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UCL Clinical Trials Unit

HIPvac Trial

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 (HIPvac Trial)

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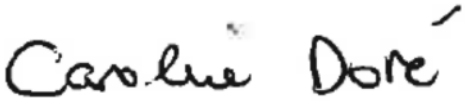
Signature	
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1 Administrative information

This document was constructed using the UCL Clinical Trials Unit (CTU) Protocol template Version 2.0. It describes the HIPvac trial, sponsored by UCL and co-ordinated by UCL CTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at UCL CTU.

UCL CTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials. The SPIRIT Statement Explanation and Elaboration document version 6 can be referred to, or a member of UCL CTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites will comply with the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable) and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and UCL CTU.

Participating sites will inform UCL CTU as soon as they are aware of a possible serious breach of compliance, so that UCL CTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants in the trial, or
- The scientific value of the trial.

1.2 Sponsor

UCL is the trial sponsor and has delegated responsibility for the overall management of the HIPvac trial to UCL CTU. Queries relating to UCL sponsorship of this trial should be addressed to the Director, UCL CTU, or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	EudraCT: 2013-002951-14
Date of Registration in Primary Registry	28 June 2013
Secondary Identifying Numbers	CTU/2012/009
Source of Monetary or Material Support	National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Sanofi Pasteur MSD (SPMSD) – supply of vaccines
Primary Sponsor	University College London
Secondary Sponsor	Sponsor responsibilities for Trial Management are delegated to UCL CTU.
Contact for Public Queries	hipvac@ucl.ac.uk
Contact for Scientific Queries	Chief Investigator: Dr Richard Gilson University College London The Mortimer Market Centre London WC1E 6JB Telephone: 020 3108 2103 email: r.gilson@ucl.ac.uk Trial Manager: Jade Meadows Clinical Trials Unit University College London, Gower Street, London, WC1E 6BT Telephone: 020 3108 3942 Email: j.meadows@ucl.ac.uk
Public Title	HIPvac: a trial of vaccination and cream treatment in patients with anogenital warts
Scientific Title	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 (HIPvac Trial)
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	Patients presenting with external anogenital warts, aged 18 years or over, males and females, with either a first or subsequent episode of anogenital warts.
Intervention(s)	Topical treatment: All participants will be randomised to receive initial treatment with either imiquimod 5% cream or podophyllotoxin 0.15% cream. Treatment allocation will be open due to the differing dosing regimen and licensed duration of therapy. • **Imiquimod:** Participants randomised to imiquimod will be asked to apply the 5% cream for three days of the week (every other day). The cream should be applied at the participant's bed time and left on overnight. The cream should be washed off after 6-10 hours. or • **Podophyllotoxin:** Participants randomised to the podophyllotoxin arm will be instructed to apply the 0.15% cream to the lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles. The licensed treatment duration is 4 weeks, but it is common practice to extend this period if there is a partial response to therapy. Participants will be randomised 1:1 to either topical treatment. Vaccines: Participants will be simultaneously randomised in a double blind fashion to one of three groups, qHPV vaccine, hepatitis A vaccine or placebo vaccine. All recipients will receive three doses at 0, 2 and 6 months. Vaccines are as follows: • **qHPV vaccine:** Quadrivalent HPV vaccine, Gardasil – Sanofi Pasteur, given according to the licenced schedule at 0, 2, and 6 months; vaccine volume 0.5ml; containing alum adjuvant. or • **Hepatitis A virus (HAV) vaccine:** inactivated whole virus vaccine, containing 25 antigen units in 0.5ml, and containing alum adjuvant (Vaqta - Sanofi Pasteur), as active control.

	or • 0.5ml normal saline vaccine as placebo control. Participants will be randomised 2:1:1 to qHPV, HAV and placebo. Participants will be randomised to one of 6 groups: A. imiquimod cream plus HPV vaccine; B. podophyllotoxin cream plus HPV vaccine; C. imiquimod cream plus HAV vaccine; D. podophyllotoxin cream plus HAV vaccine. E. imiquimod cream plus placebo vaccine. F. podophyllotoxin cream plus placebo vaccine.
Key Inclusion and Exclusion Criteria	Inclusion criteria: • Age 18 years or over • Males and females • First episode or repeat episode of anogenital warts diagnosed clinically • External anogenital warts considered, in the opinion of the investigator, to be suitable for self-administered topical wart treatment (patients with concurrent internal anogenital warts are eligible to participate) • Able to provide informed consent to participate in the trial. Exclusion Criteria: • Previous wart treatment in the last 3 months • Previous quadrivalent HPV vaccine. (Previous **bivalent** HPV vaccine is **not** an exclusion criteria). • Previous intolerance to either of the topical treatments, vaccines or their constituents • Known HIV-positivity* (HIV testing is not required for the trial). • Pregnancy or lactation** (current, or planned in the next 6 months) • Women of child bearing potential[1] not willing to use effective[2] contraception for the duration and 30 days post completion of trial treatment: see above

[1] Women of child bearing potential excludes women who are postmenopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy)

	• Unable or unwilling to complete follow-up procedures • Lesion area greater than 4 cm^2, requiring treatment under direct supervision of medical staff (in accordance with podophyllotoxin cream Summary of Product Characteristics). • Patients who have had topical steroids applied to the target area, or systemic steroids or other immunosuppressive agents, within 1 month prior to randomisation • Patients enrolled in any other trial of an Investigational Medicinal Product, without the permission of the Chief Investigator. • Any clinical condition which the investigator considers would make the patient unsuitable for the trial, including immunodeficiency conditions. *If a participant is found to be HIV positive during the course of the trial they should be withdrawn from trial treatments, but still be followed up as per protocol. Treatment should be provided as per standard treatment for HIV patients. ** Podophyllotoxin is contraindicated in pregnancy; the safety of imiquimod and qHPV vaccine in pregnancy is unknown. There are no teratogenicity risks for female partners of males being treated with either of the creams or vaccines.
Trial Type	A randomised, controlled partially blinded 2 x 3 factorial trial. The two factors are: • Type of topical cream for self-application (16 weeks of imiquimod 5%, or 4 weeks of podophyllotoxin 0.15% as active control, according to the licence) • Type of vaccination, in 3 doses at 0, 2, 6 months, starting at the same time as the topical wart treatment, and randomised 2:1:1 to: either quadrivalent HPV vaccine (Gardasil® – Sanofi Pasteur); or hepatitis A vaccine (Vaqta, 25 antigen units in 0.5ml – Sanofi Pasteur), as active control; or 0.5ml saline vaccine as placebo control.
Date of First Enrolment	January 2014
Target Sample Size	1000 participants
Primary Outcome(s)	A composite endpoint of wart clearance within 16 weeks of starting treatment and remaining wart-free between 16 and 48 weeks. This will capture both the initial clearance efficacy as well as the impact on relapse or recurrence.
Key Secondary Outcomes	1. Proportion wart-free at the end of the assigned treatment

[2] Effective contraception defined per MHRA guideline, with the addition of regular and consistent condom use without spermicide (See appendix 2).

	course (4 or 16 weeks) 2. Proportion wart-free at 16 weeks, with use of additional treatment as required 3. Quantity of additional treatment (number of cryotherapy applications, additional weeks of podophyllotoxin or imiquimod) required to achieve clearance by 16 weeks 4. Proportion wart-free at 24 weeks 5. Proportion wart-free at 24 weeks with use of additional treatment as required 6. Quantity of additional treatment (number of cryotherapy applications, additional weeks of podophyllotoxin or imiquimod) required to achieve clearance by 24 weeks 7. Proportion experiencing wart recurrence/relapse at 48 weeks after wart clearance at 24 weeks 8. Proportion experiencing complete wart clearance 9. Time to complete wart clearance 10. Proportion experiencing wart recurrence/relapse after complete wart clearance 11. Time from complete wart clearance to recurrence/relapse 12. Adverse events 13. Health-related quality of life, as measured by the Area Under the Curve for EQ-5D 14. Symptom scores 15. Total costs of treatment including prescribed agents and clinic visits

1.4 Roles and responsibilities

1.4.1 Protocol contributors

Name	Affiliation	Role
Dr Richard Gilson	University College London (UCL)	Chief Investigator (CI)
Prof Charles Lacey	University of York	Co-applicant
Dr Lewis Haddow	UCL	Co-applicant and Trial Physician
Michelle Tetlow	UCL	Clinical Project Manager
Jade Meadows	UCL	Trial Manager
Caroline Doré	UCL	Statistical Oversight
Dr Kate Soldan	Public Health England (PHE)	Co-applicant, Epidemiologist
Dr Andrew Copas	UCL	Co-applicant, Trial Statistician
Dr Mark Jit	(PHE)	Co-applicant, Health Economist
Dr Mayura Nathan	Homerton University Hospital	Co-applicant

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
National Institute for Health Research Health Technology Assessment (NIHR HTA)	NIHR HTA	Funder

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Dr Richard Gilson	UCL	Chief Investigator: overall responsibility for HIPvac Trial
Dr Lewis Haddow	UCL	Trial Physician: day-to-day clinical input
Michelle Tetlow	UCL	Clinical Project Manager: oversight of trial management
Jade Meadows	UCL	Trial Manager: day-to-day trial management

1.4.4 Trial Management Group

Name	Affiliation	Role
Dr Richard Gilson	UCL	CI (Chair)

Prof Charles Lacey	University of York	Professor of Genitourinary Medicine
Dr Andrew Copas	UCL	Trial Statistician
Caroline Doré	UCL	Trial Statistical Oversight
Yvonne Sylvestre	UCL	Trial Statistician
Dr Lewis Haddow	UCL	Trial Physician
Dr Kate Soldan	PHE	Epidemiologist
Dr Mark Jit	PHE	Health economist
Dr Mayura Nathan	Homerton University Hospital	Genitourinary Medicine Physician
Jade Meadows	UCL	Trial Manager
Nestor Salazar	UCL	Data Manager
Michelle Tetlow	UCL	Clinical Project Manager

