"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

3. STRUCTURAL SUMMARY

3.1. Synopsis of the Study

NAME OF THE TEST TECHNOLOGY	XytoTest
TITLE OF THE STUDY	"Evaluation of the quality of cervical samples obtained with self - collection vs samples taken by the medical service provider"
INDICATIONS	HPV-Hr prevalence in cervical/vaginal samples taken by both patient herself vs medical provider, determined by a follow up with a colposcopy and a biopsy on positive samples when necessary
DESIGN OF THE STUDY	Prospective, transversal, balanced, randomized, simple blind, and comparative study.
OBJECTIVE(S)	• Comparing the self-sampling method performance using XytoTest to samples taken by the service provider to detect HPV-Hr
SAMPLE SIZE	Total: 500 women • nurse practitioners working at the General Hospital of Mexico "Eduardo Liceaga" and women attending routine gynecological visit
RESEARCH CENTER	The Oncology Unit at General Hospital of Mexico "Eduardo Liceaga"
SELECTION CRITERIA OF THE SUBJECTS	• Females, 30 to 65 years of age • Women with no previous surgical procedures to treat Cervical Cancer (Cervical conization or Hysterectomy) • Women with no previous treatments such as radiotherapy, and chemotherapy to treat cervical cancer
EQUIPMENT USED	• XytoTest (self-sampling medical device). • Cervex Brush for the service provider to collect cervical samples • PCR-RT / Abbott m2000 • Abbott mSample Preparation System DNA • Abbott RealTime HR HPV Amplification Reagent Kit • Abbott RealTime HR HPV Control Kit • PreTect HPV "Proofer Next Generation" (mRNA E6/E7)
METHOD OF ADMINISTRATION AND DURATION OF TREATMENT	Dual sample of the cervix.
PRINCIPAL PARAMETERS OF EFFICACY	• Identification of DNA HPV-Hr on both self-sampling taken specimens and direct sampling by a service provider • Determine HPV-Hr infection progression on all DNA HPV-Hr positive samples by mRNA E/6-E/7 method

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

ADDITIONAL PARAMETERS OF EFFICACY	• To demonstrate that the self-collection with XytoTest is equivalent to the sample obtained by the medical service provider. • To determine the acceptability of the method of self-sampling with the medical device XytoTest.
SAFETY PARAMETER(S)	Adverse events and clinical assessment.
STATISTICAL ANALYSIS	Student's t-Distribution method
ACCEPTANCE RANGE	P<0.05
EFFECTIVE ASSESSMENT	The effectiveness will be evaluated based on the following results: DNA HPV-Hr detection via PCR-RT HPV-Hr infection progression via mRNA E6/E7 Colposcopy to all positive patients on the above-mentioned tests Biopsy to positive mRNA E6/E7 patients only

3.2. Problem approach

Cervical cancer is a non-resolved public health problem in Mexico. The Papanicolaou screening method has not had sufficient impact in the vulnerable population because of low-coverage conditions, cultural aspects, socio-economic problems and limited medical services, mainly in the rural and suburban areas. Therefore, in several parts of the world with similar problems, a self-sampling test HPV DNA with multiple benefits has been implemented: a) Greater sensitivity for high-grade lesions; b) Greater population coverage; c) Expense reduction for the medical expenses in the number of office consultations and procedures; and, d) Screening-tests specifically to people that require it;

Today, high-risk groups that have personal and health system limitations can be satisfactorily covered with the self-sampling method.

The self-sampling medical device, XytoTest, is ergonomically designed to be inserted in the vagina. Its diameter is smaller than 8mm and its length is 14 cm. It has a cell recollection area, elaborated with a class IV USP medical grade elastomer that guarantees the collection of enough quality and quantity of cervical cells to be analyzed.

3.3. Main goal

Determine the self-sampling method performance using XytoTest vs samples taken by the medical service provider to detect HPV-Hr using a DNA PCR-RT test (14 genotypes), and a mRNA E6/E7 bio-marker test (7 genotypes) to identify HPV-Hr infection progression

3.4. Secondary goal

Determining the patient's level of acceptance of the XytoTest self-collection medical device method.

