Full title: Nonavalent prophylactic HPV vaccine (Gardasil® 9) after local conservative treatment for cervical intra-epithelial neoplasia: a randomised controlled trial – The NOVEL trial

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Introduction

We would like to invite you to take part in our research study. Before you decide if you want to take part, we would like you to understand why the research is being done and what it would involve for you. Someone from our team will go through this patient information sheet with you and answer any questions you have. Please read the information carefully and talk to others, including your GP, about the study if you wish.

Part 1 tells you about the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about how we are conducting the study.

We have also included a Study Flowchart at the end which summarises the main steps involved. Please ask us if there is anything that is not clear, or if you would like more information. Take as much time as you need to decide whether or not you wish to take part. If you decide to take part, you will be asked to sign the informed consent form and you will receive a copy for your records.

Thank you for taking the time to read this information sheet.
Part 1

1 What is the purpose of the study?

Human Papilloma Virus (HPV) is a common virus and most people who are sexually active will come into contact with it, but only a few subtypes have been found to be directly associated with cervical cancer. Vaccines are highly effective in preventing HPV infection in women, and there is a national HPV vaccination programme in the UK available to all girls and more recently boys yet to reach puberty. However, vaccines are not effective against already established infections.

High grade cervical intraepithelial neoplasia (CIN), also known as high grade precancer, is caused by persistent HPV infection. These women are at high risk of developing cervical cancer. The standard local treatment is a procedure where diathermy, scalpel, or laser surgery is used to remove a cone shaped area of the cervix containing the abnormal cells.

The women who develop high-grade CIN are seen as being sensitive to HPV infection after treatment and can become rapidly re-infected. This group remain at high risk for cervical precancer, cervical cancer and other cancers related to HPV e.g. vaginal. If there is a need for repeat local treatment, this can increase the risk of premature birth in future pregnancies for women of child-bearing age.

Research has suggested that giving a HPV vaccine to women receiving local treatment for high grade precancer may reduce the rates of re-infection and development of precancer, and ultimately limit the number of cervical cancer cases as a result. However a clinical trial is needed to confirm whether this is the case.

The NOVEL trial will see whether a specific HPV-vaccine, called Gardasil®9, when started at the time of local treatment, will reduce subsequent HPV infections in women with high-grade precancer. If the study shows benefits in this high-risk population, this vaccine may be offered to all women planned for local treatment. The national vaccination programme may then consider this evidence and expand vaccination to women after local treatment as a result.

This trial is funded by the National Institute of Health Research in the UK, with additional financial support from Merck Sharp and Dohme (MSD) Ltd.

2 Why have I been invited to take part?

You have been invited to take part in this study because you are aged 18 to 55 and need to have local treatment for a presumed or confirmed high-grade cervical precancer. Your doctor thinks you may be suitable to take part in this research and, if you decide to take part, you will be one of the 1000 women recruited into the study from the UK, Finland and Sweden.

3 Do I have to take part?

Taking part in this study is entirely voluntary. It is up to you to decide whether or not to take part. Before you make your decision, your study doctor will describe the study and go through this information sheet with you. If you do decide to take part after reading this information leaflet, you will be asked to sign a consent form and you will be given a copy to take away with you together with this information sheet. If you prefer not to take part, you do not have to give a reason and your doctor will proceed with your planned treatment.
You are free to withdraw from the trial at any time, without giving a reason. This would not affect the standard of care you receive.

Your gynaecology specialist or the study sponsor (Imperial College London) may decide at any time, and for any reason, to stop study vaccine administration to trial participants, even though you may want to continue. Your study doctor will explain the reasons why you have to stop and discuss further management. Full details are included in section 8 and Part 2 of this information sheet.

4 What will happen to me if I take part?
The study is split into 3 steps. Each step is explained in this section, and there is also a Study Flowchart at the very end of the information sheet which summarises everything for you.

