PRedICT-TOPIC

Patient information folder for participation in medical scientific research

Investigating predictive factors for response to treatment with imiquimod cream in CIN abnormalities (PRedICT-TOPIC study)

Introduction

Dear madam,

You are receiving this letter because the doctor has found abnormal cells in your cervix. We would like to ask you if you would consider participating in medical research. Participation is voluntary.

In this letter you can read about the research, what it would mean for you and what the advantages and disadvantages are. This letter contains a lot of information and we would ask you to read it carefully and decide if you would be prepared to participate. If you wish to participate, you can fill in the form that you will find in appendix E: 'Consent form to participate in the study'.

Ask your questions

You can make your decision on the basis of the information in this information letter. In addition, we recommend that you do the following:

- Ask the researcher who gave you this information questions.
- Talk to your partner, family or friends about the study.
- Ask your doctor questions about the treatment.
- Request further information about your participation in this study from the independent expert.
- Read the information at: https://www.government.nl/documents/leaflets/2020/06/03/medical-research-information-for-human-subjects

1. General information

This research has been set up by the Catharina Hospital Eindhoven. Below we will refer to the Catharina Hospital Eindhoven as the 'client'. Researchers, who can be doctors (in training), researchers and research nurses, carry out the research in different hospitals.

510 participants are needed for this study.

The medical ethics review committee MEC-U has approved this study.

2. What is the aim of this study?

We wish to investigate what factors can predict the response of abnormal cells of the cervix (CIN) to imiquimod cream. We also wish to investigate what factors can predict a spontaneous disappearance of CIN without treatment.

You have recently undergone a colposcopy (examination of the cervix with a microscope), in which ‘abnormal cells' were found in the cervix. These abnormal cells are referred to as high-grade cervical intraepithelial neoplasia (also known as CIN 2 or CIN 3). CIN 2 and 3 are caused by a virus: the human papilloma virus (HPV virus). A small percentage of CIN 2 and 3 could develop into cervical cancer over a long period of time. The rest of the CIN lesions will remain a CIN or will disappear on their own. We can treat CIN by removing part of the cervix: this is called a loop excision, or with a cream: imiquimod cream. Imiquimod cream stimulates the body's immune system against viruses. This treatment has previously been tested in patients with CIN. Based on these studies, we expect that treatment with imiquimod cream will be effective in approximately 50-60% of women. With this research we want to achieve four things:

1. To investigate whether it is possible to predict which women will respond to treatment with imiquimod cream. In this way we hope to increase the effectiveness of the treatment and avoid unnecessary treatment with imiquimod.
2. Investigate whether we can predict which women with recurrent CIN will respond to treatment with imiquimod cream.
3. Investigate if we can predict in which women with CIN 2 who do not wish treatment, the CIN abnormality will disappear on its own and in who it will remain present.
4. Gain more information about the effectiveness of treatment with imiquimod cream, also on the long term.

3. What is the background of the research?

The treatment with imiquimod cream works in a percentage of patients and has some major advantages. The main advantage is for women who still want to have children.
In some cases of CIN 2 the choice can be made not to treat, but to wait for the possibility of the abnormality disappearing spontaneously.
For other CIN 2 abnormalities and all CIN 3 abnormalities, treatment is recommended. The most commonly performed treatment for CIN abnormalities is the loop excision, in which part of the cervix is removed. If you become pregnant after this treatment, the risk of the baby being born prematurely increases two fold. A premature birth can sometimes cause serious harm to the baby. Nowadays we can also treat CIN abnormalities with imiquimod cream (which means that we no longer have to remove part of the cervix). This is likely to eliminate the higher risk of preterm birth. Imiquimod is a 16 week treatment, but it does not work equally well for everyone. In addition, the treatment can have side effects. If we can predict a successful treatment in the future based on characteristics present in the CIN tissue, unnecessary side effects for patients can be prevented. In this way we can select the patients who are likely to benefit from the treatment and with that we hope to increase the effectiveness of imiquimod cream.

4. The course of the study

How long will the study take?
If you participate in this research, it will take about 20 weeks in total.