1.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Professor Graham Taylor	Imperial College London	Chair

1.4.6 Data Monitoring Committee

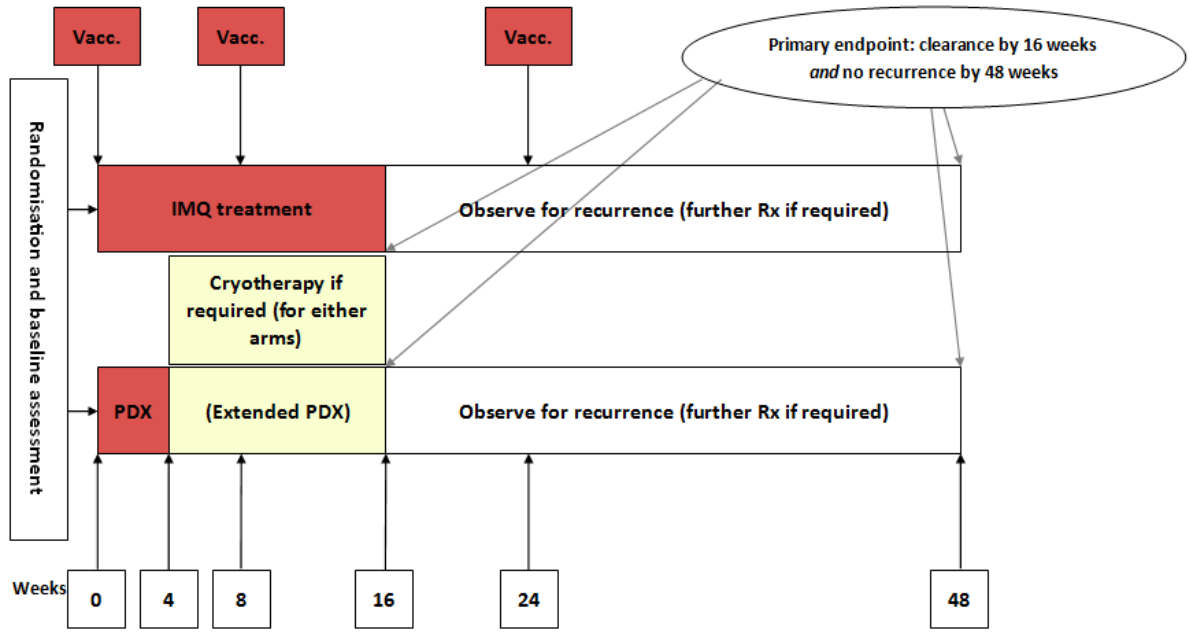
Name	Affiliation	Role and responsibilities
TBC		

1.4.6 Principal Investigator Group

Name	Affiliation	Role and responsibilities
TBC		

2 Trial Diagram

Trial visits are indicated by week numbers along the bottom of the figure. Trial-defined treatments are indicated in red boxes, with additional treatments in the event of non-response/intolerance up to week 16 in yellow.



3 Abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
AIN	Anal Intraepithelial Neoplasia
AR	Adverse Reaction
BASHH	British Association for Sexual Health and HIV
CI	Chief Investigator
CIN	Cervical Intraepithelial Neoplasia
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DSUR	Development Safety Update Report
EU	European Union
FDA	(US) Food and Drug Administration
HAV	Hepatitis A Virus
HTA	Health Technologies Assessment
HPV	human papillomavirus
JCVI	Department of Health Joint Committee on Vaccination and Immunisation
GCP	Good Clinical Practice
GUM	Genitourinary Medicine
GUMNET	a network of Genitourinary Medicine (GUM) clinics involved in sentinel public health monitoring and research
IB	Investigator Brochures
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention to Treat
MHRA	Medicines and Healthcare products Regulatory Agency
MoU	Memorandum of Understanding
NAE	Notifiable Adverse Event
NHS	National Health Service
PHE	Public Health England
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
qHPV	quadrivalent human papillomavirus
QMMP	Quality Management Plan
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RRP	Respiratory Papillomatosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
STI	Sexually Transmitted Infection
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UCL	University College London
VaIN	Vaginal Intraepithelial Neoplasia
VIN	Vulval Intraepithelial Neoplasia

4 Glossary

Adverse Event - a harmful outcome that is usually indicated by some result such as morbidity, mortality.

Anal intraepithelial neoplasia (AIN) – pre-malignant, abnormal cells in the area of the anus.

Anogenital warts - Genital warts are small fleshy growths, bumps or skin changes that appear on or around the genital or anal area.

Cervical intraepithelial neoplasia (CIN) – pre-malignant changes in the squamous cells of the cervix.

Cryotherapy – the use of liquid nitrogen to destroy cells.

Human papillomavirus (HPV) – a DNA virus that infects the skin and mucous membranes. There are more than 100 different strains of HPV.

Recurrent respiratory papillomatosis (RRP) - growths in the respiratory tract caused by HPV, which recur.

Vaginal intraepithelial neoplasia (VaIN) – pre-maligant changes to the skin cells in the area of the vagina.

Vulval intraepithelial neoplasia (VIN) – pre-maligant changes to the skin cells in the area of the vulva.

Women of child bearing potential - All women apart from those who are postmenopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy).

5 Introduction

5.1 Background and Rationale

The best and most cost-effective treatment for patients with anogenital warts is unknown. Genital warts present as lumps in the skin of the anogenital area. While usually painless with occasional irritation or bleeding, they are emotionally distressing, require prolonged, time consuming and uncomfortable treatment, and frequently relapse after apparently successful treatment. Surgery may be required in recurrent or persistent cases. About 90% of genital warts are caused by human papillomavirus (HPV) types 6 or 11, which are sexually transmitted.

There were 129,207 cases of new or recurrent genital warts treated in genitourinary medicine clinics in England in 2010 [(1)], accounting for 21% of all GUM clinic episodes[(2)]. First episode genital warts accounted for 35% of new sexually transmitted infections (STIs) diagnosed and 24% of consultations for STIs, making the infection more frequent than chlamydia. Recurrent episodes accounted for 42% of all episodes of anogenital warts reported. An estimated 7,000 additional cases per year are diagnosed and treated in primary care [(3)]. The cost to the NHS of treating anogenital warts has been estimated recently as about £17million per year, of which over £7m is for recurrent episodes.

Cryotherapy with liquid nitrogen is frequently used to treat anogenital warts, although this treatment requires equipment and facilities usually only available in hospital or specialist community settings, and appropriately trained staff. Effective treatment may be achieved with a single application, but more often requires repeated clinic attendance. Most cases of warts are now treated with self-administered topical agents, of which podophyllotoxin is the most common, with about 50% cases being treated [(4)]. Podophyllotoxin has a chemotherapeutic action believed to be based on prevention of tubulin polymerisation required for microtubule assembly and inhibition of nucleoside transport through the cell membrane, leading to inhibition of growth of virally infected cells. It is available as a solution or a cream although only the latter will be assessed in this trial. The cream (Warticon®, Glaxo SmithKline) includes the active agent at a lower concentration than the solution (0.15% versus 0.5%) but is generally considered to be easier to apply, better tolerated, and with similar efficacy. An alternative topical treatment is imiquimod, but this is more expensive and so usually reserved for second-line therapy. About 10% warts are treated with imiquimod. It is claimed that imiquimod is associated with less recurrence as a result of its unique mode of action as an immune response modifier [(5, 6)]. Imiquimod is available as a 5% cream (Aldara®, Meda). It is a Toll-like receptor (TLR) 7 agonist that acts as an immune response modifier. It directly stimulates tissue macrophages to release interferon-alpha and other cytokines which trigger a local cell-mediated response. Imiquimod has no direct antiviral activity. The treatment response may be slower than for podophyllotoxin. Imiquimod is licensed for a course of up to 16 weeks; most participants will have responded by 8 weeks. These two topical agents have never been compared in an adequately-powered trial [(7, 8)]; a comparison of the efficacy of the two treatments as initial therapy for anogenital warts is the first question addressed in this trial.
The only randomised trial comparing the two topical agents was under-powered trial (n=51) and did not report recurrence rates [(9)]. There were similar clearance rates (75% vs. 72%, 95% confidence

interval 53-98% and 52-86% respectively). A systematic review of wart treatments is currently in preparation by one of the investigators [7], the principal findings of which are reported in recent European guidelines for the treatment of genital warts [10]. The review suggests that podophyllotoxin has a similar rate of initial clearance (43-70% at 4 weeks, compared to 55-81% clearance at 16 weeks for imiquimod), but recurrence rates may be lower with imiquimod (6-26% at 6 months for imiquimod, compared to 6-55% at 8-12 weeks for podophyllotoxin). The review found no evidence of any single therapy being superior overall, largely due to the lack of high-quality comparative studies, with those reported being heterogeneous in design, and with high loss to follow-up. Until this comparison is resolved in randomised studies of sufficient size and robust design it remains impossible to firmly recommend one treatment over the other. National guidelines recommend that the choice of first line therapy be based on patient preference and morphology and distribution of lesions, with a clinic treatment algorithm to monitor treatment success[11]. The guidelines have been updated recently, but not yet published; there is no change in the recommendation on the use of podophyllotoxin or imiquimod (Gilson, personal communication).

The second question is whether the clearance or recurrence rate of genital warts can be improved by vaccination against HPV 6 and 11, initiated at the same time as topical therapy. HPV vaccines are currently licensed to prevent HPV infection and disease including anogenital warts and cancers. Quadrivalent HPV vaccine (qHPV) protects against genotypes 6, 11, 16 and 18, and from September 2012 has been the vaccine used in the national vaccination programme in the UK targeting girls before sexual debut (age 12-13 years)[12].