3.5. Primary Hypothesis

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

The self-collection with XytoTest medical device performance is comparable to the sample taken by a medical service provider for a molecular analysis via DNA HPV-Hr PCR-RT and Bio-markers mRNA E6/E7

3.6. Secondary Hypothesis

The sample collected by the participant herself using the XytoTest self-collecting medical device has a higher patient acceptance.

3.7. Methodology

The study will be monocentric, prospective, transversal, randomized, balanced, simple blinded, and comparative. It will have a participation of 500 volunteers between the ages of 30 and 65, who have not previously undergone any hysterectomy or oncology treatments for cervical cancer.

In order to carry out the study, there will be two visits, which will be numbered as 0 and 1. Visit 0 will be named Recruitment visit. During this visit, the participant's inclusion to the research protocol according to the inclusion and exclusion criteria established by the protocol will take place, and the informed consent will be explained and guided. Moreover, a dual sample will also be taken. The participant will collect her cervical/vaginal sample using the XytoTest self-collecting medical device, and the medical service provider will collect the cervical sample using the Cervex Brush that the Oncology Department from HGM has provided. Both samples will be processed via PCR (Polymerase Chain Reaction) to identify high-risk HPV DNA, and mRNA E6/E7 test will be also performed to identify women with a higher risk of developing a high-grade lesion (CIN 2+) or cervical cancer. Regarding the visit 1, this will be to pick up the results and receive the pertinent instructions from the medical service provider on an appropriate follow-up. To those patients with an HPV-Hr positive results with either method (DNA-HPV-Hr or mRNA E6/E7), a colposcopy will be performed. To all patients with a mRNA E6/E7 positive result, a biopsy will be performed.

3.8. Result Analysis

The data to be analyzed will come from the results and the final diagnostic obtained by using the XytoTest self-collection device method and from the results obtained with the sample taken by the medical service provider from the Oncology Department at the General Hospital of Mexico "Eduardo Liceaga". The patient's data collection sheet will provide the following information: general data, age, education level, occupation, marital status, number of births, number of children alive, age when started being sexually active, number of sexual partners, previous venereal diseases, previous Papanicolaou studies, previous Papanicolaou studies results, tobacco consumption, alcohol consumption and street drugs use.

The data will be introduced in tables of frequency and percentages, using statistical programs "STATA" version 14 and the Student's t Distribution statistical method. Graphics will be presented showing the representative results of the studies and, in necessary cases, variables will be crossed.

Keywords

Cervical Cancer, Papanicolaou, Self-sampling, Human Papillomavirus, HPV-Hr DNA, Cervical Bio-markers, high-grade lesion progress, XytoTest, mRNA E6/E7.

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

4. PROJECT DEVELOPMENT

4.1. Theoretical Framework

Cervical cancer is caused by a sexual transmitted infection known as Human Papillomavirus (HPV). It is estimated that 99.7% of cervical cancer cases are correlated with high-risk genotypes of HPV. Cervical cancer is the leading cause of death among women of childbearing age (38 to 44) and is also responsible for nearly 300,000 deaths annually; of which 85% occur in developing countries.

Cervical Cancer is the only cancer that can be prevented. Scientific developments ratify that early detection of the HPV DNA presence through organized screening campaigns is the best way to help lower the death rate from this disease.

Cervical cytology is a well-known technique since the 1950s, which was initially described by Papanicolaou. Its basis is the collection of cervical cells that are then analyzed by cytotechnologists who search for cell changes that could suggest a high-risk HPV infection.

Performing massive amounts of cytology testing has helped with the timely detection of cervical cancer, in that before the cancer appears and within an interval of several years, pre-malignant changes can be detected which are consistent in characteristic cell changes induced by the high-risk HPV infection.

