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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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HTA no 12/44: Treatment of anogenital warts

DRAFT PROTOCOL

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1. Project title

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

2. Name of TAR team and project 'lead'

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3. Plain English summary

Anogenital warts (AGWs) are small lumps or growths occurring in and around the anus or genital area that can cause local irritation, bleeding or discomfort. They are caused by a virus called the human papillomavirus (HPV), which is passed on by close skin-to-skin contact. There are over 100 types of HPV but AGWs are mainly caused by type 6 or type 11. AGWs are one of the most commonly occurring STIs in the UK.[1] In 2011, AGWs accounted for 17 out of 100 of new STI cases.[2] In addition, more than 50 out of 100 patients will experience recurrence of AGW within 1 year after initial clearance of their lesions. One study estimated that 148,000 episodes of AGWs were treated in England in 2008.3

Most people infected with HPV do not develop AGWs. Also, 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. Treatment for AGWs does not treat the viral infection and people can pass on HPV even after treatment or cure of AGWs.

AGWs can clear without treatment, but the frequency with which spontaneous resolution occurs is not certain. Several treatments are available for AGWs, including creams applied to the skin, a minor operation under local anaesthetic to cut out the AGW, cryotherapy (freezing) and laser treatment. AGWs can be difficult to treat and it might take several weeks of treatment, possibly even up to 6 months' treatment, to clear AGWs. Given that AGWs might clear without treatment, some people might prefer to wait for a length of time before starting treatment.

At this time, there is no resource that summarises the evidence for how effective the various treatments available are at clearing AGWs, or how the treatments compare against each other. The aim of this systematic review is to assess how well the treatments for AGW work, and how they compare with each other in curing AGWs and reducing recurrence. Another goal is to assess the adverse effects associated with the various treatments. An economic analysis will also be carried out to evaluate the cost and relative effectiveness of each intervention when used in treating AGWs and to estimate which treatments provide the most value for money. The project team will search the literature for evidence around the effectiveness of treatments for AGWs, any side effects of treatment, and information that will be required for the economic analysis (e.g., cost data and quality of life [QoL] data).

4. Decision problem

Background

AGWs are the second most commonly diagnosed STI in the UK.[1] In 2011, AGWs made up 17% of all incident STI cases presenting in genitourinary medicine (GUM) clinics in England.[2] Moreover, more than 50% of patients will experience recurrence of AGW within 1 year after initial clearance of the lesions. A study designed to evaluate the cost of care of AGWs estimated that 148,790 newly diagnosed and recurrent AGWs were treated in England in 2008.[3] Men are more likely to develop AGWs than women, with 41,333 and 34,726 new cases, respectively, in 2011 (males with unrecorded sexual orientation excluded from these figures).[2] As well as the physical discomfort caused by AGWs and the adverse effects of treatment, people may experience considerable psychological distress and most people with AGWs seek treatment for anxiety, or stress.

AGWs are benign epithelial skin lesions caused by the HPV infection.[4] HPVs, like other papillomaviruses, establish productive infections in keratinocytes of the skin or mucous membrane. Over a hundred HPV types have been identified, of which about 30 have been found to infect genital

epithelium.[5] AGWs are predominantly caused by HPV subtypes 6 and 11. The diagnosis of AGWs is typically determined by clinical examination.

AGWs occur on the external genitalia, that is, the penis, scrotum, urethral meatus, and perianal area in men, and on the introitus (vaginal opening), vulva, perineum, and perianal area in women.[6] AGWs can also develop in the anal canal.[7] The most common sites of occurrence are areas of trauma during sexual intercourse.[7] 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. Extragenital sites may be the oral cavity, larynx, conjunctivae and nasal cavity.[3]

AGWs may be single or multiple, but generally comprise from five to more than 15 lesions of 1 mm to 10 mm in diameter.[8] AGWs are typically classified as soft and non-keratinised (i.e., those on the moist, non-hair bearing skin) or firm and keratinised (i.e., those on the dry, hairy skin). Flat, plaque-like and pigmented warts are less common, and most present as soft cauliflower growths of varying size.[9] People may present with lumps or growths in the anogenital area. Other symptoms depend on the size and location of the AGWs, and include local irritation, bleeding or discomfort, and pain. Large AGWs may occur with secondary infection and maceration.[3]

Most people infected with HPV do not develop AGWs.[7] 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. Another potential route of transmission of HPV is mother-to-child transmission of HPV during labour (perinatal transmission), but this is rare.[10] Treatment of AGWs does not eliminate HPV infection directly, but most people whose lesions clear will become HPV DNA negative. Those who do not become HPV DNA negative can pass on the virus even after treatment or clearance of lesions.

