145

Author, year, country	Population	Methods	Health states	Instrument (valuation)	Utility results
Drolet 2011,[227] Canada	272 patients with first or recurrent AGWs in Canada	Between September 2006 and February 2008, patients with a first or recurrent episode of AGWs were recruited from the clinical practices of 42 physicians across Canada. QoL assessed at recruitment, month 2 and month 6. Canadian norms for the EQ-5D were also presented	QoL presented at recruitment, at follow-up dependent on clearance or not and by gender	EQ-5D (time trade-off), SF-6D (standard gamble)	See nested table below
Mennini 2011,[224] Italy	36 women with histologically confirmed diagnosis of high-grade cervical intraepithelial neoplasias in Italy	42 patients were screened at three clinical research centres in Italy. A QoL questionnaire was administered	AGWs by study centre and overall	EQ-5D (time trade-off)	Mean EQ-5D for AGWs overall: 0.71 (SD 0.35)

Utility measure	Population norm, mean	AGWs at recruitment		6 months, with clearance of warts		6 months, no clearance of warts	
		Mean	95% CI	Mean	95% CI	Mean	95% CI
Women							
EQ-5D	88.6	77.4	74.0 to 80.8	89.3	84.6 to 94.0	79.6	73.4 to 85.7
SF-6D	NA	71	69.0 to 73.0	76.7	73.8 to 79.4	71.5	67.8 to 75.2
Men							
EQ-5D	89.1	81	77.4 to 84.5	86.1	79.8 to 92.3	83.8	78.5 to 89.1
SF-6D	NA	74.2	(2.0 to 76.5	77.5	73.2 to 81.8	73.8	70.3 to 77.4

NA, not applicable.

continued

TABLE 126 Identified HRQoL data in people with AGWs (*continued*)

Author, year, country	Population	Methods	Health states	Instrument (valuation)	Utility results
Senecal 2011,[225] Canada	273 adults with initial occurrence or recurrence of genital warts in Canada	42 physicians across Canada recruited adults with genital warts. Patients completed a questionnaire collecting QoL and demographic data three times over a 6-month period (baseline, 2 months, 6 months). QoL scores were compared with Canadian population norms from a 1997 study of 3594 residents of Alberta. A further comparative analysis was carried out using US data	Disutility associated with genital warts for all patients and by covariates: gender, age, number of recurrences, time since onset of first genital warts episode, patient assessment of severity, physician assessment of severity	EQ-5D (time trade-off)	EQ-5D scores for covariates presented within the paper. Overall EQ-5D loss (mean percentage points) for genital warts: 9.9 (95% CI 7.3 to 12.5)
Woodhall 2011,[176] England and Northern Ireland	A convenience sample of 895 people aged ≥ 16 years with a current diagnosis of genital warts from seven sexual health clinics in England and one in Northern Ireland	Patients were invited to respond to demographic, clinical, behavioural and QoL questions from August 2009 to February 2010. QoL scores were compared with age group- and sex-matched average scores from the UK reference population. Consenting patients received a second questionnaire 2 weeks after their baseline visit	Utility associated with and without genital warts, by gender	EQ-5D (time trade-off)	EQ-5D score genital warts (women and men): 0.87 (95% CI 0.85 to 0.89), disutility: 0.056 (95% CI 0.038 to 0.074); EQ-5D score genital warts (women): 0.87 (95% CI 0.83 to 0.90), disutility: 0.063 (95% CI 0.029 to 0.097); EQ-5D score genital warts (men): 0.88 (95% CI 0.86 to 0.90), disutility: 0.043 (95% CI 0.021 to 0.065)

Author, year, country	Population	Methods	Health states	Instrument (valuation)	Utility results
Fiander 2010,[230] UK	Data from an observational cross-sectional study in which 1264 subjects (women and men) aged 18–64 years were recruited from 15 community and hospital health-care clinics	Women with genital warts aged 18–25 years recruited into the observational cross-sectional study. Number of patients not reported	Utility associated with genital warts	EQ-5D (time trade-off)	EQ-5D score associated with genital warts in women aged 18–25 years: 0.83
Fiander 2010,[231] UK	Data from an observational cross-sectional study of HPV-related disease in which 1264 subjects (women and men) aged 18–64 years were recruited from 15 community and hospital health-care clinics	Men with genital warts aged 18–25 years recruited into the observational cross-sectional study. Number of patients not reported	Utility associated with genital warts	EQ-5D (time trade-off)	EQ-5D score associated with genital warts in men aged 18–25 years: 0.89
Langley 2010,[228] UK, France, Spain, Italy and Germany	Internet-based survey carried out in the UK, France, Spain, Italy and Germany; 53,524 respondents in total, with 521 respondents with external genital warts	Regression analysis on SF-6D scores from respondents controlling for presence/absence of external genital warts, sociodemographic characteristics, health risk factors and Charlson Comorbidity Index	Disutility associated with external genital warts	SF-6D (standard gamble)	Disutility associated with external genital warts: –2.47 (95% CI –3.58 to –1.36)
Mennini 2011,[224] Italy	276 patients with HPV-related diseases (including genital warts) and 75 age-matched female healthy control subjects in Italy	Female patients with HPV-related diseases that were detected and managed in the preceding 18 months completed a computerised algorithm	Mean utility with and without genital warts	Time trade-off	Utility with genital warts: 0.69 ± 0.29; utility for healthy control subjects: 0.92 ± 0.19

continued

TABLE 126 Identified HRQoL data in people with AGWs (*continued*)

Author, year, country	Population	Methods	Health states	Instrument (valuation)	Utility results
Marra 2009, Canada[229]	75 participants with a history of AGWs who were recruited through a newspaper advertisement in Vancouver, Canada	Participants were asked questions about their sociodemographic and health status and filled in two QoL questionnaires. Participants were asked to consider the health state they were experiencing when they had AGWs	Utility scores with AGWs	EQ-5D (time trade-off), SF-6D (standard gamble)	EQ-5D score for genital warts: 0.76 (SD 0.19); SF-6D score for genital warts: 0.74 (SD 0.13)
Woodhall 2008,[32] England	81 adults attending the York GUM clinic with new, recurrent or persistent genital warts	Consenting participants completed questionnaires on demographic status and QoL. An EQ-5D control group was considered that included 1977 people in the same age range as the sample with genital warts	QoL with and without genital warts	EQ-5D (time trade-off)	Unadjusted: mean EQ-5D score with genital warts ($n = 81$): 0.90, mean EQ-5D without genital warts ($n = 1977$): 0.91; adjusted for age and gender, mean EQ-5D difference between people with genital warts and people without genital warts: 0.039 (95% CI 0.005 to 0.078)
Brisson 2007, Canada[226]	31 women presenting at a physician's office with genital warts	The QoL estimates from the 31 women with genital warts presenting at a physician's office were compared with average population QoL estimates, matched on age and gender	Disutility associated with genital warts	EQ-5D (time trade-off)	Disutility associated with genital warts: 0.10 (95% CI 0.05 to 0.15)

SD, standard deviation.

TABLE 127 Identified UK-based costing studies

Author, year	Studied population	Methods overview	Incidence/prevalence data	Cost year	Therapy costs	Resource use	Resource use costs	Cost per episode	Cost per population
Chapman 2013[215]	UK and devolved nations	Cost was calculated by multiplying the estimated number of people with genital warts in the UK by the expected resource use for these patients and applying UK-specific unit costs	Cases of genital warts at GUM clinics estimated using data from the HPA for the UK and England, the Information Services Division for Scotland, the Communicable Disease Surveillance Centre for Wales and the Public Health Agency for Northern Ireland. Cases of genital warts in primary care estimated using data from the Health Improvement Network database extrapolated using population statistics to estimate the number of genital wart cases at national level	Not stated	Therapy use estimated through discussions with GUM experts. Costs from the BNF were applied	Resource use estimated through discussions with GUM experts	Costs taken from the 'most recent' NHS payment by results tariffs and data from the *Unit Costs for Health and Social Care*	The cost per episode of genital warts was estimated to be £265 (UK)	£58.42M UK, £41.72M England, £1.9M Scotland, £1.87M Wales and £0.95M Northern Ireland

continued

TABLE 127 Identified UK-based costing studies (*continued*)

Author, year	Studied population	Methods overview	Incidence/prevalence data	Cost year	Therapy costs	Resource use	Resource use costs	Cost per episode	Cost per population
Lanitis 2011[51]	UK	Cost was calculated by multiplying the estimated number of people with genital warts in the UK by the expected resource use for these patients and applying UK-specific unit costs	Number of episodes estimated for GUM clinics and GP surgeries and projected to 2010. GUM clinics: number of cases estimated from HPA data; GP surgeries: number of cases estimated from Health Improvement Network data. Estimates for 2010: 173,077 GUM clinics (96,278 first episodes, 58,109 recurrent episodes and 18,690 persistent episodes); 16,782 primary care. On average, the four clinical experts felt that 2% (range 0.5– 8%) of patients were 'hard to treat'	2010	Therapy use estimated through discussions with four GUM experts. Average values were used in the base-case analysis. Costs from the BNF were applied	To estimate treatment utilisation patterns, four GUM clinicians were surveyed and each provided an estimate of the number of visits required per patient, based on the type of case (whether first episode, recurrent episode or persistent episode) and the type of wart (keratinised or non-keratinised). Most genital wart episodes were found to require two visits whereas persistent and hard-to-treat warts required three or more and eight to twelve visits respectively	Cost of attendance at GUM clinic taken from WF01B first attendance single professional, 360 GUM outpatient attendance tariff. £133 WF01A follow-up attendance single professional, 360 GUM, outpatient attendance tariff. £101 GP visit from the *Unit Costs of Health and Social Care*: £36	£276	£52.4M

Author, year	Studied population	Methods overview	Incidence/prevalence data	Cost year	Therapy costs	Resource use	Resource use costs	Cost per episode	Cost per population
Desai 2011[3]	England	Cost was calculated by multiplying the estimated number of people with genital warts in England with the expected resource use for these patients and applying UK-specific unit costs	Number of people presenting with genital warts (new and recurrent cases) was obtained for GUM clinics, GP surgeries and NHS hospitals. GUM clinics: data obtained from HPA data; data from 2008 and 2009 were averaged to provide an estimate of 141,770 cases each year. GP surgeries: the GPRD was reviewed between 2006 and mid-2008; GPRD data were extrapolated to the total population under GP care in England, resulting in an estimated 39,645 episodes of care annually. Hospital data were obtained using HES for people treated in a NHS hospital with a primary diagnosis of 'anogenital (venereal) warts', denoted by ICD-10 code A630; 1978 episodes of care were recorded to this code in 2008. To account for overlap between GPRD and HPA data, an episode with a referral code or at least one diagnostic code in the referral table and an episode with no treatment recorded were assumed to have been referred to a GUM clinic	2008–10	Costs presented by Woodhall *et al.*[176] were applied to the number of people with genital warts	Not reported	Costs presented by Woodhall *et al.*[176] were applied to the number of people with genital warts	The average cost per episode of care resolved by a GP was £79 and per episode seen by both GP and GUM clinicians was £138. The average cost per hospital care was £718. The estimated cost per episode of care for all settings was £113 (95% CI £104 to £121)	The annual cost of care in England for GP and GUM clinics combined was approximately £15.3M. The annual cost of hospital care in England was £1.4M. The total cost of care in England was £16.8M

continued

TABLE 127 Identified UK-based costing studies (*continued*)