Step 1: Eligibility & Consent and screening period (before study entry)
Your medical history will be taken during this visit to check that you are eligible for the study. If you are interested in joining the study, you will be asked to sign and date the study consent form.

Women who are confirmed to be suitable to take part in the study will then continue to Step 2 of this section.

Women who are confirmed not to be suitable to take part in the study will unfortunately not be able to take part, and their doctor will continue their management according to current recommended practice.

If you are found to be suitable to take part in this study and you wish to take part, your details will be registered with the trials office responsible for coordinating the study. The NOVEL study is a randomised clinical trial made up of two treatment groups or ‘arms’. The way we ensure that women in the two groups are as similar as possible is to randomly allocate them to one of the two groups. This means that if one group does better than the other, it is more likely to be because of the vaccine, and not because the women in each group are different from each other in some way. A computer programme is used to perform the randomisation to make sure it is done fairly. You will be told by your study doctor which group you are in.

There are two groups in this study as follows:
- **Group 1** – 500 women will receive Gardasil® 9 vaccine at the time of local treatment, then 2 after local treatment, and finally 6 months after local treatment;
- **Group 2** – 500 women will not receive the vaccine at the time of local treatment, and be followed up within the study.

Whether or not you receive the vaccine, you will remain in the study and be followed up the same way until the end of study visit which will be 24 months after your local treatment unless you explicitly withdraw your consent for this; in a small number of women the follow up period may be extended to 30 months (see Step 3 for more information on this); the follow-up and end of study visit are explained in Steps 3 and 4. Your doctor will discuss options for further management and/or treatment that may be indicated during the follow up period as appropriate.

Step 2: Study vaccine and assessments during the initial visit
Some examinations and tests done during the initial visit are standard while others are extra for the study, and this is explained below.
Routine examination, treatment & tests
• Gynaecological examination, local treatment. Information on these will be given to you by your study doctor and you may also be given separate standard patient information.

Extra examinations, treatments & tests
• As part of your diagnosis and the local treatment given at the initial visit, tissue will be collected and looked at by your hospital and this is routine. However, the tissue from local treatment will then be sent centrally to the sponsor Imperial College London for research purposes.
• A ‘smear’ test for research purposes. The sample will be sent to a HPV Laboratory in Sweden and looked at to try and find ‘markers’ that may predict effectiveness of the vaccine. This requirement is optional and you should indicate on the consent form whether you agree to it.
• Swabs for research purposes, taken from the skin around the genital area (vulva) and anal and perianal area (back passage). The swabs will be taken during the gynaecological examination just prior to local treatment. The samples will be looked at to try and find ‘markers’ that may predict effectiveness of the vaccine. This requirement is optional and you should indicate on the consent form whether you agree to it.
• A blood sample for research purposes (4 teaspoons which is 20ml). The sample will be looked at to try and find ‘markers’ that may predict effectiveness of the vaccine. This requirement is optional and you should indicate on the consent form whether you agree to it.
• If you are randomised into the vaccination group, you will get your first vaccine on the day of the local treatment and you will return at month 2 and 6 for the 2nd and 3rd injection of the vaccine. You will be asked to take a urine pregnancy test before each injection.

Step 3: Follow-up period & End of Study period
All participants will be followed up for a minimum of 24 months (2 years) after the time of local treatment, or 30 months (2 and a half years) if you are found to be positive for HPV for the first time at the 24 month visit. Follow up will be stopped if you no longer wish to participate. However, unless you explicitly withdraw your consent to take part, you will remain in the study until the end of the follow up period.

Some tests are routine and some are extra for the purpose of the study. Those tests are the same no matter what treatment group you are randomly assigned to and are described below:

Routine tests and tests
• You will be invited to return clinic 6 months after local treatment for a gynaecological examination and a routine ‘smear’ test and liquid based cytology ‘smear’. If any of these are abnormal, you will be managed according to current clinical recommendations and you may require further treatment. Your study doctor will explain this to you.