The potential role of the vaccine as therapy for anogenital warts or as secondary prevention has yet to be determined. While no randomised controlled trial (RCT) evidence exists, evidence that vaccination against HPV may be a valid therapeutic or secondary preventative strategy comes from several sources. Firstly, there are case reports that clearance of anogenital warts may be enhanced by qHPV vaccine[13,14]. Secondly, patients with anogenital warts or genital intraepithelial neoplasia (cervical [CIN], vulval [VIN] or vaginal [VaIN]) are at risk of re-infection with the same or different HPV types, or relapse of existing infection [15,16]. Thirdly, limited evidence from placebo-controlled vaccine trials appears to show that women seropositive but DNA-negative for at least one HPV type at entry were protected against subsequent disease related to the HPV type to which they were previously exposed [17]. Also, women with genital lesions treated surgically while in the vaccine trial were less likely to develop recurrent or progressive disease if they were in the vaccine arm of the trial [18]. Fourthly, preliminary evidence suggests that the qHPV vaccine may reduce recurrences of respiratory papillomatosis (RRP) in children [19], and of anal intraepithelial neoplasia (AIN) [20], both conditions caused by vaccine-type HPVs. Finally, vaccine antibody responses are much stronger than those induced by natural infection[21], so a strategy of priming or boosting anti-HPV 6/11 responses with qHPV vaccine could influence the persistence of HPV 6/11 infection and therefore the rate of disease recurrence.

Studies of the treatment cost and quality of life impact of genital warts, as well as economic analyses of vaccinating against warts have been conducted recently[4, 22, 23]. These studies have documented significant negative impacts on quality of life and substantial health care service costs. The proposed trial will evaluate the relative costs of two of the most frequently used treatments, as well as of the novel use of qHPV vaccination for both treatment and secondary prevention. Imiquimod is now out of patent protection therefore a narrowing of the current large cost differential (approximately 10-fold) compared to podophyllotoxin is anticipated. A re-evaluation of its place as a first line therapy is therefore timely. If the effectiveness of imiquimod proves superior, then an economic analysis would allow an assessment of the cost difference that would warrant its use as first line therapy. All available treatments have significant failure and recurrence rates. By maximising initial response rates and reducing recurrence rates using first-line self-administered treatment for anogenital warts, this trial has the capacity to reduce this health and quality of life burden for patients and improve cost effectiveness, now and in the future. Vaccination could add up to £260 to the cost of treatment based on the full NHS price (the tendered price for the national vaccination programme was substantially discounted). If efficacy is demonstrated, the economic analysis within this project will determine at what point increased treatment costs would be justified by reduced future healthcare costs and improved quality of life related to persistent or recurrent disease.

The adoption of a pragmatic trial design for the comparison of the two topical therapies currently in most frequent use means that the results can be generalised to the large number of health care settings where anogenital warts are treated. The topical therapies assessed and the potential (within the protocol) to use supplementary cryotherapy are closely aligned with current clinical practice.

The trial will provide the first high-quality evidence of the comparative efficacy of the two main topical treatments in current use, as well as the first randomised trial to investigate the potential therapeutic benefit of an HPV vaccine in the management of patients with anogenital warts.

5.1.1 Explanation for choice of comparators

The comparator to the qHPV vaccine is hepatitis A virus (HAV) vaccine in half the control group, and saline in the other half. The use of an active control in half the control group is preferred because it ensures double blinding as half the control recipients may have local reactions or mild systemic symptoms similar to those associated with qHPV vaccine. However some vaccine recipients will not experience any symptoms, so that having a true placebo in half the comparator will not compromise the blinding. It also means that 75% of participants have some potential health gain from their vaccine.

Hepatitis A vaccine has been used as control in a previous large phase III bivalent HPV vaccine study (PATRICIA) [24] in which three doses of HAV vaccine were given in a double blind design.

The reason for using true placebo in half of the control group is, in part, because it is possible that the observed treatment effect of HPV vaccine in anecdotal reports could have been due to a non-specific effect of the adjuvant alone. This will be examined as a secondary outcome, but the power

to determine such a difference in this study will be limited. The other reason is that proposed mechanistic sub-studies examining immune responses would be affected if all comparator patients had received adjuvant.

The dose and schedule of HAV vaccine used (Vaqta Paediatric, SPMSD) is 25 antigen units given as 0.5ml at 0, 2, 6 months, in order to match the volume and schedule of the qHPV vaccine. The licensed paediatric schedule is two doses; the licensed adult schedule is two doses of 50 antigen units. The use of a lower dose, but as three doses mirrors that used previously in the PATRICIA trial [24]. It is also consistent with the licensed combined HAV and hepatitis B vaccine, Twinrix (GSK), which is given as three doses containing 720 ELISA units HAV vaccine, while the monovalent HAV vaccine equivalent, HAVRIX Monodose contains 1440 ELISA units and is given as two doses.

5.2 Objectives

The primary objectives of the trial are:

1. To compare the effectiveness of imiquimod 5% cream versus podophyllotoxin 0.15% cream in the treatment of external anogenital warts. The primary objective will be to compare the proportions of participants receiving each treatment who have complete resolution of warts by 16 weeks and remain free of warts up to 48 weeks after starting treatment.

2. To compare the effectiveness of a course of quadrivalent HPV vaccine started at the same time as topical wart treatment with the two controls groups (active and placebo) combined, in improving wart clearance at 16 weeks and preventing recurrence up to 48 weeks.

3. To estimate the cost-effectiveness of the two topical treatments, taking into account treatment, staff and other healthcare costs of initial and recurrent warts, and reduction in participants' quality of life due to warts.

4. To estimate the cost-effectiveness of a course of quadrivalent HPV vaccine compared with placebo control, taking into account treatment, staff and other healthcare costs of initial and recurrent warts, and reduction in participants' quality of life due to warts.

Given that the cost of imiquimod is currently higher than podophyllotoxin but likely to decrease in future, the price at which it is likely to become cost-effective in comparison to podophyllotoxin will be estimated. If the HPV vaccine is more effective than control vaccine, an additional economic evaluation will be carried out to estimate the price at which it will become cost-effective.

Secondary objectives:

5. To compare wart clearance rate at interim time points corresponding to the end of the prescribed treatment course.

6. To compare the time to wart clearance in those treated with podophyllotoxin versus imiquimod with or without qHPV vaccine.

7. To compare the proportion experiencing wart recurrence/relapse (after wart clearance) at 24 and 48 weeks.

8. To compare the tolerability of all treatments as measured by reported local and systemic reactions and other adverse events, and adherence to treatment.

9. To compare health-related quality of life, as measured by the Area Under the Curve for EQ-5D.

10. To compare the requirements for additional therapy, including extension of the initial topical treatment course, treatment with cryotherapy, or recourse to other agents.

11. To compare the clearance rate in active control (hepatitis A vaccine) versus placebo control (saline vaccine) recipients.

12. To collect and store blood samples (at 0 and 48 weeks) and swab samples from genital wart lesions (at baseline and in the event of recurrence) for laboratory sub-studies, including comparison of HPV types at recurrent disease with initial lesions, and anti-HPV antibody and cell-mediated immune responses. Separate funding will be sought for this work which would be further defined according to the outcome of the main trial.

5.3 Trial Design

The trial is a randomised, controlled partially blinded 2 x 3 factorial design trial of the treatment of anogenital warts, with an accompanying economic analysis. Participants will be allocated in equal numbers to the two topical treatment groups and in a 2:1:1 ratio to the three vaccine groups. Analysis of the primary outcome will be based on logistic regression.

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to UCL CTU.

6.1.1 Trial Setting

The trial will be run at selected genitourinary medicine (GUM) clinics (about 80% of cases of genital warts treated in the NHS are treated in GUM clinics). Up to 30 sites will be invited to take part which can demonstrate that they meet the selection criteria.

6.1.2 Site/Investigator Eligibility Criteria

Site selection criteria will include the anticipated ability of the clinic to recruit patients. Based on wart cases reported from each clinic, it is anticipated that target recruitment will be 25 to 100 participants per clinic, giving an average of 40 participants per site, if 25 sites are activated.

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol and relevant Summary of Product Characteristics (SPC) or Investigator Brochures (where appropriate).

To participate in the HIPvac trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the HIPvac Trial Management Group (TMG) and that are described below.

Trial sites meeting eligibility criteria and that are accepted by the TMG as being suitable to recruit to the trial, will be issued with the HIPvac Trial Master File (TMF) documentation to use when applying for Site-Specific Approval (SSA).

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign a UCL CTU Clinical Trial Agreement or an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to UCL CTU.

6.2 Site approval and activation

The Clinical Trial Authorisation (CTA) for the trial requires that the MHRA is supplied with the names and addresses of all participating site Principal Investigators. Trial staff at UCL CTU will perform this task.

The trial manager or delegate will notify the PI in writing of the plans for site initiation. On receipt of the signed Clinical Trial Agreement, Investigator Agreement, approved delegation of responsibilities log, staff contact details, and any other documents required by the UCL CTU site activation process, written confirmation will be sent to the site PI.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority, and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at UCL CTU.

A list of activated sites may be obtained from the Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

Adult patients presenting to genitourinary medicine clinics with external anogenital warts which, in the opinion of the investigator, could be appropriately treated with either self-administered imiquimod or podophyllotoxin creams.

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

- Age 18 years or over
- Males and females

- First episode or repeat episode of anogenital warts diagnosed clinically
- External anogenital warts considered, in the opinion of the investigator, to be suitable for self-administered topical wart treatment (patients with concurrent internal anogenital warts are still eligible to participate).
- Able to provide informed consent to participate in the trial.

