CLINICAL STUDY PROTOCOL
(ICTU ADOPTED)

Study Title: Nonavalent prophylactic HPV vaccine (GARDASIL® 9) after local conservative treatment for cervical intra-epithelial neoplasia (CIN): a randomised controlled trial – The NOVEL trial

Protocol Number: C/39/2018

Product: Gardasil® 9 vaccine
Development Phase: III

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Version Number	Date Effective	Reason for update
4.0	21/01/2021	Update to long-term-follow up details Clarification of sample terms Inclusion of option interview specifics
4.1	24/03/2021	Updated flowchart
5.0	04/02/2022	Updated recruitment numbers to 1090
6.0	09/05/2022	Updated recruitment numbers to 1099
7.0	16/01/2023	Update to wording regarding sending 30-month samples. Addition of an option to send vouchers to participants as an incentive for returning self-samples.
8.0	03/05/2023	Protocol has been updated to include a new secondary HPV infection outcome
9.0	19/01/2024	Clarified primary endpoint recurrence, with removal of the non-oncogenic types 6 and 11 that aren't assayable clarified existing endpoints (wrt HPV types)

Version Number	Date Effective	Reason for update
10.0	24/04/2024	Update to stipulate that the main study analysis will commence once all participants have reached the 24 month timepoint, with updated analysis of study data to occur once all 30 month samples have been collected. Protocol has been updated to include a new secondary HPV infection outcome.

This protocol has regard for the HRA guidance

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ABBREVIATIONS

AE	Adverse Event
AGC	Abnormal Glandular Cells
AIS	Adenocarcinoma in situ
ASCH	Abnormal Squamous Cells, cannot exclude high-grade squamous intraepithelial lesions
ASCUS	Abnormal Squamous Cells of Undetermined Significance
BGSC	British Gynaecological Cancer Society
BRC	Biomedical Research Centre
BSCCP	British Society of Colposcopy and Cervical Pathology
ccfDNA	Circulating Cell-free DNA
CEO	Chief Executive Officer
CI	Chief Investigator
CIN	Cervical Intraepithelial Neoplasia
cGIN	Cervical Glandular Intraepithelial neoplasia
CRA	Clinical Research Associate
CRF	Clinical Report Form
CRUK	Cancer Research UK
CSG	Clinical Studies Group
CSR	Clinical Study Report
CTC AE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
dTaP	Combined Vaccine against Diphtheria, Tetanus, and Pertussis,
eCRF	Electronic Case Report Form
EDC	Electronic Data Collection
EFC	European Federation for Colposcopy
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus

HRA	Health Research Authority
HR-HPV	High-Risk Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesion
IARC	International Agency for Research of Cancer
ICHTB	Imperial College Healthcare NHS Tissue Bank
ICTU	Imperial Clinical Trials Unit
ICTU-Ca	Imperial Clinical Trials Unit – Cancer
IDMC	Independent Data Monitoring Committee
IM	Intramuscularly
IMD	Index of Multiple Deprivation
IMP	Investigational Medicinal Product
IPV	Inactivated Polio Vaccine
IR	Incidence Rate
ITT	Intention to Treat
LBC	Liquid-Based Cytology
NCRI-CSG	National Cancer Research Institute, Gynaecological Clinical Studies Group
LSIL	Low-grade Squamous Intraepithelial Lesion
LTFU	Long-Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MSD	Merck Sharp & Dohme
NCRI	National Cancer Research Institute
NICE	National Institute for health and Care Excellence
NIHR	National Institute for Health Research
NOAD	New-Onset Autoimmune Disease
PCR	Polymerase Chain Reaction
PERC	Patient Experience Research Centre
PI	Primary Investigator
PPE	Per Protocol Efficacy
PPI	Patient and Public Involvement
QA	Quality Assurance
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SAE	Serious Adverse Effect
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
US CDC	United States Centre’s for Disease Control and Prevention
VE	Vaccine Efficacy

VLP	Virus-Like Particle
WHO	World Health Organisation

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TRIAL SUMMARY

Title:	Nonavalent prophylactic HPV vaccine (GARDASIL® 9) after local conservative treatment for cervical intra-epithelial neoplasia (CIN): a randomised controlled trial – The NOVEL trial
Objectives:	**Primary Objective** To demonstrate that the nonavalent HPV vaccine initiated at the time of local cervical treatment reduces persistent HPV infection in women treated for high-grade CIN
Design:	Randomised (1:1) controlled multicentre trial with two parallel groups: Gardasil® 9 vaccine versus No vaccine
Study Population	Females aged between 18 and 55 years with presumed or biopsy-confirmed CIN 2, CIN3, glandular intra epithelial neoplasia (cGIN) or adenocarcinoma in situ (AIS)
Sample Size:	1099 (549 Vaccine, 550 Control) Duration: 51 months – Patient Recruitment: 12 months
Eligibility Criteria:	**Inclusion:** o Female (18-55y), attending for local treatment for - presumed CIN2 (cytological and colposcopy impression) OR - presumed CIN3 (cytological and colposcopy impression) OR - presumed cGIN/AIS (cytological and colposcopy impression) OR

	- biopsy-confirmed CIN2 OR - biopsy-confirmed CIN3 OR - biopsy-confirmed cGIN/AIS o Written informed consent obtained from the subject prior to enrolment o Free of other relevant health problems as established by medical history and clinical examination, e.g. immunosuppression o Patients who the investigator believes can and will comply with the protocol requirements (e.g. attendance at clinic appointments, return for follow-up visits) **Exclusion:** o Use of other investigational/non-registered product within 30d preceding the 1st vaccine dose o Continuous administration of immunosuppressants o Previous vaccination against HPV o Cancer or autoimmune disease under treatment. Patients who have a history of cancer or autoimmune disease but are not currently being treated for the condition will be included o Any confirmed or suspected immunosuppressive condition, including HIV infection o History of allergic disease or any neurologic disorders likely to interact with study vaccination o Acute febrile disease at enrolment (will be postponed) o Pregnant women or women intending to get pregnant during the next 6 months (if pregnant during follow-up, remaining doses will be delayed until after delivery)
Vaccine & Study Procedures:	**Vaccine Arm:** Time 0m: colposcopy + local cervical treatment + vaccine + clinic-collected research swab(s)/smear(s) + vulva/anal/perianal swabs + blood samples Time 2m: vaccine Time 6m: liquid-based cytology + local HPV test + vaccine + clinic-collected research swab(s)/smear(s) + vulva/anal/perianal swabs + blood samples Time 12m: self-sampling research swab(s) Time 18m: self-sampling research swab(s) Time 24m: liquid-based cytology (Finland only) + local HPV test (Finland only) + clinic-collected research swab(s)/smear(s) + vulva/anal/perianal swabs + blood samples Time 30m: self-sampling research swab(s) **Control arm:** Time 0m: colposcopy + cervical local treatment + clinic-collected research swab(s)/smear(s) + vulva/anal/perianal swabs + blood samples

	Time 6m: liquid-based cytology + local HPV test + clinic-collected research swab(s)/smear(s) + vulva/anal/perianal swabs + blood samples Time 12m: self-sampling research swab(s) Time 18m: self-sampling research swab(s) Time 24m: liquid-based cytology (Finland only) + local HPV test (Finland only) + clinic-collected research swab(s)/smear(s) + vulva/anal/perianal swabs + blood samples Time 30m: self-sampling research swab(s)
Endpoints:	We will commence the main analysis of study data once all participants have reached the 24 month timepoint, with an updated analysis of study data to occur once all 30 month samples have been collected. Full details are documented in the Statistical Analysis Plan (SAP). **Primary Endpoints** Weighted composite of the following 3 endpoints concerning the efficacy of the Gardasil® 9 HPV -vaccine as compared to no vaccine, all of which will be evaluated at 24 months after the first dose in female patients aged 18-55 years at the baseline local treatment: • Against persistent incident (I) (≥ 5.5 m interval) cervical infections with 7 oncogenic vaccine HPV types 16/18/31/33/45/52/58. Incident infection is defined as an HPV type not detected at baseline. • Against persistent recurrent (R) (≥ 5.5 m interval) cervical infections with 7 oncogenic vaccine HPV types 16/18/31/33/45/52/58. Recurrent is infection with a type present at baseline, but not detected on a post-treatment study test (≥ 4 m post baseline) prior to a persistent detection of the same type. • Against persistent prevalent (P) (≥ 5.5 m interval) cervical re -infections with 7 oncogenic vaccine HPV types 16/18/31/33/45/52/58. Prevalent infection is one present at baseline with a post-treatment (≥ 4 m post baseline) persistent infection of the same type without any negative tests for that type prior to the persistent infection. The hypothesised efficacy is 20% (P): 80% (I): 50% (R). We anticipate that the ratio of women with each of these outcomes (P:I:R) will be 3:2:1 in the controls, respectively. For this reason, the composite endpoint will be a weighted sum: 6 x “incident” + 3 x “recurrent” + 1 x “prevalent infection” **Secondary and Tertiary Endpoints** The efficacy of the Gardasil® 9 HPV-vaccine as compared to no vaccine against: - Persistent infection (incident, recurrent, prevalent) with any of the oncogenic HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66/68

	- Any infection, not necessarily persistent (overall and incident, recurrent, prevalent) with any of the 7 oncogenic vaccine HPV types 16/18/31/33/45/52/58 - Against any cervical infection, not necessarily persistent (overall and incident, recurrent, prevalent) with any of the oncogenic HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66/68 - CIN1+ associated with a) the 7 oncogenic vaccine HPV types; b) any oncogenic HPV types - CIN2+ associated with a) the 7 oncogenic vaccine HPV types; b) any oncogenic HPV types - To monitor the safety
Investigational Medicinal Products (IMPs):	Gardasil® 9 HPV-vaccine 3 doses Gardasil® 9 (Merck & Co.Inc. HPV6/11/16/18/31/ 33/45/52/58 L1 vaccine) intramuscularly at 0, 2, 6 months

1. BACKGROUND AND RATIONALE

1.1 Introduction

There is strong evidence that infection with Human Papillomavirus (HPV) is a necessity, but not sufficient for the development of cervical pre-invasive and invasive disease. HPV virus can infect the genital area and is sexually transmitted. A subset of those subtypes have carcinogenic potential and are therefore named high-risk HPV (hrHPV). The lifetime risk of acquiring any HPV infection likely exceeds 80%. With more sensitive testing available, studies show that HPV infection is more commonly the rule, not the exception. The majority of women clear the infection through an incompletely understood immune response and only a fraction develops persistent infection. It is persistence that can cause cervical intraepithelial neoplasia (CIN) and if not detected and treated can potentially progress to cervical cancer.