Extra tests and visits
• 6 months – In clinic will be asked to give a ‘smear’ test, swabs and blood sample for research purposes, the same as for the initial visit. The samples will be looked at to try and find ‘markers’ that may predict effectiveness of the vaccine. This requirement is optional and you should indicate on the consent form whether you agree to it.
• 12 (1 year) and 18 months (1 and a half years) - a ‘self-sampling’ swab kit for HPV testing will be posted to your home with clear instructions for the collection process and its return. You may be contacted by telephone, post or email for a reminder and to ask questions about your health and side effects.

• 24 months (2 years) - You will be asked to attend clinic for a gynaecological examination. During this examination a ‘smear’ test, swabs and blood sample will be collected for research purposes, the same as for the initial visit. The samples will be looked at to try and find ‘markers’ that may predict effectiveness of the vaccine. This requirement is optional and you should indicate on the consent form whether you agree to it.

• NB If you are unable to attend clinic for this visit at 24 months, a test kit will be sent to you by post for HPV self-sampling swab. If you test positive for HPV for the first time at 24 months, a self-sampling swab kit will also be sent in the post at 30 months (2 and a half years) after local treatment.

At each visit your study doctor or nurse will perform an assessment of any side effects that you have experienced and ask you questions about any changes to your medication or health that may have occurred since the last visit. This will take approximately 5 minutes.

5 What do I have to do?

If you take part in this study, you will need to follow the study vaccine plan, tests and clinic appointments explained in section 4. There will be one additional visit at 24 months (2 years) that is not part of routine care in most clinics. There will be an additional visit at 2 months for the second dose of the vaccine for those that are randomised to the vaccine. You should consider how these tests and visits will affect your work and family life and decide if you are able to commit to them. The care team at your clinic will ask you questions about any side effects, new medication or health problems during your visits, or contact you over the phone. You will be able to contact them in between visits if there is anything important that you wish to report.

If you are successfully enrolled in the study, whether you receive the vaccine or not:

• The study doctor or nurse will discuss with you when to come to the clinic and return self-sampling swab kits.

• You must be available for follow-up calls throughout the study to report any side effects or changes in medication or your health.

• If randomised in the vaccine arm, you will receive the vaccine, as described below:

Gardasil® 9 - (0.5ml) will be administered as a 3-dose (0, 2, 6 months) schedule. The vaccine will be administered as an intramuscular injection, usually in your upper arm or upper thigh.

6 What are the side effects of any treatment received when taking part?

Gardasil® 9 vaccine is used in vaccination programmes of girls and, in some countries boys with high efficacy in the prevention of HPV infection and precancer. Hundreds of thousands of Gardasil® 9 vaccine doses have been given and no vaccine specific serious harms or side-effects have been noticed.

There are no safety concerns. There are side effects that may develop during or immediately after the administration of Gardasil 9. The most common side effects of the vaccine Gardasil® 9 are at the injection site and include pain, swelling, redness, itching, bruising, bleeding, a lump and, rarely, infection. Women receiving the vaccine may also experience headache, fever, nausea, dizziness, tiredness, diarrhoea, abdominal pain, and sore throat. Fainting can happen after or even before receiving Gardasil® 9 (or any vaccine). Sometimes people who faint can fall and hurt themselves. For this reason, your study doctor may ask you to sit or lie down for 15 minutes after you get Gardasil® 9. Some people who faint might shake or become stiff. The study doctor may need to treat the person receiving Gardasil® 9.
Anaphylaxis is an allergic reaction to the vaccine and is a very rare side effect of the vaccine that has been reported in 2.6 per 100,000 doses of the vaccine. Anaphylaxis is potentially life-threatening, usually develops suddenly, can lead to shock and needs immediate medical help. As with all injectable vaccines, appropriate medical treatment and supervision will always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

