Sponsor: International Agency for Research on cancer (World Health Organization)
Principal Investigator: Motshedisi Sebitloane

Subject Initials: _____

Enrollment Number: _____

The study for the "Cervical cancer Screening and Treatment algorithms study using HPV testing in Africa" (CESTA)

Module 1 South Africa:
Screening Algorithms study (HPV + VIA + treat *vs.* HPV + treat)

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

Introduction

Cervical cancer is very common in this region and throughout South Africa. The University of Kwazulu-Natal; the University of Cape Town; the World Health Organization (WHO); and the International Agency for Research on Cancer are working together on a research project to study how best to implement a new test (HPV testing) which may improve the national cervical cancer prevention and control programme in South Africa, but also in other developing countries in the world.

Today you will receive information about and be invited to become a participant in this research. You do not have to decide right away whether or not you will participate and if you wish, you can talk to anyone you feel comfortable with about your participation in the study. If this form contains any words that you do not understand, please ask and they will be explained more fully to you. If you have questions later, you can ask any of the study staff.

Purpose of the research

In many parts of Africa, including South Africa, cancer of the cervix is a major killer of women and yet it is a preventable disease. Cervical cancer screening is now being conducted in South Africa using a test known as liquid based cytology (LBC). This procedure allows finding out if there are changes on your cervix so that they may be treated before they become a cancer. These changes on your cervix are commonly caused by an infection from a virus called human papillomavirus (HPV). There are tests which identify women who have this HPV infection. This test is what is being studied in this research project. We already know that the HPV test detects more lesions on the cervix, compared to Pap smear, but it is still not very clear how best to use this test in developing countries. In particular it is not yet well known if it would be better to treat all women who have the HPV infection, or if it would be better to perform still a second test if a woman is HPV-positive. The second test in this study is called "visual inspection with acetic acid" (VIA). With the VIA examination, the health provider can see if there is a change on the cervix that looks abnormal.

As is the case for cytology, both HPV test and VIA, are not 100% accurate. We know from research that almost all important cervical lesions are positive for the HPV test. However, not all women with a positive HPV test have a lesion that needs to be treated immediately. That is why we perform another VIA test and only treat when the VIA test is also positive. We call this scheme 1. The disadvantage is that some important lesions are missed by the VIA test and that is why we also collect small tissue samples called biopsies from the cervix to make sure that no lesions were missed. In scheme 2, all women with HPV-positive results are treated so we know almost all important lesions will be treated but some women will also be treated without a true lesion. Fortunately the treatment has very few side-effects and it may even protect for lesions in the future. Both schemes are recommended by the WHO.

We also want to compare 2 ways of treatment if the screening test is positive on your cervix. They are both simple treatments, called cryotherapy and thermal ablation, and are performed by the nurse who examines you when you come back for the HPV result.

In this study, we want to compare if adding a VIA is more beneficial; which treatment has more side-effects; and what is the cost for benefit.
This study requires that you agree to participate in the study. First you will be assigned to 1 of the 2 groups; in group 1 you will be treated only if your HPV test as well as your VIA test is also positive; in group 2 you will be treated if the HPV test is positive, and no VIA examination will be done. What will exactly happen to you will be explained later but you will be asked some questions; be screened for cervical cancer using the HPV test; and be treated for lesions that are not yet cancer when you come back for the HPV result. And if you are treated we will follow you up for any possible side effects. All women who had a positive HPV test or were found with a cervical lesion will be advised to come back after 1 year to the hospital for another screening.

Participant selection
You are being invited to take part in this research because you are a woman living with HIV between the ages of 25 and 54 years, and screening for cervical cancer is recommended. Women in your age group are the most likely to be affected by early cervical changes which can progress to cancer if left untreated. By providing a cervical sample today, you would be contributing to the understanding of how best to implement HPV testing in developing countries and how best to treat early lesions in women living with HIV.