Step 1: are you suitable to participate?
We first want to know if you are suitable to participate. The doctor has performed a colposcopy, in which abnormal cells (CIN 2 or CIN 3) of the cervix were found.

In this study, the standard treatment of CIN 2 or 3 abnormalities with imiquimod cream is followed. You can choose for yourself, after an explanation from your physician, how you want to be treated for your CIN abnormality; with imiquimod or with a loop excision. In the case of CIN 2, you can also opt for a wait-and-see policy with a follow-up after 6 months. If you choose for a loop excision, you cannot participate in the study. If you choose for a wait-and-see policy for CIN 2 or for treatment with imiquimod, you are eligible to participate.

If you want to participate in this study, your doctor will send you a vaginal swab by post or your doctor will give you a vaginal swab during the consultation. You can take this swab yourself at home. This is very simple. The collection instructions are included with the vaginal swab you receive. If you have opted for treatment with imiquimod, you will have to take the vaginal swab before you start treatment with imiquimod. If you have opted for a watch and wait policy, you will take the vaginal swab within 1 week after receiving the vaginal culture. After taking the vaginal swab, please send it back to us in the return envelope provided.

Step 2: Using imiquimod
You will be using imiquimod for 16 weeks. Imiquimod is a cream and is also called 'Aldara'. Imiquimod stimulates the production of certain substances in the immune system, which strengthens the defense system against viruses. Previous studies on the treatment of CIN abnormalities with imiquimod show promising results and the treatment has now been included in the Dutch Guidelines for the treatment of CIN. In appendix B: 'practical information about treatment with loop excision and imiquimod' you will find more information about the treatment with loop excision and the treatment with the imiquimod cream.

The treatment lasts 16 weeks. Four weeks after ending this treatment, a colposcopy is done to investigate whether the abnormality responds to the treatment. This involves examining the effect of the imiquimod cream on the CIN abnormality. Based on the effect of the treatment, the following options are possible:
1. The abnormality has disappeared: no further treatment, but a check-up pap smear will be taken after 6 months to check whether the abnormality remains absent.
2. The abnormality has decreased to CIN 2, or in the case of CIN 2 has remained the same: no further treatment, but a check-up pap smear will be taken after 6 months to check whether the abnormality has disappeared or remains present. If the abnormality has not decreased sufficiently, we could still perform a loop excision after 6 months.
3. The abnormality has increased to CIN 3 or, in the case of CIN 3, has remained the same: the abnormality is treated by removing the abnormal part of the cervix with a loop excision.

Step 3: examinations and measurements

While you are being treated with imiquimod, you will have a few extra check-ups, namely 3 telephone appointments and 1 colposcopy appointment in the hospital after 20 weeks. During these (telephone) appointments we will discuss your experience with the imiquimod cream, including the side effects and after 20 weeks you will be examined by means of colposcopy to view the effect of the imiquimod cream. During the colposcopy a vaginal swab will be taken by your doctor. In addition, we ask all study participants to record side effects of their treatment in an online calendar. After the treatment you will be followed-up according to the standard guidelines with a number of pap smears. We do this to make sure that the CIN abnormality stays away, and these will take place after 6 and after 24 months, or sooner if necessary. This is also the normal procedure after a loop excision. In appendix C: 'Overview of research activities with time schedule' you will find an overview of the research in a diagram. It will also show you how often you will need to come back for examinations and treatments and what will happen during those visits.

In order to find out for which women the imiquimod works best, we will examine certain proteins in the biopsies taken during the first colposcopy. We will also determine which HPV type you have. You will not notice anything of this and you will not receive the results of these examinations. We will use the vaginal swabs to look for changes in the vaginal microbiome before and after treatment with imiquimod.

In total, we want to include 310 women who have a CIN 2 or 3 abnormality for the first time, 150 women with a CIN 2 abnormality who choose watchful waiting and 50 women with a residual or recurrent CIN abnormality. The treatment takes place in your own hospital.