If you experience any side effects beyond those described above that are not known about yet or changes to your general health, you need to report them to your study doctor or research staff immediately. Your study doctor will help you manage any side effects that you experience. More information about Gardasil® 9 side effects can be found here: https://www.gardasil9.com/about-gardasil9/side-effects-and-safety/

7 Pregnancy and breastfeeding
Females who are pregnant or intending to become pregnant during the next 6 months are not eligible to take part in the study. Gardasil® 9 is not recommended for use in pregnant women, although the vaccine has not been associated causally with adverse outcomes of pregnancy or adverse events in the developing foetus. We will perform a pregnancy test before each dose for women receiving the vaccine. 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. If a vaccine dose has been administered during pregnancy, no intervention is needed. Your pregnancy will be followed if you have given us the permission to do so during the informed consent. The Pregnancy follow-up data will be shared with the Sponsor (Imperial College London) and the part funder (Merck Sharp and Dohme (MSD) Ltd).

Women who are breastfeeding may be vaccinated. There is no data to suggest harmful effects on fertility.

8 Will I be compensated for taking part in the study?
You will not be paid for taking part in the study. However, a contribution may be made towards travel expenditure for the additional visits. If you wish to find out more about this, please talk to your study doctor or nurse.

9 What are the possible benefits of taking part?
You may benefit directly as a result of taking part in this study if the vaccine is proven to be effective in preventing persistent high-risk HPV infection after treatment. The administration of the vaccine after local treatment is currently not part of the national immunisation programme and is not provided outside of this clinical trial. The results of this study will also help in understanding the benefits of Gardasil® 9 in women after treatment and if proven to be beneficial may lead to better prevention of cervical precancer and cancer in the future.

You will have additional visits in the clinic, although the results of the research tests will not be used for clinical management; it is important to have the tests and management recommended by your study doctor, and you may benefit indirectly from the closer monitoring that the additional visits will bring. The Sponsor does not intend to provide you with financial or other personal benefits that may result from the study.

10 What are the possible disadvantages and risks of taking part?
It is possible that there will be no health benefits gained by you during or following completion of this study. You may also experience side effects from the vaccine as mentioned in section 6. In addition, you may feel discomfort during some of the tests mentioned in section 4, which may include:
• **Cytology and Swabs:** the gynaecological examination can cause discomfort to some women. The collection of the liquid-based cytology sample (‘smear’) can cause some discomfort, cramps and spotting.

• **Blood samples:** As with all blood tests, there is a possibility of slight redness, inflammation and/or bruising developing at the site where the needle is placed into your arm. It is also possible that you may feel lightheaded or faint. Please tell the study doctor or nurse if you do not feel well after having your blood taken.

• **Local Treatment:**
This procedure is part of your routine treatment for the precancerous cells. The procedure refers to an excision of a cone-shaped sample of tissue containing abnormal cells from the mucous membrane of the cervix. The sample will then be sent to the histopathology laboratory for examination. This procedure is performed under a local anaesthetic (which means you are not asleep throughout) or sometimes under general anaesthetic (which means you are asleep throughout) and takes approximately 15 minutes:

**11 What are the alternatives for treatment?**
If you decide not to take part in this study, your doctor will discuss routine follow-up that does not include vaccination.

**12 What happens when the research stops?**
The study will end approximately 6 months after the last participant completes follow-up. After this point, Gardasil® 9 will not be available to patients in the clinic. In addition, Imperial College London (the sponsor), the trial’s Research Ethics Committee (REC), Regulatory Authority, or the pharmaceutical company supplying the vaccine (Merck MSD Ltd) may decide to stop the study for valid reasons not listed above. If this happens, your study doctor will discuss with you in full, including a plan for your future care as appropriate.

**13 What if there is a problem?**
Your study doctor will be there to answer any questions you might have regarding the precancer, its treatment and your participation in the study. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, then there will be several options available to you. Full details are included in Part 2 of this information sheet.