Author, year	Studied population	Methods overview	Incidence/prevalence data	Cost year	Therapy costs	Resource use	Resource use costs	Cost per episode	Cost per population
Carroll 2011[173] (linked to Lanitis 2012[51])	UK	Cost was calculated by multiplying the estimated number of people with genital warts in the UK by the expected resource use for these patients and applying UK-specific unit costs	Numbers of episodes estimated for GUM clinics and GP surgeries and projected to 2010. GUM clinics: number of cases estimated from HPA data. GP surgeries: number of cases estimated from Health Improvement Network data. Estimates for 2010: 173,077 GUM clinics (33.5% recurrent, 11% persistent), 16,882 primary care	2010	Therapy use estimated through discussions with GUM experts. Costs from the BNF applied	Number of visits required per episode estimated through discussions with GUM experts for standard and hard-to-treat patients	Resource use multiplied by UK-specific costs. NHS payment by results tariffs used for GUM costs. GP visit costs taken from *Unit Costs of Health and Social Care*	£273 female, £278 male	£52.4M
Woodhall 2011[176]	Seven GUM clinics in UK	Estimated cost of care for people with genital warts in 2010 based on review of the treatment of patients presenting at seven sexual health clinics. The authors carried out a case note review of 370 people aged ≥ 16 years attending six sexual health clinics in England and one clinic in Northern Ireland. Patients were required to have a current diagnosis of genital warts (new or recurrent episode) and have attended the clinic between April and June 2007. The authors recorded the resources used in the care of each participant and applied costs to the resource use using a mixture of standard UK unit costs and clinic estimates of cost	Not applicable	2010	Unit costs per use: podophyllotoxin cream £14.86 (source electronic drug tariff), podophyllotoxin solution £12.38 (source BNF), imiquimod £51.32 (source electronic drug tariff), cryotherapy £4.27 (clinic costing), TCAA £0.32 (clinic costing), podophyllin £0.02 (clinic costing), eutectic mixture of local anaesthetic cream £1.73 (BNF), hyfrecation £5.63 (clinic costing), curettage £4.66 (clinic costing), diode laser £143.50 (clinic costing), CO2 laser therapy £125.49 (clinic costing)	Duration of episode of care from case note review: women 37 days, men 35 days, average 36 days. Average number of visits per episode of care from case note review: 2.5. The percentage of patients attending once was 45% for women and 55% for men	Not reported	The estimated mean cost per episode of care was £94 without a STI screen and £146 with a STI screen	Not reported

Author, year	Studied population	Methods overview	Incidence/prevalence data	Cost year	Therapy costs	Resource use	Resource use costs	Cost per episode	Cost per population
Woodhall 2009[175]	189 patients with genital warts presenting at York GUM clinic	Case note review of 189 patients registered at the York clinic who were diagnosed with genital warts (first or recurrent episode). Resources used by each patient during an episode were recorded. The time taken for each procedure was estimated through interviews with nine members of the clinical team. UK costs were applied to the resources used; staff costs were taken from the *Unit Costs for Health and Social Care 2007* whereas the costs of treatments carried out in the clinic (cryotherapy, curettage, electrosurgery/hyfrecation, electrosurgery/diathermy, TCAA) were estimated from local costs of equipment and consumables	Not applicable	2007	The costs of home treatments were estimated from the BNF (2007): podophyllotoxin solution (males) \$26.47, podophyllotoxin cream (females) \$31.77, imiquimod \$105.47. The costs of clinic treatments were taken from local costs of equipment and consumables (2007): cryotherapy \$8.27, curettage \$6.04, electrosurgery/ hyfrecation \$9.70, electrosurgery/ diathermy \$8.48, TCAA 'negligable'	Number of appointments taken from case notes. The mean number of visits per episode of care (both first and recurrent) was estimated to be 2.8 (95% CI 2.4 for 3.2), with first episode mean of 2.9 and recurrent mean of 2.74. Nearly half (46%) of patients had one visit per episode of care. The average length of an episode of care was 41 days, with 3% of cases having an episode of care > 6 months. The time taken for each procedure was estimated through interviews with nine members of the clinical team. Clinician time for the first visit was estimated to be 19.2 (SD 1.9) minutes ($n = 9$) Clinician time for the follow-up visits was estimated to be 9.7 (SD 0.94) minutes ($n = 9$)	Staff costs were taken from the *Unit Costs for Health and Social Care 2007*. Staff included specialist physician (\$359.64 per hour), associate specialist (\$85.58 per hour), trainee doctor (\$84.26 per hour), band 5 nurse (\$53.43 per hour), band 6 nurse (\$61.65 per hour), band 7 nurse (\$78.09 per hour), band 2 (chaperone) (\$26.72 per hour)	Mean cost of an episode of care estimated to be \$286 (£139; 95% CI \$246 to \$327)	Not reported

continued

TABLE 127 Identified UK-based costing studies (*continued*)

Author, year	Studied population	Methods overview	Incidence/prevalence data	Cost year	Therapy costs	Resource use	Resource use costs	Cost per episode	Cost per population
Brown 2006[172]	UK	For the calculation of the costs associated with the treatment of genital warts, the authors estimated the number of people with genital warts in the UK and multiplied this by the estimated resource use and associated costs to estimate a total cost of genital wart treatment in 2003	The number of people with genital warts (first or recurrent) presenting in GUM clinics was obtained from HPA surveillance data. The number of genital wart cases reported by GUM clinics in 2003 in the UK was 76,457 for incident cases, 38,902 for recurrent cases and 16,755 for persistent cases	2003	Data for drug use and procedures were obtained from questionnaires sent to six GUM clinicians in Aberdeen, Liverpool, London ($n = 2$), Nottingham and Southampton. Telephone interviews were conducted with each respondent to review and clarify responses. For GUM clinic visits for diathermy, cryotherapy or combination treatment (procedure plus drug therapy), an all-inclusive payment was obtained from personal communication with a clinician. Costs for topical treatments were obtained from the BNF, accessed online in February 2006. GUM clinic procedures included physician time £70, loop electrosurgical excision procedure excision £280, imiquimod 5% £55.18, podophyllotoxin 5-g tube £16.62, podophyllin 10 ml £3.00	Data for number of visits per episode were obtained from questionnaires sent to six GUM clinicians in Aberdeen, Liverpool, London ($n = 2$), Nottingham and Southampton. Telephone interviews were conducted with each respondent to review and clarify responses. Responses were pooled and mean rates of events were used for costing. Length of visit was obtained from Langley *et al.*,[174] a study that carried out a retrospective chart review	GUM clinic procedures, including physician time £70	Not reported	The total annual cost for genital warts was £22.4M. When using individual physician treatment patterns the cost varied between £18M and £25.3M

Author, year	Studied population	Methods overview	Incidence/prevalence data	Cost year	Therapy costs	Resource use	Resource use costs	Cost per episode	Cost per population
Langley 2004[174]	Six GUM clinics in England and Wales	Retrospective case note review of people with external genital warts, carried out in six GUM clinics in England and Wales in 2000. At each clinic, the case notes of 100 female and 100 male patients, each with a completed episode of care, were evaluated and costs were applied to the resources consumed	Not applicable	Not reported	Not reported	Average contact time and type of professional was taken from the case note review. Initial treatment visit (minutes): doctor 16.2 males, 20.5 females; nurse 10.3 males and females; health advisor 11.5 males and females. Subsequent treatment visit (minutes): doctor 10.5 males and females; nurse 7.9 males and females; health advisor 10.3 males and females	The source of cost data was not provided within the study. Labour costs were described as estimated using annual salaries. Indirect costs were described as non-labour expenses, non-patient care expenses and direct patient care costs	Average total cost £135.77 males, £146.37 females	Not reported

EOC, episode of care; GPRD, General Practice Research Database; HES, Hospital Episode Statistics; ICD-10, *International Classification of Diseases*, Tenth edition.

Quality assessment of included economic evaluation studies

TABLE 128 Quality assessment of the included economic evaluation studies using the Philips *et al.* checklist[216]

Dimension of quality	Studies							
	Langley 2010[163]	Walczak 2009[164]	Lafuma 2003[165]	Williams 2003[166]	Alam 2001[167]	Fagnani 2000[168]	Langley 1999[169]	Langley 1999[170]
Structure								
S1: Statement of decision problem/ objective	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated
S2: Statement of scope/perspective	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated
S3: Rationale for structure	✓ Stated	✗ Not stated	✗ Not stated	✗ Not stated	✗ Not stated	✗ Not stated	✓ Stated	✓ Stated
S4: Structural assumptions	✓ Stated	✗ Not stated	✗ Not stated	✗ Not stated	✗ Not stated	✗ Not stated	✓ Stated	✓ Stated
S5: Strategies/ comparators	? Did not include the full range of comparators. Included: imiquimod	? Did not include the full range of comparators. Included: imiquimod, podophyllotoxin	? Did not include the full range of comparators. Included: imiquimod, podophyllotoxin, CO_2 laser therapy	? Did not include the full range of comparators. Included: imiquimod, podophyllotoxin	? All comparators were included with the exception of cidofovir	? Did not include the full range of comparators. Included imiquimod, podophyllotoxin, CO_2 laser therapy	? Did not include the full range of comparators. Included imiquimod, podophyllin, cryotherapy, TCAA	? Did not include the full range of comparators. Included imiquimod, podofilox, podophyllin, laser surgery, cryotherapy, TCAA
S6: Model type	✓ Decision analysis	✓ Decision analysis	✓ Decision analysis	✓ Decision analysis	✓ Stated	✓ Decision analysis	✓ Decision analysis	✓ Decision analysis
S7: Time horizon	? The time horizon for analysis 1 (one line of treatment) was 16 weeks. For analysis 2 (two lines of therapy) there was no fixed time frame	✓ 28 weeks	✓ 4–16 weeks	✓ 16–28 weeks	✗ Not stated	✗ Not stated	✗ Not stated	? Time horizon was stated for only one of the three analyses conducted
S8: Disease states/ pathways	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated	✓ Stated
S9: Cycle length	– NA	– NA	– NA	– NA	– NA	– NA	– NA	– NA

Dimension of quality	Studies							
	Langley 2010[163]	Walczak 2009[164]	Lafuma 2003[165]	Williams 2003[166]	Alam 2001[167]	Fagnani 2000[168]	Langley 1999[169]	Langley 1999[170]
Data								
D1: Data identification	✓ Reported	✗ Not reported	✓ Reported	✓ Reported	✓ Reported	✓ Reported	✓ Reported	✓ Reported
D2: Pre-model data analysis	✓ Reported	✗ Not reported	✓ Reported	✓ Reported	✗ Not reported	✓ Reported	✗ Not reported	✓ Reported
D2a: Baseline data	✓ Reported	✗ Not reported	✓ Reported	✓ Reported	✗ Not reported	✓ Reported	✓ Reported	✓ Reported
D2b: Treatment effects	✓ Reported	✓ Reported	✓ Reported	✓ Reported	✓ Reported	✓ Reported	✓ Reported	✓ Reported
D2c: Costs	✓ Reported; discounting was not discussed	✗ Not reported	✓ Reported; discounting was not discussed	✓ Reported; discounting was not discussed	✓ Reported; discounting was not discussed	✓ Reported	✓ Reported; discounting was not discussed	✓ Reported; discounting was not discussed
D2d: QoL weights (utilities)	✗ QoL not considered	✗ QoL not considered	✗ QoL not considered	✗ QoL not considered	✗ QoL was not incorporated	✗ QoL was not incorporated	✗ QoL was not incorporated	✗ QoL was not incorporated
D3: Data incorporation	✓ Reported	✗ Not reported	✓ Reported	✓ Stated	✓ Reported	✓ Reported	✓ Reported	✓ Reported
D4: Assessment of uncertainty	? Scenario analysis was carried out	✗ Not reported	? Scenario analysis was carried out	✓ One-way and probabilistic analysis	✗ Not reported	? Partial	? Partial	? Partial
D4a: Methodological	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported
D4b: Structural	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported
D4c: Heterogeneity	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported
D4d: Parameter	? Scenario analysis reported	✗ Not reported	? Scenario analysis reported	✓ One-way and probabilistic sensitivity analysis	✗ Not reported	✓ Scenario analysis was carried out	✓ Scenario analysis was carried out	✓ Scenario analysis was conducted
Consistency								
C1: Internal consistency	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported	✗ Not reported
C2: External consistency	✗ Not reported	✗ Not reported	✗ Not reported	✓ Results were compared with those of previous cost-effectiveness analyses	✓ Comparison was made with results from previous economic evaluation studies	✗ Not reported	✗ Not reported	✗ Not reported

NA, not applicable.