Voluntary Participation and right to refuse to participate or withdraw
Your participation in this research project is completely voluntary and it is your choice to participate or not. If you decide to participate, you will have the right to refuse answering to questions. Also, you are under no obligation to take part in the study and you may stop your participation for whatever reason and at any time during the study if you change your mind. If you choose not to participate in this research project, you will be offered liquid based cytology cervical screening that is routinely offered in this hospital. There will be no consequences on your future health care or result in any other form of discrimination to you if you do not wish to take part in this research study.

Procedures and Protocol of the study
After you have been explained clearly what is being done in this study you will have the opportunity to sign the Certificate of Consent and participate in this study.
The nurse will ask you some general questions such as your age, your education, if you are in a relationship and some few questions about sexual experiences. She will ask you if you like to answer some HIV-related questions, related to your treatment, CD4 counts and viral load. She will ask you also some questions on your costs and the time you spent to travel to and from the clinic; as well as your individual and household income. Then the nurse will explain how to insert a small brush in the vagina so that you can collect samples yourself.
After that, the nurse will perform a pelvic gynecological examination. For this examination, you will need to remove your underwear and lay on a special examination table. The nurse will examine you by placing an instrument called a speculum into your vagina so that your cervix can be seen. The nurse will then collect an HPV sample from your cervix with a small brush. You can expect to feel a little discomfort and a very slight pressure during this examination, but you should not feel pain. The procedure should only take a few minutes. If it hurts, be sure to tell your health provider so that adjustments can be made to make you more comfortable. All the samples will be taken to the laboratory for processing.

You will be asked to come to a CESTA study clinic after 2 weeks for the HPV result. If your HPV test is positive you will be randomized into 2 arms.
The nurse will start this second visit with a pelvic exam and collecting an endocervical swab to measure HIV shedding. Then, if you are in Arm 1, the nurse will perform an additional VIA test. VIA is a procedure where your nurse gently wets the cervix with low concentration acetic acid, which is a form of vinegar. You might feel a slight stinging sensation. After about one minute, if there is anything that could be abnormal, it will turn white. Then the nurse will collect 2 - 4 small biopsies from your cervix. The biopsies are small pieces of cervix tissue the size of a rice grain. Because the biopsies cause tiny small wounds you will be asked not to have sexual relations for 10 days or use condoms. The nurse will provide you with condoms if you wish.
Finally, if you are eligible for this treatment, and VIA positive in Arm 1, the nurse will assign you a treatment with either cryotherapy or thermal ablation. Cryotherapy is the freezing of the cervix by the application of a very cold disc to the abnormal areas, after which the abnormal area is removed and new healthy tissue can grow back. Thermal ablation is a technique in which a hot disk is put on the cervix also with the effect of removing the area so that there can be healing. You will be told which mild side-effects to expect and when you should come back to see the nurse if it would be more serious. Because the treatment causes a small wound on the cervix, you will need to let it heal and be asked not to have sexual relations for 4 weeks, or use condoms.
If you are in Arm 2, you will be treated because you are positive for HPV infection, but there will be no second VIA test performed. The nurse will still wash you cervix gently with low concentration acetic acid to examin your cervix, take 2-4 small biopsies like before and assign you to cryotherapy or thermal ablation if that is appropriate for you. A selection of women will be called back to the clinic to assess if there is more HIV virus present at the cervix after the treatment. In that case you will be asked to come back to the clinic after 1, 2, 3 and 4 weeks after treatment for the nurse to collect a brush from your cervix.Other treated women we will be called after 1 week and 1 month to ask if they had any discomfort or side effects and if they were satisfied with the treatment procedure, and only if therewere serious side effects will they be asked to come to the clinic for a check-up by the nurse and treatment if needed. After one year, you will be advised to come back to the hospital for another screening with HPV testing and VIA. All women with a positive HPV test will then have biopsies taken to make sure there is no disease left.

