EarLy dEtection of cerVical cAncer in hard-to-reach populations of women through portable and point-of-care HPV TEsting

Country-specific strategy to reach hard-to-reach women with cervical cancer screening programmes – Belgium, Brazil, Ecuador and Portugal

(June 2022)

Content

1. Introduction

ELEVATE, a five-year project conducted by an international research alliance led by Ghent University, aims to develop a new test and approach for cervical cancer screening in hard-to-reach populations. The test will combine self-sampling with a new low-cost, portable measurement device and will be validated in dedicated screening trials in Belgium, Brazil, Ecuador, and Portugal. The ELEVATE project targets women in Europe and Latin America who have never been screened or are not regularly screened. These women have a higher risk of developing cervical cancer. The project is supported by the European Union's Horizon 2020 Framework Programme for Research and Innovation Action, project number 825747.

To address the gaps in cervical cancer screening, the ELEVATE project is developing a screening strategy to make cervical screening more accessible to hard-to-reach women. This strategy will include the introduction of a new on-site HPV self-sampling screening tool and a portable testing device, able to detect the presence of HPV and cancer biomarker proteins. This portable, low-cost, on-site HPV testing tool will allow to streamline follow-up care for women at risk of developing cervical cancer.

2. Background

Even though preventive approaches and strategies are different in European and Latin American contexts, coverage levels are not sufficient in all countries. In Ecuador, coverage at national level ranges between 9 to 20% (9). In Brazil, the coverage rate for the cervical cancer-screening program (opportunistic) is estimated to be below 70% (10). In Portugal and Belgium, screening coverages reaches 70.7% and 55%, respectively (11-14). This means that in all countries a significant part of the eligible female population is not screened regularly for cervical cancer (15,16). Those women, called "hard-to-reach women", are defined as women who are eligible for cervical cancer screening and who, for specific reasons to be further clarified in this study, do not participate in screening and consequently are at higher risk for cervical cancer. They are often from minority groups or living in isolated areas and face multiple barriers in accessing preventive care.

To help define and characterize the hard-to-reach populations who do not attend cervical cancer screening in the study countries, a comprehensive literature review was conducted in each study country focusing on prevalence of HPV and cervical cancer, cervical cancer screening uptake, associated factors, current screening strategies and, in addition, an analysis of official national databases was conducted. Overall, major factors associated with low participation in cervical cancer screening found in the four countries included lower education and low income, as well as poor health literacy and lack of knowledge about cervical cancer. In Belgium and Portugal, evidence also shows that older age, being unemployed and being migrant are negatively associated with screening participation. Distance to healthcare facilities and living in remote areas were factors addressed in literature from Brazil and Ecuador. In Portugal non-regular appointments with GPs and non-adherence to mammography was associated with low participation in screening. Other barriers to screening were identified in Belgium and Ecuador's literature reviews and included fear of the test and its result, negative past experiences in healthcare services, lack of time and other life priorities. These results allowed to identify specific hard-to-reach populations for cervical cancer screening in the four countries.

To further understand barriers and facilitators to participation in cervical screening and to explore alternative strategies to promote screening among hard-to-reach populations, a focus group study has been conducted in each study country. Building on the results of these studies, a self-sampling HPV testing intervention will be launched in hard-to-reach communities in these four countries: Belgium, Brazil, Portugal and Ecuador.

This document provides a description of the country-specific strategy to reach hard-to-reach women in the acceptability study in Belgium, Brazil, Ecuador and Portugal.

3. Overall objectives

This study includes a three-arm prospective acceptability study to:

- assess **attitudes, uptake and users' experiences** related to the use of a HPV self-sampling test *(Obj 1-4)*
- assess the **impact** on looking for follow up care of self-sampling with standard cervical screening strategies *(Obj 5)*
- compare the **feasibility** of an HPV self-sampling in hard-to-reach groups versus educational sessions and standard care *(Obj 6)*

3.1. Study design

A 3-arm prospective acceptability study will be conducted with the following study arms:

Arm 1 – Assessment of screening coverage

Information about the screening coverage rates will be collected, focusing in particular on screening uptake among hard-to-reach women. The screening rates will be collected prior to the start of the study to avoid any contamination, i.e. uptake of screening that may occur through community mobilisation.

Outcome measures that will be examined for arm 1 are:

- Screening coverage at national level
- Screening coverage at local level/in hard-to-reach communities
- Follow-up rate among women who test positive (i.e., have a positive pap smear)

Arm 2 – Information session and follow-up assessment

In arm 2, a community-based researcher will educate women about sexual health and cervical cancer by using the materials that will be developed by the ELEVATE team. Women will be informed about cervical cancer screening (pap smear) and about where they can obtain these services off-site (health facilities); they will receive a contact number to make an appointment as well as information on how to reach the place of the consultation.