6.3.1.3 Participant Exclusion Criteria

- Previous wart treatment in the last 3 months
- Previous quadrivalent HPV vaccine (previous **bivalent** HPV vaccine is **not** an exclusion criterion).
- Previous intolerance to either of the topical treatments, vaccines or their constituents
- Known HIV-positivity* (HIV testing is not required for the trial).
- Pregnancy or lactation** (current, or planned in the next 6 months)
- Women of child bearing potential[c] not willing to use effective[d] contraception for the duration and 30 days post completion of trial treatment: see above
- Unable or unwilling to complete follow-up procedures
- Lesion area greater than 4 cm^2, requiring treatment under direct supervision of medical staff (in accordance with podophyllotoxin cream Summary of Product Characteristics).
- Patients who have had topical steroids applied to the target area, or systemic steroids or other immunosuppressive agents, within 1 month prior to randomisation
- Patients enrolled in any other trial of an Investigational Medicinal Product, without the permission of the Chief Investigator.
- Any clinical condition which the investigator considers would make the patient unsuitable for the trial, including immunodeficiency conditions.

*If a participant is found to be HIV positive during the course of the trial they should be withdrawn from trial treatments, but still be followed up as per protocol. Treatment should be provided as per standard treatment for HIV patients.

** Podophyllotoxin is contraindicated in pregnancy; the safety of imiquimod and qHPV vaccine in pregnancy is unknown. There are no teratogenicity risks for female partners of males being treated with either of the creams or vaccines.

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

Nursing and medical staff members of the clinical trial team at sites will have the appropriate qualifications to manage participants with genital warts as for routine clinical care. Each member of the trial team at each site will have their roles within the trial, as delegated by the PI, documented in the HIPvac site delegation log. CVs of all staff working on the trial will be collected by UCL CTU to document their qualifications and relevant experience. Protocol specific training will be given to site staff; training must be completed before a site can be activated.

[c] Women of child bearing potential excludes women who are postmenopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy)

[d] Effective contraception defined per MHRA guideline, with the addition of regular and consistent condom use without spermicide (See appendix 2).

6.3.1.5 Co-enrolment Guidance

Participants may not be enrolled in any other trial of wart treatment, or of HPV vaccination during the 48 weeks of the trial. Patients may not be enrolled in any other trial of an Investigational Medicinal Product, without the permission of the Chief Investigator of the HIPvac trial. Co-enrolment on observational studies will be accepted.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed or any blood is taken for the trial. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all participants in the same situation as part of usual standard of care, including examination and the collection of samples for tests for other sexually transmitted infections.

6.4 Interventions

6.4.1 Products

Topical treatment:

All participants will be randomised to receive initial treatment with either imiquimod 5% cream or podophyllotoxin 0.15% cream. Treatment allocation will be open due to the differing dosing regimen and licensed duration of therapy.

- **Imiquimod:** Participants randomised to imiquimod will be asked to apply the 5% cream for three days of the week (every other day). The cream should be applied at the participant's bed time and left on overnight. The cream should be washed off after 6-10 hours.

or

- **Podophyllotoxin:** Participants randomised to the podophyllotoxin arm will be instructed to apply the 0.15% cream to the lesions twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles. The licensed treatment duration is 4 weeks, but it is common practice to extend this period if there is a partial response to therapy.

Participants will be randomised 1:1 to either topical treatment.

Vaccines:

Participants will be simultaneously randomised in a double blind fashion to one of three groups, qHPV vaccine, hepatitis A vaccine or placebo. All recipients will receive three doses at 0, 2 and 6 months. Vaccines are as follows:

- **qHPV vaccine:** Quadrivalent HPV vaccine, Gardasil – Sanofi Pasteur, given according to the licenced schedule at 0, 2, and 6 months; vaccine volume 0.5ml; contains with alum adjuvant.

or

- **Hepatitis A virus (HAV) vaccine:** inactivated whole virus vaccine, containing 25 antigen units in 0.5ml, and containing alum adjuvant (Vaqta - Sanofi Pasteur), as active control.

or

- **Placebo vaccine:** 0.5ml normal saline, as placebo control.

Participants will be randomised in a 2:1:1 ratio to qHPV, HAV and placebo.

Table 1: Interventions received according to the 2 x 3 factorial trial design. Randomisation will be 1:1 between the two topical cream arms and 2:1:1 for qHPV, HAV and placebo

		Topical creams	
		Imiquimod	*Podophyllotoxin*
Vaccines	*qHPV vaccine*	Arm A n=250 Imiquimod cream for 16 weeks; qHPV vaccine at months 0, 2 and 6	Arm B n=250 Podophyllotoxin cream for 4 weeks; qHPV vaccine at months 0, 2 and 6
	HAV vaccine, active control	Arm C n=125 Imiquimod cream for 16 weeks; HAV vaccine at months 0, 2 and 6	Arm D n=125 Podophyllotoxin cream for 4 weeks; HAV vaccine at months 0, 2 and 6.
	Saline, placebo control	Arm E n=125 Imiquimod cream for 16 weeks; placebo vaccine at months 0, 2 and 6	Arm F n=125 Podophyllotoxin cream for 4 weeks; placebo vaccine at months 0, 2 and 6.

6.4.2 Treatment Schedule

Imiquimod: three times per week on alternate days for 16 weeks.

Podophyllotoxin: twice a day for three consecutive days followed by no treatment for 4 days, in weekly cycles, for up to four weeks.

qHPV vaccine or control vaccines: at months 0, 2 and 6.

6.4.3 Dispensing

Topical cream: Imiquimod and podophyllotoxin will be dispensed by the pharmacy in un-blinded packaging using an allocated participant code. It will be labelled using simplified IMP labelling. Its handling and management will be subject to standard procedures of the pharmacy. The cream will be applied by the participant. Instructions for correct application will be given by a member of the trial team at their baseline visit. The patient information will be included when the cream is dispensed; in addition the diary card will also include contact numbers in case of an emergency.

Vaccines: qHPV, HAV vaccine and placebo vaccine will be dispensed by the pharmacy in blinded packaging using pack codes. Handling and management will be subject to standard procedures of the pharmacy. The vaccines will be administered by a trained member of the trial team.

6.4.4 Dose Modifications, Interruptions and Discontinuations

Topical cream: Sites will provide participants with guidance regarding dose and frequency modifications in the event of an adverse event as per standard clinical practice. When advising the participant, sites should refer to Working Practice 1 located in section 10.3 of the HIPvac Investigator Site File (ISF).

Vaccines: If there is a severe reaction to the vaccine, as per standard care, additional doses should not be administered. Participants should still be treated and followed up as per protocol, if willing, omitting any further vaccinations.

6.4.5 Accountability

As all creams and vaccines used in this trial are classed as Investigational Medicinal Products, they will be accounted for in line with MHRA regulations.

Participants will be asked to return all unused IMP(s) that are dispensed and used or unused IMP containers, to the trial pharmacist or delegate at their next follow-up visit. In order to meet regulatory requirements, the number of remaining unopened sachets of imiquimod, and the approximate usage of each tube of podophyllotoxin cream (unused, one quarter used, half-full, three quarters used, or empty) will be recorded. The pharmacist or delegate will be responsible for maintaining and updating the accountability log in the pharmacy file, for all cream and vaccines prescribed, returned and destroyed. The reason for any IMPs or containers that are not returned should be recorded. Cream and vaccine destruction will be conducted in accordance with local pharmacy practice, once authorised by the UCL CTU. This will be documented on the drug destruction log in the pharmacy file. Destruction certificates should be requested by the pharmacy and kept in the pharmacy file. They should be sent to UCL CTU upon request.

6.4.6 Compliance and Adherence

Participants will be provided with a diary card to record their topical treatment administration. This will serve as a reminder and a record of compliance.

Non-attendances at trial visits will be followed-up with a telephone call immediately and, if a visit in person cannot be arranged before the next scheduled visit, all necessary information will be collected by telephone call. Diary cards may be completed electronically. Reminders will include email and SMS messages to participants shortly before their booked appointments, subject to prior agreement (as used at some clinics as part of routine care). Participants will be offered compensation of £20 in the event of attending for follow up at week 16, and £30 for attending at week 48. The compensation will be in the form of a high street voucher. After week 16, further treatment will be offered at the discretion of the investigator, to participants who have persistent or recurrent warts.

Participants will be asked to bring their diary and unused sachets of imiquimod or the used tube of podophyllotoxin to their next clinic visit. From this, the clinic staff will be able to estimate how much cream has been used. This should be recorded in the accountability logs. The diary card will also be reviewed with the participant to assess compliance and ensure the diary card is accurately completed.

6.4.7 Concomitant Care

Additional treatment for anogenital warts, other than cryotherapy after week 4 or extension of the randomised treatment in the case of the podophyllotoxin group, will not be permitted up to 16 weeks. Treatment of any other conditions, not including those listed in the exclusion criteria, should be given as per standard care. Any medications should be recorded in the concomitant medication section of the CRF.

Switch from podophyllotoxin to imiquimod typically occurs in clinical practice when there is non-response to the first agent, but the time until such a switch is variable between centres reflecting differences in local clinic guidelines. Switching between the allocated topical treatments will not be permitted before week 16. Sites will be asked to document any switch occurring in the CRF.

If hepatitis A and B vaccination are clinically indicated, according to standard practice for high-risk groups, vaccinations can be administered as per standard treatment. There are no safety implications associated with using HAV and HBV vaccinations with the trial vaccination. There are no data with regard to an overdose of HAV vaccination. Other vaccinations that are clinically indicated may also be given. If any vaccinations are given, this should be clearly documented in the appropriate CRF.

6.4.8 Overdose of Trial Medication

Participants will be provided with details of topical treatment overdose in the patient information sheet supplied with the topical treatment:

- Imiquimod: Wash the excess cream off using mild soap and water.
- Podophyllotoxin: Wash the excess cream off using mild soap and water. Seek medical advice.

Participants will be provided with details of vaccine overdose by a member of the trial team at the time of vaccine administration:

- HAV vaccine: No data with regard to overdose. For typical side effects see appendix 1.
- qHPV vaccine: Adverse events comparable to single doses of qHPV vaccine, see appendix 1 for a summary of side effects.
- Saline placebo: See appendix 1 for a summary of side effects.