1.2 Human Papillomavirus Vaccine (HPV Vaccine)

This vaccine gives protection against some strains of the Human Papillomavirus (HPV), including ones which cause cervical cancer. About 3,200 women are diagnosed with cervical cancer every year in the UK. It is currently the most common cancer in women under 35, killing around 850 UK women every year. Similarly, 550 cases and 170 cases of invasive cervical cancer are diagnosed in Sweden and Finland, respectively with over 150 and 50 deaths from this cancer annually.

One of the licensed vaccines used is called Gardasil® 9. Gardasil® 9 is a vaccine for children and adolescents from 9 years of age and adults. It is given to protect against diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58. Gardasil® 9 protects against the HPV types that cause most cases of cervical cancer and 90% of the cases of anogenital warts.

Gardasil® 9 is intended to prevent these diseases. The vaccine is not used to treat HPV related diseases. Gardasil® 9 does not have effect in individuals who already have a persistent infection or disease associated with any of the HPV types in the vaccine. However, in individuals who are already infected with one or more of the vaccine HPV types, Gardasil® 9 can still protect against diseases associated with the other HPV types in the vaccine.

When an individual is vaccinated with Gardasil® 9, the immune system (the body's natural defence system) stimulates production of antibodies against the nine vaccine HPV types, to help protect against the diseases caused by these viruses.

1.3 Clinical Data

Prophylactic human papillomavirus (HPV) vaccines include recombinant L1 virus-like particles lacking the viral genome. The vaccines induce high numbers of neutralizing antibodies that bind to virions and prevent infection of human cells (1). The licensed indications are to prevent anogenital cancers, and pre-invasive lesions that can lead to cervical, vaginal, vulvar or anal cancer and to prevent genital warts (2, 3). Gardasil® 9 and the two, first generation vaccines Gardasil™ and Cervarix™ have proven to be highly efficacious in preventing infection by subtypes included in the vaccine in HPV-naïve populations (4, 5), which is why the national vaccination program in the UK targets only pre-pubertal girls (6-10).

Although it has been hypothesized that the vaccine may have 'secondary' beneficial effects in HPV-infected individuals by limiting the spread of the infection to new cells or by inducing a cell-mediated

immune response that promotes clearance (11), this was not confirmed. Vaccination did not lead to clearance or reduced persistence of infections in women with ongoing infections at the time of vaccination (7, 12-15). However, the benefit from vaccination in individuals who have previously cleared the infections has been clearly documented (16-18).

There is ample prior data that HPV vaccines are much more immunogenic than the infection itself. Originally shown by Harro et al. (19) and confirmed in numerous studies, the response to the vaccine is 10-100 times higher than the response to the infection. There is strong evidence that supports the fact that a systemic administration of HPV VLPs can elicit an immune response even on those that have not been able to raise antibodies following natural HPV infection (20). This evidence comes both from the original pilot studies from the HPV positive but sero-negative women that were vaccinated but also from the 'booster' effect seen in adult women vaccination. The most widely accepted explanation is that the infection is local and lacks a viraemic phase, whereas the vaccine is given intramuscularly and directly enters the bloodstream. Furthermore, in previously infected women the vaccine is expected to further protect against other HPV subtypes that the woman has not been previously infected with.

The evidence on the value of prophylactic vaccination after local treatment (that removes a cone-shaped part of the cervix) is scarce (6, 21-24). Secondary analyses of the phase III RCTs with the quadrivalent (against HPV6/11/16/18) and the bivalent (against HPV16/18) vaccines have provided indirect evidence of a possible benefit from vaccination (6, 23). Joura et al. reported 65% reduction in the overall risk of CIN2+ lesions in women with prior cervical surgery, genital warts or vulvar or vaginal intraepithelial neoplasia in the quadrivalent vaccine recipients that had local treatment post-vaccination and a 46% reduction of any subsequent HPV-related disease (6). Garland et al. in a post-hoc analysis of the PATRICIA RCT of the HPV 16/18 AS04-adjuvanted vaccine (bivalent) demonstrated that vaccinated women who undergo local treatment continue to benefit from the vaccine with the reduced risk of subsequent CIN2+ (vaccine efficacy: all HPV 88.2% (14.8, 99.7), HPV-16/18 100% (63.1, 100)(24). Hidesheim et al. reported a possible benefit in vaccinated cohorts that went on to have local treatment against new incident infections from 16/18 and 31/33/45 types with vaccine efficacy of 58% and 37%, respectively, but no benefit on existing infections (23). Another non-randomised study reported that women vaccinated 1 week post-treatment demonstrated a 65% reduction in the risk of recurrent CIN2+ (22), while a further non-randomised study in men that have sex with men a 56% reduction in recurrent high-grade anal intra-epithelial neoplasia (21).

1.4 Rationale for the study

While local treatment for cervical high-grade pre-invasive lesions is efficacious, women after local treatment remain a high-risk group as the recurrence rate for high-grade pre-invasive disease can be as high as 5-10% (25). Despite increased surveillance, women who have been treated for high-grade cervical intraepithelial neoplasia (CIN) remain at two to four-fold increased risk of invasive cervical cancer than the general population for at least 10 years and most likely for the rest of their lives (26-30). For this reason, there is a **clinical need to find risk-reducing adjuvant treatments** for them. Local treatment for high-grade CIN seems to trigger an immune response in that most women still have detectable HPV infection immediately after treatment, but not by 6 months post-treatment. Thus, it is possible that the prophylactic vaccines **will enhance HPV clearance when given at the same time as excision** even though they are not effective when given in the absence of local treatment.

Furthermore, these women who develop CIN in the first place constitute a subgroup of the infected women who are particularly sensitive to the infection and as a result rapidly acquire re-infections post-treatment. It is plausible that the high frequency of infections place these women after local treatment at higher risk of pre-invasive or invasive recurrent disease that can be more difficult to detect and prevent (23, 31). **These women are therefore in particular need for protection against HPV re-infections by the same or different subtype as a particularly high-risk population (23).**

Media publicity has heightened public awareness that prophylactic HPV vaccination can prevent cervical pre-invasive and invasive disease. Women are increasingly aware that local treatment is associated with reproductive morbidity, increased risk of preterm birth and mid-trimester loss in subsequent pregnancies. The risk is particularly high in women requiring repeat local treatment for recurrent disease (32-36). As a result, there has been an increase in enquiries from patients and clinicians on the efficacy of the vaccine post-treatment; these questions are becoming increasingly difficult to answer.

To date, no RCTs have assessed the impact of vaccination in preventing subsequent HPV infections and pre-invasive disease after local treatment. With the recent introduction of Gardasil® 9 that includes 5 subtypes in addition to the ones in the quadrivalent vaccine cocktail, more than 90% reduction of the oncogenic HPV infections is possible (5). It is expected that the vaccine will have a substantial benefit against **new infections** not present at time of treatment, although it less likely to promote clearance of an **existing infection** in isolation. It remains an **open question** whether the vaccine a) has the potential to work in conjunction with local treatment (that removes the CIN and most of the infection) **to boost** the effect of treatment and viral clearance or b) could help following clinical clearance of the infection after local treatment to ensure that there is **no latent infection or re-occurrence of the infection** by the same subtypes.

This RCT is designed to evaluate the efficacy and safety of the new nonavalent Gardasil® 9 vaccine (against 16, 18, 31, 33, 45, 52, 58 HPV subtypes but will not evaluate vaccine types 6 and 11 as they are not oncogenic and not analysable using current standard assays) in preventing post- treatment re-infections and HPV-disease occurrence in adult female patients aged 18-55 years. This trial will further clarify whether the benefit (if any) is **a)** against *de nuovo* HPV infections and/or **b)** against *residual* infection directly (i.e. by facilitating clearance post- treatment) or indirectly by preventing clinically-detectable re-infection from sub-clinical residual infections (reduction of viral load). Advanced HPV genotyping can allow us to distinguish between the different types of infection (37-39).

1.5 Risk / Benefit Assessment

In England alone, 3.6 million women aged between 25 and 64 attended for screening in 2013-14, one in ten had abnormal results and over 23800 local treatments were carried out (40). The majority of treated women are of a young age. Establishing that HPV is causally associated with cervical cancer has revolutionised cervical cancer primary and secondary prevention but also set new challenges. National HPV prophylactic vaccination programmes targeting pre-pubertal girls (and in some, boys) are now well established in many countries. The (type-specific) efficacy of the HPV vaccines is very high in women who have not been previously exposed to HPV. In the past years, concerted efforts attempted to explore the beneficial role of vaccination in other clinical groups.

Although the vaccines do not appear to reduce the risk of progressive disease in women with ongoing infections at the time of the vaccine, there may be a role for women post-treatment, a particularly high-risk group susceptible to (new and recurrent) persistent oncogenic infection and development of (pre)invasive lesions. Evidence from non-randomised studies and secondary analyses from RCTs hint towards possible benefit in this subgroup.

If this study demonstrates benefits from vaccination, this may add a **new clinical indication** for the vaccine for this high-risk population of women after local treatment. All women post-treatment may then receive vaccination that will prevent subsequent cervical, vulvar and vaginal pre-invasive disease and anogenital warts in this high-risk population. It has now been highlighted that although the vaccine is highly efficacious, efforts should be made to accelerate the impact from vaccination. The proposed study is in line with the HPV-FASTER concept that supports the expansion of HPV vaccine indications in order to accelerate the decline in the incidence of cervical cancer (41).

2. OBJECTIVES AND ENDPOINTS

Our objective is to demonstrate that the vaccine when initiated at the time of local treatment will reduce subsequent persistent HPV infection in women with high-grade CIN.

We will carry out the main analysis of study data once all participants have reached the 24-month timepoint (main dataset). Once the remaining eligible participants have completed their 30-month (updated dataset) follow up, a second data lock will take place and an updated analysis of study data will take place. Full details are documented in the Statistical Analysis Plan (SAP).

2.1 Primary Objective

Composite primary

The primary endpoint is persistent infection. That is an HPV infection that is refractory to immunological clearance in contrast to a transient infection or a deposit. In the trial we define persistent infection as two successive positive tests of the same HPV type at least 6 months apart with the first positive test at least 4 months (122+ days) post randomisation and with no intervening negative tests between the two positive tests.

We shall calculate the persistence endpoint as a weighted composite of the following 3 persistent infection subcategories of endpoints concerning the efficacy of the Gardasil® 9 HPV-vaccine as compared to no vaccine, all of which will be evaluated at 24 months after the first dose (i.e. by Month 24) in female patients aged 18-55 years at the baseline local treatment. Patients who have an HPV type detected at 24 months which was not present at 18 months or where the same type was present at both timepoints, but they were less than 5.5m apart will be offered a 30m HPV test to assess persistence.