Step 4: Follow up after the imiquimod treatment
Treatment with imiquimod takes 16 weeks, a control colposcopy will be planned 20 weeks after the start of the treatment. After the treatment (loop excision or imiquimod treatment) control pap smears will be made as usual. This will be done at least at 6 and 24 months. If one of these pap smears shows abnormal cells again, additional smears or a colposcopy could be planned. This is not part of this study, but is care as usual after a CIN abnormality. In order to evaluate the effects of imiquimod on the long term we would like to ask for your consent to use the results of the follow up for 5 years after the start of the study also if it is done by the governmental population survey.

What is different to the normal medical care?
If you do not participate in this study you will be offered the same choice of treatment, but your tissue will not be used for research. Telephone appointments and a control colposcopy 20 weeks after the start of the imiquimod treatment will be planned according to the regular practice at your hospital. You will have the standard pap smear taken at 6 and 24 months after the imiquimod treatment.

5. What agreements do we make with you?

We want the research to go well. That is why we make the following agreements with you:

- You use the imiquimod cream according to the instructions your care giver gave you.
- You come to the appointments for treatment and examinations.
- You keep a calendar in which you note any side effects and in which you indicate when you use the cream. This calendar will be sent to you by email. That is why we ask you for your email address.
- You take the vaginal swab yourself according to the instructions and then send it back to us in the return envelope.
- You contact the care giver/researcher in these situations:
    - You are admitted to or treated in a hospital.
    - You suddenly have problems with your health.
    - You no longer want to participate in the study.
    - Your phone number, address or email address changes.
- Further you can continue to do everything you normally do.

Can you become pregnant during the study?
Women who are pregnant cannot participate in this study.
We advise you to not become pregnant during treatment with imiquimod, because it is not known how the medication will affect an unborn child. For this reason, before you use imiquimod, we will talk about pregnancy prevention by means of contraception; condoms are not reliable when using imiquimod. Your care giver can advise you on different forms of contraception. You can use imiquimod if you are breast-feeding.

Pregnant?
If you do become pregnant during the study, please inform your care giver/researcher immediately. You must then stop this research as soon as possible in consultation with the researcher.

6. What side effects, adverse effects or inconveniences may you experience?

Imiquimod can cause side effects. Few serious side effects have been reported in previous studies with imiquimod cream. The most common side effect was vaginal discharge during treatment. Other side effects that can occur are muscle pain and stiffness, tiredness, headache and a feeling of fever. A complete list of side effects can be found in Appendix D: 'Side effects of imiquimod cream'. Most patients experience one of these side effects. If you experience a side effect that worries you or you have questions about, you can contact your care giver, whose contact details can be found in the appendix A ‘Contact details’.

The following side effects are common:

- Vaginal discharge. The day after using the imiquimod, you can use a tampon or menstrual cup to prevent the cream from causing sores (change the tampon every 6 hours).

- Flu-like symptoms, such as headache, muscle aches and fever. These complaints can often be suppressed well with paracetamol, naproxen or ibuprofen. This does not affect how imiquimod works.

More information about imiquimod can be found in the medical leaflet. Are you participating in the study? Then you will receive the medical leaflet with the medicine. Please note: the package insert of the cream states that it should not be used internally, however in your case of CIN you must. This is because the imiquimod cream was not developed for CIN abnormalities, but can and may be used for your treatment.

7. What are the advantages and disadvantages of participating in this research?

Participating in the study may have advantages and disadvantages. We have listed them below. Think about this carefully, and talk about it with others.

Advantages

If you are treated with imiquimod, you may no longer need a loop excision because the abnormality has disappeared or has been adequately treated with the imiquimod cream. We expect treatment with imiquimod cream to be effective in approximately 50-60% of women. This can be an advantage if you still want to have children: then you have less chance of a premature birth and reduced fertility. Even if you no longer want to have children, it can be an advantage: sometimes bleeding or inflammation occurs during or after a loop excision, or women suffer from increased vaginal discharge after the procedure. If you don't have to undergo a loop excision, you don't have these potential drawbacks.