6.4.9 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or have it stopped early for any of the following reasons:

- Unacceptable treatment toxicity or adverse event, as defined in 6.11.3.1
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant
- Pregnancy
- Diagnosis of HIV

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

6.5 Outcomes

6.5.1 Primary Outcomes

The primary outcome is a composite endpoint of wart clearance within 16 weeks of starting treatment and remaining wart-free between 16 and 48 weeks. This will capture both the initial clearance efficacy as well as the impact on relapse or recurrence.

Secondary outcomes:

1. Proportion wart-free at the end of the assigned treatment course (4 or 16 weeks)
2. Proportion wart-free at 16 weeks, with use of additional treatment as required (primary treatment failure)
3. Quantity of additional treatment (number of cryotherapy applications, additional weeks of podophyllotoxin or imiquimod) required to achieve clearance by 16 weeks
4. Proportion wart-free at 24 weeks
5. Proportion wart-free at 24 weeks with use of additional treatment as required
6. Quantity of additional treatment (number of cryotherapy applications, additional weeks of podophyllotoxin or imiquimod) required to achieve clearance by 24 weeks
7. Proportion experiencing wart recurrence/relapse at 48 weeks after wart clearance at 24 weeks
8. Proportion experiencing complete wart clearance
9. Time to complete wart clearance
10. Proportion experiencing wart recurrence/relapse after complete wart clearance
11. Time from complete wart clearance to recurrence/relapse
12. Adverse events
13. Health-related quality of life, as measured by the Area Under the Curve for EQ-5D
14. Symptom scores
15. Total costs of treatment including prescribed agents and clinic visits

6.6 Participant Timeline

6.6.1 Baseline Assessment Visit

After assessing eligibility and obtaining consent, information on the following will be collected: the date of first presentation; dates of previous episodes, and treatment of warts; history of sexually transmitted infections and co-morbidities; history of recent sexual contacts; concomitant medication; and quality of life questionnaire. Baseline assessment will include examination of the anogenital area and documentation of the position and approximate number of warts. The estimated maximum diameter of the largest wart will be recorded as per Working Practice 3 (please refer to section 10.8 of the ISF).

A symptom-directed general physical examination will be performed if appropriate. A blood sample and a swab of the lesions (for HPV DNA) will be taken and stored. Additional blood samples may be taken for participants who have consented to trial sub-studies. For instructions on how to take and process the blood and swab samples, please refer to Working Practice 2 in section 10.3 of the ISF. Randomised treatments will be prescribed/administered and participants will be supplied with information on their use, risks and side-effects. Participants will be offered safer sex advice, free condoms, and access to other sexual and reproductive health services as per routine care. For women of child bearing potential[e], a pregnancy test will be performed. Simple diary cards will be provided for the participant to provide a reminder of when the treatment should be applied, record its use, record if/when warts have cleared and record symptom scores related to the topical treatment. A follow-up appointment will be arranged.

6.6.2 Follow-up Assessment Visits

Routine follow up will be for 48 weeks in total, with visits at 4, 8, 16, 24 and 48 weeks. Further topical treatment will be issued according to the randomisation/reassessment at weeks 4 and 8, vaccine will be administered at weeks 8 and 24. Alternative treatments (i.e. cryotherapy) should only be administered from 4 weeks (visit 2) onwards. If a participant is unable to tolerate the allocated treatment, after dose modifications as appropriate (per working practice 1, in section 10.3 of the ISF), alternative treatment can be administered at the discretion of the investigator. Any alternative treatment prescribed should be recorded in the appropriate CRF. For the purposes of the trial, early use (within 4 weeks of the start of randomised treatment) of alternative treatments and topical treatment switch to the opposite arm before 16 weeks will be considered a primary treatment failure and result in withdrawal of the participant from their randomised topical treatment arm. Participants should continue to be followed up and receive vaccinations as per protocol.

Participants will be encouraged to return to the clinic before their next appointment if they notice a recurrence of their warts, recording the date they first noticed the recurrence in their diary card.

[e] Women of child bearing potential excludes women who are postmenopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy)

Presence of warts will be determined on examination by a member of the trial clinical team at each study visit to confirm clearance/recurrence. Participants will be asked to return to the clinic early if they notice a recurrence so that this can be documented (and the onset timed) and further treatment offered according to standard of care, as above. If warts recur within the first 16 weeks the participant should be prescribed the treatment that they were randomised to at baseline.

After week 16, topical treatment can be changed at the discretion of the investigator, including a switch to the other randomised topical treatment. Any treatment changes must be recorded in the appropriate CRF. Timing of eventual wart clearance will be recorded for the secondary analysis (time to clearance).

Participants will be provided with a diary card to record treatments applied and the date the warts are last seen and/or recur, and if there are additional visits between week 16 and 48 for clinical care, a record of presence/absence of warts will be made.

Assessment at routine visits will include an assessment of treatment response, as reported by the participant, and observed by the clinician, adherence to the treatment regimen, tolerability, quality of life, and the need for additional or extended treatment. Participants will also be asked about work days lost due to clinic visits. Diary cards will be collected. An end of trial blood sample will be collected at week 48, and lesion swab for HPV detection (archive) will be collected in the event of recurrence. An additional blood test may be taken at 16 weeks for participants who have consented to additional blood tests. For instructions on how to take and process the blood and swab samples, please refer to Working Practice 2.

Additional visits will be arranged in the event of recurrences or other indications for additional treatment or review in line with routine clinical practice, or if significant adverse events occur that require medical assessment.

6.6.3 Further Treatment

In those participants randomised to the podophyllotoxin group, further podophyllotoxin cream can be prescribed if there is persistence of warts at week 4, with treatment continued up to week 16. Treatment provided up to week 16 will be classed as IMP.

At weeks 16, 24 and 48, or at any intervening time point in the event of patient attendance, further treatment will be provided at the discretion of the investigator if persistent/recurrent warts are present. This could involve continuation of the randomised treatment, but usual clinical practice would be to switch to an alternative at this time on the basis of a lack of response. Participants on imiquimod might therefore be switched to podophyllotoxin and vice versa. Details of any switch in treatments should be carefully documented in the appropriate CRF, according to site working practice instructions.

Any topical wart treatment received after week 16, and any treatment given earlier which is not the randomised treatment will **not** be classed as an IMP. Such treatments will be supplied from routine clinic stock and will not require trial labelling. There will be no requirement for the participant to return any unused or partially used containers of these treatments for accountability purposes, but a record of the treatment used should be recorded in the CRF.

Safety reporting should continue, to take into account the fact that participants will also be receiving one of the vaccines, but a causality assessment should still take place for the creams if they are being provided as standard treatment.

Alternatively participants may be offered treatment with other ablative therapies (for example cryotherapy or excision). The same discretion as to which treatment can be offered would apply to participants whose warts had cleared before or after week 16, and who then experience a recurrence up to week 48.

Table 2: Baseline and follow up assessments and procedures

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**Extra visits**
Week	**0 (baseline)**	**4**	**8**	**16**	**24**	**48**	**if warts recur**
Give PIS and go through trial with participant	x						
Check eligibility, complete and sign Consent Form	x						
Randomisation	x						
Record wart treatment	x	x	x	x	x	x	x
Review and record concomitant medication	x	x	x	x	x	x	x
Examine and record approximate number and location of warts/the absence of warts	x	x	x	x	x	X	x
Symptom-directed general examination	x						
Urine pregnancy test (βhCG) (women of child bearing potential only[f])	x	x*	x*	x*	x*	x*	x*
Quality of life questionnaire	x	x	x	x	x	x	x
Assessment of tolerability		x	x	x	x	x	
Assessment of Adverse Events (and pregnancy)	x	x	x	x	x	x	x
Assessment of treatment response and need for additional / altered treatment		x	x	x	x	x	x
Lesion swab for HPV detection (all participants, samples to be archived)	x						x
Blood sample for plasma (all participants, samples to be archived)	x					x	
Blood sample for peripheral blood mononuclear cells (subset of 120 consenting participants)	x			x			
Supply trial wart treatment	x	x	x				
Supply/apply additional/alternative wart treatment if required and as permitted in the protocol		x	x	x	x	x	x (from week 4 onwards)
Vaccination	x		x		x		
Provide diary card for self-treatment and self-examination record	x	x	x	x	x		
Collect/review diary card		x	x	x	x	x	x
Completion/review of electronic trial documentation	x	x	x	x	x	x	x
* Pregnancy test to be completed, if the participant has not adhered to using effective contraception[g] and is being prescribed any trial topical treatment.							

[f] Women of child bearing potential excludes women who are postmenopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy)

6.6.4 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the schedule in table 2. They should be encouraged and facilitated to continue with trial follow up, even though they no longer take the trial treatment. If, however, the participant indicates that they no longer wish to be followed up, this must be respected and the participant withdrawn from further follow up. UCL CTU should be informed of the withdrawal in writing using the appropriate HIPvac trial CRF. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Participants who stop trial follow-up early will be replaced only if they have not yet received any of the allocated treatments.

6.6.5 Participant Transfers

If a participant moves from the area making continued follow up at their consenting site inappropriate, every effort should be made for them to be followed up at another participating trial site. Written consent should be taken at the new site and then a copy of the participant's CRFs should be provided to the new site. Responsibility for the participant remains with the original consenting site until the new consent process is complete.

6.6.6 Loss to Follow-up

Every effort should be made to minimise loss to follow-up as these are a threat to the integrity of the trial. Procedures to minimise loss are detailed in section 6.4.6 and 6.8.2.

6.6.7 Trial Closure

Trial closure is defined as the date when all data having been received, cleaned and all queries resolved at all sites.