Risk factors for AGW include a high number of sexual partners, a history of STIs, smoking, the use of oral contraceptives, and high parity (number of children).[11,12] Susceptibility is generally increased among patients who are immunocompromised, such as people who have undergone organ transplantation or those with human immunodeficiency virus (HIV).[11,12] Hormonal factors and male circumcision have also been investigated as risk factors for genital HPV infection, with inconclusive results.[13,14]

In the UK, AGWs are managed predominantly at GUM clinics. Individuals may seek care directly or be referred to GUM clinics by their general practitioners (GPs). AGWs can spontaneously resolve, but the reported proportion of people who experience spontaneous remission varies widely from 0% to 50%.[15] On this basis, some clinicians and patients may prefer to wait a period of time before starting treatment.[16] 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.[3] The goal of treatment is to reduce symptoms and visible lesions, not to treat the virus. Treatments are divided into provider (clinic-based) and patient-applied (home-based) therapy groups. For mild, early lesions, topical therapies suitable for application by the patient at home are typically preferred. Podophyllotoxin (Warticon® [available as a 0.5% solution or 0.15% cream], GlaxoSmithKline or Condylline® [available as a 0.5% solution or cream], Nycomed) and imiquimod (Aldara® [available as a 5% cream], Meda Pharmaceuticals) 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 due to their adverse effects.[3] Destructive methods that require administration by a clinician, such as electrosurgery (cautery, hyfrecation), cryotherapy, laser therapy, and trichloroacetic acid (TCA), act to debulk the visible lesions.

Soft, non-keratinised AGWs typically respond well to treatment with podophyllotoxin and TCA, whereas physical ablative methods are more effective for treating keratinised lesions. In some settings, topical treatments and ablative therapies may be used in combination. However, treatments, and in particular topical treatments, are associated with high failure and relapse rates.

The evidence base to direct first- and second-line treatment is limited, with a paucity of randomised controlled trials (RCTs) in this area. Guidelines produced by the British Association for Sexual Health and HIV (BASHH) in 2007 recommended that clinics develop individual treatment algorithms for different types of AGW.[7] Implementation of locally developed and monitored treatment algorithms has been found 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.

The rising prevalence and high rate of recurrence of AGWs places a significant cost burden in terms of treatment on the National Health Service (NHS). In a 2010 study based on Health Protection Agency (HPA) data from GUM clinics and primary care, the estimated national cost of managing AGWs was £52.4 million (£276 per treated genital wart episode).[17] There is evidence to show a reduction in the presentation rate of AGWs in the years after initiation of national vaccination programmes.[18] The adoption of such programmes could contribute to a reduction in the incidence and prevalence of AGWs in the UK.

At this time, there is no resource that summarises the evidence for how effective the various treatments available are at clearing AGWs, or how the treatments compare against each other. The objectives of this systematic review are to:

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

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

Planned PICO criteria

The review will 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, counselling), prevention of transmission, and screening for other STIs are also not addressed by this systematic review.

As a result of the anticipated lack of RCTs evaluating treatments, it may be necessary to include observational data.

The planned criteria pertaining to population, intervention, comparators, and outcomes are summarised in the table below.

PICO	**Criteria**
Population	Patients aged 16 years and over with clinically diagnosed AGWs (irrespective of biopsy confirmation)
Intervention	Topical treatments (any licensed dose, or formulation) evaluated will be: • podophyllotoxin; • imiquimod; • podophyllin; • TCA; • cidofovir. Physical ablation methods evaluated will include: • cryotherapy (liquid nitrogen spray or cryoprobe); • surgical excision (under local anaesthetic); • electrotherapy (electrocautery, hyfrecator surgery); • laser therapy. Combination or sequential therapy (e.g., cryotherapy followed by podophyllotoxin) will also be included.

Comparators	The interventions listed above versus each other (either as monotherapy or combination therapy), placebo or no intervention
Outcomes	Clinical effectiveness (expressed in terms of clearance, recurrence, and volume of wart), HRQoL and adverse effects (local and systemic). Specifically: *Primary outcomes* • Wart clearance at completion of treatment (e.g., 4 weeks for podophyllotoxin; up to 16 weeks for imiquimod) and at later time points (e.g., 3 months, 6 months); • Recurrence rate (time point will be that 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); • Adverse effects; • Malignancy.
Study design	RCTs and observational studies (prospective matched control studies, case series and case control studies). Should RCTs be identified, the decision might be taken to exclude observational data.
Abbreviations used in table: AGWs, anogenital warts; HRQoL, health-related quality of life; QoL, quality of life; RCTs, randomised controlled trials; TCA, trichloroacetic acid.	

Interventions not recommended in the BASHH guideline for routine management of AGWs and not typically used in NHS clinical practice have been 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).

Based on feedback from clinical experts, patients with AGWs and HIV with a CD4+ cell count of less than 200 cells/mm^3 typically respond less well to treatment and could be considered as a clinically distinct population. Data from studies in this patient group will be reported separately for the primary analysis. A sensitivity analysis combining the full data set will be carried out.

Subgroup analyses

If the evidence allows, use of the interventions in the subgroups listed below will be considered separately:

- Soft, moist, non-keratinized AGWs;
- Dry, keratinized AGWs;
- Number of AGWs, which will be grouped as (i) single, (ii) few (2–5), or (iii) multiple (≥6);
- Site of AGW;
- 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 more than 6 months);
- Immune status (immunosuppressed vs not immunosuppressed).

5. Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the PRISMA statement (formerly the QUOROM statement).[19] A flow diagram illustrating the flow of information through the systematic review process will be presented according to the PRISMA reporting guidelines.

Search methods for identification of studies

The search strategy will comprise the following main elements:

1. Searching of electronic bibliographic databases;
2. Contact with clinical experts in the field;
3. Review of the reference lists of retrieved papers.

Electronic searches

The electronic databases that will be searched are:

- MEDLINE (draft search strategy provided in Appendix 10.1);
- EMBASE;
- The Cochrane Central Register of Controlled Trials (CENTRAL);
- Web of Science(R).

Clinical trial registers will also be searched to identify relevant ongoing clinical trials that when completed may have an impact on the results of this review. Registers to be searched include:

- WHO International Clinical Trials Registry Platform;
- ClinicalTrials.gov (http://clinicaltrials.gov/);

The website of the US Food and Drug Administration (FDA) will also be searched to identify unpublished data.

Contacting clinical experts

Clinical experts in the relevant therapy area will be contacted to request details of trials (published and unpublished) of which they may be aware. Experts will be allowed 28 days to provide an initial response, with any additional time allowed being dependent on whether the data analysis stage of the review has been reached.

Review of the reference lists of retrieved papers

The references from any relevant review papers or RCTs identified by the search will be examined for additional, potentially relevant references.

Abstract appraisal

Titles and abstracts of studies identified by the search process will be assessed independently by two reviewers for inclusion. In cases where the reviewers are unable to reach a consensus as to whether the full text should be obtained for further appraisal, the full text will be obtained.

When potentially relevant data are available in only an abstract format, attempts will be made to contact the corresponding author to obtain the full publication. A deadline for response to the initial contact of 1 calendar month will be imposed. Additional time might be allowed should the author be able to supply the data requested. Information supplied after the deadline will potentially be included in only the discussion section of the report.

Inclusion criteria

For the review of clinical effectiveness, only RCTs will be included. Criteria might be relaxed should insufficient data be identified, as well as for consideration of adverse events, for which observational studies (prospective matched control studies, case series and case control studies) may be included. No language restriction will be imposed.

Studies not meeting the PICO criteria outlined in the table above will be excluded. Studies will also be excluded if they are:

- trials reporting only post-crossover results: study authors will be contacted to attempt to obtain pre-crossover results. If pre-crossover results cannot be obtained, study will be excluded;
- animal models;
- preclinical or biological studies;
- narrative reviews, editorials, opinions;
- reports published as only meeting abstracts, where insufficient methodological details are reported to allow critical appraisal of study quality.

Study inclusion assessment

Two reviewers will independently assess the full text of the trials identified during the abstract assessment stage for inclusion and any differences in opinion will be arbitrated by a third reviewer. Studies rejected at this or subsequent stages will be recorded in a 'characteristics of excluded studies table', and reasons for exclusion recorded.

Data extraction and management

Data will be extracted independently by one reviewer using a standardised data extraction form (provided in Appendix 10.4). The data extraction form will be piloted on 5 studies and modified as required before use. A pragmatic decision for data validation will be made depending on the number of trials identified due to the time constraints. Should 10 or less studies be identified as relevant for inclusion in the review, data will be extracted by two review authors independently. Should more than 10 studies be identified, data will be extracted by two reviewers for 10 studies, after which data would be extracted by one reviewer and validated by the second. Discrepancies in the data extracted by the two reviewers will be resolved through discussion, with involvement of a third reviewer if necessary.

Data from intention-to-treat (ITT) analyses will be extracted. Should a trial not report ITT data, missing data will be treated as treatment failures to allow analysis to conform to an ITT analysis. For the purpose of this review, ITT will be defined as patients being analysed in the treatment group they were allocated to at randomisation irrespective of whether they received the allocated intervention, withdrew or were lost to follow-up.

Quality assessment

Outcomes from the studies that meet the inclusion criteria will be assessed using the updated risk of bias tool developed by the Cochrane Collaboration (March 2011).[20] Two reviewers will independently rate the trial outcomes for inclusion and any differences in opinion will be arbitrated by a third reviewer. An outcome from an RCT will be considered appropriate for inclusion unless the trial demonstrates some feature that necessitates the exclusion of that outcome. Seven domains will be assessed for each included study:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcomes assessment;
5. Incomplete outcome data;
6. Selective reporting;
7. 'Other bias'.

Based on these criteria, a risk of bias assessment will be carried out for each outcome extracted. The three bias assessment categories used will be: low, high and unclear risk. Unclear risk is likely to be assigned due to poor reporting of how the trial was conducted rather than a poorly conducted trial.[21] Trials that are deemed to be at low or unclear risk of bias will be included in the main analysis and the trials rated high risk will be included in a sensitivity analysis.