Developed countries whom have implemented screening programs using new molecular technologies for the early detection of high-risk HPV infections, showed greater advance in reducing morbid-mortality rates compared to developing countries where conventional screening programs based only on yearly pap-smear tests are used. This constitutes a great development for those countries, being that cervical cancer affects women in the middle of their life, when they are still very productive in many aspects (family, working, social, etc.). Life span gained contributes to a major prosperity of any society. This is why the timely detection of cervical cancer should be considered a top-priority health goal.

4.2. Past history

In Mexico, through the National Institute of Public Health, Dr. Eduardo Lazcano, pioneer on the self-sampling initiative in combination with molecular technologies for the identification of DNA of high-risk HPV, verified its usefulness in rural areas. Self-sampling showed a high acceptance among participants and also, showed concordance between the self-collected samples and the samples collected by the service provider, with high sensitivity for the diagnosis of high-grade lesions. This model was replicated in different parts of the world, being an excellent alternative to screen high-risk patients, in rural and suburban areas.

The intention of this study is to confirm the usefulness of a new medical device for self-collection, Mía by XytoTest, and to compare the quality and quantity of specimens collected to the conventional sampling done by the service provider for the detection of DNA high-risk HPV 14 genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using Abbott's PCR-RT technology. Furthermore,

during the study, all samples will also be subject to a mRNA E6/E7 analysis with the intention of stratifying women who are at a higher risk of developing high-degree lesions (NIC 2+) or cancer.

4.3. Problem approach

Cervical cancer is a non-resolved public health problem in Mexico. The Papanicolaou screening method has not had sufficient impact in the vulnerable population because of low-coverage conditions, cultural aspects, socio-economic problems and limited medical services, mainly in the rural and suburban areas. Therefore, in several parts of the world with similar problems, a self-collection initiative combined with a molecular test for HPV DNA has been implemented delivering multiple benefits such as: a) Greater sensitivity for high-grade lesions; b) Greater population coverage; c) Cost-effectiveness in medical expenses specially those related to the number of office visits and procedures.

Today, high-risk groups that have multiple personal and health system limitations can be satisfactorily covered with the self-collection method.

The XytoTest self-collecting medical device is ergonomically designed to be inserted in the vagina. Its diameter is smaller than 8mm and its length is 14 cm. It has a cell collection area, elaborated with an IV USP medical grade elastomer that guarantees the collection of enough quality and quantity of cervical/vaginal cells by the patient herself to be analyzed via PCR-RT.

4.4. Justification

The sensitivity of the XytoTest self-collecting device when used alone with Abbott Laboratory's m2000 system has not been studied; in addition, the same goes to the sensibility of self-collected specimens using Mía by XytoTest and a molecular mRNA E6/E7 method. Therefore, this study was designed to compare the sensitivity of the self-sampling method to the sample taken by the service provider for the high-risk HPV DNA analysis.

4.5. Main Hypothesis

The performance of the medical device Mía by XytoTest for the self-collection of cervical/vaginal cells is comparable to the sample obtained by the medical provider to perform a real-time PCR analysis of the DNA high-risk HPV.

4.6. Secondary Hypothesis

Self-sampling for DNA high-risk HPV using the medical device Mía by XytoTest has a higher acceptance among patients.

4.7. Main Goal

Determining the performance of the self-sampling method by using the medical device Mía by XytoTest versus a sample that was obtained by the medical provider using a molecular real-time PCR test for DNA high-risk HPV analysis and a Bio-marker based on mRNA (E6/E7).

4.8. Secondary Goal

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

To evaluate the self-sampling method done with the medical device Mía by XytoTest by participants in this study.