Appendix 3 Excluded studies

TABLE 129 Table of excluded clinical studies with rationale

Excluded study	Reason for exclusion
Clinical observation of treatments for condyloma acuminatum. *Chin J Dermatol* 1989;**22**:114–15	Not a RCT
Genital warts reduced with imiquimod. *Aids Patients Care STDS* 1998;**12**:409	Not a RCT
Imiquimod (Aldara) for the treatment of external genital and perianal warts. *Geneesmiddelenbulletin* 2000;**34**:148–9	Not a RCT
Imiquimod cream for genital warts. *Am Fam Phys* 1997;**55**:2348	Not a RCT
Aigner F, Conrad F, Widschwendter A, Zangerle R, Zelger B, Haidenberger A, *et al.* [Anal HPV infections.] *Wien Klin Wochenschr* 2008;**120**:631–41	Not a RCT
Audisio T, Roca FC, Piatti C. Topical imiquimod therapy for external anogenital warts in pregnant women. *Int J Gynaecol Obstet* 2008;**100**:275–6	Not a RCT
Augustovski F, Pichon RA, Bardach A, Colantonio L, Ferrante D, Garcia MS, *et al.* Cryotherapy to anogenital warts. *Health Technol Assess Database* 2009;**3**. URL: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32009100592/frame.html (accessed 21 December 2015)	Not a RCT
Bashi SA. Cryotherapy versus podophyllin in the treatment of genital warts. *Int J Dermatol* 1985;**24**:535–6	Not a RCT
Batista CS, Atallah AN, Saconato H, da Silva EM. 5-FU for genital warts in non-immunocompromised individuals. *Cochrane Database Syst Rev* 2010;**4**:CD006562	Not a RCT
Bianco V, Erba P, Remotti G. [Florid vulvar condylomatosis. Comparison of therapeutic schedules.] *Ann Ostet Ginecol Med Perinat* 1991;**112**:247–56	Not a RCT
Billingham RP, Lewis FG. Laser versus electrical cautery in the treatment of condylomata acuminata of the anus. *Surg Gynecol Obstet* 1982;**155**:865–7	Not a RCT
Chen HF. Photodynamic therapy with aminolevulinic acid (ALA-PDT) for urethral condyloma acuminatum: a clinical observation. *J Clin Dermatol* 2009;**38**:193–4	Not an intervention of interest (photodynamic therapy plus aminolaevulinic acid)
Chen K, Chang BZ, Ju M, Zhang XH, Gu H. Comparative study of photodynamic therapy vs CO_2 laser vaporization in treatment of condylomata acuminata: a randomized clinical trial. *Br J Dermatol* 2007;**156**:516–20	Not an intervention of interest (photodynamic therapy plus aminolaevulinic acid)
Chopra K, Lee P, Tyring SK, Arany I, Mcdemott D. Vehicle-controlled study investigating the mechanism of action of 5% imiquimod cream applied three times a week for the treatment of patients with genital/perianal warts. *Australas J Dermatol* 1997;**1320**:113–14	No outcomes of interest reported
Coremans G, Margaritis V, Snoeck R, Wyndaele J, de Clercq E, Geboes K. Topical cidofovir (HPMPC) is an effective adjuvant to surgical treatment of anogenital condylomata acuminata. *Dis Colon Rectum* 2003;**46**:1103–8	Not a RCT
Coremans G, Wyndaele J, Dockx S, Vandenbussche FG, Geboes K, de Clercq E, *et al.* Eradication of intra-anal condylomata acuminata and histologically dysplasia with combined intralaesional cidofovir and coagulations. *Gastroenterology* 2008;**134**:A318	Not a RCT
Damstra RJ, van Vloten WA. Cryotherapy in the treatment of condylomata acuminata: a controlled study of 64 patients. *J Dermatol Surg Oncol* 1991;**17**:273–6	Not a RCT
de Luca, Kharaeva Z, Raskovic D, Pastore P, Luci A, Korkina L. Coenzyme q(10), vitamin E, selenium, and methionine in the treatment of chronic recurrent viral mucocutaneous infections. *Nutrition* 2012;**28**:509–14	Not an intervention of interest
Desai A, Saple DG, Baliga V. Assessment of efficacy, safety, and tolerability of imiquimod cream 5% in adult patients with external genital warts: a first Indian study. *J Am Acad Dermatol* 2006;**54**:135	Not a RCT

continued

TABLE 129 Table of excluded clinical studies with rationale (*continued*)

Excluded study	Reason for exclusion
Di Stefano, Facchini D, de Paulis AL, Cappa F, Moscarini M. [Vulvar lesions caused by papillomavirus (HPV): effectiveness of thymopentin (syntomoduline). First results and experiences.] *Minerva Ginecol* 1991;**43**:53–6	Not interventions of interest
Dominguez GJ, Simon RD, Abreu DA, Zlenkova H. Effectiveness of glycyrrhizinic acid (glizigen) and an immunostimulant (viusid) to treat anogenital warts. *ISRN Dermatol* 2012;**2012**:863692	Not interventions of interest
Duus BR, Philipsen T, Christensen JD, Lundvall F, Sondergaard J. Refractory condylomata acuminata: a controlled clinical trial of carbon dioxide laser versus conventional surgical treatment. *Genitourin Med* 1985;**61**:59–61	Not a comparator of interest (comparator is conventional surgery and includes a mixture of electrocautery and surgical excision; results are not reported separately for the individual techniques)
Duus BR, Dahl JC, Philipsen T. [Surgery and laser treatment of podophyllin-resistant condylomata acuminate.] *Ugeskr Laeger* 1986;**148**:1212–14	Not a RCT
Einarson A, Costei A, Kalra S, Rouleau M, Koren G. The use of topical 5% imiquimod during pregnancy: a case series. *Reprod Toxicol* 2006;**21**:1–2	Not a RCT
Ferenczy A. Laser treatment of patients with condylomata and squamous carcinoma precursors of the lower female genital tract. *CA Cancer J Clin* 1987;**37**:334–47	Not a RCT
French LN. What is the most effective treatment for external genital warts? *J Fam Pract* 2014;**51**:313	Not a RCT
Goldmeier D, Madden P, Lacey C, Legg K, Tamm N, Cowen M. Complementary therapy and genital warts. *Sex Transm Infect* 2005;**81**:360	Not a RCT
Gollnick H, Barasso R, Jappe U, Ward K, Eul A, Carey-Yard M, *et al.* Safety and efficacy of imiquimod 5% cream in the treatment of penile genital warts in uncircumcised men when applied three times weekly or once per day. *Int J STD AIDS* 2001;**12**:22–8	Not a RCT
Gori J, Castano R, Dominguez J, Puga A. Laser vaporization, cryotherapy and trichloroacetic application in the therapy of ectocervical condylomatous lesions: a comparison of clinical results. *Cervix Low Fem Genit Tract* 1992;**10**:217–19	Not a RCT
Graversen PH, Bagi P, Rosenkilde P. Laser treatment of recurrent urethral condylomata acuminata in men. *Scand J Urol Nephrol* 1990;**24**:163–6	Not a RCT
Greenberg MD. A double-blind, randomized trial of 0.5% podoflox and placebo for the treatment of genital warts in women. *Genitourin Med* 1991;**67**:359	Not a RCT
Heim K, Krause P, Huter O, Wartusch B, Holbock E, Conrad F, *et al.* [Laser therapy of condylomata of the female genitals.] *Gynakol Rundsch* 1989;**29**(Suppl. 2):96–100	Not a RCT
Jensen SL. Comparison of podophyllin application with simple surgical excision in clearance and recurrence of perianal condylomata acuminata. *Genitourin Med* 1986;**62**:212	Not a RCT
Jiang RF, Shi TN. [123 cases curative effect observation of podophyllin resin solution improved for external use in treating condyloma acuminatum.] *Chin J Dermatovenereol* 1991;**15**:191	Not a RCT
Johnson R, Stockfleth E. Imiquimod 5% cream for the treatment of cutaneous lesions in immunocompromised patients. *Acta Derm Venereol Suppl (Stockh)* 2003;**214**:23–7	Not a RCT
Khawaja HT. Podophyllin versus scissor excision in the treatment of perianal condylomata acuminata: a prospective study. *Br J Surg* 1989;**76**:1067–8	Not a RCT
Kressenstein S. Treatment of condyloma acuminata by patient-applied cream. *Arztliche Praxis Dermatol* 2000;**5**:37	Not a RCT
Lassus A. Comparison of podophyllotoxin and podophyllin in treatment of genital warts. *Lancet* 1987;**2**:512–13	Not a RCT
Lewis MI. Treatment of extensive condyloma acuminata of the anal canal. *Int Surg* 1973;**58**:412–14	Not a RCT
Li CH, Lu ZZ. [The different ways of CO_2 laser or electric burn therapy for condyloma acuminatum.] *Chin J Dermatovenereol* 1994;**8**:98	Not a RCT

TABLE 129 Table of excluded clinical studies with rationale (*continued*)

Excluded study	Reason for exclusion
Lim KB, Lee CT, Koh YL, Yeo WL, Tan T. Self-application of podophyllin resin for penile condylomata acuminata. *Ann Acad Med Singapore* 1987;**16**:167–9	Not a RCT
Lwegaba A, Phillips A, Kiraru R. Silver nitrate may be far superior to podophyllin in clearing HPV external anogenital warts. *West Indian Med J* 2008;**57**:63–5	Not a RCT
Maier H, Donath P, Cabaj A, Honigsmann H. Successful pulsed dye laser treatment of genital warts. 24th Annual Meeting of the American Society for Laser Medicine and Surgery, Dallas, TX, 31 March 31–4 April 2004. Abstract 66	Not a RCT
Mazurkiewicz W, Jablonska S. [Comparative studies between 0.5 percent podophyllotoxin preparations (condyline) and 20 percent podophyllin dissolved in alcohol, in the therapy of raised condylomas.] *Z Hautkr* 1986;**61**:1387–95	Not a RCT
Orlando G, Fasolo MM, Beretta R, Cargnel A. Combined surgical–medical treatment of genital warts in HIV positive patients. *Tumori* 2001;**87**:s11–12	Not a RCT
Potocnik M, Bartenjev I. Genital warts treatment – ultrapulse CO_2 or argon laser. *Australas J Dermatol* 1997;**38**(Suppl. 2):30–1	Not a RCT
Renziehausen K. [Cryotherapy of condylomata acuminata and other benign vulvar neoplasms.] *Zentralbl Gynakol* 1974;**96**:1135–9	Not a RCT
Sait MA, Garg BR. Treatment of warts – a study of one hundred and six cases. *Indian J Dermatol Venerol Leprol* 1985;**51**:96–8	Not a RCT
Schofer H, Van Ophoven A, Henke U, Lenz T, Eul A. Randomized, comparative trial on the sustained efficacy of topical imiquimod 5% cream versus conventional ablative methods in external anogenital warts. *Eur J Dermatol* 2006;**16**:642–8	Not an intervention of interest (all ablative therapies analysed together)
Seo JY, Park SC, Oh SJ, Rim JS. Urethroscopic ND:YAG laser therapy for urethral condyloma acuminata in men. *Int J Androl* 2005;**28**:100	Not a RCT
Song W. [Combination therapy in the treatment of 68 cases of condyloma acuminatum.] *Chin J Dermatol* 1994;**27**:173	Not a RCT
Stefanaki C, Katzouranis I, Lagogianni E, Hadjivassiliou M, Nicolaidou E, Panagiotopoulos A, *et al.* Comparison of cryotherapy to imiquimod 5% in the treatment of anogenital warts. *Int J STD AIDS* 2008;**19**:722	Not a RCT (erratum)
Stefanaki C, Hadjivassiliou M, Katzouranis I, Bethimoutis G, Nicolaidou E, Anyfantakis V, *et al.* Prognostic factors for the response to treatment in males with genital warts. *J Eur Acad Dermatol Venereol* 2009;**23**:1156–60	Not a RCT
Stragier I, Snoeck R, De Clercq E, Van den Oord JJ, Van Ranst M, De Greef H. Local treatment of HPV-induced skin lesions by cidofovir. *J Med Virol* 2002;**67**:241–5	Not a RCT
Thivolet J. Treatment of warts. *Concours Med* 1982;**104**:4957–66	Not a RCT
Usman N, Udayashankar K Subramanian S, Thyagarajan SP. Autoimplantation technique in the treatment of anogenital warts: a clinico-immunological study. *Int J STD AIDS* 1996;**7**:55–7	Not a RCT
Van Ophoven A, Schofer H, Henke U, Lenz T, Eul A. Randomized, comparative trial on the sustained efficacy of topical imiquimod 5% cream versus conventional ablative methods in external anogenital warts. *J Urol* 2007;**177**:36	Not a RCT
Von Krogh G. Topical treatment of penile condylomata acuminata with podophyllin, podophyllotoxin and colchicine. A comparative study. *Acta Derm Venereol* 1978;**58**:163–8	Not a RCT
Von Krogh G. Podophyllotoxin for condylomata acuminata eradication. Clinical and experimental comparative studies on podophyllum lignans, colchicine and 5-fluorouracil. *Acta Derm Venereol Suppl (Stockh)* 1981;**98**:1–48	Not a RCT
Von Krogh G. Topical self-treatment of penile warts with 0.5% podophyllotoxin in ethanol for four or five days. *Sex Transm Dis* 1987;**14**:135–40	Not a RCT
Ward BG, Thomas IL. Randomized prospective intervention study of human cervical wart virus infection. *Aust N Z J Obstet Gynaecol* 1994;**34**:182–5	Not a population of interest (no AGWs)

continued

TABLE 129 Table of excluded clinical studies with rationale (*continued*)