**14 Will my taking part in the study be kept confidential?**
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Full details are included in Part 2 of this information sheet.

If the information in Part 1 has interested you and you are considering taking part in the study, please read the additional information in Part 2 before making your decision.
Part 2

15 What if new information becomes available?
Sometimes we get new information about the vaccine being studied. If this happens, your study doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your study doctor will make arrangements for your care to continue. If you decide to continue in the study your doctor may ask you to sign an updated consent form.

Also, on receiving new information your study doctor might consider it to be in your best interests to withdraw you from the study. They will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

16 What will happen if I don’t want to carry on with the study?
You must tell your doctor immediately if you no longer wish to take part in the study. Your doctor will discuss further management with you as appropriate. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will not collect any new information about you, but we will keep the information about you that we have already obtained including any optional research samples i.e. ‘smear’ tests, swabs, and blood and tissue samples unless you specifically withdraw your consent for their use. To safeguard your rights, we will use the minimum personally-identifiable information possible. Your study doctor can also stop study intervention at any time e.g. if this is clinically indicated, or another condition develops that may mean you are unable to carry on receiving study treatment.

17 What if there is a problem?

Complaints
If you have a concern about any aspect of this study, you should contact your study doctor whose number is on the first page of this information sheet, who will do their best to answer your questions. If you wish to complain or have any concerns about the way that you have been approached or treated during the course of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact your study team on (xxxxx). If you remain unhappy and wish to complain formally, the usual complaint mechanisms will be available to you. Details can be obtained from the hospital or clinic (please insert country specific information) or via [insert telephone number]. If you are still not satisfied with the response, you may contact the sponsor, Imperial College Joint Research Office on +44 (0)20 7594 9459.

What happens if I am injured as a result of taking part in this research study?
Every care will be taken in the course of this clinical trial. However, in the unlikely event that you are injured by taking part, compensation may be available. If you suspect that the injury is the result of the Sponsor’s (Imperial College London) or the hospital’s negligence, then you may be able to claim compensation. After discussing with your study doctor, please make the claim in writing to Dr Maria Kyrgiou who is the Chief Investigator for the clinical trial and is based at Imperial College London. The Chief Investigator will then pass the claim to the Sponsor’s Insurers, via the Sponsor’s office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.
Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of Imperial College London or another party. You should discuss this possibility with your study doctor in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical trial, the normal (please insert country specific organisation) complaints mechanisms are available to you. Please ask your study doctor if you would like more information on this. Details can also be obtained from the Department of Health website (Please insert country specific information).

18 Will my taking part in this study be kept confidential?

Imperial College London is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep identifiable information about you for 10 years after the study has completed in relation to primary research data.

Further information on Imperial College London’s retention periods and Imperial College London’s data protection please contact Imperial College London’s Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on +44 (0)20 7594 3502 and via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

YOUR RIGHTS

Your usual statutory rights to access, change or move your information are limited, because of exceptions applicable to some types of research, and also because we need to manage your information in specific, lawful ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

LEGAL BASIS Country specific

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

INTERNATIONAL TRANSFERS

There may be a requirement to transfer information to countries outside the European Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection
standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

**CONTACT US Country specific**

If you wish to raise a complaint on how we have handled your personal data or if you want to find out more about how we use your information, please contact Imperial College London’s Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on +44 (0)20 7594 3502 and via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner’s Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

[Please enter site name] will collect information from you and/or medical records for this research study in accordance with our instructions.

[Please enter site name] will keep your name, NHS number and contact details confidential and will not pass this information to Imperial College London. [please enter site name] will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the study sponsor, Imperial College London and its representatives, Imperial College Healthcare NHS Trust and its contractors, MSD Company Ltd., contracted companies conducting laboratory tests, and regulatory authorities may look at your medical notes and data collected where it is relevant to your participation in the study. These individuals will not receive any data that will enable them to identify you. This also applies to the individuals who will be involved in the analysis of study data at the end of the trial.