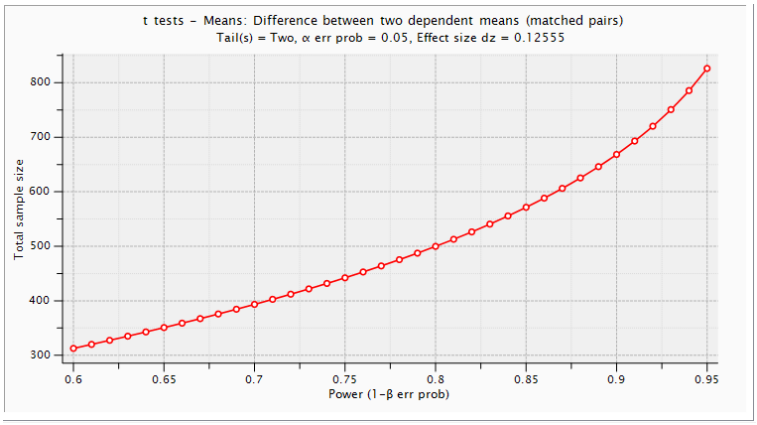
4.9. Methodology

4.9.1. Study Type and Design

The study will be monocentric, prospective, transversal, randomized, balanced, simple blinded and comparative.

4.9.2. Sample size and population

The size of the sample was determined by using the compared matched method. The two comparison groups will use the same cell collection techniques for a later determination of DNA of high-risk HPV. The required sample size was carried out based on the accuracy of the paired diagnostic tests (same number of subjects for each one of the tests). For these types of calculations, sensitivity and specificity values were used for each one of the tests; a fixed 95% confidence level (error alpha of .05) was established with a statistic testing power of 80% (beta of .20), and the effect size (d de Cohen) of 0.12555. The size of the sample was equal to 500 women of which, 250 women will go for self-sampling of cervical/vaginal cells first, and then for the conventional method to obtain cervical cells after the self-sampling takes place; while the other group of 250 women will do the opposite of the first group. It is important to highlight that the sample taken will be randomized. The GPower 3.1.9.2 software was used to determine the final size of the sample for this study.



Graphic 1. Size of the sample

4.9.3. Inclusion criteria

A. The participation of the subjects will be voluntary according to the proposed guidelines under the General Health Law and an informed consent will be obtained according to the above-mentioned law. Therefore, the rules established by the Declaration of Helsinki, the Revision of Japan and the Good Clinical Practice will be followed.

B. Women older than 30 years of age and younger than 65 will be included.

C. Those without a previous surgical procedure to treat cervical cancer. (LEED – Conization)

D. Those without cervical cancer treatments (radiotherapy – chemotherapy)

4.9.4. Exclusion criteria

A. Women non-sexually active.

B. Subjects who underwent a uterine surgery.

C. Pregnant women.

D. Women on their menstrual cycle.

E. Having had sex 24 hours previous to taking the sample.

4.9.5. Criteria of Elimination

A. Proof of non-cooperating attitude during the study.

B. Not having signed the informed consent.

4.9.6. Identification of the Investigational Product

The XytoTest self-collecting device is ergonomically designed to be inserted in the vagina. It has a diameter smaller than 8mm and a length of 14cm. It includes a cell collection area, with an IV USP medical grade elastomer, that guarantees a sufficient quantity and quality of self-collection cervical cells to be analyzed via PCR.

4.10. Procedure

This is a Prospective, transversal, balanced, randomized, simple blind, and comparative study, of the General Hospital of Mexico.

The inclusion criteria for this study consists of female patients between the ages of 30 and 65 years of age, sexually active, who have not undergone a surgical procedure (hysterectomy) or an oncological treatment to reduce cervical cancer.

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

a. General Procedure

Candidate patients who participate in the study will be asked to sign the informed consent letter to later cross-check the adherence to the instructions that were given to them, and the compliance of the criteria of inclusion and lack of criteria of exclusion according to the established points in 4.9.3 and 4.9.4 of the present documents.

b. Planned activities during the study

A total of two (2) visits will be made (including the recruitment visit), and for those with positive results a total of three (3) visits would be necessary; for which will be numbered 0 to 2.