Excluded study	Reason for exclusion
Webb DGK. Management of external genital warts: a comparison of podophyllin and podophyllotoxin. *Pharm J* 2014;**252**:291–3	Not a RCT
Weinberg JM, Stewart A, Stern JO. Successful treatment of extensive condyloma acuminata of the inguinal area and thigh with topical imiquimod cream. *Acta Derm Venereol* 2001;**81**:76–7	Not a RCT
Wiltz OH, Torregrosa M, Wiltz O. Autogenous vaccine: the best therapy for perianal condyloma acuminata? *Dis Colon Rectum* 1995;**38**:838–41	Not a RCT
Xie FM, Zeng K, Chen ZL, Li Gf, Lin ZF, Zhu XL, *et al.* [Treatment of recurrent condyloma acuminatum with solid lipid nanoparticle gel containing podophyllotoxin: a randomized double-blinded, controlled clinical trial.] *Nan Fang Yi Ke Da Xue Xue Bao* 2007;**27**:657–9	Not an intervention of interest
Zeng K, Li GF, Xu CY, Chen ZL, Wang ZF. A double-blind randomized controlled trial of podophyllotoxin liposomes ointments in the treatment of condylomata acuminata. *J First Military Med Univ* 1998;**18**:246	Not an intervention of interest
Zhou SJ, Li ZW, Li B, Cheng P. [Observation on effects of 27 cases of condyloma acuminatum treated by combined therapy.] *Chin J Leprosy Skin Dis* 2014;**16**:61	Not an intervention of interest

Appendix 4 Codes for fixed-effects and random-effects models in the mixed-treatment comparisons

Fixed effects

```
model{

for(i in 1:ns){

        delta[i,t[i,1]]<-0

        mu[i] ~ dnorm(0,.0001)


        for (k in 1:na[i]) {

                r[i,t[i,k]] ~ dbin(p[i,t[i,k]],n[i,t[i,k]])

                logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]


   rhat[i,t[i,k]]<- p[i,t[i,k]] * n[i,t[i,k]]

   resdev[i,k]<- 2 * (r[i,t[i,k]] * (log(r[i,t[i,k]]) - log(rhat[i,t[i,k]])) + (n[i,t[i,k]] - r[i,t[i,k]]) * (log(n[i,t[i,k]] - r[i,t[i,
k]]) - log(n[i,t[i,k]] - rhat[i,t[i,k]])))

   }

   sumdev[i]<-sum(resdev[i,1:na[i]])
```

```
for (k in 2:na[i]) {
            delta[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]]     # trial-specific LOR
            }
}
sumdevtot<- sum(sumdev[])
d[1]<-0
for (k in 2:nt){
            d[k] ~ dnorm(0,.0001)
            }
for (i in 1:ns) {
            mu1[i] <- mu[i] * equals(t[i,1],1)
            }

for (k in 1:nt) {
            logit(T[k])<- sum(mu1[])/nb +d[k]
            }
for (k in 1:nt) {
            rk[k]<-nt+1 - rank(T[],k)
            best[k]<-equals(rk[k],1)
   }

for (c in 1:(nt-1)) { for (k in (c+1):nt) { or[c,k] <- exp(d[k] - d[c] ) }}
}
```

Random effects

```
model{

for(i in 1:ns){



        w[i,1] <-0

        delta[i,t[i,1]]<-0

        mu[i] ~ dnorm(0,.0001)



        for (k in 1:na[i]) {

                r[i,t[i,k]] ~ dbin(p[i,t[i,k]],n[i,t[i,k]])

                logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]

        rhat[i,t[i,k]]<- p[i,t[i,k]] * n[i,t[i,k]]

        resdev[i,k]<- 2 * (r[i,t[i,k]] * (log(r[i,t[i,k]]) - log(rhat[i,t[i,k]])) + (n[i,t[i,k]] - r[i,t[i,k]]) * (log(n[i,t[i,k]] - r
        [i,t[i,k]]) - log(n[i,t[i,k]] - rhat[i,t[i,k]])))

        }

        sumdev[i]<-sum(resdev[i,1:na[i]])



for (k in 2:na[i]) {

          delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

          md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]

          taud[i,t[i,k]] <- tau*2*(k-1)/k

          w[i,k] <- (delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]])/(k-1)

          sw[i,k] <-sum(w[i,1:k-1])/(k-1)

          }

}

sumdevtot<- sum(sumdev[])

d[1]<-0
```

```
for (k in 2:nt){
            d[k] ~ dnorm(0,.0001)
            }
sd~dunif(0,2)
tau<-1/pow(sd,2)
for (i in 1:nt) {
            mu1[i] <- mu[i] * equals(t[i,1],1)
           }


for (k in 1:nt) {
            logit(T[k])<- sum(mu1[])/nb +d[k]
            }
for (k in 1:nt) {
            rk[k]<-nt+1 - rank(T[],k)
            best[k]<-equals(rk[k],1)
            }
for (c in 1:(nt-1)) { for (k in (c+1):nt) { or[c,k] <- exp(d[k] - d[c] ) }}
for (c in 1:(nt-1)) { for (k in (c+1):nt) { lor[c,k] <- (d[k] - d[c] ) }}
```

Appendix 5 Results of mixed-treatment comparison for complete clearance at end of treatment

TABLE 130 Primary analysis

Intervention	Comparator, OR (95% CrI)[a]						
	Podophyllin 20–25% (clinician applied)	Placebo/no treatment	Imiquimod 5% cream for 12 or 16 weeks (patient applied)	Podophyllotoxin 0.5% solution (patient applied)	Podophyllotoxin 0.3% solution (patient applied)	Podophyllotoxin 0.5% cream (patient applied)	Podophyllotoxin 0.3% cream (patient applied)
Podophyllin 20–25% (clinician applied)	–	–	–	–	–	–	–
Placebo/no treatment	0.053 (0.007 to 0.1626)	–	–	–	–	–	–
Imiquimod 5% cream for 12 or 16 weeks (patient applied)	1.07 (0.15 to 3.45)	24.54 (7.28 to 73.04)	–	–	–	–	–
Podophyllotoxin 0.5% solution (patient applied)	11.65 (2.65 to 38.50)	389.2 (51.6 to 1821)	18.97 (2.27 to 83.18)	–	–	–	–
Podophyllotoxin 0.3% solution (patient applied)	28.50 (0.97 to 143.4)	1008 (23.96 to 5253)	51.02 (1.07 to 243.7)	2.17 (0.13 to 10.08)	–	–	–
Podophyllotoxin 0.5% cream (patient applied)	2.68 (0.37 to 9.19)	65.81 (14.42 to 234)	3.48 (0.51 to 13.03)	0.30 (0.04 to 0.99)	0.45 (0.01 to 2.29)	–	–
Podophyllotoxin 0.3% cream (patient applied)	1.84 (0.07 to 8.35)	45.73 (2.68 to 225)	2.33 (0.10 to 11.55)	0.19 (0.007 to 0.874)	0.31 (0.003 to 1.56)	0.66 (0.06 to 2.9)	–
Podophyllin solution (patient applied)	4.57 (0.11 to 25.49)	219.6 (2.07 to 1161)	9.59 (0.10 to 50.16)	0.61 (0.008 to 3.52)	1.23 (0.004 to 5.50)	3.77 (0.04 to 20.59)	16.46 (0.06 to 77.65)
TCAA	1.23 (0.30 to 3.56)	49.91 (4.27 to 245.7)	2.30 (0.20 to 10.2)	0.17 (0.02 to 0.63)	0.37 (0.005 to 1.40)	0.94 (0.07 to 4.12)	3.99 (0.09 to 19.0)
Cryotherapy	2.11 (0.39 to 6.90)	88.66 (6.00 to 438.9)	4.02 (0.28 to 18.73)	0.29 (0.02 to 1.15)	0.54 (0.008 to 2.46)	1.67 (0.10 to 7.29)	7.16 (0.13 to 33.6)
Surgical excision	13.08 (0.48 to 70.51)	604.9 (8.47 to 3200)	26.07 (0.41 to 142.2)	1.82 (0.03 to 9.90)	3.28 (0.014 to 16.97)	11.92 (0.16 to 59.99)	54.34 (0.24 to 229.9)
CO_2 laser therapy	104.6 (3.35 to 505.2)	6533 (65.49 to 25,760)	247.0 (3.03 to 1087)	14.9 (0.24 to 72.79)	39.21 (0.10 to 123.0)	103.1 (1.11 to 430.7)	412.3 (1.62 to 1735)
TCAA plus podophyllin 25%	2.14 (0.50 to 6.16)	86.98 (7.42 to 414.5)	3.99 (0.33 to 17.76)	0.30 (0.03 to 1.08)	0.56 (0.009 to 2.43)	1.62 (0.12 to 7.11)	7.35 (0.15 to 33.3)
Cryotherapy plus podophyllotoxin 0.15% cream	6.63 (0.28 to 29.42)	346.6 (5.47 to 1585)	15.2 (0.25 to 66.81)	0.96 (0.02 to 4.13)	2.96 (0.008 to 7.30)	5.97 (0.09 to 26.41)	37.92 (0.13 to 104.9)
Cryotherapy plus podophyllin 25%	3.42 (0.51 to 12.05)	152.7 (8.16 to 745.1)	6.79 (0.37 to 31.24)	0.47 (0.03 to 1.91)	0.88 (0.01 to 3.90)	2.72 (0.14 to 12.72)	13.28 (0.18 to 55.53)

a OR > 1 favours the intervention and OR < 1 favours the comparator.
Shading represents statistically significant results.