- Against persistent incident (I) (≥ 5.5 months, interval) cervical infections with vaccine HPV types /16/18/31/33/45/52/58. Incident infection is defined as an HPV type not detected at baseline.
- Against persistent recurrent (R) (≥ 5.5 months interval) cervical infections with vaccine HPV types /16/18/31/33/45/52/58. Recurrent is infection with a type present at baseline, but not detected on a post-treatment (≥ 4 m, > 121 days post baseline) study test prior to a persistent detection of the same type.
- Against persistent prevalent (P) (≥ 5.5 months interval) cervical re-infections with vaccine HPV types /16/18/31/33/45/52/58. Prevalent infection is one present at baseline with a post-treatment (≥ 4 m, > 121 days post baseline) persistent infection of the same type without any negative tests for that type prior to the persistent infection.

The hypothesised efficacy is 20% for prevalent, 80% for incident and 50% for recurrent infection (50). Additionally, we anticipate that the ratio of women with each of these outcomes (P:I:R) will be 3:2:1 in the controls. In order to maximise the power under these assumptions (see **Section 8.1** for details), the composite endpoint will be a weighted sum: 6 x “incident” + 3 x “recurrent” + 1 x “prevalent infection”.

2.2 Secondary Objective

- To evaluate the three components of the composite primary endpoint separately

- Against post-treatment persistent cervical infection (incident, recurrent, prevalent) with any of the oncogenic HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66/68
- Against any cervical infection, not necessarily persistent (overall and incident, recurrent, prevalent) with any of the 7 oncogenic vaccine HPV types 16/18/31/33/45/52/58
- Against any cervical infection, not necessarily persistent (overall and incident, recurrent, prevalent) with any of the oncogenic HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66/68
- Against new, post-treatment, CIN2+ lesions (high-grade squamous intra-epithelial lesions (HSIL)) associated with vaccine HPV types 16/18/31/33/45/52/58.
- Against new, post-treatment, CIN2+ lesions (HSIL) associated with any oncogenic HPV types.
- To monitor the safety of Gardasil® 9 with the first dose given at localised cervical treatment.

2.3 Tertiary Objective

- Against new, post-treatment, CIN1+ associated with the vaccine HPV types 16/18/31/33/45/52/58.
- Against new, post-treatment, CIN1+ overall (irrespectively of HPV type).

The expert workshop convened by the International Agency for Research on Cancer (IARC) and the US National Cancer Institute in September 2013 has stated that persistent HPV infections should be the recommended end-point for future trials on licensure and clinical indications of HPV vaccination (42).

Table 1: Summary of Objectives and Endpoints

Objectives	Endpoints	Time point(s) of evaluation
Primary	• Persistent HPV infections (incident, prevalent, recurrent) for vaccine types	24m (+6)
Secondary	• Components of overall composite endpoint separately • HPV infections (I, P, R) with any types • Persistent HPV infection (incident, recurrent, prevalent) with any of the oncogenic HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66/68 • Any cervical infection, not necessarily persistent (overall and incident, recurrent, prevalent) with any of the 7 oncogenic vaccine HPV types 16/18/31/33/45/52/58 • Against any cervical infection, not necessarily persistent (overall and incident, recurrent, prevalent) with any of the oncogenic HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66/68 • CIN2+ associated with vaccine types • CIN2+ associated with any of the oncogenic HPV types • Safety	24m (+6)
Tertiary / Exploratory	• CIN1+ associated with vaccine types • CIN1+ associated with any of the oncogenic HPV types	24m (+6)

3. STUDY DESIGN

3.1 Overall Study Design

This is a phase III, observer- blind randomised study consisting of two arms to which patients will be randomised 1:1, as depicted in **Figure 1**. The patients and clinicians will not be blinded but the laboratory staff performing the HPV assays on vaccinated and non-vaccinated arms will be blinded. The trial will be performed at approximately 16 investigational sites in the UK, Finland and Sweden. Arm 1 (vaccine) will enrol 549 and arm 2 (no vaccine) will enrol 550 patients, for a total of 1099 patients in the entire study.

- Arm 1 – Vaccine: Gardasil® 9 vaccine (N=549): administered at 0, 2 and 6 months.
- Arm 2 – Control: no vaccine (N=550)
  Participating patients in the trial will be advised not to obtain vaccine outside the trial while participating in the study.

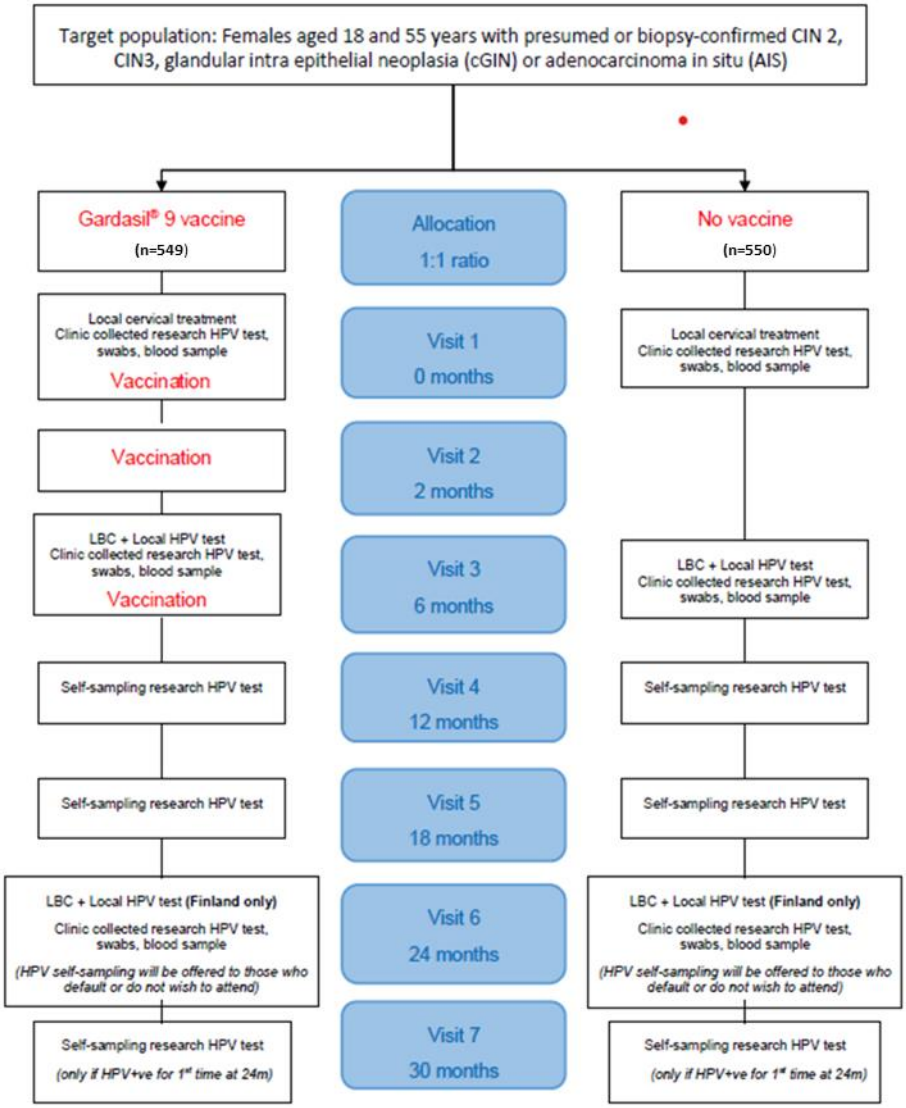
We will stratify by country and study site (clinic).

3.2 Treatment regimens

Table 2: Summary of treatment groups

Treatment Arm	Number of Patients	Treatment	Treatment schedule
Arm 1	549	Vaccine (Gardasil® 9)	Gardasil® 9 will be supplied as a liquid in individual pre-filled syringes to be administered (0.5 ml) intramuscularly (IM) into the deltoid of the non-dominant arm on a 0, 2, 6-month schedule.
Arm 2	550	No vaccine	Observation only

Figure 1: Study flow chart



4. PARTICIPANT ENTRY

4.1 Study setting and population

This trial will be performed at investigational sites in the UK, Finland and Sweden and recruit women attending for local treatment for presumed CIN2/CIN3/cGIN/AIS or biopsy confirmed CIN2/CIN3/ cGIN/AIS.

4.2 Inclusion Criteria

Patients who meet all of the following inclusion criteria will be considered eligible for this study:

1. Female (18-55y) attending for local treatment for presumed CIN2 (cytological and colposcopy impression) OR presumed CIN3 (cytological and colposcopy impression) OR presumed cGIN/AIS (cytological and colposcopy impression) OR biopsy-confirmed CIN2 OR biopsy-confirmed CIN3 OR biopsy-confirmed CGIN/AIS
2. Written informed consent obtained from the subject prior to enrolment

3. Free of other relevant health problems as established by medical history and clinical examination, e.g. immunosuppression
4. Patients who the investigator believes can and will comply with the protocol requirements (e.g. attendance at clinic appointments and return for follow-up visits)

4.3 Exclusion criteria

Patients who meet any of the following exclusion criteria will **not** be eligible for this study:

1. Use of other investigational/non-registered product within 30 days preceding the 1st vaccine dose
2. Continuous administration of immunosuppressants
3. Previous vaccination against HPV
4. Cancer or autoimmune disease under treatment. Patients who have a history of cancer or autoimmune disease but are not currently being treated for the condition will be included
5. Any confirmed or suspected immunosuppressive condition, including HIV infection
6. History of allergic disease or any neurologic disorders likely to interact with study vaccination
7. Acute febrile disease at enrolment (will be postponed)
8. Pregnant women or women intending to get pregnant during the next 6 months (if pregnant during follow-up, remaining doses will be delayed until after delivery)

5. PROCEDURES AND MEASUREMENTS

5.1 Identification and recruitment of patients

Potential patients will be identified either by their direct care team at a participating investigational site (i.e. principal and/or co-investigator), or as the result of referral to the principal and/or co-investigator by another doctor based within or outside of that investigational site. Recruitment will take place as part of routine outpatient clinic visits at participating investigational sites.

5.2 Screening and pre-randomisation evaluations

Written informed consent will be obtained before the patient undergoes any study specific procedures. Once consent has been obtained the patient will be added to the study Electronic Case Report Form (eCRF), where a unique Screening ID will be allocated, which will be used in all correspondence during the screening period.