Visit 0 will be the recruitment visit. Visit 1 will be to pick up the results and to perform any histological studies to all women with positive results. The activities that will take place on each visit are described below:

Visit 0

- **Patient recruitment**

In total, 500 women will be recruited to participate in this study. Both, nurses working for the General Hospital of Mexico, "Eduardo Liceaga", and women from general population attending the Oncology department of said hospital for the timely detection of cervical cancer. During this first visit, the following data will be compiled: date, demographic data, age, level of education, occupation, marital status, number of births, number of children alive, age in which started to be sexually active, number of sexual partners, have you ever had a sexual transmitted disease? Have you ever had a Pap smear done? Do you have a Pap smear done annually? Do you smoke? Do you drink alcohol? Do you use street drugs? Do you take any medication?

Once the previous step concludes, the patients will begin de dual sampling. The sample collection method will take taken place in a randomized order. As for the self-collecting method, the patient will be given a medical device kit named Mía by XytoTest® to be use in a discrete and comfortable place by the patient herself following manufacturer's instructions as follows: a) remove the device from its plastic hygiene package ; b) remove the cap from the top of the device and discarded immediately; c) with one hand separate the vagina labia majora; d) with the other hand introduce the medical device into the vagina until the wing of the device touched the labia majora; e) rotate the device clockwise 3 times 360 degrees; f) slowly remove the device and hand delivery it to the nurse assistant. Once the device is delivered to the nurse assistant, it will be placed into a tube containing 5 mL of preserCyt, a liquid transport medium, the device should be stir-up for 30 seconds before is removed from the liquid transport medium to be discarded. Lastly, the tube containing the collected cells by the patient herself using the medical device Mía by XytoTest, should be firmly closed and hand delivery to the personnel in charge of the processing.

Regarding the direct sampling done by the service provider, the patient will be placed in gynecological position and then a vaginal speculum will be inserted into the vagina and a Cervex Brush will be used by the service provider to collect the cervical cells. Said device will be place in a

tube containing 20 mL of preservCyt, a liquid transport medium, as recommended by the manufacturer of the Cervex Brush. After the patient has completed the sampling by the two methods, she will be asked to answer a short questionnaire about her experience with self-sampling for the prevention of cervical cancer.

At the 13:00 hours of each day when patients have been recruited to participate in this study, nurses working at the oncology department of the general Hospital of Mexico, "Eduardo Liceaga", will logged the collected samples into the study's record. As previously described, the samples taken by the service provider were diluted into 20 mL preservCyt solution, the next step is for the nurse assistant to place the tube containing the 20 mL solution in a cellular agitator to secure sample homogenization before 5 mL are extracted and transferred into a new tube. The objective of this process is to send to the lab, two identical samples which it will be only labeled as sample A and sample B.

The collected samples will be transported on Wednesday and Friday of each week until the study is completed at 14:00 hours. Both, sample A and sample B will be process for the identification of DNA of HPV-HR using a Abbott PCR technology. The system m2000 will determine the presence of HPV-HR types 16, 18, 31, 33,35, 39, 45, 51, 52, 56, 58, 59,66, and 68. The remaining preservCyt solution containing at least 3 mL of samples A and B will be sent via DHL to an ISO 13485 certified laboratory located in Norway to process the samples by using the second molecular analysis for the identification of mRNA E6/E7 for specific set of HPV-HR genotypes as follows: 16, 18, 31, 33, 45, 52, and 58.

Visit 1

The laboratories' result of the two molecular analysis will be delivered to each patient at the oncology unit of the General Hospital of Mexico, "Eduardo Liceaga" 15 working days after the samples were taken. Each patient will be receiving alone with her results, the appropriate indications and directions on the next steps to follow according to the test results. All patients with positive results for DNA of HPV-HR will be subject to a colposcopy and a biopsy if necessary; while all patients positive for mRNA E6/E7 will go under a colposcopy and biopsy.

Visit 2

The visit will happen 10 workings days after the colposcopy and biopsy were taken. At this time, results of the colposcopy and biopsy (whenever it applies) will be delivered to patients. The medical doctor will be discussing with her patient the treatment procedure if any and/or instructions to follow.