Podophyllin solution (patient applied)	TCAA	Cryotherapy	Surgical excision	CO_2 laser therapy	TCAA plus podophyllin 25%	Cryotherapy plus podophyllotoxin 0.15% cream	Cryotherapy plus podophyllin 25%
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–
2.18 (0.03 to 11.86)	–	–	–	–	–	–	–
3.69 (0.05 to 20.3)	1.87 (0.55 to 4.73)	–	–	–	–	–	–
23.98 (0.09 to 128.7)	16.53 (0.36 to 93.16)	11.35 (0.20 to 61.91)	–	–	–	–	–
211.3 (0.61 to 986.4)	86.15 (4.05 to 415.3)	44.61 (3.30 to 201.7)	78.35 (0.22 to 254.9)	–	–	–	–
3.80 (0.05 to 19.95)	2.32 (0.39 to 7.86)	1.53 (0.21 to 5.53)	1.01 (0.02 to 4.75)	0.13 (0.003 to 0.59)	–	–	–
13.85 (0.05 to 59.66)	5.76 (0.33 to 24.0)	2.86 (0.27 to 11.39)	4.10 (0.02 to 15.09)	0.26 (0.004 to 1.10)	4.23 (0.14 to 19.05)	–	–
6.06 (0.06 to 33.04)	3.56 (0.46 to 13.2)	2.37 (0.25 to 9.36)	1.80 (0.02 to 8.29)	0.22 (0.004 to 0.94)	2.23 (0.22 to 8.83)	2.91 (0.07 to 11.3)	–

TABLE 131 Sensitivity analysis

Intervention	Comparator, OR (95% CrI)[a]								
	Podophyllin 20–25% (clinician applied)	Placebo/no treatment	Imiquimod 5% cream for 12 or 16 weeks (patient applied)	Podophyllotoxin 0.5% gel (patient applied)	Podophyllotoxin 0.5% solution (patient applied)	Podophyllotoxin 0.3% solution (patient applied)	Podophyllotoxin 0.5% cream (patient applied)	Podophyllotoxin 0.3% cream (patient applied)	Podophyllotoxin 0.15% cream (patient applied)
Podophyllin 20–25% (clinician applied)	–	–	–	–	–	–	–	–	–
Placebo/no treatment	0.05 (0.01 to 0.15)	–	–	–	–	–	–	–	–
Imiquimod 5% cream for 12 or 16 weeks (patient applied)	1.09 (0.23 to 3.03)	24.02 (6.68 to 64.4)	–	–	–	–	–	–	–
Podophyllotoxin 0.5% gel (patient applied)	2.15 (0.04 to 12.24)	41.41 (1.34 to 222.5)	2.45 (0.05 to 13.77)	–	–	–	–	–	–
Podophyllotoxin 0.5% solution (patient applied)	4.33 (1.45 to 10.88)	112.0 (25.54 to 377.8)	5.58 (1.16 to 19.20)	17.11 (0.31 to 99.45)	–	–	–	–	–
Podophyllotoxin 0.3% solution (patient applied)	22.98 (0.99 to 122.1)	602.3 (21.46 to 3299)	31.13 (0.97 to 168.5)	98.1 (0.42 to 558.9)	5.32 (0.29 to 27.34)	–	–	–	–
Podophyllotoxin 0.5% cream (patient applied)	2.24 (0.58 to 5.95)	53.1 (13.26 to 158.1)	2.80 (0.53 to 9.41)	7.90 (0.16 to 44.5)	0.62 (0.13 to 1.74)	0.42 (0.01 to 2.12)	–	–	–
Podophyllotoxin 0.3% cream (patient applied)	3.63 (0.41 to 14.87)	91.48 (9.07 to 416.9)	4.77 (0.40 to 21.66)	15.88 (0.15 to 87.83)	0.91 (0.11 to 3.44)	0.60 (0.02 to 3.29)	1.96 (0.23 to 8.14)	–	–
Podophyllotoxin 0.15% cream (patient applied)	1.09 (0.15 to 3.84)	28.24 (3.01 to 118.8)	1.42 (0.14 to 6.05)	4.37 (0.05 to 24.91)	0.28 (0.04 to 0.90)	0.18 (0.005 to 0.87)	0.63 (0.07 to 2.49)	0.49 (0.05 to 1.83)	–
Podophyllin solution (patient applied)	4.04 (0.27 to 19.00)	113.2 (5.21 to 598.4)	5.54 (0.24 to 29.03)	17.62 (0.10 to 107.2)	1.04 (0.07 to 4.69)	0.75 (0.01 to 4.52)	2.47 (0.12 to 12.57)	2.33 (0.07 to 12.45)	6.91 (0.23 to 37.19)

Intervention	Comparator, OR (95% CrI)[a]								
	Podophyllin 20–25% (clinician applied)	Placebo/no treatment	Imiquimod 5% cream for 12 or 16 weeks (patient applied)	Podophyllotoxin 0.5% gel (patient applied)	Podophyllotoxin 0.5% solution (patient applied)	Podophyllotoxin 0.3% solution (patient applied)	Podophyllotoxin 0.5% cream (patient applied)	Podophyllotoxin 0.3% cream (patient applied)	Podophyllotoxin 0.15% cream (patient applied)
TCAA	1.56 (0.30 to 4.98)	43.66 (4.89 to 182.5)	2.08 (0.25 to 8.51)	6.85 (0.08 to 39.64)	0.46 (0.05 to 1.63)	0.32 (0.007 to 1.75)	0.98 (0.11 to 3.88)	0.97 (0.05 to 4.53)	2.88 (0.19 to 13.18)
Cidofovir 1.0%	26.79 (0.29 to 162.8)	756.0 (6.86 to 4375)	37.02 (0.30 to 224.9)	175.3 (0.16 to 612.3)	7.86 (0.07 to 43.84)	5.40 (0.01 to 29.88)	16.77 (0.14 to 100.8)	16.41 (0.08 to 95.29)	57.72 (0.26 to 307.2)
Cryotherapy	2.65 (0.60 to 7.83)	71.05 (10.44 to 274.1)	3.36 (0.55 to 12.41)	11.39 (0.15 to 63.8)	0.77 (0.11 to 2.63)	0.53 (0.01 to 2.86)	1.62 (0.23 to 6.03)	1.61 (0.10 to 7.21)	4.79 (0.38 to 21.58)
Surgical excision	18.03 (0.30 to 109.6)	586.5 (5.45 to 3466)	27.05 (0.26 to 166.3)	130.5 (0.13 to 477.3)	5.30 (0.06 to 32.21)	3.68 (0.01 to 23.75)	12.14 (0.13 to 71.5)	11.96 (0.07 to 70.48)	36.41 (0.24 to 209.5)
CO_2 laser therapy	171.2 (3.03 to 991.7)	4986 (64.22 to 28,480)	222.2 (3.18 to 1344)	821.2 (1.49 to 4056)	49.81 (0.66 to 284.3)	34.11 (0.12 to 207.8)	111.2 (1.36 to 638.5)	103.6 (0.75 to 629.4)	329.5 (2.59 to 1920)
Electrotherapy	32.72 (3.15 to 150.08)	877.2 (64.38 to 4685)	44.47 (2.91 to 239.5)	168.7 (1.16 to 898.3)	9.30 (0.70 to 44.14)	6.51 (0.10 to 38.37)	20.12 (1.38 to 102.5)	20.18 (0.73 to 108.2)	64.83 (2.82 to 338.4)
TCAA plus podophyllin 25%	2.61 (0.37 to 9.22)	76.0 (6.18 to 351.7)	3.68 (0.31 to 16.71)	11.65 (0.10 to 71.06)	0.78 (0.07 to 3.12)	0.55 (0.008 to 3.09)	1.66 (0.14 to 7.18)	1.66 (0.07 to 8.15)	4.92 (0.26 to 24.35)
Cryotherapy plus podophyllotoxin 0.15% cream	10.58 (0.23 to 61.07)	305.3 (5.41 to 1779)	14.38 (0.26 to 82.42)	56.03 (0.12 to 273.9)	3.06 (0.06 to 17.57)	2.60 (0.01 to 13.28)	6.77 (0.11 to 39.36)	6.48 (0.06 to 38.94)	21.41 (0.22 to 120.4)
Cryotherapy plus podophyllin 25%	4.58 (0.35 to 20.36)	136.0 (6.45 to 702.9)	6.53 (0.31 to 33.15)	23.76 (0.12 to 126.9)	1.36 (0.07 to 6.41)	0.97 (0.01 to 5.71)	2.89 (0.14 to 14.73)	2.86 (0.07 to 15.36)	8.69 (0.27 to 47.89)

continued

TABLE 131 Sensitivity analysis (*continued*)

Intervention	Comparator, OR (95% CrI)[a]									
	Podophyllin solution (patient applied)	TCAA	Cidofovir 1.0%	Cryotherapy	Surgical excision	CO_2 laser therapy	Electrotherapy	TCAA plus podophyllin 25%	Cryotherapy plus podophyllotoxin 0.15% cream	Cryotherapy plus podophyllin 25%
Podophyllin 20–25% (clinician applied)	–	–	–	–	–	–	–	–	–	–
Placebo/no treatment	–	–	–	–	–	–	–	–	–	–
Imiquimod 5% cream for 12 or 16 weeks (patient applied)	–	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.5% gel (patient applied)	–	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.5% solution (patient applied)	–	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.3% solution (patient applied)	–	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.5% cream (patient applied)	–	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.3% cream (patient applied)	–	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.15% cream (patient applied)	–	–	–	–	–	–	–	–	–	–

Intervention	Comparator, OR (95% CrI)[a]									
	Podophyllin 20–25% (clinician applied)	TCAA	Cidofovir 1.0%	Cryotherapy	Surgical excision	CO_2 laser therapy	Electrotherapy	TCAA plus podophyllin 25%	Cryotherapy plus podophyllotoxin 0.15% cream	Cryotherapy plus podophyllin 25%
Podophyllin solution (patient applied)	–	–	–	–	–	–	–	–	–	–
TCAA	1.26 (0.04 to 6.82)	–	–	–	–	–	–	–	–	–
Cidofovir 1.0%	24.65 (0.07 to 132.9)	25.95 (0.19 to 165.5)	–	–	–	–	–	–	–	–
Cryotherapy	2.14 (0.08 to 11.38)	2.19 (0.50 to 6.34)	1.33 (0.11 to 8.04)	–	–	–	–	–	–	–
Surgical excision	15.87 (0.06 to 92.61)	19.51 (0.17 to 121.9)	10.73 (0.01 to 63.98)	10.56 (0.10 to 66.12)	–	–	–	–	–	–
CO_2 laser therapy	147.4 (0.66 to 855.7)	144.2 (2.51 to 838.1)	88.94 (0.12 to 516.4)	63.39 (1.88 to 343.1)	145.8 (0.16 to 636.9)	–	–	–	–	–
Electrotherapy	27.8 (0.57 to 160.5)	32.23 (2.02 to 166.0)	8.71 (0.22 to 48.15)	15.79 (1.39 to 75.41)	25.87 (0.11 to 137.7)	2.03 (0.01 to 10.53)	–	–	–	–
TCAA plus podophyllin 25%	2.22 (0.06 to 12.11)	2.45 (0.22 to 9.98)	1.51 (0.008 to 9.23)	1.37 (0.14 to 5.42)	1.72 (0.01 to 9.87)	0.15 (0.001 to 0.84)	0.21 (0.007 to 0.97)	–	–	–
Cryotherapy plus podophyllotoxin 0.15% cream	9.04 (0.06 to 52.16)	8.81 (0.20 to 49.16)	5.50 (0.01 to 32.31)	3.89 (0.16 to 19.83)	9.04 (0.01 to 41.94)	0.44 (0.002 to 2.51)	0.70 (0.008 to 4.13)	7.83 (0.10 to 43.69)	–	–
Cryotherapy plus podophyllin 25%	3.76 (0.06 to 22.37)	4.16 (0.26 to 19.44)	2.49 (0.009 to 16.29)	2.35 (0.14 to 10.98)	3.63 (0.01 to 18.04)	0.28 (0.001 to 1.47)	0.35 (0.008 to 1.84)	3.15 (0.13 to 15.92)	3.27 (0.03 to 18.34)	–

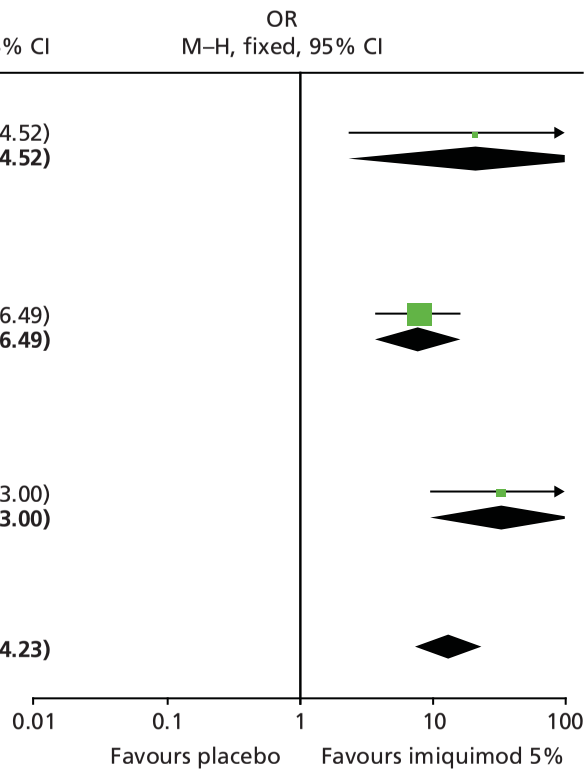
a OR > 1 favours the intervention and OR < 1 favours the comparator.
Shading represents statistically significant results.