Within a study, a summary assessment of low risk of bias will be given when there was a low risk of bias for all key domains, unclear risk of bias when there is an unclear risk of bias for one or more key domains, and high risk of bias when there is a high risk of bias for one or more key domains. Across studies, a summary assessment of the risk of bias for the primary outcome (across domains) will be undertaken.[17]

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be implemented to estimate a summary measure of effect on relevant outcomes based on ITT analyses. For dichotomous outcomes, odds ratio will be used as the summary statistic, and for continuous outcomes weighted mean difference will be the summary statistic. Meta-analyses will be conducted only if there are clinically homogeneous studies of similar comparisons reporting the same outcome measures. Standard pair-wise meta-analysis will be conducted when more than one trial is identified for inclusion for any pair of treatments under investigation. This will be carried out using a fixed effects model with the Mantel-Haenszel method.[22] Sensitivity analysis will be conducted using a random effects model with the DerSimonian & Laird method.[23] Subgroup analyses will be performed for the subgroups outlined in Section 4, should the evidence allow.

Should sufficient data be identified to facilitate a mixed treatment comparison (MTC), the MTC will be carried out based on a fixed effects and a random effects model with the most appropriate model identified as the one with the lowest deviance information criterion (DIC).[24]

Heterogeneity

For pair-wise meta-analysis, heterogeneity will be explored through consideration of the study populations, methods and interventions, by visual inspection of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic. Statistically significant heterogeneity will be defined as p <0.10. Levels of inconsistency will be assessed using I^2 and will be defined as follows: I^2 of: 0%–25% = low level of inconsistency; 26%–50% = moderate level of inconsistency; and >50% = high level of inconsistency.[25]

If statistically significant heterogeneity is detected in any of the analyses, hypothesis-generating subgroup analysis will be conducted, but the results from such analyses will be treated with caution. Meta-regression will be attempted if significant statistical heterogeneity is identified among trials analysed and there are 10 or more trials in the comparison.

For the MTC, where a random effects model is deemed the best fit, the degree of heterogeneity will be investigated by evaluating the posterior mean of tau-squared. Where possible, any closed loops formed by the network of trials will be assessed separately to determine if the results from the "direct" evidence is coherent with the "indirect" evidence when the wider network is introduced. Any incoherence identified will be investigated.

Sensitivity analysis

Sensitivity analyses will be carried out for aspects of the review that might have an impact on the results, for example, including studies where there is a high risk of bias, and inclusion of studies in patients with co-morbid HIV and a CD4+ cell count of less than 200 cells/mm^3. Sensitivity analysis will carried out for only the primary outcomes listed.

Publication bias

For each of the primary pair-wise meta-analyses, a funnel plot will be used to assess publication bias. A regression of normalised effect versus precision will also be calculated as a test for small study effects (using a p <0.10 as an indicator of a significant result).[26]

6. Report methods for synthesising evidence of cost-effectiveness

Identifying and systematically reviewing published cost-effectiveness studies

Identification of published economic evaluations will be attempted through searches of the following databases:

- MEDLINE;
- EMBASE;
- The Cochrane Central Register of Controlled Trials (CENTRAL);
- NHS Economic Evaluation Database (NHS EED);
- Health Technology Assessment (HTA) Database.

Search filters, specific to MEDLINE, EMBASE and CENTRAL, used to identify clinical evidence (Appendix 10.1) will be adapted with the removal of RCT filters and application of economic search filters (Appendix 10.2). In addition, search strategies specific to NHS EED and HTA databases will be designed and applied.

The inclusion and exclusion criteria for economic evaluations will be similar to those used in the systematic review of clinical effectiveness, with the following differences:

- non-randomised studies will be included (e.g., decision-model based analysis or analysis of person-level cost and effectiveness data alongside observational studies);
- full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost consequence analyses will be considered for inclusion;
- stand-alone costing studies will also be sought and appraised (with a preference for UK specific studies).

The titles and abstracts (where available) of all reports identified through the electronic search will be assessed independently and screened for possible inclusion by two health economists. The full publication of studies identified as potentially relevant, by either reviewer, will be obtained and assessed independently by two health economists. Any disagreements will be resolved by a third health economist. Studies rejected at this or subsequent stages will be recorded in a 'characteristics of excluded studies table', and reasons for exclusion recorded.

Evaluation of costs and cost effectiveness (may include development of a *de novo* economic model)

Information on data inputs, methodology, assumptions and results of any economic evaluations identified for final inclusion will be extracted into a data extraction form, collaboratively designed by two health economists. The methodological quality of included economic evaluations will be assessed

according to internationally accepted criteria such as the Consensus on Health Economic Criteria list questions developed by Evers *et al.* [27] (2005). Any studies based on decision models will be assessed using the checklist developed by Philips *et al.*[28] (2004). The applicability to the UK of each included study and the comparability of results across different economic evaluations will be considered, and summarised in tabular or narrative form.