The biopsies are processed in the laboratory later and will tell afterwards if there was indeed a cervical lesion or not. In case the nurse did not see any abnormal lesion with VIA but the biopsy result shows a lesion that needs to be treated, you will be called back to the clinic to receive the treatment you need.

In case you need another kind of treatment, you will be referred for another examination which is called colposcopy and you will get. A colposcopy is an examination like the VIA examination, only this time the doctor will look through a magnifying lens so he/she can better observe your cervix and treat you with the right treatment for you according to the recommendations of the South African Ministry of Health. It is possible that at the colposcopy examination you require a treatment called “Large Loop Excision of the Transformation Zone” (LLETZ), during which the abnormal lesion is cut out under local anesthesia. This treatment may cause bleeding, pain for a few days, and in some occasions may cause infection; rarely, it may affect the capacity to get pregnant or to complete pregnancies in the future. This LLETZ treatment will only be performed if it is clinically recommended.

During this CESTA study, several kinds of samples will be collected that will be used only for this research: HPV specimens and biopsies. The sample leftover will be stored at the laboratory at the University of Kwazulu-Natal Medical School or send to the Internal Agency for research on Cancer and we would like to ask your consent about using it for other molecular tests that could be of interest to better understand the disease. Your samples will not be labeled with information that identifies you. Samples will be coded to allow them to be associated with your other data and if the result from additional testing needs further examination, you may be called back to the clinic. We ask your authorization to allow that the specimens and tissues collected during the study, as well as your medical records can be reviewed by the study investigators.

Pictures

If you are HPV positive and depending on the clinic you are assigned to, the nurse will take 2-3 pictures of your cervix. These pictures will be anonymized and used for two purposes: continued training for the nurses to perform diagnosis in reviewing the pictures with experts, and publishing these pictures and the training results for a research purpose. At any time you have the possibility to tell the nurse that you do not want her to make pictures.

Contact phone number

The study team will ask your phone number for contact purpose and your number will only be accessible by the study team. In some clinics, you may also be asked if you want to receive appointment reminders and other study-related information on your phone through a smartphone application called SEVIA.

Anticipated risks, discomfort or adverse effects

What is offered to you specifically for the research purposes, and that is not routine care practices in South Africa are the HPV and VIA tests and treatment with cryotherapy or thermal ablation.

By participating in this research, you should not be at any physical risks when HPV samples are collected; when the VIA procedure is performed; or when you are treated. These tests and treatments have been used in practice and in research with many women with a good safety record. However, you may find the procedure slightly uncomfortable or perhaps embarrassing. Every effort will be made to assure your privacy and address your concerns. If you prefer that your examination is performed by a woman, then you should let us know and we will make arrangements. Like any other test, HPV and VIA testing are not perfect and it may be possible for the tests to give a "false positive" result when everything is normal or "false negative" results, when there is a cervical lesion present. However, this can also happen with Pap smear and that is also why we take the biopsies to make sure we did not miss a lesion when doing VIA.

The pelvic exam is uncomfortable and in very few occasions may cause light spotting afterwards that disappears spontaneously. The VIA inspection requires the application of some drops of common vinegar that could produce a slight stinging sensation that will disappear spontaneously. When biopsies are taken it may cause mild discomfort, small amount of bleeding (spotting) from the vagina for 1-2 days, and mild to moderate cramping for 5 minutes that is similar to mild menstrual pain. You will be asked to refrain from intercourse or practice safer sex for 10 days to reduce risk of sexually transmitted infections including HIV during the healing process. Similarly in the case of cryotherapy treatment you may experience mild abdominal cramps in for less than 10 minutes or some burning sensation at the cervix during the 30 seconds treatment with thermal ablation. A watery discharge

from the vagina is possible for usually less than 2 weeks after treatment. You will be asked to refrain from intercourse or practice safer sex for 4 weeks.

