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

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## Scientific summary

Interventions for the treatment of anogenital warts

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# 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.

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