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

4.11. Activity timeline

VISITS

	RECRUITMENT	**Visit 1**	**Visit 2**
ACTIVITIES	**Day 0**	**15 working days**	**25 working days**
Execute informed consent	*		
Demography	*		
Clinical records	*		
Physical exam	*		
Tolerability	*		
Study explanation to patient	*		
Inclusion Criteria	*		
Exclusion Criteria	*		
Elimination Criteria	*		
Self-sampling for Hr-HPV with XytoTest	*		
Sample taken by the medical service provider	*		
Tests results collection by patient		*	
Colposcopy and biopsy when tests results are positive		*	
Test results collection and discussion on process to follow			*

4.13. Statistical Analysis

The information to be analyzed will come from the results and the final diagnosis obtained from the self-collecting method using the XytoTest and the Mexican General Hospital "Eduardo Liceaga" Oncology Department's service provider. On the data collection sheet the following information will be obtained: general data, age, level of education, marital status, number of births, number of children alive, age that became sexually active, number of sexual partners, venereal disease history, previous Pap smear testing, results of previous Pap smear testing, smoking, alcohol, and drug use.

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

The information will be recorded on tables of frequency and percentages, using statistical programs in the presentation, and the analysis of the results through the T of Student. Graphics showing the most representative results of the tests will be presented and variables will be crossed-marked in those necessary cases.

4.14. Closing of the Study

The final evaluation of the volunteers will be performed seven days after the self-collection was taken. Also, the global efficiency and the quantified satisfaction from the patient and the main researcher will be evaluated, as well as the global safety (only from the researcher). Therefore, the corresponding areas will be filled out in the Case Report Form.

4.15. Validation of Safety

All volunteers who participate in the study will contribute to provide safety information. Any adverse event will be classified according to its severity, treatment and the relation with the sampling taken in the study.

4.15.1. Adverse Events

Definitions

An adverse event/experience (AE) is any medical occurrence in a patient or participant subject during a clinical investigation to whom a pharmaceutical product is administered and which (reaction) does not necessarily have a causal relation to this product.

An adverse event (AE) can be an unfavorable non-intentional sign (including abnormal laboratory findings) symptom or disease that can temporarily be associated with the usage of a pharmaceutical and cannot or is not related to it.

A severe Adverse Event (SAE) is any medical occurrence that at any dose:

- Causes death
- Endangers life
- Results in a permanent or significant disability
- Results in or prolongs hospitalization
- Causes a congenital anomaly or a birth defect

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

An unexpected adverse reaction is that reaction whose nature or severity is neither described in the scientific literature, nor in the information given in the sticker or in the prescribing information, nor in the documentation presented for its registration, and additionally is not possible to infer it from its pharmacological activity.

During the development of the study, any adverse events that occur will be classified according to the intensity of the clinical manifestation (severity) as:

- Mild: presenting as easily tolerated signs and symptoms, no treatment needed, no prolonged hospital stays and can or cannot require stopping the medication.

- Moderate: It interferes with normal activity (with possibility of causing work time off work or school) without directly threatening the patient's or volunteer's life. It requires pharmaceutical treatment and may or may not require stopping the medication causing the adverse reaction.

- Severe: any presenting morbid manifestation with the administration of any dose of medication and that: (1) puts life in danger or caused the death of a patient and/or volunteer (2) makes hospitalization necessary or prolongs the hospital stay, and (3) causes a persistent or a significant disability.

Under both sampling method modalities, the self-sampling and the sample taken by the service provider, no side-effects have been reported

4.15.2. Report and Documentation of Adverse Events

In the presence of any adverse event, this shall remain documented in the corresponding CRF section for each volunteer.

It is important to report any adverse event that based on the previous definitions could be considered severe, even if it is not significant as per the researcher's opinion or related to the medication used during the study.

For the severe adverse events report, the corresponding format (official format for suspicious adverse reactions to medications (SSA-03-021) will be used.

The non-severe adverse events (mild and moderate) that present during the study will be registered with the study final report, as established in the above mentioned rule/guideline.