Appendix 6 Results of standard pairwise meta-analysis for complete clearance at end of treatment

Imiquimod 5% compared with placebo

Primary analysis

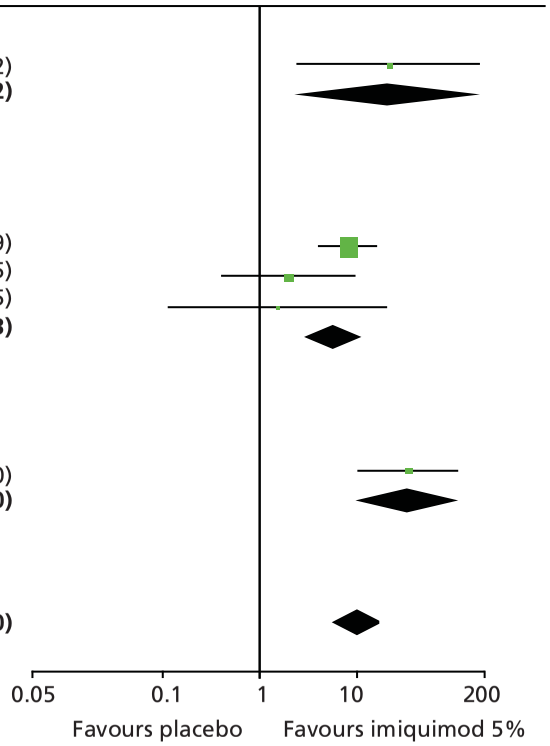
Study or subgroup	Imiquimod 5% Events	Total	Placebo Events	Total	Weight	OR M–H, fixed, 95% CI
Imiquimod 5% (3×day) for 12 weeks						
Arican 2004[112]	23	34	1	11	6.3%	20.91 (2.37 to 184.52)
Subtotal (95% CI)		**34**		**11**	**6.3%**	**20.91 (2.37 to 184.52)**
Total events	23		1			
Heterogeneity: Not applicable						
Test for overall effect: $z=2.74$ ($p=0.006$)						
Imiquimod 5% (3×day) for 16 weeks						
Edwards 1998[118]	54	109	11	100	75.1%	7.94 (3.83 to 16.49)
Subtotal (95% CI)		**109**		**100**	**75.1%**	**7.94 (3.83 to 16.49)**
Total events	54		11			
Heterogeneity: Not applicable						
Test for overall effect: $z=5.56$ ($p<0.00001$)						
Imiquimod 5% (1×day) for 16 weeks						
Beutner 1998[116]	49	94	3	95	18.5%	33.39 (9.87 to 113.00)
Subtotal (95% CI)		**94**		**95**	**18.5%**	**33.39 (9.87 to 113.00)**
Total events	49		3			
Heterogeneity: Not applicable						
Test for overall effect: $z=5.64$ ($p<0.00001$)						
Total (95% CI)		**237**		**206**	**100.0%**	**13.48 (7.50 to 24.23)**
Total events	126		15			
Heterogeneity: $\chi^2=4.30$, df=2 ($p=0.12$); $I^2=53\%$						
Test for overall effect: $z=8.70$ ($p<0.00001$)						
Test for subgroup differences: $\chi^2=4.18$, df=2 ($p=0.12$); $I^2=52.2\%$						



df, degrees of freedom; M–H, Mantel–Haenszel.

Sensitivity analysis

Study or subgroup	Imiquimod 5% Events	Total	Placebo Events	Total	Weight	OR M–H, fixed, 95% CI
Imiquimod 5% (3×day) for 12 weeks						
Arican 2004[112]	23	34	1	11	4.5%	20.91 (2.37 to 184.52)
Subtotal (95% CI)		**34**		**11**	**4.5%**	**20.91 (2.37 to 184.52)**
Total events	23		1			
Heterogeneity: Not applicable						
Test for overall effect: z=2.74 (p=0.006)						
Imiquimod 5% (3×day) for 16 weeks						
Edwards 1998[118]	54	109	11	100	52.8%	7.94 (3.83 to 16.49)
Gilson 1999[119]	7	65	2	35	21.1%	1.99 (0.39 to 10.15)
Tyring 1998[125]	7	16	1	3	8.6%	1.56 (0.12 to 20.85)
Subtotal (95% CI)		**190**		**138**	**82.5%**	**5.75 (3.02 to 10.93)**
Total events	68		14			
Heterogeneity: χ^2=3.36, df=2 (p=0.19); I^2=40%						
Test for overall effect: z=5.34 (p<0.00001)						
Imiquimod 5% (1×day) for 16 weeks						
Beutner 1998[117]	49	94	3	95	13.0%	33.39 (9.87 to 113.00)
Subtotal (95% CI)		**94**		**95**	**13.0%**	**33.39 (9.87 to 113.00)**
Total events	49		3			
Heterogeneity: Not applicable						
Test for overall effect: z=5.64 (p<0.00001)						
Total (95% CI)		**318**		**244**	**100.0%**	**10.02 (5.88 to 17.10)**
Total events	140		18			
Heterogeneity: χ^2=10.33, df=4 (p=0.04); I^2=61%						
Test for overall effect: z=8.46 (p<0.00001)						
Test for subgroup differences: χ^2=6.88, df=2 (p=0.03); I^2=71.0%						



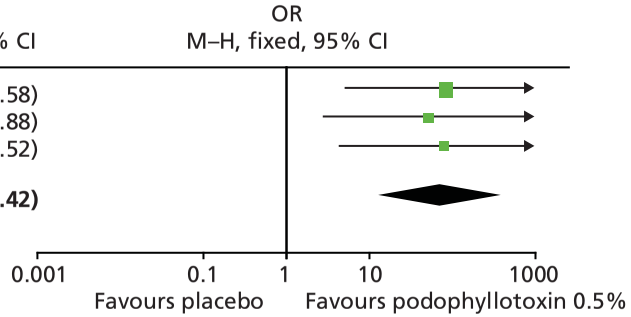
df, degrees of freedom; M–H, Mantel–Haenszel.

Podophyllotoxin 0.5% solution compared with placebo

Primary analysis

Study or subgroup	Podophyllotoxin 0.5 solution Events	Total	Placebo Events	Total	Weight	OR M–H, fixed, 95% CI
Beutner 1998[115]	25	56	0	53	43.1%	86.62 (5.10 to 1472.58)
Kirby 1990[61]	11	19	0	19	32.3%	52.76 (2.78 to 1001.88)
von Krogh 1994[127]	13	19	0	19	24.7%	81.00 (4.20 to 1561.52)
Total (95% CI)		**94**		**91**	**100.0%**	**74.31 (13.39 to 412.42)**
Total events	49		0			

Heterogeneity: $\chi^2=0.07$, df=2 ($p=0.97$); $I^2=0\%$
Test for overall effect: $z=4.93$ ($p<0.00001$)



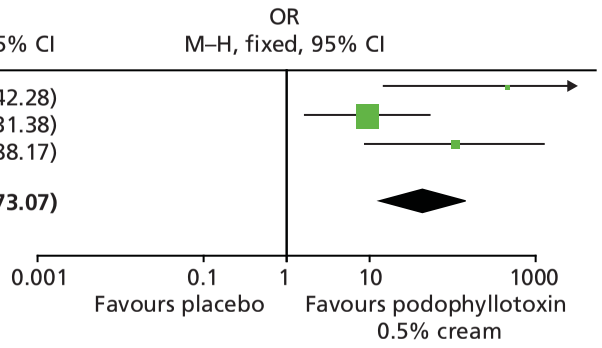
df, degrees of freedom; M–H, Mantel–Haenszel.

Podophyllotoxin 0.5% cream compared with placebo

Primary analysis

Study or subgroup	Podophyllotoxin 0.5 cream Events	Total	Placebo Events	Total	Weight	OR M–H, fixed, 95% CI
Syed 1994[122]	25	30	0	20	6.1%	190.09 (9.92 to 3642.28)
Syed 1995[123]	11	20	3	20	78.4%	6.93 (1.53 to 31.38)
von Krogh 1992[126]	40	48	1	12	15.5%	55.00 (6.20 to 488.17)
Total (95% CI)		**98**		**52**	**100.0%**	**25.62 (8.98 to 73.07)**
Total events	76		4			

Heterogeneity: $\chi^2=5.12$, df=2 ($p=0.08$); $I^2=61\%$
Test for overall effect: $z=6.06$ ($p<0.00001$)

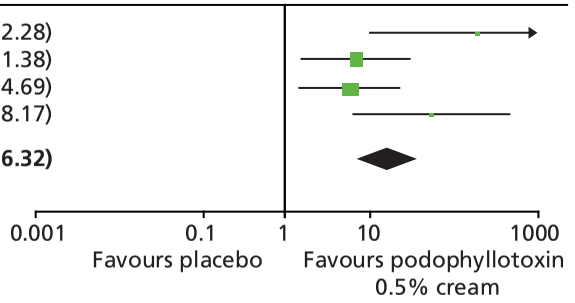


df, degrees of freedom; M–H, Mantel–Haenszel.

Sensitivity analysis

Study or subgroup	Podophyllotoxin 0.5 cream Events	Total	Placebo Events	Total	Weight	OR M–H, fixed, 95% CI
Syed 1994[122]	25	30	0	20	3.2%	190.09 (9.92 to 3642.28)
Syed 1995[123]	11	20	3	20	40.6%	6.93 (1.53 to 31.38)
Syed 1995[124]	12	20	4	20	48.2%	6.00 (1.46 to 24.69)
von Krogh 1992[126]	40	48	1	12	8.0%	55.00 (6.20 to 488.17)
Total (95% CI)		**118**		**72**	**100.0%**	**16.17 (7.20 to 36.32)**
Total events	88		8			

Heterogeneity: $\chi^2=6.98$, df=3 ($p=0.07$); $I^2=57\%$
Test for overall effect: $z=6.74$ ($p<0.00001$)



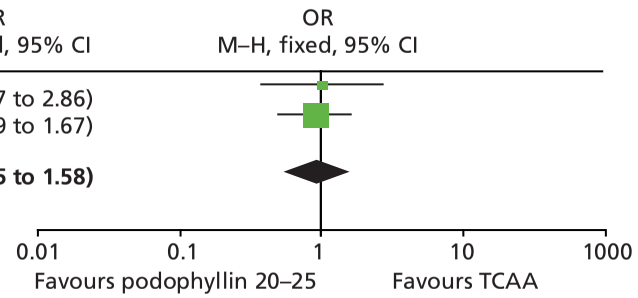
df, degrees of freedom; M–H, Mantel–Haenszel.