Furthermore, should the published economic evidence be insufficient to determine the cost-effectiveness of medical or surgical treatments for AGW, a *de novo* economic evaluation will be carried out. The *de novo* economic analysis will use a decision analysis model (such as a decision tree, Markov or hybrid model) as a framework for the estimation of the cost-effectiveness of treatments used in the management of AGWs. Analysis will be carried out from the perspective of the UK NHS and personal social services (PSS). In accordance with NICE guidance,[29] an annual discount rate of 3.5% will be applied to both costs and benefits. Clinical expert opinion, received during protocol development, stated that recurrence and persistence of warts are key issues in the pathway of care. Expert advice highlighted that treatment usually continues until full clearance of AGWs is achieved; however, the number of treatments required to achieve clearance is highly variable. Based on this, it is envisaged that any *de novo* economic analysis required to address the decision problem will incorporate health states related to full clearance, recurrence and persistence of warts. In addition, the time horizon of the analysis should be sufficient to capture the goal of patient care, that is, achievement of complete clearance.

Review of NHS EED and HTA databases indicated that previously published economic evaluations in this area have used shorter time horizons. Preliminary review of NHS EED and HTA databases, using the single search term of "anogenital warts", was carried out on the 26th April 2013; four economic evaluations were identified. Of these, one presented a cost consequence analysis of imiquimod (followed if necessary by carbon dioxide [CO_2] laser treatment) or podofilox (followed if necessary by CO_2 laser treatment) in the treatment of anogenital warts; 38 out of 100 patients were estimated to require further treatment, following completion of first and second line therapy.[30] A further study[31] reported the results of a costing exercise carried out on case series data for the clearance rates of AGWs in patients treated with silver nitrate (n = 14) and patients treated with podophyllin (n = 34). The final two studies[32,33] were UK-based and presented treatment-specific costs alongside RCT efficacy data. White *et al.*[30] considered only the cost of drug acquisition (podophyllotoxin 0.5%, podophyllin 0.5% and podophyllin 2.0%). Lacey *et al.*[31] calculated the cost associated with podophyllotoxin 0.5% solution, podophyllotoxin 0.15% cream and 25% podophyllin (clinic applied) based on resource use data collected as part of a 12-week RCT. In addition, Lacey *et al.*[31] applied a one-off additional cost (average cost of treatments considered) to patients relapsing within 12 weeks or dropping out of treatment as a result of adverse events.

The absence of longer term extrapolation in previously published economic evaluations may suggest a paucity of data to inform economic modelling over the longer-term. However, should the need for a *de novo* economic analysis arise, every effort will be made to find data, for example, from observational studies (see Section 5), to inform the longer-term outcomes of treatment. Model structure, assumptions and data inputs will be determined in consultation with clinical experts to ensure they reflect the best current clinical practice and evidence. To allow assessment of the impact of parameter uncertainty on any cost-effectiveness results, all model parameters (that are associated with a level of uncertainty) will be incorporated into the decision analytic model as distributions, rather than mean estimates; i.e., probabilistic sensitivity analysis (PSA) will be carried out. In addition, univariate (one-way) and scenario sensitivity analyses will be carried out to assess the impact of individual parameters and assumptions on the cost-effectiveness results.

The benefits of treatment will be assessed with respect to QoL data expressed as a measure of utility. Utility values will be assigned to each model health state and used to determine the relative quality adjusted life-years (QALYs) gained per treatment. The impact of adverse events will be accounted for either through the use of additional health states or through the application of disutility values. Ideally, utility data will be available from RCTs included within the clinical effectiveness review. However, in the absence of such evidence, a systematic literature review will be carried out with the aim of identifying published utility data for the health states and adverse events incorporated within the economic model. The clinical search filters (Appendix 10.1) will be adapted with the removal of RCT filters and application of quality of life search filters (Appendix 10.3). Searches of MEDLINE, EMBASE and CENTRAL, NHS EED and HTA databases will be carried out. Two health economists will perform abstract appraisal, full text appraisal and data extraction. Only studies reporting utility data for patients with AGWs will be included, with a preference given to studies using time-trade off (TTO, in particular EQ-5D) or standard gamble valuation methodologies (in line with the NICE reference case[27]). Utility data used in the economic model will be adjusted for age using data from the Health Survey of England.[34]

Deterministic and probabilistic base case results will be presented as fully incremental cost-effectiveness ratios (ICERs). That is, interventions will be ordered with respect to cost (from lowest to highest) and the value of any QALYs gained assessed relative to the next cheapest intervention; interventions that are more expensive and less effective than their predecessor will be ruled out on the basis of dominance and interventions that provide less value for money than their predecessor will be ruled out on the basis of extended dominance. Probabilistic results will be presented in scatter plots in the cost-effectiveness plane and cost-effectiveness acceptability frontiers. In addition, the probability of being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 will be reported for each treatment. Sensitivity analysis results will be tabulated and presented as tornado diagrams. For treatments associated with a notable paucity of data, value of information (VOI) analysis, examining the potential value of a clinical trial investigating treatment effectiveness and safety, will be carried out.