If you don't benefit from this study yourself, the research may provide useful data in the future and benefit other women. If we can predict a good outcome of treatment with imiquimod cream in CIN, we can select patients who will benefit from imiquimod therapy and avoid unnecessary treatment with imiquimod and the possible side effects.

Disadvantages

- You may experience the side effects as described in section 6.
- Participating in the study will cost you extra time. If you are being treated with imiquimod, we ask you to have 2 extra contacts by telephone with the hospital for this study and to make one extra visit to the hospital. An additional colposcopy will be performed. These appointments last approximately 15 minutes.
- We advise you not to become pregnant during the first 20 weeks of treatment, so this may mean that you have to postpone any desire to have children for 20 weeks.

We do not expect your CIN abnormality to develop into cervical cancer while you are being treated with imiquimod. The worsening of CIN is very gradual; in general it takes many years for a CIN abnormality to develop into cervical cancer. Because we do an extra colposcopy after 20 weeks, we can keep a close eye on any worsening of the abnormality and if the

treatment has no effect on your CIN 3, we will treat the CIN 3 abnormality immediately with a loop excision.
In very rare cases it happens that cervical cancer is already present before the start of the use of the imiquimod cream, without this being diagnosed at the first colposcopy. This has not been seen in previous studies with Imiquimod. Imiquimod is not a treatment for cervical cancer, so if in doubt a loop excision will be performed and you will not be eligible for imiquimod treatment. If there was no doubt at the start, but the abnormality has worsened, a loop excision will still be performed during the colposcopy after 20 weeks,

You don't want to participate?
You decide whether you want to participate in the study. Participation is voluntary. If you decide not to participate, you don't need to do anything. You don't have to sign anything. You also don't have to say why you don't want to participate. You will simply receive the treatment that you would receive otherwise. If you do participate, you can always change your mind and stop anyway; also during the study. Your participation in the study can also be terminated by the researcher, if he/she has reasons to do so. You can read more about this in the general brochure.

8. When does the research end?

The researcher will let you know if there is new information about the study that is important to you. The researcher will then ask you whether you will continue to participate.

In these situations, the study will stop for you:

- All extra examinations according to the study schedule are over.
- The end of the entire investigation has been reached. The study will end when 310 women with primary CIN abnormalities, 50 women with residual or recurrent CIN abnormalities and 150 women with CIN 2 who chose expectative management have been examined.
- You have become pregnant.
- You want to stop the research yourself. That is possible at any time. Report this immediately to the researcher. You do not have to say why you are stopping. You will then receive the usual treatment for the CIN abnormality.
- The researcher thinks it is better for you to stop. The researcher will still invite you for a follow-up check.
- One of the following authorities decides that the investigation should stop:
    - Catharina Hospital Eindhoven,
    - the government, or
    - the medical ethics committee that assesses the research.

What happens if you stop the study?
The researchers use the data and body material collected up to the moment of stopping. If you wish, collected body material can be destroyed. In this case the researcher should be informed.

The entire study ends when all participants have completed the treatment.

9. What happens after the research?

Can you continue to take the medicines?

You cannot continue to use the medicines that you have taken during the examination, because the duration of the treatment is 16 weeks. The researcher will discuss with you what other medical care you will receive.

Will you get the results of the research?

About 2 years after your participation, you can ask your attending physician about the most important results of the study. You can then request a patient newsletter via the treating centre.

10. What do we do with your data and tissue?

Are you participating in the study? Then you also give permission to collect, use and store your data and tissue in a biobank.

What data do we keep?

We will keep the following data:

- Your name
- Your gender
- Your address
- Your date of birth
- Data about your health
- (medical) data that we collect during the research

What bodily material do we keep?

We save samples of tissue (biopsies) from the cervix that were collected during the colposcopy. We also store the vaginal cultures that are taken at different time points during the study.

Why do we collect, use and store your data and body material?

We collect, use and store your data and your body material to answer the questions of this research. And to be able to publish the results.

How do we protect your privacy?

