Research Study: A randomized controlled trial comparing cure rates of cervical intraepithelial neoplasia grade 2 and higher (CIN2+) treated with CO_2-based cryotherapy, CryoPen®, and thermoablation

Research Team

Principal Investigator
Name, title and contact information
of Principal Investigator at each site

Study Coordinator
Name, title and contact information
of Principal Investigator at each site

Co- Principal Investigator
Dr. Miriam Cremer
Department of Obstetrics & Gynecology
Cleveland Clinic, USA

We are asking you to be in a research study

A research study is a way to test new ideas or to learn about how or why certain things happen. Researchers from El Salvador, Colombia and China and the Cleveland Clinic in the United States are leading this study. Women in [location of other study sites] will also participate. There will be about 1,200 women in this study between three different countries.

You are being asked to join this study because you are 18 or older and have pre-cancer cells on your cervix. The cervix is a part inside your body that connects the vagina and the womb and can be seen in a regular gynecological exam. When a woman has pre-cancer cells in the cervix, it means that you have an infection that puts you at risk of developing cervical cancer. It does not mean you already have cancer, but you may develop cancer in the future if it is not treated.

This form explains what this study is about and what will happen if you choose to be in it. After you read or someone reads this form to you, please ask any questions you have. Then you can decide if you want to be in the study or not. You can ask questions now or at any time during the study. If you join the study, you can quit at any time and nothing will happen to you.

Your participation in this study is voluntary. You are free to say no to any part of the study or to leave the study at any time. Whether you join the study or not will not affect your medical care. You will receive your scheduled treatment anyway and without delay, whether you decide to take part in the research study or not.

We will give you a copy of this consent form to take home with you and keep.

What we are trying to learn in this study

The purpose of this research study is to see how well two new machines work at curing cervical pre-cancer compared to the usual machine that is used for treatment in many hospitals.

When women have pre-cancer on the cervix, they may receive a treatment called cryotherapy. This treatment freezes the area of the cervix where the pre-cancer is located. This is a common

treatment for cervical pre-cancer. Providers use a gas called carbon dioxide to freeze the tissue during cryotherapy.

The new medical instruments we are testing are called the CryoPen® and the WISAP C3 thermoablator. The CryoPen® is approved for use in the United States for treating cervical pre-cancer. The thermoablator is approved for use in Europe for the same thing. The CryoPen® and the thermoablator are not yet approved for use in hospitals in [country name] and are considered investigational. This means that these machines are only allowed for use in research studies like this one.

In this research, we will compare the CryoPen® and thermoablator with the gas-based cryotherapy instrument that is normally used. The CryoPen® works like cryotherapy to freeze and destroy tissue with a metal attachment that is cooled to a very cold temperature. The thermoablator uses an attachment with heat instead of cold to destroy the area with pre-cancer. The cold or hot attachment is covered and does not touch any part of the body except the pre-cancer area of the cervix. You will only receive one of these three treatments.

Six weeks after you receive the treatment, we will ask you to return for a visit so we can check for any side effects and so you can tell us about any concerns you may have about the treatment. Twelve months after treatment, we will ask you to come again to see if any cervical pre-cancer cells still exist. We will use different types of tests to learn which test is best at finding pre-cancer cells after treatment in case any are still there.

If you are in El Salvador or Colombia, some of the samples taken during the study visits will be sent to two labs in the United States to be analyzed by experts. These labs are located in the National Institutes of Health in Maryland and the Medical College of Wisconsin in Wisconsin. The labs will only receive samples labeled with an identification code but none of your personal information. The results of these analyses will only be used for this study. After being analyzed, the samples will be destroyed. Samples from China will be analyzed at local hospitals and local laboratories.

Will this study help you or others?

Being in this research study will not help you personally. But what we learn in this study may help other women in this country and around the world in the future. We hope to learn how to improve treatment of cervical problems. Better treatment would allow more women to be treated before they develop cervical cancer and could save lives.

What we are asking you to do

If you decide to participate in the study you will sign this consent form or provide a fingerprint.

You will be taken to an examination room in the hospital and asked to answer a short set of questions about some personal and medical information. You do not have to answer any questions if you do not want to do so. Then you will be asked to take a pregnancy test. This is important because you cannot have the treatment if you are pregnant. You can only participate in the study when you are not pregnant.

If the pregnancy test is negative, the doctor will put an instrument called a speculum in your vagina so the cervix can be seen. The doctor will look at your cervix to see if you are able to have the treatment. If the doctor cannot see your cervix or it is difficult to reach, you will not be able to participate in the study. He or she will also take a small sample from your vagina to analyze it and see if you have any infections. Women do not usually receive numbing medication for these treatments. If you are having pain or are uncomfortable at any moment, please let the doctor know. You can tell the doctor at any time if you do not wish to continue and the doctor will stop the procedure.