A complete record of all patients who enter screening for the study, and also those who go on to be enrolled, must be maintained at each site. The local investigator is responsible for ensuring that this record includes the allocated trial ID as well as the patient identifiable data including name, hospital number and date of birth.

Eligible patients who take part in the study must meet all of the listed inclusion criteria and none of the exclusion criteria.

5.3 Randomisation

After eligibility has been confirmed, patients will be randomised to the trial. Randomisation will be performed centrally using the eCRF; there is no option available for manual randomisation. Upon randomisation each patient will be allocated a unique ID which should be used in all future correspondence.

Randomisation will be stratified by country and study site (clinic).

Please refer to the eCRF Completion Manual for further details on patient randomisation.

5.4 Vaccine Period

Patients will receive three doses of the vaccine (Gardasil® 9) throughout the course of the study. The vaccine will be administered intramuscularly at month 0 if a randomised subject is not able to receive the vaccine on the day of treatment this can be administered within 7 days of treatment, month 2, and then at month 6. Women participating in the trial will be asked not to obtain the vaccine outside the trial. We will record data at 24 months on whether any other vaccine was taken during the trial period (date, name and number of doses). Please refer to **Figure 1**.

5.5 Follow-Up

Patients will be followed up at 6, 12, 18, 24 months (some participants will also be sent a self-sample 6 months later ie. at 30 months). We considered that a bi-annual follow-up for 24 months is sufficient to observe incident and/or persistent infections/recurrent lesions in Gardasil® 9 recipients (6, 22) with PCR (38, 39). There will be no additional colposcopies beyond clinical indications and guidelines. The results of the research test will not be used for clinical management. All patients will be sent a letter as a reminder at study completion to ensure that they attend their normal screening test and research tests will not be used to inform clinical decisions.

A) 'Test of cure' at 6 months

Around 15-20% of women will fail the 'test of cure' (i.e. abnormal HPV DNA test and/or cytology (48) (audit data from Imperial College - Barts & Whipps Cross NHS Trust for this age group report a rate of 17.5%).

The decision to perform colposcopy +/-biopsies will follow national guidelines.

In the UK, all women post-treatment have cytology and HPV test ('test of cure') at 6m

- Women with cytology sample reported as negative, borderline, or low-grade, and whose HR-HPV test is negative should be recalled in three years, whatever their age.
- Women with cytology sample reported as negative, borderline, or low-grade, and whose HR-HPV report is positive should be referred to colposcopy.
- Women with cytology sample reported as high-grade dyskaryosis or possible invasion must be referred for colposcopy – an HR-HPV test is not necessary.

In Finland, all women post-treatment have cytology and HPV test at 6m

- If the HPV test is negative and cytology is normal/ASCUS/LSIL, HPV test and cytology is repeated at 24m. At 24m, if HPV is negative and cytology is normal/ASCUS, the woman returns to 5-yearly routine recall. If HPV test is negative and cytology LSIL, HPV test and cytology is repeated at 36m.
- If the HPV test is positive, or the colposcopy LSIL+, or cytology ASCH, HSIL or AGC, treatment is offered if indicated and if not indicated women are followed up with repeat testing in 6m.

In Sweden, all women have cytology and HPV test at 6m

- If HPV test is positive but cytology negative **or** HPV negative but cytology ASCUS or LSIL, cytology and HPV test is repeated in 6m. If either is positive, colposcopy is indicated.
- If the HPV is positive and cytology ASCUS or LSIL, women are referred to colposcopy.
- If the cytology is high-grade, women are referred to colposcopy.

5.6 Vaccine and Treatment after Study Termination

Patients enrolled in the study will not be receiving any additional vaccination and/or treatment once all the study related visits are completed by participants.

5.7 Study Schedule

Vaccination is divided into 7 events, as per **Figure 1**. Protocol mandated visits, the required assessments and self-sampling are provided per trial arm in **Tables 3 and 4**. The patient information sheet will be sent by post with the invitation to attend for local cervical treatment.

The minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third doses, and 5 months between the first and third doses. If a vaccine dose is administered after a shorter interval, it should be re-administered after another minimum interval has elapsed since the most recent dose. If the vaccination schedule is interrupted, vaccine doses do not need to be repeated (no maximum interval). We cannot guarantee giving the remaining doses of the vaccine after 24 months from trial initiation.

We should aim that the scheduled follow-up assessments take place within 6-month intervals and at 6, 12, 18 and 24 months. For the purposes of persistent infection, we will count visits between 4-8 months apart (6+/-2 months). Two consecutive short or long intervals on the same patient should be avoided. If a visit is missed for over 2 months, we would revert to the next normal expected visit (for example, if the woman does not attend by 8months for her 6-month visit, the next visit will be reset for at 12months).

Table 3. Schedule of Assessments – Vaccine Group

Events	S	1	2	3	4	5	6	7
Timing (months)	-28 to -1	0m	2m	6m	12m	18m	24m	30m
Informed consent	●							
Inclusion / Exclusion criteria	●							
Demographics	●							
Pregnancy test		●	●	●				
Medical history / Concomitant medical conditions	●	●	●	●	●	●	●	●
Concomitant / Prohibited medication review		●	●	●				
Randomisation		●						
Colposcopy prior to local cervical treatment		●						
Local Cervical Treatment		●						
Histology data (grade, margins)		●						
Liquid-based Cytology (LBC)				●			● Finland only	
Local Clinic HPV test				●			● Finland only	
Clinic-collected research HPV test[1]		●		●			●	
Self-sampling research HPV test					●	●		●
Vulva, anal, perianal sample[2]		●		●			●	
Research Blood sample		●		●			●	
Vaccination[3]		●	●	●				
Colposcopy[4]								
Adverse Events (AEs)[5]		●	●	●	●	●	●	●
End of study follow-up								●

[1]*self-sampling research HPV test at 24m also an option for those that default or do not wish to attend the clinic*
[2]*optional.*

[3] Vaccine administered into the deltoid of the non-dominant arm. If the randomised subjects are not able to receive the vaccine on the day of treatment it can be administered within 7 days of treatment. In the event of failure to deliver the first dose within 7 days, the first does may be given up to 30 days after treatment. Such delayed vaccination must be justified and signed-off by the local PI.

[4]Colposcopic examination will be conducted in cases of persistent infection, high grade cytology or if clinically indicated

[5] The following AEs require reporting:

- ***Related and unexpected adverse events (AEs) and serious adverse events (SAEs) from the vaccine** i.e. events assessed by investigator as **at least possibly causally related to the vaccine** and **not** listed as undesirable effects in the Summary of Product Characteristics (SPC) for Gardasil® 9 (see Appendix A), that **may or may not** meet at least one SAE seriousness criteria (see section 7.4.1)*
- ***Related and expected SAEs from the vaccine** i.e. events assessed by investigator as **at least possibly causally related to the vaccine and** listed as undesirable effects in the SPC for Gardasil® 9 (see Appendix A), that meet **at least one** SAE seriousness criteria (see section 7.4.1);*
- ***Related and expected SAEs from local cervical treatment** (see Appendix B) i.e. events assessed by investigator as **at least possibly causally related to local cervical treatment and** listed in Appendix B, that meet **at least one** SAE seriousness criteria (see section 7.4.1).*

If patients are not coming for clinic visits AEs will be collected through telephone calls.

Table 4. Schedule of Assessments – Observation Group (No vaccine)

Events	S	1	2	3	4	5	6	7
Timing (months)	-28 to -1	0m	2m	6m	12m	18m	24m	30m
Informed consent	●							
Inclusion / Exclusion criteria	●							
Demographics	●							
Medical history / Concomitant medical conditions	●	●	●	●	●	●	●	●
Randomisation		●						
Colposcopy prior to local cervical treatment		●						
Local Cervical Treatment		●						
Histology data (grade, margins)		●						
Liquid-based Cytology (LBC)				●			● Finland only	
Local Clinic HPV test				●			● Finland only	
Clinic-collected research HPV test[1]		●		●			●	
Self-sampling research HPV test					●	●		●
Vulva, anal, perianal sample[2]		●		●			●	
Research Blood sample[2]		●		●			●	
Colposcopy [3]								
Adverse Events[4]		●	●	●	●	●	●	●
End of study follow-up								●

[1] *self-sampling research HPV test at 6m and 24m also an option for those that default or do not wish to attend the clinic*

[2] *optional.*

[3] *Colposcopic examination will be conducted in cases of persistent infection, high grade cytology or if clinically indicated*

[4] *Only the following AEs require reporting:*

- ***Related and expected SAEs from local cervical treatment*** *(see Appendix B) i.e. events assessed by investigator as* ***at least possibly causally related to local cervical treatment and*** *listed in Appendix B, that meet* ***at least one*** *SAE seriousness criteria (see section 7.4.1).*

If patients are not coming for clinic visits AEs will be collected through telephone calls.

5.8 Procedures and Measurements

5.8.1 Demographic Data

Patient month and year of birth and information on ethnicity, smoking status, Index of Multiple Deprivation (IMD) and mode of contraception will be collected at screening.

5.8.2 Medical History / Concomitant Medical Conditions

A complete medical history will be taken by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years including vaccines, cancer diagnoses and prior anti-cancer therapies that are considered to be clinically significant by the Investigator. Any other relevant medical history and treatments will also be recorded. Concurrent diseases, i.e. other medical conditions that are ongoing from the start of the study, will be documented as adverse events if they qualify as a reportable AE as per section 7 **and** worsen from the start of the study. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

Patients may be contacted to be offered to give an interview for qualitative research to assess their responses to having an HPV vaccination following treatment. This might include their reflections on the process, perceived risk of disease recurrence / HPV persistence, information needs, beliefs about the efficacy of the vaccine in this context, ongoing anxieties, feelings about follow-up results. This is optional (see 5.8.11).

5.8.3 Concomitant / Prohibited Medications

All medications being taken at the time of the month 2 and 6 visits will be documented as a concomitant medication by the investigator or qualified designee. The following details will be collected: drug name, reason for therapy, therapy dosage / units, frequency of therapy, route of administration, start and end date of therapy.

5.8.4 Local Cervical Treatment

Local cervical treatment will involve removal or ablation of a cone-shaped part of the cervix containing the transformation zone with diathermy, scalpel, cold coagulation, cryotherapy or laser. More specifically, conservative treatment for CIN is by 8 different excisional or ablative techniques. The excisional techniques include cold knife conisation (CKC), laser conisation (LC), large loop (LLETZ, also known as LEEP) or needle excision of the transformation zone (NETZ, also known as SWETZ). The ablative techniques include radical point diathermy (RD), cryotherapy (CT), cold coagulation (CC) or laser ablation (LA).