To protect your privacy, we give all your data and your body material a code. We will only use this code on your data and body material. We will keep the key of the code in a secure place in the Catharina Hospital Eindhoven. If we process your data and body material, we use only this code. Before your biological material and data are stored in the biobank, all identifiable information is removed. These data will no longer be used and will be replaced by a code. In

reports and publications about the investigation, no one will be able to recall to whom a code refers.

Who can see your data?
Some people can view your name and other personal information without a code. These are people who check whether the researchers are conducting the research properly and reliably. These people can access your data:

- Members of the committee that monitors the safety of the investigation.
- An inspector who works for the Catharina Hospital Eindhoven.
- The coordinating researcher of the Catharina Hospital Eindhoven
- National supervisory authorities, for example the Health and Youth Care Inspectorate.

These persons keep your data secret. We ask you to give permission for this inspection.

Your biological material is stored in the biobank. The biobank has no commercial purpose. Your (medical) data and biological material will never be sold.

Research using your biological material is conducted under the responsibility of researchers working at the Catharina Hospital Eindhoven. Collaboration with other organizations or companies may also occur. However, the Catharina Hospital Eindhoven will always remain involved in the research.

In order to carry out the research properly, it may sometimes be necessary to share (medical) data and biological material with collaborating organizations. They will not be able to identify that the data belongs to you. They will also not be able to identify that the biological material comes from you.

A proposal for collaboration is always submitted to the Medical Ethical Review Committee (METC) MEC-U.

How long do we keep your data and body material?
We will keep your data for 15 years in the hospital. Afterwards, we will destroy the biological material and the data stored in the biobank. If the researchers wish to retain the biological material and data for a longer period, you will be informed about this.

We will store your body material in the hospital. It will be kept for 15 years in order to be able to answer possible further questions related to this research in the course of this project. As soon as this is no longer necessary, we will destroy your body material.

May we use your data and body material for other research?
Your data and your (remaining) body material may also be important after this study is finished, and used for other research in the field of your condition and/or for the further development of the treatment method. For this purpose, your data and body material will be

stored in the hospital for 15 years. In the consent form you indicate whether you agree with this. If you do not give permission? Then you can still participate in this study. You will get the same care.

What happens with unexpected discoveries?
During the investigation, we may happen to find something that is important to your health or to the health of your family members. The researcher will then contact your treating doctor. You will then discuss what needs to be done with your treating doctor. With the form you give permission to inform your general practitioner or doctor.

Can you withdraw your consent to the use of your data?
You can withdraw your consent to the use of your data at any time. This applies to use in this study and to use in other studies. But beware: if you withdraw your consent after the researchers have collected data for a study, they can still use this data. The researchers will destroy your body material after you withdraw your consent. But have measurements have already been done on your body material, the researcher may continue to use the results.

Would you like to know more about your privacy?

- Would you like to know more about your rights when processing personal data? Then look at https://www.autoriteitpersoonsgegevens.nl/en.
- Do you have questions about your rights? Or do you have a complaint about the processing of your personal data? Please contact the person responsible for the processing of your personal data, in the first instance with the investigation team.
    - See Appendix A for contact details.
- You can also contact the JBZ Data protection officer. The JBZ Data protection Officer can be researched by email at privacy@jbz.nl, or you can file a complaint with the Dutch Data Protection Authority.

11. Will you be compensated if you participate in the study?

You will not be compensated for participating in the study nor for travel expenses, because during the study standard care is offered. The treatment is covered by the standard care that is reimbursed through your health insurance. Your compulsory personal contribution to your the health insurance still exists despite participating in this study.

12. Are you insured during the investigation?

You are not additionally insured for this research, because participating in the study does not carry any additional risks. That is why the MEC-U granted exemption to the Catharina Hospital Eindhoven from taking out additional insurance.

13. We inform your general practitioner

The researcher will send your general practitioner a message to let you know that you are participating in the study.