If the physician sees that the treatment can be performed, you will be placed in one of three groups. The procedure you receive is random which means it will be determined by chance. You and your doctor cannot choose which treatment you will get. Women in each group will receive one of three different procedures to destroy the pre cancer area of the cervix:

- Standard cryotherapy (usual treatment). The cervix tissue is treated with a double freeze application of the CO_2. This means the area of the cervix with precancer is given a 3-minute freeze, followed by a 5-minute rest and another 3-minute freeze). This is the method recommended by the WHO (World Health Organization) for this machine.
- CryoPen® cryotherapy (new machine). The cervix tissue is treated with one 5-minute freeze application. This means the area of the cervix with precancer is given only one 5 minute freeze. We think this is the best method for this machine because in past studies it seems to freeze as well as the double application. In some cases, the doctor may decide that the treatment has to be repeated to make sure the whole area is treated.
- Thermoablation (new machine). The cervix tissue is treated once (in most cases) with a probe that heats up to 100°C for 40 seconds. In some cases, the doctor may think one application is not enough to treat the whole area. He or she may decide to do one or more 20 second applications until the whole area is treated.

Most patients who undergo these procedures experience mild to moderate pain during the application, but some patients experience severe pain during the application. A few women also may feel dizzy or faint during the procedure. In most women, pain, dizziness and faintness go away as soon as the procedure is finished.

The complete procedure will take about 10 to 15 minutes. It is normal to have vaginal discharge for several weeks after the study. Some women may develop vaginal infections. It is recommended that after any of the treatments, women do not take a bath, douche, introduce tampons or other objects into the vagina, or have sexual intercourse for at least four weeks.

If you agree, photographs will be taken of your cervix. Photographs may be used for training purposes and for quality control. They may also be used to help build an artificial intelligence system to diagnose pre-cancer. This means a computer program may be able to identify cervical precancer using pictures like the ones we are taking of your cervix. No other photographs of any other parts of your body will be taken. Your name will not be on the photographs of the cervix. No woman can be identified by photographs of the cervix. If you do not wish to have photographs taken of your cervix, you may have all other procedures without photographs.

You will also be asked to rate any pain you might have felt during the treatment.
Six weeks after treatment, you will be asked to return for a gynecological exam and to answer some questions about how you have been feeling since the treatment so that we can see if there are any common side effects. We will ask you your opinion of the treatment you received. At this visit, the doctor will also take another vaginal sample to make sure there are no infections. If there are safety measures in place due to COVID-19, you may have a telemedicine appointment (a phone call) instead of an in-person visit.

Twelve months after treatment, you will be asked to return for another examination so that we can we can see if there is remaining of cervical precancer. At this visit, we will ask you again what is your opinion of the treatment you received. The doctor will perform a minor procedure to remove tissue from your cervix. We will be using three types of tests to see if any pre-cancer cells are still there after the treatment and to determine which test is best at finding any cervical pre-cancer left after treatment. We will also take pictures of your cervix again. As before, these images will be used to train providers in ablation treatment, to help us see how well the treatment worked, and may also be used help develop a computer program to diagnose cervical precancer. If you do not wish to have photographs taken of your cervix, you may have all other procedures without photographs. This is the last part of your participation in the study.

If any pre-cancer cells are left on your cervix, you will be referred to the appropriate unit within the hospital for any necessary further treatment. If additional treatment is needed, it will not be part of the study.

Can anything bad happen to you from being in this study?

You can expect to feel pain or cramping during treatment and during the exams at the six week and twelve month visits. Most patients experience mild to moderate pain during the treatment application, but some patients experience severe pain during the treatment application. We will provide pain medication after each procedure if you need it.

You may have some vaginal discharge and mild vaginal bleeding or spotting after each procedure. Some women develop vaginal infections and receive antibiotic treatment. Most treatment related infections would occur within 2-5 days following the procedure. You should seek medical attention if the discharge is foul smelling, if you have a fever or bleeding more than a normal period or pain that is not eased with over the counter pain medication.

Freezing or heating areas of the cervix cells to destroy precancer tissue does not affect any other part of your body and it has not been shown to have any negative effects.

Women who have had cryotherapy or thermoablation treatment continue to have their period as they did before and can become pregnant and have children in the future.

Women who have these treatments have not reported pain or discomfort during sexual relations after waiting for the recommended time after having the treatment.

If the probe is placed in the wrong location, it could lead to additional pain and tissue damage.