The local treatment is performed under local anaesthetic in the outpatient setting in the majority of the cases or under general anaesthetic less frequently.

5.8.5 Histology Data

The histology of the patient biopsy and local excision will be reported locally and then slides will be provided for each patient to enable a central pathology review at Imperial College London. Tissue from the paraffin blocks may be used for further research.

Further details on sample processing, handling and shipment are provided in the NOVEL study Laboratory Manual.

5.8.6 Liquid Based Cytology (LBC) Sampling for HPV test

Local Clinic HPV test will be tested at 6 months from the LBC solution locally as per regional recommendation and the result will be recorded. In Finland the local HPV test will also be repeated at 24 months.

5.8.7 Clinic-collected or self-sampling research samples

Additional samples (swabs/smears) will be collected for research purposes with an ultrasensitive specific HPV assay (MALDI-TOF high-throughput PCR that will determine the exact HPV genotype and whether the incident is recurrent or prevalent infection. These sample may be used for further biomarker (ie. microbiome, methylation, HPV integration, immune response). Self-sampling swabs will be undertaken by the study patients at 12 and 18 months. The self-sampling kits will be posted to the patient with a prepaid envelope to post back. Reminders will be sent to the patient if the kit is not returned within 2 weeks. Self-sampling swabs will also be sent at 6 and 24 months if the patients fail or decline to attend. Some participants may be sent a self-sample 6 months later, ie. at 30 months if this is required (for example to define persistent hrHPV infection). For each self-sample that is returned by a participant, a voucher will be offered as an incentive. These vouchers will be to the value of between £10 to £15 and will be purchased using funds from study grants.

5.8.8 Vulva, Anal and Perianal Sample

This part of the study is optional, where patients consent to have vulva, anal and perianal swabs taken at months 0, 6 and 24. All swabs will be stored for future assessment.

5.8.9 Research Blood

This part of the study is optional, where patients consent to have 20ml of blood taken at months 0, 6 and 24. This will enable us to collect up to 3,000 samples to provide a minimum of 4 ml of serum (four 1ml aliquots). The blood will be stored at Imperial College London for future research.

5.8.10 Chain of Custody of Biological Samples

In all cases, patients will be consented for the collection and use of their biological samples and a full chain of custody will be maintained for all samples throughout their lifecycle.

The investigator at each site is responsible for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal. Any person(s) responsible for temporarily holding samples, e.g. sub-contracted service provider keeps full traceability of samples from initial receipt of sample to further shipment or disposal (as appropriate).

Imperial College keeps overall oversight of the entire lifecycle through internal procedures and monitoring of study sites.

Samples retained for further use will be registered with the Imperial College Healthcare NHS Tissue Bank (ICHTB).

5.8.11 Qualitative Interviews

This part of the study is optional, and patients will consent separately. All women who participate in the trial will be offered the opportunity to participate by the PI or qualified designee at their baseline visit. Participants will be informed of the opportunity to participate in an interview when they return for their 6-month visit and asked to opt in to being contacted about this. Women who opt in will be contacted by telephone 2-3 weeks before their 6-month visit to confirm interview participation. We aim to interview 20-30 women across the 10 UK sites. If more than 30 women agree to an interview, we will use purposive sampling to recruit women from a range of age-groups.

Interviews will take place at a room in the clinic with a research assistant or research nurse. The interviews will be semi-structured and a topic-guide will be used to ensure key issues are covered. This will include exploring women's reflections on the process, perceived risk of disease recurrence / HPV persistence, information needs, beliefs about the efficacy of the vaccine in this context, ongoing anxieties and feelings about follow-up results. Interviews will be recorded and transcribed verbatim (by an external transcription company, after being securely transferred). Once transcriptions have been checked, the audio recordings will be destroyed. Framework Analysis will be used to analyse the data. Analysis involves five stages: familiarisation, identifying a framework, indexing, charting, mapping and interpretation. Two members of the research team will be involved in each of these stages to ensure reliability and reduced interpretation-bias. It should be noted, that the qualitative data resulting from women's interviews will be fully anonymised and will not be linked to their trial data.

6. TREATMENTS

6.1 Investigational Medicinal Product Details

Gardasil® 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) by Merck Vaccines.

6.2 Labelling and Packaging

Gardasil® 9 will be provided by MERCK SHARP & DOHME LIMITED and packaged, re-labelled and distributed by Sharp Clinical. Labels will be prepared in accordance with Good Manufacturing Practice Annexe 13 requirements and local regulatory guidelines.

Gardasil® 9 will only be dispatched to sites after receipt of confirmation that the regulatory checklist is complete.

Please refer to the IMP Handling Manual for further details.

6.3 Storage and Dispensing

6.3.1 Condition on Arrival

- Refrigerate on arrival.
- Should not have been frozen.

6.3.2 Storage

- Store refrigerated at 2°C to 8°C (36°F to 46°F); DO NOT FREEZE.
- Protect from light.
- Administer as soon as possible after being removed from refrigeration.
- Rotate stock so that the earliest-dated vaccine is used first. Ensure that the refrigerator is plugged into an outlet in a protected area where it cannot be disconnected accidentally. Record refrigerator temperatures in a temperature log.
- For guidance on how to dispose of expired, used, or damaged vaccines, please contact your vaccine supplier or manufacturer.

6.3.3 Temperature Excursions

- GARDASIL® 9 can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperature between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

6.3.4 Handling

- **Vial use:** Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.
- Gardasil® 9 should not be diluted or mixed with other vaccines.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. After thorough agitation, Gardasil® 9 is a white, cloudy liquid. Do not use the product if particulates are present or if it appears discoloured.
- Most vaccines are produced in single-dose vials or pre-filled syringes by the manufacturer. Needles should be disposed of properly and should not be recapped.

Table 5: Dosage, Administration and Duration

Vaccine	Formulation	Presentation	Volume	N° doses
Gardasil® 9 vaccine	30 μg HPV6 L1 VLP 40 μg HPV11 L1 VLP 60 μg HPV16 L1 VLP 40 μg HPV18 L1 VLP 20 μg HPV31 L1 VLP 20 μg HPV33 L1 VLP 20 μg HPV45 L1 VLP 20 μg HPV52 L1 VLP 20 μg HPV58 L1 VLP 500 μg of aluminium hydroxyphosphate sulfate	Liquid in pre-filled syringes	0.5 ml	3

Three doses of Gardasil ®9 (Merck & Co.Inc. HPV6/11/16/18/31/ 33/45/52/58 L1 vaccine) will be administered intramuscularly according to a 0, 2, 6month schedule. This vaccine has an excellent safety and immunogenicity profile both in monitored clinical trials (5).

6.4 Accountability

In accordance with local regulatory requirements, the investigator / appropriately delegated site staff will document the amount of Gardasil® 9 vaccine received, the amount dispensed to patients and the amount destroyed.

Product accountability records will be maintained throughout the course of the study and filed with delivery documentation. Destruction will be documented as per local policy.

Please refer to the IMP Handling Manual for further details.

6.5 Drug interactions / Precautions / Contraindications

6.5.1 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in **table 5.**
Individuals with hypersensitivity after first administration of Gardasil® 9 will not proceed with further doses of Gardasil® 9.

6.5.2 Special warnings and precautions for use

The decision to vaccinate an individual should take into account the risk for previous HPV exposure and potential benefit from vaccination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.
Syncope (fainting), sometimes associated with falling, can occur following, or even before, any vaccination, especially in adolescents as a psychogenic response to the needle injection. This can be

accompanied by several neurological signs such as transient visual disturbance, paraesthesia, and tonic-clonic limb movements during recovery. Therefore, vaccines should be observed for approximately 15 minutes after vaccination. It is important that procedures are in place to avoid injury from fainting.

Vaccination should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a mild upper respiratory tract infection or low-grade fever, is not a contraindication for immunisation.

As with any vaccine, vaccination with Gardasil® 9 may not result in protection in all vaccine recipients.

The vaccine will only protect against diseases that are caused by HPV types targeted by the vaccine. Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

The vaccine is for prophylactic use only and has no effect on active HPV infections or established clinical disease. The vaccine has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical, vulvar, vaginal and anal cancer, high-grade cervical, vulvar, vaginal and anal dysplastic lesions or genital warts. It is also not intended to prevent progression of other established HPV-related lesions.

Gardasil® 9 does not prevent lesions due to a vaccine HPV type in individuals infected with that HPV type at the time of vaccination.

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Gardasil® 9 will not provide protection against every HPV type, or against HPV infections present at the time of vaccination, routine cervical screening remains critically important and should follow local recommendations.

There are no data on the use of Gardasil® 9 in individuals with impaired immune responsiveness. Safety and immunogenicity of a qHPV vaccine have been assessed in individuals aged 7 to 12 years who are known to be infected with human immunodeficiency virus (HIV).

Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may not respond to the vaccine.

This vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals. Long-term follow-up studies are currently ongoing to determine the duration of protection.

There is no safety, immunogenicity or efficacy data to support interchangeability of Gardasil® 9 with bivalent or quadrivalent HPV vaccines.

6.5.3 Interaction with other medicinal products and other forms of interaction

Safety and immunogenicity in individuals who have received immunoglobulin or blood-derived products during the 3 months prior to vaccination have not been studied in clinical trials.

Use with other vaccines

Gardasil® 9 may be administered concomitantly with a combined booster vaccine containing diphtheria (d) and tetanus (T) with either pertussis [acellular, component] (ap) and/or poliomyelitis [inactivated] (IPV) (dTap, dT-IPV, dTap-IPV vaccines) with no significant interference with antibody response to any of the components of either vaccine. This is based on the results from a clinical trial in which a combined dTap-IPV vaccine was administered concomitantly with the first dose of Gardasil® 9.

Use with hormonal contraceptives

In clinical studies, 60.2% of women aged 16 to 26 years who received Gardasil® 9 used hormonal contraceptives during the vaccination period of the clinical studies. Use of hormonal contraceptives did not appear to affect the type specific immune responses to Gardasil® 9.

6.6 Permanent Discontinuation of Study Vaccine and Withdrawal from Study

6.6.1 Permanent discontinuation of study vaccine

A patient may be permanently discontinued from study treatment for the following reasons:

- Patient decision
- Significant adverse events or unacceptable toxicities
- Severe non-compliance to this protocol as judged by the Investigator
- Allergic reaction to study medication
- If the investigator considers that a patient's health will be compromised due to adverse events or concomitant illness that develop after entering the study.
- Use of any investigational or non-registered product other than the study vaccine during the study
- Patients with history of cancer or autoimmune disease who has relapsed following vaccination
- Continuous administration of immune-suppressants
- Newly diagnosed immunosuppressive condition, including HIV infection

Date of permanent discontinuation and the reason will be recorded.
Once study medication is permanently discontinued it cannot be restarted.