7. Expertise in the TAR team

The BMJ-TAG is one of the Centres of Excellence identified by NIHR to undertake HTA. As a team dedicated to meeting contractual obligations to the NIHR, the BMJ-TAG has a strong record of submission of high-quality reports to tight deadlines. A brief description of the experience of the individual members of the BMJ-TAG who will contribute to this project is provided.

Dr Steven J. Edwards DPhil MSc BSc (Hons), Head of Health Technology Assessment

Steve has performed clinical and economic evaluations for over 15 years in a range of therapeutic areas, including cardiovascular, central nervous system, gastroenterology, infection, oncology, ophthalmology, respiratory medicine, and urology. He has in-depth experience of applying evidence synthesis methods within the context of health technology assessment. His interests are in the use of the best available evidence for decision making with an emphasis on the design and conduct of clinical trials, systematic reviews, meta-analyses, adjusted indirect comparisons and their subsequent use in economic evaluations. His postgraduate research in this area at the University of Oxford resulted in him being awarded the first doctorate of evidence based health care in 2010. Steve is a standing member of the Diagnostic Advisory Committee for the National Institute for Health and Care Excellence (NICE) and a reviewer of research applications for the National Institute for Health Research (NIHR). In addition, Steve is an honorary lecturer in health economics at the London School of Hygiene & Tropical Medicine, a member of the Cochrane Statistical Methods Group, the Campbell & Cochrane Economics Methods Group, and an Editorial Board member of the *International Journal of Clinical Practice*.

Dr Samantha Barton PhD BSc (Hons), Senior Health Technology Assessment Analyst

Sam has extensive experience in the critical appraisal of studies. Over the past 7 years, she has contributed to the publication of over 50 systematic reviews on prevention and treatment of various clinical conditions. She has worked on reviews in the areas of mental health, sexual health, infectious diseases, cardiovascular disorders, respiratory disorders and oncology. Sam has acted as lead on the clinical effectiveness components of several Single Technology Appraisals as part of the Technology Appraisal process.

Ms Nicola Trevor MSc BSc (Hons), Health Economics Lead

Nicola has a strong mathematical background, with a Masters in analytical, numerical and statistical modelling techniques, which over the past 4 years she has applied in the field of health economics, conducting economic evaluations and statistical analysis for systematic review in disease areas such as multiple sclerosis, cardiovascular disease, Gaucher's disease, mental health and oncology. Her interests are in the use of the best available techniques for decision making with an emphasis on survival analysis, meta-analysis, modelling approaches and the use of Bayesian methods in economic evaluations.

Dr Charlotta Karner PhD MSc, Health Technology Assessment Analyst Lead

Since 2011 Charlotta has developed, conducted, and published over 9 systematic reviews as a member of the Cochrane Airways Group. She has worked in a variety of conditions but has a special interest in pharmacological interventions for chronic obstructive pulmonary disease and asthma. Charlotta has also conducted primary research to understand the role of Transient Receptor Potential channels in airway smooth muscle cells. Charlotta has an active interest in translating complex research concept into a format suitable for the general public.

Elizabeth Thurgar MSc BSc (Hons), Senior Health Economist

Elizabeth has a Masters in Economics and a Masters in Health Economics. Previously, Elizabeth has worked as an Assistant Economist with the UK Government, and has worked within NHS Trusts, assisting decision-makers to use evidence to inform their choices. Elizabeth has over 5 years' experience in economic evaluation, statistical analyses and modelling in a wide range of disease areas.

Recent publications from the team members

Edwards SJ, Barton S, Nherera L, Trevor N, Krause T, Thurgar E. Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma: A Single Technology Appraisal. BMJ-TAG, London, 2013.

Edwards SJ, Karner C, Trevor N, Barton S, Nherera L. Mirabegron for the treatment of symptoms associated with overactive bladder. BMJ-TAG, London, 2013.

Edwards SJ, Hamilton V, Nherera L, Trevor N. Lithium or an atypical anti-psychotic in the management of treatment resistant depression: systematic review and economic evaluation. BMJ-TAG, London, 2012.

Edwards SJ, Barton S, Thurgar E, Nherera L, Hamilton V, Karner C, *et al*. Bevacizumab for the treatment of recurrent advanced ovarian cancer: A Single Technology Appraisal. BMJ-TAG, London, 2012.

Edwards SJ, Barton S, Nherera L, Trevor N, Hamilton V. Ivabradine for the treatment of chronic heart failure: a Single Technology Appraisal. BMJ-TAG, London, 2012.

External Clinical Expert Advisors

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Consultant physician in Genito-Urinary Medicine and HIV, with a special interest in treatment and prevention of anal neoplasia.

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Relevant publications include:

Nathan M, Sheaff M, Fox P, Goon P, Gilson R, Lacey C. Early treatment of anal intraepithelial neoplasia. *BMJ* 2011:343; d7717.

Bissett SL, Howell-Jones R, Swift C, De Silva N, Biscornet L, Parry JV, *et al*. Human papillomavirus genotype detection and viral load in paired genital and urine samples from both females and males. *J Med Virol* 2011:83; 1744-51.