6.7 Sample Size

The trial will recruit 1000 participants with equal numbers randomised to each of the two topical cream arms and a ratio of 2:1:1 for the three vaccine groups in a 2x3 factorial design, so that allowing for 20% loss to follow-up 800 participants will contribute primary outcome data. For the primary endpoint analysis, the two control groups (HAV vaccine and placebo vaccine) will be combined, giving 4 groups. The anticipated proportion achieving the primary endpoint in the less favourable topical treatment group is 35%, assuming a wart clearance rate of 50% within 16 weeks and a 30% subsequent recurrence rate. The proposed sample size provides 80% power (at the 5% significance level) to detect an increase to 45% with the better treatment. This sample size also provides 80% power to detect an increase from 35% to 45% in the primary endpoint from vaccination, as would arise if vaccination reduces the recurrence rate from 30% to 10% whilst leaving the wart clearance rate unchanged at 50%.

[g] Effective contraception defined per MHRA guideline, with the addition of regular and consistent condom use without spermicide (See appendix 2).

6.8 Recruitment and Retention

6.8.1 Recruitment

Participants will be recruited from selected GUM clinics, as detailed in section 6.1.1, by trained trial doctors or nurses present on the trial delegation log. Participants will be approached after it has been confirmed that they have genital warts and meet the eligibility criteria.

6.8.2 Retention

If participants do not attend for protocol follow-up visits they will be contacted immediately by a member of the trial team to arrange a further appointment. If they cannot attend, follow-up information will be obtained over the telephone.

It is recognised that loss to follow up is a threat to the integrity of the trial. Participants will therefore be offered compensation of £20 if they attend the follow up at week 16, and £30 for attending at week 48. The compensation is in the form of a High Street voucher.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

Participants will be allocated in equal proportions to the two topical cream arms but in a ratio of 2:1:1 to the vaccine arms, with twice as many receiving qHPV as either HAV vaccine or placebo (see Table 1 above) using minimisation with a random element, with gender (male vs female), previous occurrences of warts (no previous occurrences vs one or more previous occurrences) and site as stratification factors.

A participant identification number and the trial arm allocation, as detailed above, will be computer generated by a randomisation service provider (Sealed Envelope) accessed by the investigator through a password-protected, secure web-based system. To enrol and randomise a participant the investigator will be required to enter the participant's initials, date of birth, and confirmation that they meet the eligibility/exclusion criteria. The allocation to topical treatment is not blinded so the investigator will write the allocated cream on a prescription for the participant to take to pharmacy for dispensing. Randomisation procedures should take place immediately prior to dispensing study supplies and during pharmacy opening hours.

6.9.1.2 Allocation concealment mechanism

Allocation to the vaccine arms will be blinded. Blinded trial vaccine supplies will be labelled with pack numbers by Sanofi Pasteur MSD. The list of pack numbers with the key will be provided to Sealed Envelope by the SPMSD. The randomisation system will issue the relevant pack number to be dispensed based on the randomisation group and the register of packs supplied to each site. Full accountability will be maintained from receipt of trial treatments in pharmacy, through dispensing and return of trial containers or packs and to destruction of unused trial treatments. The pharmacist, clinic staff and participant will be blind to the allocated vaccine.

6.9.1.3 Allocation Implementation

The responsibility for enrolling participants and prescribing trial treatments lies with the PI. Eligibility decisions will be made in line with the approved protocol. Other physicians employed at the same clinical site may enrol and prescribe trial treatments to participants only if they have received appropriate training on the trial and appear on the HIPvac Trial Delegation log, approved by the PI. The randomised treatment allocation will be generated by Sealed Envelope as described in 6.9.1.1. Members of the trial team will not have access to the randomised vaccine treatment.

6.9.2 Blinding

Sealed Envelope will provide the randomised cream and allocated vaccine pack code, through the Sealed Envelope internet based randomisation service, to the trained member of the trial team performing the randomisation. The blinding of the vaccines will be performed by Sanofi Pasteur MSD which will ensure blinding of the qHPV vs control vaccine/placebo to all investigators, participants and the dispensing pharmacy staff on the trial. The labelling strategy ensures that the unblinding of one participant will not unblind the entire trial arm.

The podophyllotoxin vs imiquimod portion of the trial will be open-label, and all participants, physicians, and members of the trial team will be aware of the participant's treatment assignment. It is not deemed feasible to blind those assessing trial outcomes, and so they will be aware of the participant's treatment assignment.

6.9.3 Emergency Unblinding

The IMPs in this trial are licensed products used in routine clinical care or prevention. Only the vaccines are blinded and these are in world-wide use for population level prevention programmes. It is not anticipated that there will be a need for unblinding in an emergency situation. It is anticipated that for the majority of instances, appropriate clinical management can proceed without unblinding, as the management of an SAE would be the same regardless of the vaccine that the participant received. Unblinding is likely only to be required in association with a Suspected Unexpected Serious Adverse Reactions (SUSAR). In order to minimise any risks to participants, site PIs will be provided with password-protected access to the Sealed Envelope website to enable them to unblind a participant under follow-up at their site. This should only be used when information on the treatment allocation is essential for a participant experiencing a Serious Adverse Event (SAE). Wherever possible, UCL CTU staff will be available for discussion of the process prior to unblinding, this will include access to a clinical opinion if required. The appropriate adverse event reporting procedures should be followed and details of any unblinding should be documented.

The Chief Investigator and the UCL CTU should be informed of the reason why emergency unblinding was considered necessary. Early unblinding will not be permitted solely at the request of the participant. All participants will be unblinded when data have been analysed.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

Data will be collected by the investigator or delegate on the appropriate CRF or questionnaire. All trial staff completing or correcting CRFs or questionnaires should be delegated this function by the PI on the HIPvac trial specific delegation log. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the person making the alteration. The CRF/questionnaire should be sent to UCL CTU for entry into the trial database preferably by scanning the document and e-mailing it to the HIPvac specific CTU e-mail address: hipvac@ucl.ac.uk. Copies of the paper CRF can also be posted to UCL CTU, if required. Post relating to the trial should be sent to:

HIPvac Trial Manager
Clinical Trials Unit
UCL
Gower Street
London
WC1E 6BT

At each visit, the presence of warts will be recorded in the visit CRF. Participants will also record wart clearance and recurrence on their diary card which will be collected at each visit.

Additional treatment will be captured on a visit CRF. Adverse events will be captured on an adverse event CRF.

Quality of life will be assessed and recorded on the EuroQoL EQ-5D-5L questionnaire.

6.10.2 Non-Adherence and Non-Retention

Follow-up of participants in person after clearance of warts may be difficult. Trial team members should attempt telephone follow-up to confirm the clearance of the warts by the participant, if they fail to attend follow-up assessment visits. The reason for loss to follow-up and subsequent management, including presence/absence of warts and additional treatment, will be recorded where possible. Attempts to obtain this information will be made by telephone and/or notes review and recorded in the appropriate CRF as detailed in 6.6.6.

Withdrawal of consent will be documented in the Withdrawal CRF. Once consent has been withdrawn follow-up will cease.

Reasons for topical treatment discontinuation will be recorded by the participant in their diary. The diary and reasons for discontinuation will also be discussed with a member of the trial team at the next follow-up visit.

Participants will be asked to contact their trial team if they experience any problems and advice will be given as to how to adjust the dose of cream to limit the side effects if appropriate. Dose

modifications will be recorded by site trial staff in the appropriate CRF. Data on wart presence will be recorded for all participants being followed up as per protocol.

If a participant does not receive one of the scheduled vaccinations and is not re-scheduled within the one week window the non-adherence should be recorded on the appropriate CRF. The participant can receive their next vaccination at the next scheduled visit, even if a vaccine is not scheduled. For example, if the week 8 vaccination is missed, the vaccine can be given at week 16 or if the week 24 vaccine is missed it can be given at week 48. Every effort should be made for the participant to complete their vaccination course.

6.10.3 Data Management

Once the paper CRFs have been completed by the site and send to the CTU, they will be entered into the HIPvac database by the HIPvac Trial Manager or delegate. The database will contain validation checks to promote data quality.

The data that is sent to UCL CTU should only contain the participant identification number (PID), date of birth and initials as identifiers. Only members of the HIPvac Trial Team will have access to the inbox. Sites posting CRFs to UCL CTU should address the envelope to the HIPvac Trial team.

6.10.4 Statistical Methods

6.10.4.1 Statistical Methods – Outcomes

Analysis will be by intention-to-treat (where participants are analysed according to the treatment arm to which they were randomised), and will include all participants for whom an outcome is observed. The primary analysis for both factors (podophyllotoxin vs imiquimod, and qHPV vs control vaccines) will be based on comparisons at the margins of the 2 x 2 table (combining the two control vaccine arms HAV vaccine and placebo - Table 1), meaning all participants randomised to podophyllotoxin will be compared with all participants randomised to imiquimod, and all participants randomised to qHPV vaccine will be compared with all participants randomised to HAV vaccine/placebo.

We do not anticipate a substantial interaction between topical treatment and vaccination. However, as a secondary analysis, we will perform an interaction test between the two factors, and present results from a six-arm analysis (where each of the six treatment groups is regarded as a separate treatment arm), as is recommended for factorial trials [25,26].

The primary outcome (the composite endpoint of wart clearance within 16 weeks of starting treatment and remaining wart-free between 16 and 48 weeks) will be analysed using a logistic regression model, and will be adjusted for gender, previous occurrence of warts, and site as stratification factors [27,28], and will include both treatment factors (topical treatment and vaccination) as covariates.

Multiple [29] imputation using chained equations will be used to account for missing follow-up visits. Data will be imputed separately within each treatment group. The imputation model will include the

presence of warts at weeks 4, 8, 16, 24, and 48, gender, and previous occurrence of warts and indicators of recorded compliance problems with the initially allocated treatment, second-line treatment applied, or unscheduled visits during follow-up. The number of imputations will be specified in the statistical analysis plan. Imputation results will be combined using Rubin's rules. Participants who do not attend any follow-up visits will be excluded from the analysis.