[Please enter site name] will keep identifiable information about you from this study for 10 years after the study has finished.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research. For more information please contact your site on___________.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

19 Involvement of the General Practitioner (GP) (UK participants only)

With your permission, indicated on the consent form, we will inform your GP about your involvement in this study. Should you experience any side effects or symptoms outside your clinic appointment days and been in touch with your GP, he/she will share this information with your study doctor.

20 What will happen to any samples that I give?

This is explained below. Samples will be kept for a maximum of 15 years from the end of the whole study, after which point they will be destroyed. If you are confirmed not to be suitable to take part in the study, the study doctor will arrange to have the samples destroyed. If you are suitable to take part then you may
withdraw your consent for their use at any time without giving a reason and without your medical treatment or legal rights being affected, and the study doctor will arrange to have the samples destroyed.

**Cytology, swab and tissue samples:** Your samples will be analysed for HPV DNA typing, presence of precancerous cells and other biomarkers that may influence the development of cervical disease or show how people respond to the study vaccine. The data may be used to develop a diagnostic or predictive test: a medical procedure performed to help diagnosis or prediction of response to the vaccine, or to guide treatment decisions. Archival samples will be reviewed and then returned to the local hospital pathology department for archiving; slides may be kept in the Central Pathology Laboratory of the Trial at Imperial College London after the study completion. Tissue from local treatment will be kept for at least the duration of the study and used for further ethically approved commercial and/or non-commercial research in the field of HPV research. This further research may involve International partners.

**Research Blood Samples** Research bloods will be used to examine DNA and various biomarkers. These biomarkers may predict who would benefit the most from the vaccine. As the samples are being taken before, during and after the vaccine, they will help us understand how the vaccine works. This will also enable us to learn whether or not the treatments have the desired effect, and to understand if these effects may be beneficial for the prevention of cervical disease. This information may also be used to develop and test other new treatments in the future. The research samples will be kept for the duration of the study and, if you consent, used for further ethically approved commercial and/or non-commercial research in this field of research on HPV. This further research may involve international partners.

20.1 **What rights do I have to see the results of the biomarker research and personal data?**

These parts of the study are for exploratory research purposes only. You will be provided with results of tests that may be important for clinical management. You will not otherwise be provided with your test results, nor will any results be made available to any insurance company, your employer, your family, your study doctor, your GP, or any other doctor who treats you now or in the future.

20.2 **What rights do I have to the results of the biomarker research?**

Any information derived directly or indirectly from this research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research, are the sole property of the study sponsor (and its successors and licensees) and may be used for commercial purposes. You will have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing the consent form and offering samples for research, you do not give up any rights that you would otherwise have as a participant in research.

21 **Data collection from NHS Digital**

We will ask if you are happy to allow follow up of your health status over time. This will be done by linking your name and NHS number with records held by NHS Digital and maintained by the NHS Central Register or any applicable NHS information system. NHS Digital is part of the Department of Health. It aims to provide high quality patient information for health and social care services to meet the country’s needs and plan for the future, in order to give you the best possible care. Further details are available at [https://digital.nhs.uk](https://digital.nhs.uk)
The study researchers would like to know whether you have further health problems after your enrolment in this study. Specifically, we would like to know about whether you return to hospital after your study treatment and, if so, whether any health problems have developed. Furthermore, we would like to know whether the postcode that you live in affects the health problems and medical care that you will receive – known as Index of Multiple Deprivation or IMD. In order to find this out, we will send your NHS number, date of birth and postcode to NHS Digital – this identifiable information will not be sent to Imperial College London or any other individuals who may look at your medical notes and data collected for the study, meaning that your confidentiality will be protected. NHS Digital can then provide us with details of your past and future hospital records, current health status and survival status. These data will be supplied by NHS Digital on behalf of the Office of National Statistics. Other details that may be requested include attendance in the Emergency or Outpatient Department, or admission to the hospital wards and hospital critical care units and mental health data. This information will be used to decide whether we are giving the right amount of medical attention to the patients who will go on to need medical care the most.