6.6.2 Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- Patient decision
- Loss to follow-up
- Death
- Investigator decision

If a patient dies whilst participating in the study a “Statement of Death” eCRF must be completed. The following details will be collected: date of death, whether autopsy performed, whether death

was related to the disease under investigation, primary cause of death, secondary cause of death, and any other details.

6.6.3 Procedures for Withdrawal from Study

If the patient is withdrawn from the study the date of withdrawal and the reason must be recorded. Where the patient has withdrawn due to an AE, the investigator should follow the procedures in section 7.

6.6.4 Product Complaints

Any quality complaints or comments concerning the commercial stock for the study should be sent to ukmisp_general@merck.com. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Merck representative.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, the investigator should follow the procedures in **section 7**.

7. PHARMACOVIGILANCE

In this trial, we will record:

- In the vaccine arm, **related and unexpected adverse events (AEs) and serious adverse events (SAEs) from the vaccine** i.e. events assessed by investigator as **at least possibly causally related to the vaccine** and **not** listed as undesirable effects in the Summary of Product Characteristics (SPC) for Gardasil® 9 (see Appendix A), that **may or may not** meet at least one SAE seriousness criteria (see section 7.4.1);
- In the vaccine arm, **related and expected SAEs from the vaccine** i.e. events assessed by investigator as **at least possibly causally related to the vaccine and** listed as undesirable effects in the SPC for Gardasil® 9 (see Appendix A), that meet **at least one** SAE seriousness criteria (see section 7.4.1);
- In both the vaccine and no vaccine arm, **related and expected SAEs from local cervical treatment** (see Appendix B) i.e. events assessed by investigator as **at least possibly causally related to local cervical treatment and** listed in Appendix B, that meet **at least one** SAE seriousness criteria (see section 7.4.1).

In this trial, we will **not** record:

- In the vaccine arm, **any AE that is not assessed by investigator as at least possibly related to the vaccine, regardless of seriousness or whether or not it is listed in the SPC for Gardasil® 9**;
- In the vaccine arm, **related and expected AEs from the vaccine that do not meet at least one SAE seriousness criteria** (see section 7.4.1); in both the vaccine and no vaccine arm, **related and expected AEs from local cervical treatment that do not meet at least one SAE seriousness criteria** (see section 7.4.1)

7.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory

finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP.

7.2 Adverse Event recording

Reportable AEs and SAEs will be recorded throughout the study, from the point of consent until the end of follow-up; they will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner.

Any reported SAEs which remain unresolved at the patient's last visit in the study should be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF.

If an Investigator learns of any reportable SAEs at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to study IMP, the Investigator should notify the Clinical Trials Unit (CTU).

The following details will be collected in the eCRF for each reportable AE:

- Description / diagnosis
- Date of onset and date of resolution
- CTCAE grade maximum intensity
- Seriousness
- Investigator causality rating against the study medication (yes or no)
- Action taken with regard to study medication
- Outcome

7.2.1 Severity of Adverse Events

Severity is a measure of intensity; whereas seriousness is defined by the criteria in **section 7.4.1**

Severity will be assessed using the grading scales found in the National Cancer Institute CTCAE version 4.03 (June 2010) for all adverse events with an assigned CTCAE term. For those events without assigned CTCAE grades, the recommendation on page 1 of the CTCAE that converts mild, moderate and severe into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

7.2.2 Causality of Adverse Events

The Investigator will assess causal relationship between the study treatment and each AE.

Unrelated:	No evidence of any causal relationship
Unlikely:	There is little evidence to suggest there is a causal relationship (e.g. 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 patient's clinical condition, other concomitant treatment).
Possible:	There is some evidence to 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 patient's clinical condition, other concomitant treatments).

Probable:	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite:	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.3 Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as adverse events where they also qualify as reportable. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

7.4 Serious Adverse Events (SAE)

7.4.1 Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

7.4.2 Reporting of SAEs

Rapid reporting of all reportable SAEs i.e. within 24 hours of the Principal Investigator or designee becoming aware of the event occurring during the study must be performed as detailed in the Pharmacovigilance Manual. If the investigator becomes aware of safety information that appears to be drug related and is reportable, involving a patient who participated in the study, even after an individual patient has completed the study, this should be reported to the Sponsor.

All reported SAEs will be reviewed by the Chief Investigator (CI) or a designated medically qualified representative to confirm expectedness and causality. Reporting of SAEs and review by the CI will be via the trial data collection system (eCRF) as detailed in the Pharmacovigilance Manual.

Following documented assessment by the CI, the completed SAE form will be sent by email to the Sponsor at jrco.ctimp.team@imperial.ac.uk by the study team at ICTU-Ca within the pre-specified timelines.

Regardless of expectedness or causality, all reported SAEs must also be reported in English to MSD Pharmacovigilance or designee as follows:

All reported Serious Adverse Events (SAEs) - within 24 hours of the sponsor-investigator's observation or awareness of the event

The ICTU-Ca will send all SAE reports to MSD Pharmacovigilance (or designee) within 24 hours as per any agreements.
See below for contact information for the reporting of SAEs to MSD Pharmacovigilance.
Follow-up information on the SAE may be requested by MSD Pharmacovigilance (or designee).
In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to MSD Pharmacovigilance (or designee) from all sites participating in the study.
Sub-investigators must report all reportable SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to MSD Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).
Relationship to all study drugs for each reportable SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Safety Contact Information - Merck
Drug Surveillance Department
Fax number: 0032 2402 5990
E-mail: pv.uk@merck.com via password protected method

7.5 Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the subject.

7.6 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC).

7.6.1 Reporting of SUSARs

SUSARs should be notified to the appropriate regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements. SUSARs which are fatal or life-threatening will be reported not later than seven days after alerting the sponsor to the reaction. Any additional relevant information will be sent within eight days of the report.

A SUSAR which is not fatal or life-threatening will be reported within 15 days.

Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

7.7 Development Safety Update Reports (DSURs)

Development Safety Update Reports (DSURs) will be submitted to the Sponsor, the relevant Ethics Committees and Regulatory Authorities in accordance with regulatory requirements.

7.8 Pregnancy, Breastfeeding, Fertility

Pregnancy

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformative nor foeto/neonatal toxicity of Gardasil® 9. Animal studies do not indicate reproductive toxicity. However, these data are considered insufficient to recommend use of Gardasil® 9 during pregnancy. Patients will have urine pregnancy test prior to every vaccine dose.

Females who are pregnant, trying or intending to become pregnant are not eligible to take part in the study. HPV vaccines are not recommended for use in pregnant women, although they have not been associated causally with adverse outcomes of pregnancy or adverse events in the developing foetus.

The (US) CDC advises "HPV vaccines are not recommended for use in pregnant women. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed."

If a woman become pregnant during the study, the study vaccine will be stopped. The woman will remain in the study and will receive the remaining doses of the vaccine after delivery.

Pregnancies occurring in patients during the study may represent a safety issue and must be reported via the eCRF. Site staff should notify ICTU-Ca (who will in turn notify the Sponsor) of a pregnancy in a trial patient and the estimated due date. Where a pregnancy is known, this will be followed up for outcome and any adverse outcome of pregnancy assessed for causality to the vaccine received. ICTU-Ca will provide copies of all pregnancy reports to MSD and the Sponsor.

Breast-feeding

Gardasil® 9 can be used during breast-feeding.

A total of 92 women were breast-feeding during the vaccination period of the clinical studies of Gardasil® 9. In the studies, vaccine immunogenicity was comparable between breast-feeding women and women who did not breast-feed. In addition, the adverse experience profile for breast-feeding women was comparable to that of the women in the overall safety population. There were no vaccine-related serious adverse experiences reported in infants who were breast-feeding during the vaccination period.

Fertility

No human data on the effect of Gardasil® 9 on fertility are available. Animal studies do not indicate harmful effects on fertility.

7.9 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant regulatory authority i.e. MHRA in UK, FIMEA in Finland, MPA in Sweden and the relevant national REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1 Sample Size, power considerations and planned recruitment rate

Enrolling 500 patients per arm and using a two-sided alpha level of 0.05 will give 90% power to detect a significant effect of vaccination on composite measure of persistent HPV infections post-treatment under the following assumptions:

1. Percentage of patients with persistent (i.e., test positive twice at least 6 months apart) infection with one of the seven high-risk HPV types in the vaccine starting between 6 and 24 months post local cervical treatment in the control arm: 12%
2. Relative proportion of persistent infections that are prevalent (i.e., a type present at diagnosis or in the excised cone and at 6 and 12 months or the first tests at 4+ months from baseline) without a preceding negative test: incident (i.e., a type not present at diagnosis nor in the excised cone): recurrent (i.e., a type present at diagnosis or in the excised cone but NOT at a timepoint at 4+ months prior to a persistent recurrence of the same as at baseline) in the control arm is: 3:2:1 (corresponding to 6% persistent, 4% incident, 2% recurrent).
3. The effectiveness of vaccination using Gardasil® 9 with the first dose at local treatment is:
A) 20% for prevalent; B) 80% for incident; C) 50% for recurrent infections
4. The composite measure is P+6I+3R where P, I and R are the proportions of patients with prevalent, incident and recurrent infections, respectively. The test statistic will be based on comparison between randomised women in the two arms (ITT) using the variance estimate (for each arm) of P(1-P)+36I(1- I)+9R(1-R) and comparing the normalised test statistic to a standard normal deviate.
5. Drop-out and compliance:
a. All patients randomised to the vaccine arm will receive the first dose
b. 97% of those in the vaccine arm will receive at least two, and 92% will receive all three doses
c. 78% of randomised patients will provide samples for HPV testing at baseline, 6, 12, 18 and 24 months (or until being found to have a persistent infection, whichever is first).