14. Do you have questions?

Questions about the study can be directed to your hospital's executive investigator or the principal investigator. Questions about the treatment with imiquimod or loop excision can be directed to your treating doctor. Would you like advice from someone who has no interest in this research? Then contact Dr. B. Slangen, gynecologist. She knows a lot about the investigation, but does not participate in it. The contact details can be found in Appendix A 'Contact details'.
Do you have a complaint? Then discuss this with the researcher or the care giver who is treating you. Would you rather not? Then go to your hospital's complaints mediator.

15. How do you give permission for the research?

You can consider this research first. After that, your treating care giver, hospital research coordinator or coordinating researcher (Caroline Muntinga) will contact you and ask you whether you understand the information and whether or not you want to participate. Would you like to participate? Then fill in the consent form that you will find in Appendix E of this information letter and return it in the enclosed return envelope. You and the researcher will both receive a signed version of this consent form.

Thank you for your time.

16. Attachments to this information

A. Contact details
B. Practical information about treatment with loop excision and imiquimod
C. Overview of research activities with time schedule
D. Side effects of imiquimod cream
E. Consent form to participate in this study

Appendix A: Contact details

Contact details coordinating investigator

Drs. C.L.P. Muntinga
MD, researcher
Catharina Ziekenhuis Eindhoven
Afdeling Gynaecologie en Verloskunde
Michelangelolaan 2
5623 EJ Eindhoven
T 040 - 239 93 00 (secr)
E predict-topic@catharinaziekenhuis.nl

Contact details principal investigator

Dr. E.M.G. van Esch, MD, PhD
Gynaecologist-oncologist
Catharina Ziekenhuis Eindhoven
Department of Obstetrics and Gynaecology
Michelangelolaan 2
5623 EJ Eindhoven
T 040 - 239 93 00 (secr)
E edith.v.esch@catharinaziekenhuis.nl

Contact details independent doctor

Dr. B. Slangen, MD, PhD
Gynaecologist-oncologist
Maastricht Universitair Medisch Centrum (MUMC+)
Department of Obstetrics and Gynaecology
P. Debyelaan 25
6202 AZ Maastricht, The Netherlands
T 043 – 387 47 67 (secr)
E brigitte.slangen@mumc.nl

Contact details executive researchers

Jeroen Bosch Ziekenhuis

B.M. Pijlman
Gynaecologist
Jeroen Bosch Ziekenhuis
Department of Obstetrics and Gynaecology
Henri Dunantstraat 1
5223 GZ ‘s-Hertogenbosch
T 073 553 62 50
E b.pijlman@jbz.nl

For questions and more information about the processing of your personal data:

Drs. C.L.P. Muntinga, MD
Coordinating investigator PRedICT-TOPIC study
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Afdeling Gynaecologie en Verloskunde
Michelangelolaan 2
5623 EJ Eindhoven
T 040 - 239 93 00 (secr)
E predict-topic@catharinaziekenhuis.nl
Availability: Monday to Friday between 9:00 AM and 5:00 PM.

Complaints Mediator of the Jeroen Bosch Hospital

For more information and to access the online complaint form, please visit: https://www.jeroenboschziekenhuis.nl/contact-afspraak-maken/als-de-zorg-anders-loopt-dan-verwacht/een-klacht

Mailing address for the complaints mediator

Jeroen Bosch Hospital, Attn: Complaints Mediator(s)
Antwoordnummer 176
5200 VB ’s-Hertogenbosch (no postage stamp required)

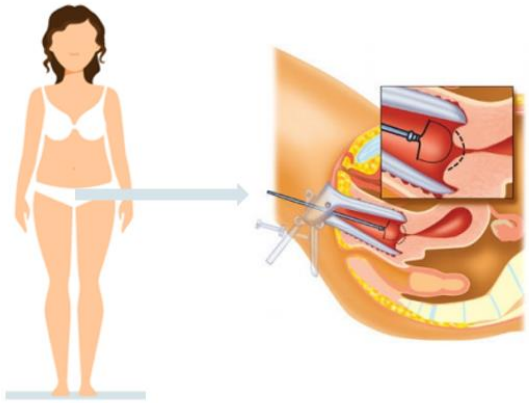
Visiting address for the complaints mediator

Information Center,
Building B, Ground Floor, along the Boulevard, location ’s-Hertogenbosch
You can reach the complaints mediator(s) by phone at (073) 553 26 39 on weekdays from 09:00 to 13:00.