Fox PA, Nathan M, Francis N, Singh N, Weir J, Dixon G, *et al*. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. *AIDS* 2010:24; 2331-35.

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Relevant publications include:

Lanitis T, Carroll S, O'Mahony C, Charman F, Khalid JM, Griffiths V, Brown RE. The cost of managing genital warts in the UK. *Int J STD & AIDS* 2012:23(3); 189-94.

O'Mahony C, Reeve-Fowkes A, Worthen E, Mallinson H. Three years of using Aptima Combo 2 (AC2) transcription-mediated amplification for gonorrhoea in a district hospital genitourinary medicine clinic shows it to be superior to culture and has a specificity of almost 100%. *Int J STD & AIDS* 2008:19; 67-9.

O'Mahony C. Genital warts: current and future management options. *Am J Clin Dermatol* 2005:6; 239-43.

8. Competing interests of authors

None.

9. Timetable/milestones

Send progress report to NETSCC, HTA – 2nd April 2014

Submit assessment report to NETSCC, HTA – 2nd May 2014

The timetable is based on an 11-month working time-frame, commencing in June 2013 assuming that the final approval of the protocol has been received by this time.

10. Appendices

10.1. Draft MEDLINE search strategy (Clinical)

10.2. Draft MEDLINE economic search filters

10.3 Draft MEDLINE quality of life search filters

10.4. Data extraction form

10.5. Team members' contributions

10.6 References

10.1 Draft MEDLINE (via OVID) search strategy (including RCT filter)

As a result of the small number of RCTs identified in the scoping search, the decision was taken to omit search terms for interventions from the scoping search.

1. exp Condylomata Acuminata/ (4,427)
2. (genital$ adj3 wart$).tw. (1,671)
3. (anogenital$ adj3 wart$).tw. (402)
4. (peni$ adj3 wart$).tw. (61)
5. (venereal adj3 wart$).tw. (79)
6. (condyloma$ adj3 acuminat$).tw (1,918)
7. (anal adj3 wart$).tw (129)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (5,821)
9. Randomized Controlled Trials as Topic/ (85,104)
10. randomized controlled trial/ (347,234)
11. Random Allocation/ (77,090)
12. Double Blind Method/ (119,540)
13. Single Blind Method/ (17,406)
14. clinical trial/ (476,841)
15. clinical trial, phase i.pt. (13,095)
16. clinical trial, phase ii.pt. (20,959)
17. clinical trial, phase iii.pt. (7,843)
18. clinical trial, phase iv.pt. (797)
19. controlled clinical trial.pt. (85,791)
20. randomized controlled trial.pt. (347,234)
21. multicenter study.pt. (155,524)
22. clinical trial.pt. (476,841)
23. exp Clinical Trials as topic/ (265,156)
24. or/9–23 (959,357)
25. (clinical adj trial$).tw. (181,773)
26. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (116,996)
27. PLACEBOS/ (31,591)
28. placebo$.tw. (142,147)
29. randomly allocated.tw. (14,393)
30. (allocated adj2 random$).tw. (16,744)
31. or/25–30 (367,609)
32. 24 or 31 (1,069,995)
33. case report.tw. (172,936)
34. letter/ (769,425)

35. historical article/ (291,530)
36. or/33–35 (1,223,179)
37. 32 not 36 (1,041,844)
38. 8 and 37 (561)

10.2 Draft MEDLINE (via OVID) economic search filters

1. exp economics/
2. exp Costs and Cost Analysis/
3. Cost Benefit Analysis/
4. value of life/
5. exp models economic/
6. exp fees/and charges/
7. exp budgets/
8. (economic adj2 burden).tw.
9. (expenditure* not energy).tw.
10. budget*.tw.
11. (economic* or price* or pricing or financ*or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw.
12. (decision adj1 (tree* or analys* or model*)).tw.
13. Resource Allocation/
14. (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.
15. ((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.
16. Markov Chains/
17. exp Decision Support Techniques/
18. (resource adj2 (use* or utili* or allocat*)).tw.
19. (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* or charges)).tw.
20. or/1–19

10.3 Draft MEDLINE (via OVID) quality of life search filters

1. exp quality of life/
2. quality of life.tw
3. life quality.tw
4. (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
5. (euroqol or eq5d or eq 5d).tw
6. quality adjusted life$.tw
7. (QALY$ or lifeyear$ or life year$ or ((qualit$3 or value) adj3 (life or survival))).tw.
8. ((burden adj3 (disease or illness)) or (resource adj3 (allocation$ or utilit$)) or (value adj5 money)).tw.
9. (budget$ or cost$ or econom$ or expenditure$ or financ$ or fiscal$ or funding or pharmacoeconomic$ or price or prices or pricing).tw.