Benefits or reimbursements

If your cervical screening examinations are normal, then you will be followed up according to the National cervical screening and treatment policies. If any of your screening tests or biopsies were positive, you will be treated or referred for treatment as soon as possible. This will greatly reduce your chances of developing cervical cancer. But, if cancer is suspected during this examination, you will be referred for appropriate care.

The HPV test is known to detect more easily serious abnormalities on the cervix than Pap smear, so the possibility of missing a lesion is lower with HPV testing, compared to Pap smear. The one year follow-up screening if you were treated will make sure that you had no cancerous disease left on the cervix. Your participation in the study will contribute to find the answer to how best to implement HPV screening in developing countries. Then it may be introduced in other health facilities throughout South Africa and other countries and benefit many more women around the world.

When you are invited to visit the CESTA study clinic for the first time, you will be reimbursed 50 Rand the help with your transport expenses. In case you would have to come back to the clinic for a reason that is not part of routine care but needed only for the research we will reimburse your transport costs to an amount of 200 Rand. You will not be given any other money or gifts to take part in this research.

Confidentiality

Your privacy is very important. The principal investigator is responsible for assuring that all the information gathered from you will be kept with utmost confidentiality. You will be identified using a unique participant number which will be entered into a computer for analysis and program monitoring. The computer that contains your data will be secured by passwords. Only the researchers and staff dedicated to this study including your health care provider will have access to this information. Your name will only be used by your health provider for contact purposes, but not for any other purpose. No publication or any other communication from the researchers to other researchers will bear your name or identification number.

Sharing the research findings

The research findings from the CESTA study may be presented at scientific conferences or published in scientific publications.

Contact information

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact:

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This proposal has been reviewed and approved by the International Agency for Research on Cancer Ethics Committee (IEC).

This proposal has also been reviewed and approved by the Biomedical Research Ethics committee (BREC) at the University of KwaZulu-Natal.
If you wish to find out more about the BREC:

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CERTIFICATE OF CONSENT

Study Protocol Title: The study for the "Cervical cancer Screening and Treatment algorithms study using HPV testing in Africa" (CESTA)

PARTICIPATION IN THE STUDY

I, **[name of the participant]**, have been given the foregoing explanation of the nature and purpose of the study and what I will be expected to do. I understand that the tests and procedures may have some complications, and that I am free to withdraw from the study at any time without the need to justify the decision. This will not affect me or my family availing health care from the Institution and public health services in any way.
I understand that my personal records will be seen by research investigators and I agree to disclosure of this report and any results to them. All data will be treated as confidential and kept for as long as required by law.

I hereby give my voluntary, free and informed consent to take part in the study and comply with all the regulations, procedures and interventions stipulated in the study protocol.

[ ] YES, I want to participate in this study, including HIV testing, HPV testing and treatment by cryotherapy or thermal ablation.
[ ] NO, I don't want to participate in this study.

PERMISSION TO STORE AND USE SAMPLES OR DATA FOR FUTURE STUDIES

I agree to permit archival of HPV and biopsy specimens for future research purposes. I consent to the transfer/use of my coded data by the International Agency for Research on Cancer even if I withdraw from the study.

I authorize my samples to be stored in an anonymous way for possible future studies: [ ] [YES] ; [ ] [NO]
I authorise that my coded data can be used for future studies: [ ] [YES] ; [ ] [NO]
I authorise the study staff to share my personal phone number to receive appointment reminders and study-related information through the SEVIA smartphone application: [ ] [YES] ; [ ] [NO]

Printed Name of **Participant** _____
Signature or Finger Print of Participant _____*Date* _____

If illiterate
Thumb Print of **Participant** | | *Date* _____

I have witnessed the accurate reading of the consent form to the potential participant who has had the opportunity to ask questions. I confirm that consent was given freely.
Printed Name of **Testimony** _____
Signature of Testimony _____*Date* _____

I confirm that consent was given freely and that a copy of this ICF has been provided to the participant.

Printed Name of **Researcher/person taking the consent**_____
Signature of Researcher/person taking the consent _____*Date* _____