Appendix B: Practical information about treatment with loop excision and imiquimod

The loop excision

CIN abnormalities are usually treated by removing the abnormal tissue. This is called a loop excision. The treatment is performed by the gynecologist (in training) and takes place in the hospital. In this case (as with a colposcopy) a speculum is first inserted and fluid is applied to the cervix to visualize the abnormality. The cervix is then locally anaesthetized. The gynecologist then removes a strip of tissue from around the opening of the cervix. He or she uses a thin metal loop that is heated electrically. This can be seen in the picture below. After this, the speculum is removed. The procedure takes about 20 minutes. You can go home the same day. The removed tissue is examined by a pathologist (a doctor who examines tissue). Within two weeks you will hear whether the treatment by loop excision has been sufficient. If the treatment is sufficient, you will come back after 6 months for a Pap smear. Depending on this result, it will be determined whether you should come back for another smear after 12 or 24 months. Depending on this result, you will be checked further or referred back to the population screening.



Imiquimod cream: the treatment that this research focuses on

Imiquimod is a medicine that stimulates the body's immune response against viruses. CIN abnormalities are caused by viruses. It is also used to treat certain warts and certain types of skin cancer.

You carry out the treatment yourself at home. You apply the cream yourself, with a vaginal applicator, which is an applicator sleeve for the cream, or by applying the cream on top of a vaginal tampon. First you put the cream from a bag in the applicator sheath or on the tampon. Then you insert the insertion sheath or tampon vaginally. Inserting the introducer sheath is similar to inserting a tampon. After leaving the cream in the sheath, remove the applicator sheath. In the picture below you can see how this insertion works. You apply the cream three times a week, in the evening before going to bed. You should not have sexual intercourse after applying the cream. In the morning, rinse off the remnants of the cream on the labia under the shower. We recommend inserting a tampon the morning after applying the imiquimod cream to prevent any residue of the imiquimod from getting on the labia. This can give side effects to the labia.

The treatment lasts a total of 16 weeks. After treatment with imiquimod, your doctor will perform a colposcopy to see if the CIN abnormality responds to the treatment. We do this 20 weeks after the start of the treatment. You will hear whether the treatment has been successful within two weeks after the colposcopy. If the colposcopy shows that the treatment has been successful, you will come back for a smear after 6 months and depending on the results possibly after 12 months and after 24 months. If this colposcopy shows that the treatment has not worked (sufficiently) after 20 weeks, a loop excision will still be performed (see above for the description).

It is important to know that you should not become pregnant during the treatment with imiquimod cream.

Appendix C: Overview of research activities with time schedule

Moment:	**Activity that takes place:**
Colposcopy appointment	Standard examination after an abnormal Pap smear. Biopsies will be taken for further examination of the cervix You will receive information about the possible treatment of CIN with a loop excision or imiquimod treatment or, in the case of CIN 2, a wait and see policy. You will receive information about possible participation in this study, the PRedICT-TOPIC study.
Appointment before treatment	You will get the results of the biopsies from your doctor. You can opt for a loop excision or imiquimod, or in the case of CIN 2 a wait and see policy. If you opt for a loop excision, it will be performed immediately, you will not participate in this study. If you choose imiquimod, the doctor will ask you to participate in this study. Once you have signed the consent form, your doctor or the coordinating researcher or research nurse will write down a few details. You will receive information about the treatment and appointments will be made. You should not be or become pregnant if you are going to take imiquimod and your doctor will therefore discuss contraception with you.
Week 0	A vaginal swab will be sent to you by your doctor or given to you. You must take this yourself before you start using imiquimod. Start of treatment: imiquimod cream, inserted vaginally 3 times a week
Week 2	Telephone appointment: the use of imiquimod and possible side effects will be discussed.
Week 8	Telephone appointment: the use of imiquimod and possible side effects will be discussed
Week 16	Telephone appointment: the use of imiquimod and possible side effects will be discussed Instructions to quit imiquimod treatment.
Week 20	Colposcopy, treatment (loop excision) if the abnormality has not sufficiently reduced or disappeared. A vaginal swab will be taken by your doctor.
6 months after treatment, a pap smear and a vaginal swab are taken by your doctor.	
1 year after treatment: a pap smear is taken if necessary	
2 years after treatment: a pap smear is taken	
5 years after treatment: data of participation in the population screening will be requested	