The justification for the assumptions are as follows:

1. The percentage of patients who are high-risk HPV positive 6 months after local treatment in England is about 17.5% (audit data for this age group from Imperial College - Barts & Whipps Cross NHS Trust: 17.5%; Kitchener 2008 total: 14.6%) (48). Approximately 85% of these infections will be one of the seven vaccine types (16, 18, 31, 33, 45, 52 or 58) (50, 53). Approximately 65% of these infections will be persistent at 12 months (50, 53). Based on the study by Soderlund-Strand et al (50) about 80% of women with infections 6-24 months post treatment will have infections at 6 months post treatment. Thus, we take the percentage with persistent infection (in the control arm) over the course of the study to be 17.5 x 0.85 x 0.65 / 0.80 = 12%. There is some heterogeneity in the literature as to the proportion of infections at 6 months post treatment that will be persistent (and it may depend on the assay), the proportion of those that are one of the vaccine types and the frequency of new persistent infections (12-24 months after treatment) but we consider our estimate of 12% of treated women having a persistent infection with a vaccine type over the two years of follow up to be reasonable and erring on the side of caution (I.e. being on the low side).
2. In the paper by Soderlund-Strand et al (50), there were 25 prevalent, 17 Incident and 9 recurrent. Thus the percentages of infections P:I:R were 49%:33%:18% (corresponding to 2.97:2.00:1.09).
3. The three assumptions:
a. Many would hypothesise that vaccines based on L1 virus like particles would have no effect on prevalent infections based the prophylactic trials results. However, we allow for a modest effect (20%) based on the fact that local treatment does not generally clear the HPV immediately, but it does lead to clearance in the majority of patients by 6 months. Thus, it is clear that excision

stimulates the immune system and it is possible that vaccination given at the same time as excision will boost this process.
b. The efficacy of HPV vaccines to persistent infection with vaccine types in women who are naïve to the particular type until receiving their third dose is well over 95% (7, 54). This very high efficacy is expected for type specific persistent infection; in women naïve to that type (both DNA negative and sero-negative at entry); mostly age 9-15 at immunisation (and immunogenicity bridging studies show that the immune response is not as great in 16-20-year as in 9-15 year olds girls); remained HPV negative until receiving all 3 vaccine doses. In our population we assume 80% efficacy partly to allow for: some women only receiving one dose of vaccine; some women having been exposed to the type prior to treatment and being DNA negative but not being truly naïve; women being considerably older; potential for some apparent incident
Infections being prevalent infections that were missed at baseline due to masking by other HPV type.
c. The efficacy of the vaccine in preventing types cleared through local treatment is unknown. We power the study assuming that it is in between that for incident and that for prevalent infections. Anecdotal reports (e.g. the non-randomised study of Kang et al 2013) (22) support a beneficial effect of concurrent vaccination in preventing recurrent high-grade CIN in treated women.
4. This composite maximises the power under the assumptions made here. The optimal weighting for a composite outcome gives weights proportional to the expected difference in the proportions divided by the variance of that difference. Here we have (p1-p0)/[p1(1-p1)+p0(1-p0)], p1 is the proportion in the vaccinated and p0 in the control arm. Note that if an individual has more than one type of persistent infection they will only count towards the type that has the biggest contribution to the composite score.
5. We expect high compliance in women randomised to the vaccine with almost 100% receiving the 1st dose based on interviews (and taking into account that they will only just have consented to participate). We anticipate that virtually all women (97%) will return at 6 months (since this is a standard post-treatment visit) and that compliance with the 2-month visit will be very high. We will not exclude women that have not had all three doses. We note that in women aged 9-14 two doses of vaccine given 6 months apart are non-inferior to three doses. We anticipate that 85% of women will provide at least one follow-up sample (at 12, 18 or 24 months), with 82% providing two samples and 78% three.
The expected value of the composite in controls is 0.36 and in vaccinated women it is 0.126 (giving an efficacy for the composite of 65%) and the variance of the composite is 1.62 (SD=1.27) in controls and 0.42
(SD = 0.648) in vaccinated women. Treating these are normal random variable, the sample size required for 90% power is 391 per arm (total 782). We will recruit 1000 patients (500 per arm) to allow 22% dropout/non-supply of self-samples.

To cover drop outs due to the COVID-19 pandemic, up to an additional 90 patients (45 each arm) will be recruited.

We expect to complete recruitment within 12 months and follow-up by 36 (+6) months.
across 3 countries: UK (up to 10 sites); Finland (1 site) and Sweden (up to 5 sites).

8.2 Statistical analysis

(i) Efficacy Analysis

Analysis of baseline characteristics Demographic characteristics of the patients will be tabulated. The mean age (with range and standard deviation) of the enrolled patients, as a whole and per group, will be calculated. The distribution of patients enrolled among the study sites will be tabulated.

(ii) Primary Endpoint Analysis

Intention to treat cohort (ITT): The ITT cohort will include randomised patients according to their random allocation. The ITT cohort for analysis of efficacy will include randomised patients for whom data concerning efficacy endpoint measures are available. The ITT cohort analyses will be performed per randomisation actually administered.

Per Protocol Efficacy (PPE) cohort: The PPE cohort for analysis of efficacy will include all evaluable patients (i.e. those meeting all eligibility criteria, complying with the procedure defined in the protocol, with no elimination criteria during the study) for whom data concerning efficacy endpoint measures are available.
This will include patients for whom assay results are available for HPV DNA.

The primary analysis will be based on the ITT cohort for analysis of efficacy. A second analysis based on the PPE cohort will be performed to complement the ITT analysis.

(iii) Secondary Endpoints Analysis

Subgroup analyses: We will perform a subgroup analysis to explore the efficacy of vaccination against prevalent, incident and recurrent infections and assess the subgroup that benefits the most. We will further perform analysis in subgroups of women with negative or positive HPV test at 6months posttreatment, according to the resection margins and grade of CIN treated. We will further perform a subgroup analyses according to age.

We will evaluate the three components of the composite primary endpoint separately.

We will evaluate the composite endpoint of post-treatment persistent cervical infections (incident, recurrent, prevalent) with any of the oncogenic HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66/68.

We will evaluate the composite endpoint of post-treatment persistent cervical infections (incident, recurrent, prevalent) with any of the 7 oncogenic vaccine HPV types 16/18/31/33/45/52/58

We will also perform analysis of any infection by vaccine types, not necessarily persistent, as overall composite and prevalent, incident and recurrent infections by both the 7 oncogenic vaccine HPV types 16/18/31/33/45/52/58 and all the ongogenic HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66/68.

(iv) Safety Analysis

Occurrence of reportable AEs and SAEs will be reported. Safety data analysis will be conducted on all patients receiving at least 1 dose of Gardsil9™. Analyses will consist of data summaries for clinical parameters, and for AEs. The number and percentage of patients experiencing 1 or more AEs will

be summarised by the relationship to study vaccine and severity. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. All available safety data will be provided to an IDMC at the interim and final efficacy analyses (see below). Periodic safety reviews will be conducted by the IDMC as described in the IDMC Charter.

We will commence the main analysis of study data once all participants have reached the 24-month timepoint, with an updated analysis of study data to occur once all 30-month samples have been collected. Full details are documented in the Statistical Analysis Plan (SAP) which will be finalised prior to the main analysis. Any deviation(s) from the final statistical plan will be described and justification given in the final report.

9 REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 1964 Declaration of Helsinki, and any relevant revisions.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 R2guidelines).

9.3 Independent Ethics Committee Approval

9.3.1 Initial Approval

Prior to the shipment of IMP and the enrolment of patients in each country, a REC must provide written approval of the conduct of the study in that country at named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the patients, any advertisements that will be used and details of any subject compensation.

9.3.2 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Amendments, including whether the changes are substantial or non-substantial, will be made in accordance with HRA and/or REC guidance as appropriate, with the decision being made by the Trial Management Group (TMG). Changes will be appropriately version controlled. In the case of protocol amendments, the amended protocol must be reviewed by all members of the Protocol Development Group prior to finalising, while amendments affecting stakeholders e.g. patient groups will require review prior to finalising where appropriate.

9.3.3 Annual Progress Reports

The REC will be sent annual progress reports in accordance with national requirements.

9.3.4 Annual Safety Reports and End of Trial Notification

The REC will be sent annual safety updates in order to facilitate their continuing review of the study and will also be informed about the end of the trial, within the required timelines.

9.4 Regulatory Authority Approval

The study will be performed in compliance with each country's regulatory requirements. Clinical Trial Authorisation from the appropriate Regulatory Authorities must be obtained prior to the start of the study. In addition, the Regulatory Authorities must approve amendments prior to their

implementation (as instructed by the Sponsor), receive SUSAR reports, DSURs, and be notified of the end of the trial.

9.5 HRA Approval – UK only

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.
The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.6 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.
An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.
A serious breach is defined as:
A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the trial patients; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the relevant competent authorities and ethics committees in the participating countries within 7 days of becoming aware of the serious breach.

9.7 Insurance and Indemnity

The Sponsor has civil liability insurance, which covers this study in the UK, Sweden and Finland.

9.8 Trial Registration

The study is registered on a trial database EudraCT 2018-004662-33 and Clinicaltrials.gov NCT03979014 in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

9.9 Informed Consent

The Principal Investigator at each site will:

- Ensure that each patient is given full and adequate oral and written information about the study including the background, purpose and risks/benefits of participation
- Ensure that each patient is notified that they are free to withdraw from the study at any time
- Ensure that each patient is given the opportunity to ask questions, allowed sufficient time to read and understand the information sheet, and given sufficient time to decide whether or not to take part
- Ensure each patient provides signed, dated informed consent before undergoing any study specific procedure
- Ensure the original copy of the signed, dated Informed Consent Form is stored in the patient's medical records and a copy is also filed in the Investigator site file

- Ensure that each patient receives a copy of the signed, dated Informed Consent Form

9.10 Contact with General Practitioner

It is the investigator's responsibility to inform the patient's General Practitioner (where applicable) by letter that the patient is taking part in the study provided the patient agrees to this, and information to this effect is included in the Patient Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

9.11 Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsors, patients will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to patients' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and RECs.

9.12 Data Protection and Patient Confidentiality

The investigator will preserve the confidentiality of all patients taking part in the study, which will be conducted in accordance with the Data Protection Act and EU General Data Protection Regulation (GDPR). The Patient Consent form will identify those individuals who will require access to patient data and identifiable details and obtain appropriate permission from the consenting patient.

9.13 End of Trial

The end of the trial is defined as the date of last data capture for the last patient active on study.

9.13.1 Post Study Follow Up

All patients recruited to the study, will be asked to give consent to be part of a follow-up cohort observational study with a follow-up period of 20 years. This will permit the assessment of long-term outcomes through national registries such as the incidence of invasive cervical/vaginal and other HPV-related cancers, recurrent high-grade precancer etc. Their samples may also be used for 20 years after the end of the trial. Patient will be unblinded and patient identifiable data will be required to link the name and national insurance number to national registries. If patients do not wish to give their consent to the follow-on study, they can still participate in the main study.