Patient follow-up will take place during the following two weeks after the completion of the study, mainly to watch the onset of any adverse event that could be considered in relation with itself and, if it applies, will also have to be reported.

4.16. Premature Suspension or Termination of the Study

The main researcher will be able to suspend or interrupt the study at any moment for security, administrative or other reasons.

The reasons to interrupt a study should be properly documented and notified to the Ethics and Research committee. In case of early termination of a study, a complete final evaluation of the patients will have to take place in order to ensure their health conditions, and if necessary, take appropriate measures.

The conditions for the suspension of a study at an early stage are summarized as follow:

Patients can be removed from the study for any of the following reasons:

- Because of a self-decision and there is no need to give any explanation.
- A decision taken by the clinical researcher due to patient's security reasons or disability to meet the protocol requirements.

4.17. Assurance of Information Quality

4.17.1. Monitoring

The researcher is responsible for ensuring that the study is run according to protocol and good clinical practices and that the information generated is accurately documented.

4.17.2. Data management

Quality Control is responsible for the first step to validate the results received from the researcher. All corrections made in the case report forms (CRF) have to be legible and signed by the person who performed it. Each result revision must include the signature and date of the revision. Quality Control will perform an independent revision to proof the accuracy of the results, documenting the process with a signature and date of the revision.

To maintain the confidentiality of the volunteer, all registered data during the course of the study will be identified only with initials and the volunteer number. However, the researcher agrees to register

the volunteer's identification on a list. This list will be treated with strict accuracy to the guidelines of confidentiality and will be archived.

4.18. Documentation of the Study

4.18.1. Case Report Form

The Main researcher will elaborate a corresponding Case Report Form before the beginning of the study, which will contain: protocol title, number of the study, number of protocol, date, volunteer identification (name, and patient number) and tests done.

4.18.2. Master Archive of the Study

The Master Archive of the Study will contain the following documents:

- The protocol of the study
- Monography of the researcher
- Approval of the Protocol by the Ethics and Research Committee, including the outgoing correspondence
- Approval/Notification
- Approval/Notification of the Health Authority (if it applies)
- Guidelines of the ICH-GCP and local law (if applicable)
- Information/Identification of the volunteers and Informed Consent
- Informed consent duly signed
- Patient instructions
- Patient identification (selection, identification lists, etc.).
- Special instructions referring to the conduction of the study (for example, instructions to perform the self-sampling and the sampling).
- Case Report Form
- Adverse Events Report
- Proof of turning in and reception of the biological fluid samples.
- Clinical history

4.18.3. Final Report

Once the study concludes, the researcher will have to elaborate a final report of it.

4.18.4. Document Archive

Documentation must be saved for a period of up to 3 years after conclusion of the study.

4.18.5. Documentation

Documentation generated from the planning to conclusion of the study will have to be filed in the corresponding Master Document.

4.19. Ethical and Legal Aspects for the Development of the Study

The study will be performed according to the Helsinki Declaration (1964) revised in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West, RSA (1996) and Edimburg (2000), Washington (2002) and the revisions that were made in the WMA General Assembly, in Tokyo (2004).

The study will be conducted according to:

ICH E 6: Note for Guidance on Good Clinical Practice (CPMP/ ICH/ 135/95).

ICH E 3: Note for Guidance on Structure and Content of Clinical Study Reports, Step 4 (CPMP/ICH/137/95).

Ethics and Research Independent Committee

A copy of the protocol or amendments of the study, a copy of the consent form letter and a copy of the researcher pamphlet will be provided to the Ethics and Research Committee. All this documentation will come accompanied with a formal application for the protocol approval and an authorization so it can be performed.

In the case that an amendment to the protocol is presented once authorized, these will be approved by the Committee previous to the implementation of such changes, unless the modifications are of administrative type and do not affect the participant volunteers.