Treatment effect estimates, 95% confidence intervals, and two-sided p-values will be reported for each outcome measure.

A detailed statistical analysis plan will be written prior to final analysis.

6.10.4.2 Economic evaluations

Economic outcomes will be collected in the same way as previous studies by the investigators [4]. Health-related quality of life will be assessed using the EuroQol EQ-5D-5L. Information on types of treatments given, staff attending and number of visits made will be collected. These will be combined with unit costs from standard NHS sources as well as previous economic studies [4] to evaluate treatment costs. Clinical, quality of life and cost data will be used to assess the relative cost-effectiveness of alternative treatment options, with or without vaccination. Cost-effectiveness analyses will be conducted according to the reference case used by the National Institute for Health and Care Excellence to ensure comparability with other economic evaluations.

6.10.4.3 Additional Analyses - Subgroup

Two planned subgroup analyses will be performed for gender (male vs. female), and previous occurrences of warts (no previous occurrences vs. one or more previous occurrences). Subgroup analyses will be performed for the primary outcome only, by adding interaction terms to the model for the primary outcome. This will consist of four interaction terms:

- topical treatment and gender
- topical treatment and previous occurrences of warts
- vaccination (HPV versus control) and gender
- vaccination (HPV versus control) and previous occurrences of warts

Further subgroup analyses will only be performed if one or more of these interaction terms are found to be statistically significant ($P<0.05$).

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

The Trial Steering Committee will convene an independent Data Monitoring Committee (IDMC) consisting of a clinician with expertise in HPV disease, a clinical trialist and a statistician. No member

of the IDMC will be an investigator linked to the trial. The IDMC will receive safety and efficacy reports and advise the TSC on the continuation of the trial.

Further details of the roles and responsibilities of the IDMC including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the HIPvac IDMC Terms of Reference (ToR).

6.11.2 Interim Analyses

No formal interim analysis is planned, but periodic reports concerning participant safety and key outcomes will be prepared for the IDMC. The IDMC may request an interim analysis if a report raises concerns.

6.11.3 Data Monitoring for Harm

All adverse events will be recorded by site staff and reported to UCL CTU as detailed in 6.11.3.4 and 6.11.3.5.1. A trained member of the trial team will report the events, according to the reporting timelines detailed in 6.11.3.5.2. Additional notifiable events are stated in 6.11.3.2.

6.11.3.1 Safety reporting

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

Table 3: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***
Suspected Unexpected Serious	A serious adverse reaction, the nature of severity of which is **not**

Adverse Reaction (SUSAR)	**consistent** with the known potentially expected events associated with the applicable trial treatment. The event is evaluated as having a possible, probable or definite relationship to a trial treatment **and** is unexpected for that trial treatment.

* the term life threatening here refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction)

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial treatment administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial treatment administration.)
- continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment

Adverse events do NOT include:

- Local reactions to topical treatment or vaccinations
- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Overdose of medication without signs or symptoms
- Complications of standard therapy that are prescribed in addition to investigational trial treatments
- Elective abortions

6.11.3.2 Other Notifiable Adverse Events

Pregnancy

Participants will be reminded during the trial of the importance of avoiding pregnancy. Female participants of child bearing potential should use effective contraception for the duration and for 30 days post completion of trial treatment. If a participant becomes pregnant whilst on treatment they will be withdrawn from further treatment as part of the trial. If a participant does become pregnant while on treatment, this needs to be reported as a Notifiable Adverse Event (NAE) in the same way as an SAE, and immediately of awareness at site. At the end of the trial participants will continue to have specialised follow-up at an appropriate clinic. Should it become apparent that a participant has conceived whilst on trial treatment then this may be brought to the attention of the general practitioner and local obstetric services.

Follow-up of pregnancy

Pregnancies will be followed up until birth, and the pregnancy outcome reported on a pregnancy outcome form. Participants should be asked to contact the research nurse if they become pregnant at any time whilst on in the trial. Pregnancy follow-up will be closely monitored using the trial database. The trial team at UCL CTU will regularly check the database for pregnancy outcome forms that have not been received within 10 months of notification of pregnancy. In the event of an outstanding pregnancy outcome form a request for the form will be sent, as a matter of urgency, to the site. If there is no response to the query within the timelines given, UCL CTU will perform a triggered on site monitoring visit. Participants should be aware that if their last vaccine dose is delayed to week 48, they should monitor for safety events and pregnancies for 30 days after the date of receipt of the vaccine. Any pregnancies or safety events should be reported to the research nurse immediately. The research nurse may contact the participant to check for any safety events or pregnancies.

In the event of spontaneous abortion, this should be reported as a separate serious adverse event and causality and expectedness assessed by the PI or medical delegate. This can also be reported as a resolution to the original pregnancy report, but it must also be reported separately as a new event.

In the event of elective abortion, this does not need to be reported as an SAE. The site staff should document all details of a participant's pregnancy, reporting and follow-up and details of any forms sent to UCL CTU including the pregnancy outcome form, in the source notes.

6.11.3.3 Procedures to follow in the event of female participants becoming pregnant

Participants, who become pregnant on the trial, should be withdrawn from treatment. Further treatment will be according to local procedures. The participant should continue to be followed up as detailed above.

6.11.3.4 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the participant's medical notes. They should then be reported in the AE CRF and sent to UCL CTU within 7 days. SAEs and SARs should be notified to UCL CTU immediately.

6.11.3.4.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 3. If the event is classified as 'serious' then an SAE form must be completed and UCL CTU notified immediately.

6.11.3.4.2 Severity or grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the Common Terminology Criteria for Adverse Events (CTCAE):

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.11.3.4.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 4.

Table 4: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to	SAR

	suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment, and treatment is discontinued, interrupted or the dose modified, refer to the relevant Interventions sections of the protocol.

6.11.3.4.4 Expectedness

If there is at least a possible involvement of the trial medications (including any comparators), the investigator and UCL CTU must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the current IB or SPCs, or one that is more frequently reported or more severe than previously reported. See appendix 1 for a list of expected toxicities associated with the treatments being used in this trial. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) MHRA and REC reporting guidelines apply (see Notifications sections of the protocol).

6.11.3.5 Notifications

6.11.3.5.1 Notifications by the Investigator to UCL CTU

UCL CTU must be notified of all SAEs immediately of the investigator becoming aware of the event.

Investigators should notify UCL CTU of any SAEs and other Notifiable Adverse Events (NAEs), as defined in section 6.11.3.2, occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to UCL CTU until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (**https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/**).

The SAE form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to UCL CTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the patient identification number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the trial team at UCL CTU on:

hipvac@ucl.ac.uk

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to UCL CTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by participant identification number, date of birth and initials only. The participant's name should never be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

6.11.3.5.2 UCL CTU responsibilities

Medically qualified staff at UCL CTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The delegated staff at UCL CTU will review the assessment of expectedness and, based on possible wider knowledge of the reference material for the treatment or comparator, and after discussion with the CI, may over-rule the investigator assessment of expectedness for the purposes of onward reporting.

UCL CTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs to the regulatory authorities (MHRA) and the RECs as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within seven days of UCL CTU becoming aware of the event; other SUSARs must be reported within 15 days.

UCL CTU will keep investigators informed of any safety issues that arise during the course of the trial.

UCL CTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the HIPvac trial are based on the standard UCL CTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.11.4.2 Central Monitoring at UCL CTU

UCL CTU staff will review CRFs for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the HIPvac trial Data Management Plan.

6.11.4.3 Quality Management and Monitoring Plan

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the HIPvac Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports.

6.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the UCL CTU trial oversight policy.

In multi-site trials this oversight is considered and described both overall and for each recruiting site by exploring the trial dataset or performing site visits as described in the HIPvac Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.2 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, UCL CTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.3 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its independent Chair.

6.11.4.4.4 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to UCL CTU.

7 Ethics and Dissemination

7.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the

treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Competent Authority Approvals

This protocol will be submitted to the UK Regulatory Authority (MHRA).

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the Competent Authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices.

7.3 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the local R&D approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to UCL CTU before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the UCL CTU Protocol Review Committee.

7.4 Protocol Amendments

Approval for substantial amendments to the Protocol will be sought by the trial team at UCL CTU from the REC and the appropriate regulatory bodies. Approved protocol amendments will be communicated by the Trial Team at UCL CTU to all investigators.

7.5 Consent

Patients will be provided with an information sheet and given time to read it fully. After a discussion with a medically qualified investigator or suitably trained and authorised delegate, and when all questions have been satisfactorily answered, written informed consent will be obtained, if the patient agrees to participate. In order to avoid delay in providing treatment, provision of information about the trial, consent and initiation of treatment/vaccination may all be undertaken at the same clinic visit. However, where a patient prefers to have longer to consider the trial, information about the trial may be provided and consent and initiation of treatment may be delayed until a later date. Participation in the trial should not be a cause of undue delay in providing treatment.

For non-native speakers, an interpreter may be provided by the clinical service to assist with routine clinical care. In this event, they may assist the potential participant in understanding the information provided about the trial. The interpreter must not have any conflicts of interest i.e. must not be a member of the trial team or related to the participant. Any illiterate patients/participants will be

given assistance by a member of staff at the site who is not involved in the trial or in the patients/ participant care.

During the consent process it will be made completely and unambiguously clear that the patient is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use. A copy of the approved consent form is available from the UCL CTU trial team.

7.5.1 Consent or Assent in Ancillary Studies

Selected participants may be asked to consent to additional blood tests in their main trial consent for future research into immune responses to HPV.

Participants will be asked to consent to being contacted in connection with continued follow-up beyond 48 weeks, should the trial be extended.

7.6 Confidentiality

Paper copies of personal trial data will be kept at the participating site in a secure location with restricted access. Only non-identifiable data will be kept at the UCL CTU office with only authorised UCL CTU staff members having access. Only staff working on the trial will have password access to this information.