Appendix D – Side effects of imiquimod cream

The following text is a simplified version of the information in the Farmacotherapeutisch Kompas, published by the Health Insurance Board.

Side effects
Depending on the treatment schedule, some side effects may occur more or less frequently.

Very common (> 10%): itching and pain on application and application site reactions (including bleeding, rash, redness, discharge, burning, irritation, swelling, inflammation, bumps, blisters, numbness, scaling, open wound, crusting, scar).

Common (1-10%): headache, nausea, muscle aches, fatigue and infections (viral or bacterial infection or fungal infection).

Uncommon (0.1-1%): rash, itching, hives, increased sweating. Flu-like symptoms, malaise, fever, muscle weakness, muscle stiffness, swollen lymph nodes. Gastrointestinal disorders, loss of appetite or weight loss. Drowsiness or insomnia, dizziness, migraine, depression. Ringing in the ears, flushing, runny nose, strep throat, painful joints and (back) pain. Local, severe inflammatory reactions (with general malaise, fever, nausea and myalgia) have been reported after only a few administrations. Hair loss can occur. Also reported are: pigment abnormalities, serious skin reactions, liver function disorders decrease in certain blood values such as hemoglobin (blood iron), number of white blood cells and platelets.

For genital warts: uncommon (0.1-1%): dysuria, genital pain, erectile dysfunction, pain during intercourse, disorders of the penis, vulva or rectum.
In skin cancer: uncommon (0.1-1%): dry mouth, drowsiness and irritability.
In actinic keratosis: uncommon (0.1-1%): superficial oedema, eye irritation, sore throat.

Appendix E: Consent form to participate in this study

Related to Investigation of predictive factors for response to treatment with imiquimod cream in CIN abnormalities (PRedICT-TOPIC study). We ask you to fill in the form below and send it with the enclosed return envelope. No stamp is required.

- I have read the information letter. I could also ask questions. My questions have been answered well enough. I had plenty of time to decide whether to participate.
- I know that participation is voluntary. I also know that I can decide at any time not to participate in the study, or to stop. I don't have to say why I want to stop.
- I give the researcher permission to let my general practitioner know that I am participating in this study.
- I give the researcher permission to provide my general practitioner or specialist with information about unexpected findings from the study that are important to my health.
- I give the researchers permission to collect and use my data and/or body material and store it in the biobank. The researchers only do this to answer the research question of this study.
- I understand that my (medical) data and biological material will be treated confidentially.
- I know that for the purpose of monitoring the study, some people can see all my data. Those people are listed in this information letter. I give these people permission to view my data for this monitoring.
- I am aware that it is advised not to become pregnant during treatment with imiquimod.
- The researcher discussed with me the best way to avoid becoming pregnant.

− Can you tick yes or no in the table below?

I give permission to keep my data to use it for other research, as stated in the information letter.	Yes☐	No☐
I give permission to store my (remaining) body material to use it for other research, as stated in the information letter. The body material is stored for 15 years.	Yes☐	No☐
I give permission to ask me after this study if I want to participate in a follow-up study.	Yes☐	No☐

- I want to participate in this study.

My name is (study subject): ……..

Email address:…….

Signature: …… Date (DD-MM-YYYY): __ / __ / __

To be completed by doctor/researcher:

I declare that I have fully informed this subject about the PRedICT-TOPIC study.

Will information become known during the study that could influence the subject's consent?

Then I will let the subject know in time.

Name researcher (or its representative):…….

Signature:…… Date (DD-MM-YYYY): __ / __ / __

The subject receives a complete information letter, together with a signed version of the consent form.