Trichloroacetic acid compared with podophyllin 20–25%

Primary analysis

Study or subgroup	TCAA Events	Total	Podophyllin 20–25% Events	Total	Weight	OR M–H, fixed, 95% CI
Nath 1990[148]	39	48	38	47	25.1%	1.03 (0.37 to 2.86)
Sherrard 2007[149]	49	88	46	79	74.9%	0.90 (0.49 to 1.67)
Total (95% CI)		**136**		**126**	**100.0%**	**0.93 (0.55 to 1.58)**
Total events	88		84			

Heterogeneity: $\chi^2=0.05$, df=1 ($p=0.83$); $I^2=0\%$
Test for overall effect: $z=0.26$ ($p=0.80$)



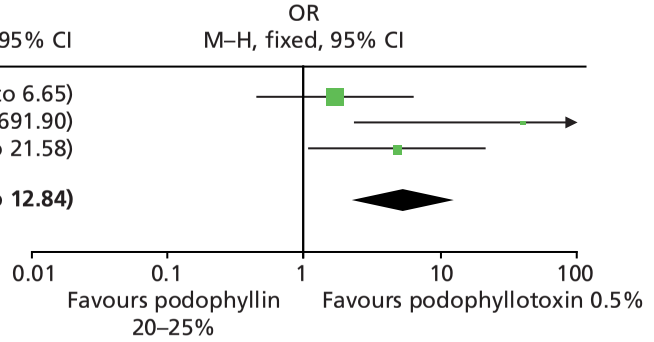
df, degrees of freedom; M–H, Mantel–Haenszel.

Podophyllotoxin 0.5% solution compared with podophyllin 20–25%

Primary analysis

Study or subgroup	Podophyllotoxin 0.5% solution Events	Total	Podophyllin 20–25% Events	Total	Weight	OR M–H, fixed, 95% CI
Kar 2003[138]	33	37	29	35	62.5%	1.71 (0.44 to 6.65)
Lassus 1984[140]	48	48	37	52	7.1%	40.09 (2.32 to 691.90)
Mazurkiewicz 1990[60]	11	16	5	16	30.3%	4.84 (1.09 to 21.58)
Total (95% CI)		**101**		**103**	**100.0%**	**5.40 (2.27 to 12.84)**
Total events	92		71			

Heterogeneity: $\chi^2=4.68$, df=2 ($p=0.10$); $I^2=57\%$
Test for overall effect: $z=3.81$ ($p=0.0001$)

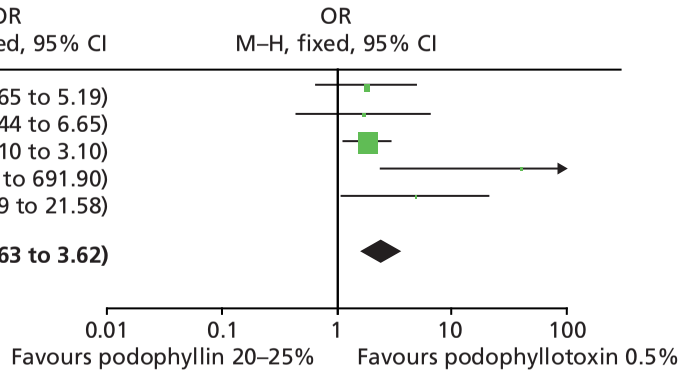


df, degrees of freedom; M–H, Mantel–Haenszel.

Sensitivity analysis

Study or subgroup	Podophyllotoxin 0.5% solution Events	Total	Podophyllin 20–25% Events	Total	Weight	OR M–H, fixed, 95% CI
Edwards 1988[136]	28	42	12	23	16.4%	1.83 (0.65 to 5.19)
Kar 2003[138]	33	37	29	35	10.2%	1.71 (0.44 to 6.65)
Lacey 2003[64]	72	120	52	116	67.2%	1.85 (1.10 to 3.10)
Lassus 1984[140]	48	48	37	52	1.2%	40.09 (2.32 to 691.90)
Mazurkiewicz 1990[60]	11	16	5	16	5.0%	4.84 (1.09 to 21.58)
Total (95% CI)		**263**		**242**	**100.0%**	**2.43 (1.63 to 3.62)**
Total events	192		135			

Heterogeneity: $\chi^2=6.15$, df=4 ($p=0.19$); $I^2=35\%$
Test for overall effect: $z=4.35$ ($p<0.0001$)



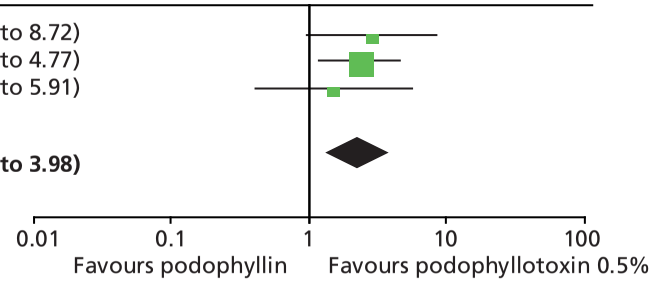
df, degrees of freedom; M–H, Mantel–Haenszel.

Podophyllotoxin 0.5% cream compared with podophyllin 20–25%

Sensitivity analysis

Study or subgroup	Podophyllotoxin 0.5% cream Events	Total	Podophyllin Events	Total	Weight	OR M–H, fixed, 95% CI
Hellberg 1995[137]	23	30	16	30	22.2%	2.88 (0.95 to 8.72)
Kinghorn 1993[63]	115	138	42	62	57.5%	2.38 (1.19 to 4.77)
Mazurkiewicz 1990[60]	9	22	5	16	20.3%	1.52 (0.39 to 5.91)
Total (95% CI)		**190**		**108**	**100.0%**	**2.32 (1.35 to 3.98)**
Total events	147		63			

Heterogeneity: $\chi^2=0.52$, df=2 ($p=0.77$); $I^2=0\%$
Test for overall effect: $z=3.05$ ($p=0.002$)



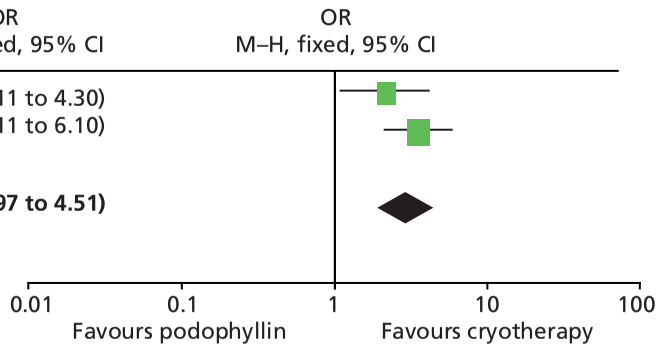
df, degrees of freedom; M–H, Mantel–Haenszel.

Cryotherapy compared with podophyllin 20–25%

Sensitivity analysis

Study or subgroup	Cryotherapy Events	Total	Podophyllin Events	Total	Weight	OR M–H, fixed, 95% CI
Sherrard 2007[149]	61	81	46	79	43.4%	2.19 (1.11 to 4.30)
Stone 1990[151]	68	154	26	144	56.6%	3.59 (2.11 to 6.10)
Total (95% CI)		**235**		**223**	**100.0%**	**2.98 (1.97 to 4.51)**
Total events	129		72			

Heterogeneity: $\chi^2=1.28$, df=1 ($p=0.26$); $I^2=22\%$
Test for overall effect: $z=5.16$ ($p<0.00001$)



df, degrees of freedom; M–H, Mantel–Haenszel.

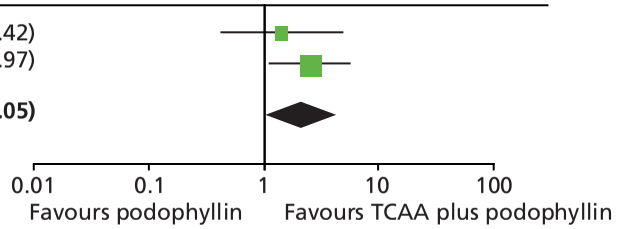
DOI: 10.3310/hta20240

Trichloroacetic acid plus podophyllin 20–25% compared with podophyllin 20–25% alone

Sensitivity analysis

Study or subgroup	TCAA plus podophyllin Events	Total	Podophyllin alone Events	Total	Weight	OR M–H, fixed, 95% CI
Gabriel 1983[145]	21	35	20	38	38.3%	1.35 (0.53 to 3.42)
Sherrard 2007[149]	63	85	46	79	61.7%	2.05 (1.06 to 3.97)
Total (95% CI)		**120**		**117**	**100.0%**	**1.78 (1.04 to 3.05)**
Total events	84		66			

Heterogeneity: $\chi^2=0.52$, df=1 ($p=0.47$); $I^2=0\%$
Test for overall effect: $z=2.11$ ($p=0.03$)



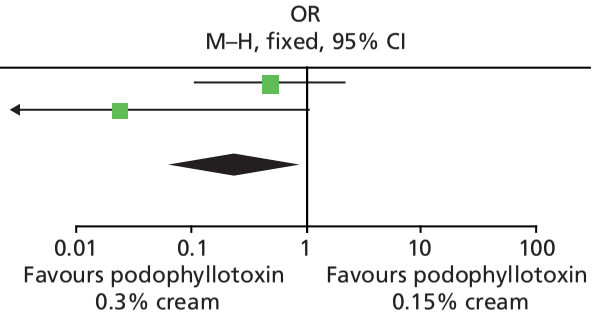
df, degrees of freedom; M–H, Mantel–Haenszel.

Podophyllotoxin 0.15% cream compared with podophyllotoxin 0.3% cream

Sensitivity analysis: fixed effects

Study or subgroup	Podophyllotoxin 0.15% cream Events	Total	Podophyllotoxin 0.3% cream Events	Total	Weight	OR M–H, fixed, 95% CI
Strand 1995[142]	21	30	25	31	53.8%	0.56 (0.17 to 1.83)
Syed 1993[143]	14	20	20	20	46.2%	0.05 (0.00 to 1.04)
Total (95% CI)		**50**		**51**	**100.0%**	**0.33 (0.12 to 0.91)**
Total events	35		45			

Heterogeneity: $\chi^2=2.21$, df=1 ($p=0.14$); $I^2=55\%$
Test for overall effect: $z=2.15$ ($p=0.03$)

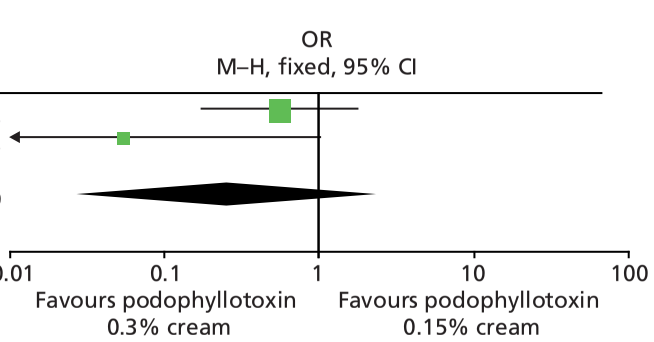


df, degrees of freedom; M–H, Mantel–Haenszel.

Sensitivity analysis: random effects

Study or subgroup	Podophyllotoxin 0.15% cream Events	Total	Podophyllotoxin 0.3% cream Events	Total	Weight	OR M–H, fixed, 95% CI
Strand 1995[142]	21	30	25	31	66.3%	0.56 (0.17 to 1.83)
Syed 1993[143]	14	20	20	20	33.7%	0.05 (0.00 to 1.04)
Total (95% CI)		**50**		**51**	**100.0%**	**0.26 (0.03 to 2.39)**
Total events	35		45			

Heterogeneity: $\tau^2=1.60$, $\chi^2=2.21$, df=1 ($p=0.14$); $I^2=55\%$
Test for overall effect: $z=1.20$ ($p<0.23$)



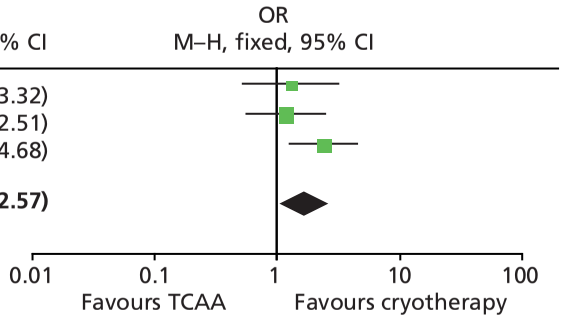
df, degrees of freedom; M–H, Mantel–Haenszel.