Steps we take to protect your privacy

- Your medical record will be checked by your doctors to make sure it is fine for you to be in this study.
- The only information that will be taken from your medical records will be the information that shows that you are able to be in the research study. No other information will be taken, and no information about this research will be included in your medical records.
- If the doctor for the research study finds any important medical information during our study, this information will be given to the doctor in charge of your care at the hospital so that your health team can take care of you.
- Your name will not be recorded on the study information collected about you. Your study information will be identified only by a randomly generated study number.
- We will only have one document that includes your name, how to contact you, and your code number. We will keep this document in a place different from where we keep other study information. It will be stored in a locked file cabinet, where only the research team can access it. We will destroy this document with names five years after the study is over.
- Study records will be kept on files protected by a password that only the research team knows. Any paper documents will be kept in a locked storage room at the study sites. They will be destroyed after 5 years. Copies will be sent electronically to the United States and stored with a password that only the research team will know. If you agree to have photographs taken of your cervix, they will not have your name on them. These images may be kept for more than 5 years to complete the development of the computer program to diagnose cervical precancer.
- Your name will not be used in any report or publication of the results of this study.
- We will use your cervical tissue only for this research.
- Researchers working on the study will have access to the study records. The only other people who may look at our study records are people who review studies to make sure they are safe and protect your rights. This could include members of the Cleveland Clinic Institutional Review Board or Ethics Committees at the study sites, Cleveland Clinic, MobileODT, National Institutes of Health (NIH), National Cancer Institute (NCI), National Library of Medicine, or officials in [country] who approve the use of new medical instruments. These people are not allowed to share private study information about you with anyone else.
- This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that most people outside the research team will not see your name on your research information. This includes people who try to get your information using a court order. One exception is if you agree that we can give out research information with your name on it. Other exceptions are information about child abuse or neglect and harm to yourself or others.

Are there any costs to you if you join the study?

There are no costs to you if you join the study. The costs of the study procedures are paid by the study. None of the investigators will earn any money from sales of any of the devices.

If you believe that you have suffered an injury from being in this study, contact [name of person according to site] (telephone number listed below).

Information about your rights

- **You do not have to be in this research study.** If you say no, you will not lose any rights that you normally have. If you say yes, you will not gain any rights that you did not have before.
- **You may say yes now and change your mind later.** You may stop or leave at any time during the study.
- **If you do not want to be in the study, your regular medical care will not change.**

Conflict of Interest Disclosure

The Co-Principal Investigator of this project, Dr. Miriam Cremer, is the founder of the non-profit Basic Health International, Inc. (BHI). BHI is a collaborator on this study. BHI and Dr. Cremer could benefit financially from positive publicity if this research is successful. Neither Dr. Cremer nor Basic Health International have any financial interest in CryoPen®, Inc., or WISAP and will not profit from sales of the devices. These financial interests are being managed and are within permissible limits established by the local institution Conflict of Interest Policy. If you have any questions regarding conflict of interests, please ask your doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924.

Who to contact if you have questions

- If you have questions about this study or if you believe you have been hurt as a result of this study, please call:
  [name and contact information at each site]
- If you have questions about your rights as a research participant, please call:
  [Ethics Committee or IRB at each site]

Confirmation of consent

The volunteer and the investigator/delegate must each SIGN, DATE and TIME this consent form.

Research participant:

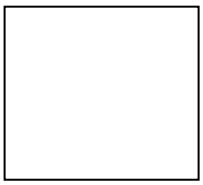
I have read, or had read to me, this entire consent for research. I have had the opportunity to ask all my questions about the study. All of the questions I asked were answered to my satisfaction. If I do not choose to participate in this research, or if I choose to withdraw from this research at any time, this will not affect my ability to receive medical care outside of this research study. I hereby volunteer to participate in this research.

☐ YES. I agree to have photographs taken of my cervix during my procedure. The photographs will not identify me in any way.

☐ NO, I do not agree to have photographs taken of my cervix during my procedure.

Research participant signature:

_____



Name:

_____

Print Name

Date: (DD/MM/YR):_____ Time: _____

Thumbprint
(If non-literate)

Consent witness (for non-literate participants)**:**
I was present for the entire consent process and observed that the potential volunteer had an opportunity to ask questions, appeared to understand what was involved and voluntarily agreed to take part in the research.

Consent witness signature: _____

Name: _____

Print Name

Date: (DD/MM/YR): _____ Time: _____

Research investigator or delegate:
I have fully explained to the potential participant the nature and purpose of this research study. I have explained the potential benefits. I have explained the possible discomforts and risks. I believe that the potential volunteer understands the nature, purposes, benefits, and risks of participation in this research. I have also offered to answer any questions and have fully and completely answered all such questions. I have provided the participant with a copy of the consent form.

_____

Signature of Investigator/Delegate (person who obtained consent)

_____

Print Name of person who obtained consent Title

Date: (DD/MM/YR): _____ Time: _____