HIPvac: a trial of vaccination and cream treatment in patients with anogenital warts

Human papillomavirus infection: a randomised controlled trial of Imiquimod cream (5%) versus Podophyllotoxin cream (0.15%), in combination with quadrivalent human papillomavirus or control vaccination in the treatment and prevention of recurrence of anogenital warts

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ECONOMIC EVALUATION ANALYSIS PLAN (EEAP)

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Abbreviations

Abbreviation	Definition
BNF	British National Formulary
HPV	Human papillomavirus
IMP	Investigational Medicinal Product
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial

Background

HIPvac is an RCT with a 2x2 factorial design comparing the efficacy of two options for topical treatment (imiquimod or podophyllotoxin), with or without HPV vaccination, in treating anogenital warts and preventing recurrence. Patients enrol in the trial receive either imiquimod or podophyllotoxin according to current clinical practice, and in addition may receive three doses of quadrivalent HPV vaccine administered at 0, 8 and 24 weeks after recruitment of each patient. In addition to the treatment indicated by randomisation, cryotherapy can be administered from 4 weeks onwards in some cases based on investigator judgment. Topical treatment (imiquimod or podophyllotoxin) provided up to week 16 is classified as an IMP. After week 16, the topical treatment can be changed on the basis of lack of response.

This document outlines the plan for economic evaluation alongside this RCT.

Aim and objectives:

To assess the incremental costs, QALYs and cost-effectiveness of the following options for anogenital warts patients:

A. imiquimod cream without HPV vaccination;
B. podophyllotoxin cream without HPV vaccination;
C. imiquimod cream with HPV vaccination;
D. podophyllotoxin cream with HPV vaccination

Economic evaluation methodology

Economic evaluation methodology will follow the reference case for NICE health technology appraisals 2013 (1), including the following:

Category	Methodology
Type of analysis	Cost-utility analysis.
Cost-effectiveness threshold	£20,000 - £30,000 per QALY gained.
Perspective on costs	The cost perspective will be that of the NHS and personal and social services.

Time horizon	In the trial, participants will be followed-up for 48 weeks, with routine visits expected at 4, 8, 16, 24 and 48 weeks. However, for the economic evaluation, costs and health outcomes will be extrapolated to the lifetime of the patient.
Costs reference year and currency	All costs will be inflated to GBP 2016/17 prices.
Discounting	Discounting of future costs will be at 3.5% for both costs and QALYs, for the base case. Sensitivity analysis at 1.5% for both costs and QALYs will be conducted.

Outcomes

The primary outcome of the RCT is the effectiveness of each of the four interventions (imiquimod or podophyllotoxin with or without HPV vaccine) in treating anogenital warts, through the measure of the proportion of participants in each arm with complete anogenital warts resolution at 16 weeks (warts clearance) and remain free of warts up to 48 weeks after starting treatment (preventing recurrence).

The primary economic outcome is the cost-effectiveness of each intervention. A full incremental analysis will be performed. The most effective option which is below the cost-effectiveness threshold will be calculated after taking out dominated and extendedly dominated intervention arm(s). The uncertainty around this choice will also be estimated.

If the HPV vaccine is more effective than control vaccine, an additional economic evaluation will be carried out to estimate the threshold price at which it will become cost-effective.

Measurement of resource use:

Health care resources used to deliver the intervention in HIPvac may not necessarily be representative of clinical practice. Hence costs of resources used will be obtained from the results from the QOLIGEN observational study of anogenital warts treatment in sexual health clinics(2). Patients in QOLIGEN will be stratified according to whether they received imiquimod or podophyllotoxin; patients receiving both or neither topical treatments will be excluded. HPV vaccine costs will be added separately. The information provided from the QOLIGEN study includes clinic attendance frequency and treatment received, but the overall duration of warts treatment will follow that found in HIPvac, dependent on each of the four potential treatment combinations (podophyllotoxin or imiquimod with or without HPV vaccination).

Where possible, unit cost data will be updated from national tariffs or published prices, such as NHS supply chain, the British National Formulary (BNF), and unit staff costs reported by the Personal Social Services Research Unit (PSSRU). An expert panel of clinicians will be consulted to find out if resource use is likely to have changed since the QOLIGEN study was conducted.

If patient-level QOLIGEN data cannot be obtained, then HIPvac trial data will be used and combined with standard data sources and assumptions about resource use.

Measurement of utility scores:

Health-related quality of life outcomes will be collected using the EQ-5D-5L questionnaire at each study visit (weeks 0, 4, 8, 16, 24, and 48). Utility values informed by the EQ-5D-5L scores will be calculated based on the English value set, stratified by age (3).

Multiple imputation will be used in the case of missing data points. Extrapolation beyond the trial period (week 48) will be managed using suitable extrapolation functions, e.g. splines, with the final choice of function chosen based on standard model selection criteria e.g. Aikaike Information Criterion. Splines will be fitted to data points including uncertainties from the imputation process using maximum likelihood estimation.

Patients who clear warts and have no recurrences will be assumed to have EQ-5D-5L scores returning to population norms. Duration of warts will be estimated using survival analysis.

The quality adjusted life years (QALYs) in each arm will then be estimated based on the area under the curve of quality of life as a function of time since recruitment. This will be done using both the 5-dimension questionnaire and the visual analogue scale of the EQ-5D-5L. Uncertainty around QALYs due to both sampling and imputation will be estimated.

Uncertainty analysis:

Uncertainty around all outcomes and conclusions will be estimated using probabilistic sensitivity analysis. Uncertainty distributions for all cost and QALY outcomes will capture uncertainty due to sampling, imputation, extrapolation and survival analysis.

References

1. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal [Internet]. 2013 [cited 2016 Jan 15]. Available from: https://www.nice.org.uk/article/pmg9/chapter/foreword
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3. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2018 Jan;27(1):7–22.