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

4.20. Relevance and Expectations

This project intends to show proof through a pilot study to identify if applying a low-dose radiotherapy previous to the conventional therapy could have benefits in the reduction of the inflammatory processes and reduction on the recovery time caused by conventional radiation.
The results will be useful for the following products:

-Results will be presented at the Oncology Congress of Research.
-New research lines in the cancer treatment will be created.
-An article will be published in a Scientific Journal.

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

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ANNEX 1

PATIENT CHARACTERISTICS SHEET

SALUD
SECRETARÍA DE SALUD

HOSPITAL GENERAL de MÉXICO
DR. EDUARDO LICEAGA

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

Date: Click here to type a date.

City: Click here to type text. **State:** Click her to type text.
Country: Click here to type text. **Hospital:** Click here to type text.

Patient reference number: Click here to type text.

1. Generalizations

First Last Name: Click here to type text. Second Last Name: Click here to type text.
Name: Click here to type text. .
IFE No.: Click here to type text. Date of birth: Click here to type a date.
Address: Click here to type text. Zip code: Click here to type text.
Telephone: Click here to type text.

2. Age Group

30 – 40 ☐ 41 – 50 ☐ 51 – 65 ☐

3. Level of Education

None ☐ Incomplete Elementary ☐ Completed Elementary☐
Incomplete High School ☐ Completed High School ☐ Technical School ☐
College Degree ☐ Masters Degree or more ☐

4. Occupation: Choose an option.

If you are employed, please indicate your profession or your trade: Click here to type a text

5. Family information

Marital status: Choose one Number of births: Choose one Number of children alive: Choose one

6. Sexual History

a. Age of your first sexual encounter: Choose one

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

b. Number of sexual partners: Choose one
c. Have you ever had any Sexually Transmitted Infection: Choose an option

7. Visit to the Gynecologist

a. Have you ever had a cytology or a Pap smear done? Yes ☐ No ☐
b. If your previous answer is yes, indicate when was the last time you had a vaginal cytology done: Choose one.
c. Do you have a cytology or Pap smear done annually? Yes ☐ No ☐

Observations: Click here to type text.

8. Personal Habits

a. Do you smoke? Yes ☐ No ☐
b. If you answered yes, how many cigarettes do you smoke a day? Choose an option.
c. Do you drink alcohol? Yes ☐ No ☐
d. If the answer is yes, how much alcohol do you drink a week? Choose an option.
e. Do you consume any street drugs? Yes ☐ No ☐
f. Do you take any medication? Yes ☐ No ☐

9. Observations

Click here to type text.
Medical Service Provider initials: Choose an option.

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"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

ANNEX 2

QUESTIONNAIRE TO EVALUATE THE SELF-COLLECTING EXPERIENCE

Dear patient:

Thank you for participating in the study "Evaluation of the quality of the cervical samples obtained with self-collecting method versus samples taken by a medical service provider." In reference to the self-collecting method, that is the objective of this study, we would like to learn your opinion based on your personal experience.

1. Please, mark with an X the level of discomfort caused by the self-collecting method. "1" is equivalent to no discomfort, and "10" is equivalent to an unbearable discomfort.

1	2	3	4	5	6	7	8	9	10

2. Please, mark with an X the level of difficulty you had using self-collection. 1 is equivalent to no difficulty and 10 is equivalent to a difficulty that makes it impossible to perform the test.

1	2	3	4	5	6	7	8	9	10

3. If self-collecting is equally valid to the sample taken by the doctor, would you take the self-sample device home and bring the sample back?
   Yes ☐ No ☐

4. Do you feel comfortable and confident by taking the cervical/vaginal sample by yourself?
   Yes ☐ No ☐

Name: _____ Signature:_____

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

ANNEX 3

RESULTS FORMAT

Study results with self-sampling:

_____
_____
_____

Study results from the Service Provider:

_____
_____
_____

"EVALUATION OF THE QUALITY OF CERVICAL SAMPLES OBTAINED WITH SELF COLLECTION VS SAMPLES TAKEN BY THE MEDICAL SERVICE PROVIDER"

ANNEX 4

RESULTS FORMAT

Final diagnosis:

_____
_____
_____
_____