Cryotherapy compared with trichloroacetic acid

Primary analysis

Study or subgroup	Cryotherapy Events	Total	TCAA Events	Total	Weight	OR M–H, fixed, 95% CI
Abdullah 1993[153]	37	53	21	33	24.3%	1.32 (0.53 to 3.32)
Godley 1987[154]	43	61	46	69	39.6%	1.19 (0.57 to 2.51)
Sherrard 2007[149]	61	81	49	88	36.1%	2.43 (1.26 to 4.68)
Total (95% CI)		**195**		**190**	**100.0%**	**1.67 (1.09 to 2.57)**
Total events	141		116			

Heterogeneity: $\chi^2=2.27$, df=2 ($p=0.32$); $I^2=12\%$
Test for overall effect: $z=2.33$ ($p=0.02$)

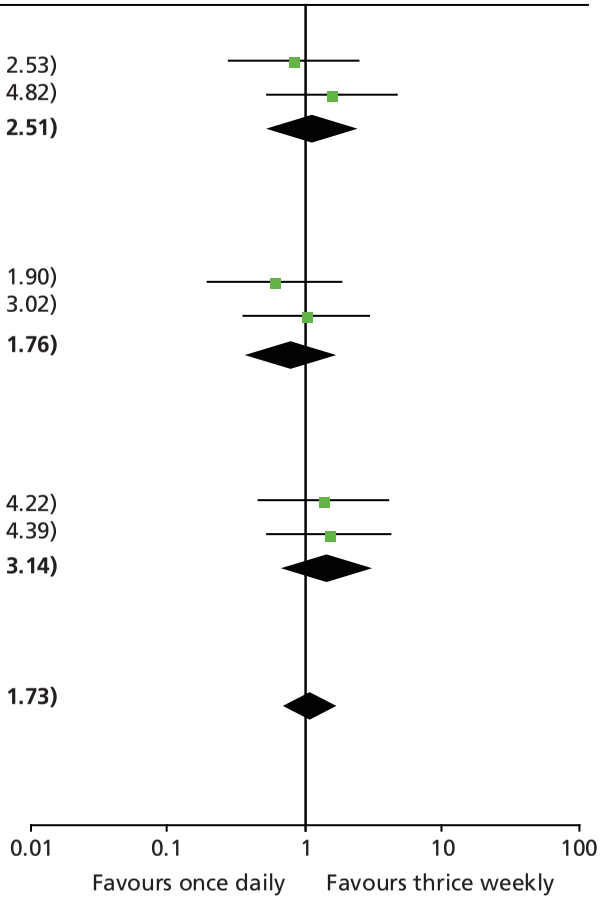


df, degrees of freedom; M–H, Mantel–Haenszel.

Appendix 7 Results of standard pairwise meta-analysis for complete clearance at another time point

Imiquimod 5% cream applied three times weekly, once daily or twice daily

Study or subgroup	Imiquimod 5% once daily Events	Total	Imiquimod 5% 3 times per week Events	Total	Weight	OR M–H, fixed, 95% CI
Imiquimod once daily vs. thrice weekly						
Fife 2001[129]	10	29	10	26	18.7%	0.84 (0.28 to 2.53)
Trofatter 2002[134]	23	32	16	26	13.4%	1.60 (0.53 to 4.82)
Subtotal (95% CI)		**61**		**52**	**32.1%**	**1.16 (0.53 to 2.51)**
Total events	33		26			
Heterogeneity: χ^2=0.65, df=1 (p=0.42); I^2=0%						
Test for overall effect: z=0.37 (p=0.71)						
Imiquimod twice daily vs. thrice weekly						
Fife 2001[129]	8	29	10	26	20.6%	0.61 (0.20 to 1.90)
Trofatter 2002[134]	20	32	16	26	17.9%	1.04 (0.36 to 3.02)
Subtotal (95% CI)		**61**		**52**	**38.5%**	**0.81 (0.37 to 1.76)**
Total events	28		26			
Heterogeneity: χ^2=0.46, df=1 (p=0.50); I^2=0%						
Test for overall effect: z=0.53 (p=0.59)						
Imiquimod once daily vs. twice daily						
Fife 2001[129]	10	29	8	29	14.2%	1.38 (0.45 to 4.22)
Trofatter 2002[134]	23	32	20	32	15.2%	1.53 (0.54 to 4.39)
Subtotal (95% CI)		**61**		**61**	**29.4%**	**1.46 (0.68 to 3.14)**
Total events	33		28			
Heterogeneity: χ^2=0.02, df=1 (p=0.89); I^2=0%						
Test for overall effect: z=0.97 (p=0.33)						
Total (95% CI)		**183**		**165**	**100.0%**	**1.11 (0.71 to 1.73)**
Total events	94		80			
Heterogeneity: χ^2=2.26, df=5 (p=0.81); I^2=0%						
Test for overall effect: z=0.47 (p=0.64)						
Test for subgroup differences: χ^2=1.14, df=2 (p=0.57); I^2=0%						



df, degrees of freedom; M–H, Mantel–Haenszel.

Appendix 8 Data on clinical effectiveness used to inform the cost-effectiveness analysis

TABLE 132 Results of MTC for recurrence used to inform the cost-effectiveness analysis

Intervention	Podophyllin 20–25% (comparator), OR (95% CrI)[a]	Probability of recurrence (95% CrI) (%)[b]
Podophyllin 20–25%	NA	41.2 (31.3 to 51.6)
Imiquimod 5% cream	0.3 (0.04 to 1.07)	16.5 (2.8 to 43.9)
Podophyllotoxin 0.5% solution (patient applied)	0.8 (0.4 to 1.5)	34.6 (20.0 to 51.4)
Podophyllotoxin 0.3% solution (patient applied)	12.3 (0.8 to 60.6)	76.2 (36.1 to 97.7)
TCAA	0.3 (0.09 to 0.87)	18.4 (6.3 to 36.4)
Surgical excision	0.2 (0.03 to 0.44)	9.7 (2.2 to 24.7)
TCA 50% plus podophyllin 25%	1.1 (0.3 to 3.1)	39.4 (17.2 to 65.3)

NA, not applicable.
a OR < 1 favours the intervention and OR > 1 favours podophyllin 20–25%.
b To calculate 3-month probability estimates of recurrence, the baseline estimate for podophyllin 20–25% was calculated based solely on those trials reporting this outcome at 3 months.
Cells shaded indicate statistically significant results.

Appendix 9 Results of mixed-treatment comparison for recurrence

TABLE 133 Recurrence at < 6 months: primary analysis

Intervention	Comparator, OR (95% CrI)[a]				
	Podophyllin 20–25% (clinician applied)	Podophyllotoxin 0.5% solution (patient applied)	Podophyllotoxin 0.3% solution (patient applied)	TCAA	TCAA 50% plus podophyllin 25%
Podophyllin 20–25% (clinician applied)	–	–	–	–	–
Podophyllotoxin 0.5% solution (patient applied)	1.37 (0.03 to 7.15)	–	–	–	–
Podophyllotoxin 0.3% solution (patient applied)	67.8 (0.07 to 261.5)	36.15 (0.39 to 208.7)	–	–	–
TCAA	0.81 (0.02 to 4.45)	5.31 (0.01 to 26.05)	3.43 (< 0.001 to 8.91)	–	–
TCAA 50% plus podophyllin 25%	2.63 (0.05 to 16.64)	18.03 (0.04 to 83.35)	14.35 (0.001 to 31.02)	35.71 (0.06 to 145.3)	–

a OR < 1 favours the intervention and OR > 1 favours the comparator.

TABLE 134 Recurrence at < 6 months: sensitivity analysis

Intervention	Comparator, OR (95% CrI)[a]										
	Podophyllin 20–25% (clinician applied)	Podophyllotoxin 0.5% solution (patient applied)	Podophyllotoxin 0.3% solution (patient applied)	Podophyllotoxin 0.5% cream (patient applied)	Podophyllotoxin 0.3% cream (patient applied)	Podophyllotoxin 0.15% cream (patient applied)	Podophyllin 0.5% solution (patient applied)	TCAA	Cryotherapy	Electrotherapy	TCAA 50% plus podophyllin 25%
Podophyllin 20–25% (clinician applied)	–	–	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.5% solution (patient applied)	0.87 (0.47 to 1.49)	–	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.3% solution (patient applied)	13.8 (0.94 to 65.21)	15.71 (1.25 to 74.3)	–	–	–	–	–	–	–	–	–
Podophyllotoxin 0.5% cream (patient applied)	1.02 (0.09 to 4.22)	1.27 (0.11 to 5.51)	0.26 (0.005 to 1.46)	–	–	–	–	–	–	–	–
Podophyllotoxin 0.3% cream (patient applied)	1.16 (0.19 to 3.77)	1.35 (0.24 to 4.22)	0.27 (0.009 to 1.37)	2.88 (0.12 to 14.81)	–	–	–	–	–	–	–
Podophyllotoxin 0.15% cream (patient applied)	1.40 (0.57 to 2.92)	1.64 (0.74 to 3.22)	0.33 (0.02 to 1.44)	3.46 (0.25 to 15.5)	1.93 (0.37 to 6.42)	–	–	–	–	–	–
Podophyllin 0.5% solution (patient applied)	62.5 (0.27 to 202.2)	73.95 (0.35 to 236.0)	15.64 (0.02 to 45.73)	127.8 (0.25 to 468.0)	95.13 (0.24 to 282.2)	52.68 (0.21 to 165.9)	–	–	–	–	–
TCAA	0.35 (0.09 to 0.88)	0.44 (0.10 to 1.21)	0.09 (0.003 to 0.43)	0.87 (0.05 to 4.13)	0.54 (0.05 to 2.26)	0.30 (0.06 to 0.90)	0.21 (0.001 to 1.33)	–	–	–	–
Cryotherapy	0.61 (0.20 to 1.41)	0.76 (0.21 to 1.98)	0.15 (0.007 to 0.72)	1.51 (0.10 to 7.03)	0.94 (0.11 to 3.75)	0.52 (0.12 to 1.48)	0.37 (0.002 to 2.33)	2.41 (0.42 to 7.92)	–	–	–
Electrotherapy	0.74 (0.25 to 1.68)	0.93 (0.26 to 2.37)	0.19 (0.008 to 0.88)	1.85 (0.13 to 8.41)	1.15 (0.13 to 4.57)	0.64 (0.15 to 1.81)	0.46 (0.003 to 2.87)	2.96 (0.53 to 9.69)	1.30 (0.65 to 2.36)	–	–
TCAA 50% plus podophyllin 25%	1.10 (0.25 to 3.13)	1.37 (0.27 to 4.21)	0.27 (0.01 to 1.37)	2.71 (0.15 to 13.22)	1.70 (0.15 to 7.4)	0.93 (0.16 to 3.09)	0.67 (0.004 to 4.34)	4.35 (0.56 to 16.28)	2.29 (0.34 to 8.01)	1.85 (0.28 to 6.49)	–

a OR < 1 favours the intervention and OR > 1 favours the comparator.
Shading represents statistically significant results.

TABLE 135 Recurrence at ≥ 6 months: primary analysis

Intervention	Comparator, OR (95% CRI)[a]			
	Podophyllin 20–25% (clinician applied)	Imiquimod 5% cream	Podophyllotoxin 0.5% solution (patient applied)	Surgical excision
Podophyllin 20–25% (clinician applied)	–	–	–	–
Imiquimod 5% cream	0.31 (0.04 to 1.06)	–	–	–
Podophyllotoxin 0.5% solution (patient applied)	1.56 (0.46 to 4.08)	9.64 (0.89 to 42.07)	–	–
Surgical excision	0.16 (0.03 to 0.43)	0.97 (0.07 to 4.34)	0.14 (0.02 to 0.50)	–

a OR < 1 favours the intervention and OR > 1 favours the comparator.
Shading represents statistically significant results.

EME
HS&DR
HTA
PGfAR
PHR

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