Confidentiality of participant's personal data is ensured by not collecting participant names on CRFs that will be sent to UCL CTU and storing the data in a pseudonymised fashion at UCL CTU. At trial randomisation the participant will be issued a participant identification code and this will be the primary identifier for the participant, with secondary identifiers of date of birth and initials.

The participant's consent form will carry their name and signature but these will be kept at the trial site (participant's hospital) and not with the participant's data at the UCL CTU. The patient consent forms will only be accessed by UCL CTU staff for purposes of monitoring the consent procedure at the site.

Trial specific blood samples will be labelled with only participant ID, date of birth and initials.

7.7 Declaration of Interests

The investigators named on the protocol will each sign a declaration of interests statement as part of the HIPvac Trial Management Group Terms of Reference.

7.8 Archiving

The investigators agree to archive and/or arrange for secure storage of HIPvac trial materials and records for a minimum of 10 years after the close of the trial unless otherwise advised by the UCL CTU.

7.9 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG with permission from the TSC. Considerations for approving access are documented in the TSC Terms of Reference.

7.10 Ancillary and Post-trial Care

Post-trial care will be as per standard care.

7.11 Publication Policy

7.11.1 Trial Results

Feedback to participating sites will be sent after analysis of the results. Sites will then feedback to participants and staff involved in the trial directly, or through publication of the results according to local procedure.

Release of information will be timed to coincide with the first public presentation of the findings at a scientific conference.

Publication, initiated at the same time as submission to conferences will be in peer reviewed journals with general readership to ensure an impact on those working in primary care as well as specialist centres. The results will be submitted to the guidelines group at British Association for Sexual Health and HIV (BASHH) to ensure they are considered in reviews of the national treatment clinical guidelines.

The findings of the vaccine aspect of the research will be submitted to the sub-committee of the Department of Health Joint Committee on Vaccination and Immunisation (JCVI) or other policy groups which review HPV vaccine policy.

The institutions leading the research (UCL, PHE, University of York and Homerton University Hospital) will publicise the presentation and publication of the trial findings through their media streams (institutional websites, press releases etc.). The results of the trial will be disseminated regardless of the direction of effect.

7.11.2 Authorship

The TMG will nominate a writing group, which will consist of members of the TMG and will be responsible for drafting the manuscript for publication. These individuals will be named on the final publication.

7.11.3 Reproducible Research

If the public request access to HIPvac trial information, a request must be sent to the TSC. The request can be forwarded to hipvac@ucl.ac.uk .

8. Indemnity

University College London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

9 Ancillary Studies

No ancillary studies have been finalised. Collection and archiving of samples to allow ancillary studies is included in the main protocol. Ancillary study proposals will be subject to separate review and approval.

10 Protocol Amendments

This is the first version of the protocol and therefore there have not been any amendments.

11 References

1. HPA. Sexually transmitted infections in England, 2011. London, UK: Health Protection Agency, 2011.

2. HPA. Total number of STI diagnoses & other episodes of care seen at genitourinary medicine clinics in England: 2009 - 2011. London, UK: Health Protection Agency, 2012.

3. HPA. Infection reports. HIV-STIs. Genital Warts. . London, UK: Health Protection Agency, 2011.

4. Woodhall SC, Jit M, Soldan K, Kinghorn G, Gilson R, Nathan M, et al. The impact of genital warts: loss of quality of life and cost of treatment in eight sexual health clinics in the UK. Sex Transm Infect. 2011;87(6):458-63.

5. Moore RA, Edwards JE, Hopwood J, Hicks D. Imiquimod for the treatment of genital warts: a quantitative systematic review. BMC Infect Dis. 2001;1:3.

6. Arany I, Tyring SK, Stanley MA, Tomai MA, Miller RL, Smith MH, et al. Enhancement of the innate and cellular immune response in patients with genital warts treated with topical imiquimod cream 5%. Antiviral Res. 1999;43(1):55-63.

7. Woodhall SC, Lacey CJ. Systematic review of treatment for anogenital warts. 2012; Manuscript in preparation.

8. Yan J, Chen SL, Wang HN, Wu TX. Meta-analysis of 5% imiquimod and 0.5% podophyllotoxin in the treatment of condylomata acuminata. Dermatology. 2006;213(3):218-23.

9. Komericki P, Akkilic-Materna M, Strimitzer T, Aberer W. Efficacy and safety of imiquimod versus podophyllotoxin in the treatment of anogenital warts. Sex Transm Dis. 2011;38(3):216-8.

10. Lacey CJ, Woodhall SC, Wikstrom A, Ross J. European guideline for the management of anogenital warts. J Eur Acad Dermatol Venereol. 2012;Mar 12. doi: 10.1111/j.1468-3083.2012.04493.x. [Epub ahead of print].

11. BASHH. United Kingdom National Guideline on the Management of Anogenital Warts, 2007. London, UK: British Association for Sexual Health and HIV, 2007.

12. Kmietowicz Z. UK will use Gardasil in its HPV vaccination programme from next September. BMJ. 2011;343:d7694.

13. Venugopal SS. Recalcitrant cutaneous warts treated with recombinant quadrivalent human papillomavirus vaccine (types 6, 11, 16, and 18) in a developmentally delayed, 31-year-old white man. Arch Dermatol. 2010;146(5):475-7.

14. Lee HJ. Condyloma accuminatum treated with recombinant quadrivalent human papillomavirus vaccine (types 6, 11, 16, 18). J Am Acad Dermatol. 2011;64(6):e130-2.

15. Hogewoning CJ, Bleeker MC, Van Den Brule AJ, Voorhorst FJ, Snijders PJ, Berkhof J, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. Int J Cancer. 2003;107:811-6.

16. Bleeker MC, Berkhof J, Hogewoning CJ, Voorhorst FJ, van Den Brule AJ, Starink TM, et al. HPV type concordance in sexual couples determines the effect of condoms on regression of flat penile lesions. Br J Cancer. 2005;92(8):1388-92.

17. Olsson SE, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Hum Vaccin. 2009;5(10):696-704.

18. Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. BMJ. 2012;344:e1401.

19. Fromm T, Stőlzel K, Gross M, Schädlich L, Kaufmann AM, Albers AE. Laryngeal papillomatosis: immunological and clinical responses to HPV and vaccination. 27th International Papillomavirus Conference and Clinical Workshop; September 17-22, 2011; Berlin, Germany2011.

20. Goldstone SE, Vuocolo S. A prophylactic quadrivalent vaccine for the prevention of infection and disease related to HPV-6, -11, -16 and -18. Expert Rev Vaccines. 2012;11(4):395-406.

21. Rose RC, Reichman RC, Bonnez W. Human papillomavirus (HPV) type 11 recombinant virus-like particles induce the formation of neutralizing antibodies and detect HPV-specific antibodies in human sera. J Gen Virol. 1994;75:2075-9.24.

22. Desai S, Wetten S, Woodhall SC, Peters L, Hughes G, Soldan K. Genital warts and cost of care in England. Sex Transm Infect. 2011;87(6):464-8.

23. Jit M, Chapman R, Hughes O, Hong Choi Y. Comparing bivalent and quadrivalent human papillomavirus vaccines: economic evaluation based on transmission model. BMJ. 2011;343:d5775.

24. Jorma Paavonen, David Jenkins, F Xavier Bosch, Paulo Naud, Jorge Salmerón, Cosette M Wheeler, Song-Nan Chow, Dan L Apter, Henry C Kitchener, Xavier Castellsague, Newton S de Carvalho, S Rachel Skinner, Diane M Harper, James A Hedrick, Unnop Jaisamrarn, Genara AM Limson, Marc Dionne, Wim Quint, Bart Spiessens, Pascal Peeters, Frank Struyf, Susan L Wieting, Matti O Lehtinen, Gary Dubin, for the HPV PATRICIA study group, Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007; 369: 2161-2170.

25. McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: a systematic review. JAMA. 2003 May 21;289(19):2545-53.26.

26. Kahan BC. Bias in randomised factorial trials, Stat Med. 2013; 32, 4540-4549.

27. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med. 2012 Feb 20;31(4):328-40. doi: 10.1002/sim.4431. Epub 2011 Dec 4.

28. Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. BMJ. 2012 Sep 14;345:e5840. doi: 10.1136/bmj.e5840.

29. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011 Feb 20;30(4):377-99. doi: 10.1002/sim.4067. Epub 2010 Nov 30.

12 Appendices

Appendix 1: Summary of Side effects

Note: Use of the word "site" in the tables below refers to an anatomical site.

Cream	Very Common (≥1/10)	Common (≥1/100 to <1/10)
Imiquimod	Application site pruritus	Infection
	Application site pain	Headache
	Application site redness	Nausea
	Application site erosion	Myalgia
	Application site excoriation/flaking/scaling	Application site burning
	Application site oedema	Application site irritation
		Fatigue
Podophyllotoxin	Skin erosion	
	Application site erythema	
	Application site Pruritus	
	Application site burning	

Vaccine	Very Common (≥1/10)	Common (≥1/100 to <1/10)
qHPV (Gardasil)	Headache	Nausea
	Erythema, pain, swelling at the injection site	Pain in extremity
		Pyrexia Hematoma, pruritus at the injection site
Hepatitis A (Vaqta)	Injection site pain, erythema, tenderness	Headache
		Injection site erythema and swelling, warmth, bruising and ecchymosis
		Irritability
		Fever
Placebo (saline)	Local discomfort at the site of injection	

Appendix 2: Effective contraception

1. Established use of oral, injected or implanted hormonal methods of contraception.
2. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
3. Female condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
4. Regular and consistent use of male condoms.
5. Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
6. True abstinence: When this is in line with the preferred and usual lifestyle of the subject.

These are according to MHRA guidelines with the addition of regular condom use alone (the MHRA guidelines specify condoms require to be used with spermicide[h])

[h] http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033037.pdf