We will collect your data from NHS Digital for 20 years.

For more information about how NHS Digital uses your personal data including their lawful basis for processing, how long they hold it for and your rights, please contact your site on ______.

All of the above are optional and you do not have to give your consent. If you do not wish to give permission, you can still participate in the study.

22 What will happen to the results of the research study?

After completion of the study the results may be presented at national/international scientific meetings or published in a leading medical journal by your gynaecology specialists, the study team and the sponsor Imperial College London, lay summaries will be published on websites as appropriate. Individual patient results will not be available as this treatment is not standard of care in this population group. Published results will be available if requested. At no point in the analysis or publication will any information about the identity of individual patients be revealed. A copy of the results will be circulated to your GP/Doctor. Please note that if any inventions resulting in commercial gain emerge from any of the above research, you will not be eligible to benefit financially from these discoveries.

23 Who is organising and funding the research?

Imperial College London is the legal sponsor of this study and is organising the study through the Imperial Clinical Trials Unit – Cancer (ICTU-Ca). The trial is primarily funded by the National Institute of Health Research (NIHR), with some additional funding and the vaccine being provided by a pharmaceutical company, Merck MSD Ltd.

Imperial College London will offer financial support to your hospital for including you in this study, but your doctor will not receive any personal financial payment if you take part.
24 Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by London – Brent Research Ethics Committee.

25 Further information and contact details
If you have additional questions during the course of this study about the research or your rights as a research patient, you may address them to the study doctor(s) <insert name of doctor and tel.no> or the study staff <insert name and tel. no.> Out of office Hours <insert name and tel.no> please contact this study doctor in the event of the following occurring:

a) If you suffer an illness or a possible study related injury
b) If you feel different in any way
c) If you are admitted to hospital for any reason
d) If you are seen at a casualty (accident/emergency department) for any reason

Thank you for taking the time to read this information sheet.

If you decide you would like to take part, you will be given a copy of this information sheet to keep together with a copy of your signed consent for
**Figure 1: Study flow chart**

**Multicentre randomised controlled trial**
**UK, Finland, Sweden**

Target population: Females aged 18 and 55 years with presumed or biopsy-confirmed CIN 2, CIN 3, glandular intra epithelial neoplasia (cGIN) or adenocarcinoma in situ (AIS)

- **Gardasil® 9 vaccine (n=500)**
  - Local cervical treatment
  - Clinic collected research HPV test, swabs, blood sample
  - Vaccination

- **Allocation 1:1 ratio**
  - Visit 1
  - 0 months

- **No vaccine (n=500)**
  - Local cervical treatment
  - Clinic collected research HPV test, swabs, blood sample

- **Vaccination**
  - Visit 2
  - 2 months

- **LBC + Local HPV test**
  - Clinic collected research HPV test, swabs, blood sample
  - Vaccination

- **Visit 3**
  - 6 months

- **Self-sampling research HPV test**

- **Visit 4**
  - 12 months

- **Self-sampling research HPV test**

- **Visit 5**
  - 18 months

- **LBC + Local HPV test (Finland only)**
  - Clinic collected research HPV test, swabs, blood sample
  - HPV self-sampling will be offered to those who default or do not wish to attend

- **Visit 6**
  - 24 months

- **Self-sampling research HPV test (only if HPV+ve for 1st time at 24m)**

- **Visit 7**
  - 30 months

- **LBC + Local HPV test (Finland only)**
  - Clinic collected research HPV test, swabs, blood sample
  - HPV self-sampling will be offered to those who default or do not wish to attend

- **Self-sampling research HPV test (only if HPV+ve for 1st time at 24m)**