10.4 Pilot data extraction form

Item	**Details**
Section 1: Reviewer and study information	
Reviewer name	
Date of completion of form	
Study ID	
Study details (journal, year, volume, page range)	
Language of publication	
Type of report (full paper/only abstract/conference abstract)	
Section 2: study eligibility (If answer is NO to any questions in this section do not proceed to Section 3)	
Type of study (RCT, prospective matched control study, case series, case control)	
Population: adults ≥16 years old with clinically diagnosed AGW	
Interventions: Compares interventions listed versus placebo, no intervention, or another listed intervention, either as a monotherapy or in combination	
Outcomes At least one of the listed outcomes evaluated: • clearance of AGW at completion of treatment or other time point; • recurrence rate; • time to complete clearance;	

• volume of wart clearance; • relief of symptoms during treatment; • appearance of new warts during treatment; • QoL; • adverse effects; • malignancy.		
Section 3: study information		
Location and number of sites		
Trial sponsor		
Conflicts of interest		
Patient enrolment (how patients were enrolled, and date to date of enrolment)		
Trial design (e.g., RCT, cross-over RCT)		
Line of therapy (first, recurrent, persistent)		
Inclusion criteria		
Exclusion criteria		
All outcomes reported		
Subgroups evaluated		
Stratification		
Measurement of disease		
Ethnicity		
Treatment	**Intervention [NAME]**	**Comparator [NAME]**
Randomised, N		
Withdrawals (specify reasons for withdrawal), n (%)		
Treatment regimen (delivery, dose, and formulation)		
Treatment duration (length of treatment, with SD/SE if given)		
Treatment discontinuation		
Concomitant medications		
If the comparator was placebo, was the formulation and appearance matched to that of the other intervention?		
Did both groups experience the same care except for the two interventions under investigation?		
Baseline patient characteristics		
Age, years (range)		
Previous treatment		
Site of AGW, n (%)		
Type of AGW (e.g., non-keratinsed, keratinised), n (%)		
Comments (e.g., power calculation, important changes to protocol, type of analysis)		

Section 4: Outcomes	
Outcome	*Definition*
AGW clearance at completion of treatment	
AGW clearance at other time points	
Recurrence of AGW	
Time to complete clearance	
Volume of wart clearance (e.g., proportion of patients with 50% clearance)	
Relief of symptoms during treatment	
Appearance of new warts during treatment	
Quality of life (trial scale used)	
Adverse events (please specify)	
Malignancy	

Section 5: ITT data extraction form						
Outcome	**Timeframe**	**Intervention**		**Comparator**		**Estimate of effect (CI and p value)**
AGW clearance at completion of treatment		n	N	n	N	
AGW clearance at other time points						
Recurrence of AGW						
Time to complete clearance						
Volume of wart clearance (e.g., proportion of patients with 50% clearance)						
Relief of symptoms during treatment						
Appearance of new warts during treatment						
Quality of life (trial scale used)						
Adverse events (please specify and use multiple rows)						
Malignancy						

Section 6: Clinical trial quality	
Method of randomisation	
Method of allocation concealment	
Method of masking and who was masked	

Number of patients lost to follow up (the overall number and number by treatment group, give reasons for loss to follow up)	
Section 7: Additional comments	
Additional comments	
Further information that could be requested from authors	
Abbreviations used in table: AGW, anogenital wart; CI, confidence interval; n, number of patients with the outcome; N, number of patients assessed; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SE, standard error.	

Summary of the trials design to minimise bias for (please tick)

Outcome	**Risk of bias**	**Low risk**	**Unclear risk**	**High risk**	**Comments**
AGW clearance at completion of treatment and at other time points	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Recurrence of AGW	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Time to complete clearance	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				

	7) 'Other Bias'				
Volume of wart clearance (e.g., proportion of patients with 50% clearance)	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Relief of symptoms during treatment	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Appearance of new warts during treatment	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Quality of life	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				

Adverse events	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Malignancy	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Overall rating of bias					

10.5 Team members' contributions

Steve Edwards, Head of HTA, will contribute to the development of the protocol, act as the third reviewer for assessment of trials and cost-effectiveness studies, validate data extraction and any data analysis required, validate the economic model, contribute to writing/editing of the report, be overall lead of the project and act as guarantor of the report.

Samantha Barton, Senior HTA Analyst, will contribute to the development of the protocol, act as co-reviewer for assessing trials on clinical effectiveness for inclusion and data extraction, and contribute to the writing/editing of the report.

Charlotta Karner, HTA Analyst Lead, will act as co-reviewer for assessing trials on clinical effectiveness for inclusion and data extraction, and contribute to the writing/editing of the report.

Nicola Trevor, Health Economist Lead, will contribute to the development of the protocol, act as co-reviewer of the cost-effectiveness studies, develop the economic model, and contribute to the writing/editing of the report.

Elizabeth Thurgar, Senior Health Economist, will contribute to the development of the protocol, act as co-reviewer of the cost-effectiveness studies, and contribute to the writing/editing of the report.

Dr Colm O'Mahony and Dr Mayura Nathan, Clinical Expert Advisors, will provide clinical advice throughout the protocol development and review processes.

10.6 References

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