Individually-consented participants in the Trial may have their longer-term heath status followed up via data held by NHS Digital, NHS Health and Social Care Information Centre (HSCIC) or its successor, the Office of National Statistics, Public Health England and other national databases via a linkage completed by ICTU as the holder of the identifiable data. This is in line with the requirements for safety monitoring, funding conditions and maximising the individual's contribution to research. In such cases long term cancer registration and mortality data will be obtained from NHS Digital and the NHS Health and Social Care Information Centre (HSCIC) or

equivalent. A sophisticated encryption mechanism will be used to transfer patient details directly from practices to HSCIC.

It will enable the direct care team to invigilate if patients had further health problems after their enrolment in this study with specific focus on whether the patient returned to hospital and what further health problems developed in that period of time. Furthermore, it will also enable the direct care team to annotate whether the postcode that a patient lives in affects the health problems and medical care that they will receive.

In Sweden and Finland, similar national registries will be used for long-term outcomes and data collection.

9.14 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Patient files and other source data (including copies of protocols, CRFs/eCRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

10.1 Source Data

All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial are classified as source data. Source data are contained in source documents; these are defined as: original documents, data, and records e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

10.2 Language

eCRFs will be in English and must be completed in English. Generic names for concomitant medications should be recorded in the eCRF wherever possible. All written material to be used by patients must use vocabulary that is clearly understood and be in the language appropriate for the study site.

10.3 Database

The study eCRF was built in InForm. Data management will be performed using the electronic data capture (EDC) and management system. The system allows for real time oversight of trial activity including adverse event reporting, rapid data validation and data aggregation.

In 2023 the ECRF was migrated from InForm to OpenClinica.

AE data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, and CTCAE grade.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trial.

10.4 Data Collection

In compliance with Good Clinical Practice (GCP), the medical records/medical notes should be clearly marked and allow easy identification of a patient's participation in the clinical trial.

The Investigator (or delegated member of the site study team) must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy data into the trial electronic data collection (EDC) system.

Details of procedures for eCRF completion will be provided in the eCRF Completion Manual.

10.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

11. STUDY MANAGEMENT STRUCTURE

11.1 Trial Oversight Committees

11.1.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including an independent Chair, two independent clinicians, a patient representative, the Chief Investigator, Country Lead Investigators and the Trial Co-ordinator. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.1.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, Country Lead Investigators, co-investigators, key collaborators, trial statistician and trial co-ordinator. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.1.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be convened to monitor data collected during the study and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue. It will consist of an independent Chair, an independent statistician and an independent clinician. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.2 Early Discontinuation of the Study

In case of early discontinuation of the study, the end of treatment assessments should be performed for each patient remaining on study treatment.

11.3 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Trial Coordinator and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

11.4 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 R2 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data. Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

11.5 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

11.6 Peer Review

This study has undergone peer review by the following bodies:

- Imperial College London Cancer Clinical Trials Committee and the research team at Imperial College London (Chief Investigator's host institution)
- NCRI CSG
- Merck Pharmaceutical Company
- National Institute of Health Research Efficacy and Mechanism Evaluation Programme

11.7 Patient and Public Involvement (PPI)

11.7.1 Previous PPI Involvement

The team has actively involved patients and the wider public from the outset in determining the importance of the research question and in preparing the application. Increasing queries from patients about the value of vaccination after local treatment led to this trial as this has been identified as major scientific gap. Their views were explored through 20 informal interviews that helped prioritisation of the research questions. We discussed means of dissemination of findings and explored how the results may influence them. We discussed the project with the CEO of Jo's Trust (cervical cancer charity) and we intend not only to engage the charity but also patients and the public through this organisation. The Jo's Trust has conducted pioneering projects on patient information and the information needs of patients with precancer and invasive cervical cancer. Advice was taken from two patient representatives through the Jo's Trust, who had personal experience of pre -invasive and invasive disease and raises funds for research in cervical disease and prevention. The proposed project has also been discussed amongst leading academics at the BSCCP and IFCPC research committee and was also endorsed by the NCRI Gynaecological CSG.

11.7.2 Plans for future PPI Involvement

During the conduct of the trial, PPI will be actively involved in the proposed research in the following ways: Design of the research; developing participant information resources; Contributing to the reporting of the research and Dissemination of research findings.

We will form a PPI group with 4 representatives. We will also invite a PPI representative to be a member of the study TSC.

We will meet annually and will establish email communications. We will organise one annual meeting with a larger patient group, lay members, healthcare staff and carers. At the outset we will provide lay summaries and ensure the patients have clear understanding of the project. We will answer subsequent queries that may arise. The CI will be available to provide support by email to the patients' representatives. The lay advisory group that supports public engagement in health research will help to phrase research reports and information sheets in plain language so that these are best received and understood by the public, disseminated through Jo's Trust and HEI's websites, patients' forums and through the media (e.g. radio, interviews).

We will invite the group to offer feedback on how the summary findings could be best disseminated to the public. The group will help us to summarise reports on the research findings in lay language so that this will be better understood by the wider public. Materials will be sent to the PPI representatives by email ahead of the planned meetings so that the representatives are allowed sufficient time to prepare their comments. More specifically, we will ensure that we will receive

feedback from the representatives on the results that they consider important, that we have captured all the questions that are important to them and that the results are available in a usable and understandable format. If all the questions are not captured, that will inform priority research questions for further research. We will share our findings and the lay summaries and receive feedback. Based on this feedback, we will change and update the documents of the summary of research findings on the method of communication and dissemination of the findings. The representatives will also be invited to support public engagement events where the research findings will be presented and discussed.

We will evaluate the PPI involvement. We will do this by evaluating the PPI members' expectations of how their involvement will make a difference to the project before they undertake the next PPI steps and then again afterwards including their perspective of being involved in the project. We will also ask the researchers involved in the project to complete similar 'before and after' evaluation forms personalised to the project. Patient Experience Research Centre (PERC) has example templates.

The NIHR Imperial BRC Patient Experience Research Centre (PERC) has provided advice and will provide ongoing support with the proposed PPI. More specifically, our PPI team can facilitate and support PPI involvement and provide key documents that may be required to formalise the role of the PPI group. These include documents on how to reimburse expenses, consent forms, examples of evaluation forms for the impact of PPI on this project and for feedback generally and examples of agendas for the planned meetings. They further provide terms of reference for the PPI group to confirm the scope of the involvement of the members and the planned responsibilities within the group in order to manage expectations. These documents will soon be live in the PPI support section at Imperial College London. PERC can also provide PPI training for patients, public and researchers. We will offer appropriate PPI training to our patient representatives depending on their needs.

11.8 Publication and Dissemination policy

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TSC.

The results may be published or presented by the investigator(s), but only with the permission of the Sponsor and/or Funder.

A Clinical Study Report summarising the study results will be prepared and submitted to the ethics committees and competent authorities of the participating countries within one year of the end of study. The results will also be submitted to the EudraCT results database in accordance with regulatory requirements.

Appendix A

The undesirable effects as documented in section 4.8 the Summary of Product Characteristics released on 16th May 2019. Please always check the link below for any updates:
https://www.medicines.org.uk/emc/product/7330/smpc

4.8 Undesirable effects

A. Summary of the safety profile

In 7 clinical trials, individuals were administered Gardasil 9 on the day of enrolment and approximately 2 and 6 months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of Gardasil 9. A total of 15,776 individuals (10,495 subjects aged 16 to 26 years and 5,281 adolescents aged 9 to 15 years at enrolment) received Gardasil 9. Few individuals (0.1%) discontinued due to adverse experiences.

The most common adverse reactions observed with Gardasil 9 were injection-site adverse reactions (84.8% of vaccinees within 5 days following any vaccination visit) and headache (13.2% of the vaccinees within 15 days following any vaccination visit). These adverse reactions usually were mild or moderate in intensity.

B. Tabulated summary of adverse reactions

Clinical trials

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)

Table 1: Adverse reactions following administration of Gardasil 9 occurring with a frequency of at least 1.0% from clinical trials

System organ class	**Frequency**	**Adverse reactions**
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Common	Nausea
General disorders and administration site conditions	Very common	At the injection site: pain, swelling, erythema
	Common	Pyrexia, fatigue, At the injection site: pruritus, bruising

In a clinical trial of 1,053 healthy adolescents aged 11 to 15 years, administration of the first dose of Gardasil 9 concomitantly with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine showed that more injection-site reactions (swelling, erythema), headache and pyrexia were reported. The differences observed were < 10% and in the majority of subjects, the adverse events were reported as mild to moderate in intensity (see section 4.5).

Post-marketing experience

The following adverse experiences have been spontaneously reported during post-approval use of qHPV vaccine and may also be seen in post-marketing experience with Gardasil 9. The post-marketing safety experience with qHPV vaccine is relevant to Gardasil 9 since the vaccines contain L1 HPV proteins of 4 of the same HPV types.

Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure.
Infections and infestations: Injection-site cellulitis.
Blood and lymphatic system disorders: Idiopathic thrombocytopaenic purpura, lymphadenopathy.
Immune system disorders: Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm and urticaria.
Nervous system disorders: Acute disseminated encephalomyelitis, Guillain-Barré syndrome, syncope sometimes accompanied by tonic-clonic movements.
Gastrointestinal disorders: Vomiting.
Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.
General disorders and administration site conditions: Asthenia, chills, malaise.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Appendix B

Local cervical treatment has been associated with a number of complications that, were they to occur and a) be related to local cervical treatment and b) meet the definition of serious as per section 7.4.1, will require reporting to sponsor. These events are listed as follows and taken from information available at https://www.nhs.uk/conditions/colposcopy/treatment/:
- pain and discomfort
- primary haemorrhage
- secondary haemorrhage
- infection
- per vaginum discharge
- vasomotor symptoms

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13. SIGNATURE PAGES

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: NOVEL: Nonavalent HPV vaccine after local conservative treatment for cervical intra-epithelial neoplasia: A randomised controlled trial

Protocol Number: C/39/2018

Signed: _____

Dr Maria Kyrgiou
Clinical Reader and Honorary Consultant

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: NOVEL: Nonavalent HPV vaccine after local conservative treatment for cervical intra-epithelial neoplasia: A randomised controlled trial

Protocol Number: C/39/2018

Signed: _____

Ruth Nicholson
Head of Research Governance and Integrity
Joint Research office
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: NOVEL: Nonavalent HPV vaccine after local conservative treatment for cervical intra-epithelial neoplasia: A randomised controlled trial

Protocol Number: C/39/2018

Signed: _____

Professor Peter Sasieni
Professor of Cancer Epidemiology
Queen Mary University of London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: NOVEL: Nonavalent HPV vaccine after local conservative treatment for cervical intra-epithelial neoplasia: A randomised controlled trial

Protocol Number: C/39/2018

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____