Outcome measures that will be examined for arm 2 are:

- Participation rate (i.e., women invited/women who attend the session)
- Knowledge, willingness and uptake of cervical cancer screening prior to the session
- Acceptability of self-sampling
- Uptake of cervical cancer screening through standard services: A 3-month follow-up by phone is proposed to check:

    - whether the woman made an appointment; if no appointment was made, we will ask why; if an appointment was made, we will ask if she was able to attend the appointment
- Knowledge of as well as willingness to get screened for cervical cancer screening will also be assessed during the follow-up phone call
- Feasibility

Arm 3 – Information session and self-sampling

A community-based researcher will educate women about sexual health and cervical cancer by using the materials that will be developed by the ELEVATE team. In addition, women will receive information about self-sampling and will be instructed by the community-based researcher on how to take a self-sample using an illustrative cartoon. Women will then be asked to take a sample on-site. The researcher will collect all samples and bring them to the laboratory of UZ Ghent for analysis by an HPV test (yet to be decided which one). Sample analysis is expected to take 2 weeks time. Women who tested positive for HPV will receive a follow-up phone call to notify their result and will again be informed about cervical cancer screening (pap smear) and about where they can obtain these services; they will receive a contact number to make an appointment as well as information on how to reach the place of the consultation.

Outcome measures that will be examined for arm 3 are:

- Participation rate (i.e., women invited/women who attend the session)
- Knowledge, willingness and uptake of cervical cancer screening prior to the session
- Acceptability of self-sampling
- Uptake of the self-sampling test (women who attend the session/women who take the self-sample)
- Attitudes towards self-sampling (reasons to accept/decline the self-sample; advantages and disadvantages versus conventional screening)
- User experiences among those who took a self-sample (easy/difficult; painless/painfull; trustworthy/untrusty; etc.)
- Uptake of cervical cancer screening through standard services:
    - A 3-month follow up is proposed to check whether the woman made/went to the appointment
- Knowledge of as well as willingness to get screened for cervical cancer screening will also be assessed during the 3 month follow-up phone call
- Feasibility and cost of the intervention

3.2. Specific objectives

Objective 1: Assess and compare **attendance rates** following invitation to participate to the study

Hypothesis 1.1: Attendance will be higher when women are offered self-sampling compared to when women are only offered an educational session.

Objective 2: Evaluate the current **knowledge, willingness and uptake** of cervical cancer screening among participants of the acceptability study (arm 2 & 3); assess knowledge improvement and willingness to get screened 3 months after the intervention

Hypothesis 2.1: Knowledge and willingness to get screened will be poor and uptake of cervical cancer screening among the participants will be lower than the national average (but similar to results found in arm 1)

Hypothesis 2.2: After the information sessions, women will be able to link cervical cancer with HPV and will understand the benefit of screening; willingness to be screened will have increased

Objective 3: Assess **attitudes towards and users' experiences** of the HPV self-sampling test among hard-to-reach women (i.e. participants in arm 3)

Hypothesis 3.1: Attitudes towards on-site HPV self-sampling will be overall positive

Hypothesis 3.2: Women who use the self-sampling tool will have positive users' experiences related to the self-sampling device.

Objective 4: Compare the uptake of the on-site HPV testing (arm3) with the current national screening services (arm1) and with off-site referrals (arm2)

Hypothesis 4.1: Uptake of on-site HPV self-sampling will result in an increase in screening coverage compared to standard practices. (arm 3 vs arm 1)

Hypothesis 4.2: On-site HPV self-sampling will have higher uptake than referrals to off-site screening. (arm 3 vs arm 2)

Hypothesis 4.3: Referral to off-site screening following participation in an educational session on cervical cancer will result in higher screening coverage compared to current practices. (arm 2 vs arm 1)

Hypothesis 4.4: Uptake of off-site screening among those who refuse the self-sampling in arm 3 will be lower than uptake of off-site screening in arm 2

Objective 5: Examine the impact of HPV self-sampling on follow-up testing and care

Hypothesis 5.1: Women whose on-site HPV testing came out positive will go for follow-up testing and care

Objective 6: Assess the **feasibility** of the information session and the self-sampling test

Hypothesis 6.1: Providing cervical cancer screening information and offering on-site HPV self-sampling in hard-to-reach communities will be feasible.

4. Methodology: acceptability study (arm 2 & 3)

4.1. Study setting/context

Organizations and community-based associations working with socio-economically vulnerable women will be invited to participate. These organizations will be randomly allocated to invite women to either arm 2 or arm 3.

We aim to link the information sessions of the acceptability study to group activities that are offered by the organizations. This was suggested by the community health workers during the focus group discussions as a good way to motivate women to participate. It was reported that it is difficult to gather women for the sole purpose of an information session about their health (especially about cervical cancer that is often not known) and that linking it to an activity for which they are gathered will increase the participation rate.

We are paying attention that organisations and their catchment areas are not too close to each other to avoid spillover.

4.2. Inclusion criteria

4.2.1. Participants

Women who are in a socio-economically vulnerable situation and therefore visit one of the abovementioned organizations. Women from the abovementioned hard-to-reach communities will be invited. They are eligible for inclusion if they meet the following criteria:

- are between the ages of 25 to 65 years of age, in line with the European Guidelines for initiating and stopping cervical cancer screening
- (ever been) sexually active;
- not diagnosed or in treatment for cervical cancer;
- not having had a hysterectomy
- not being pregnant
- Speaking the local language

4.2.2. Community-based researchers offering the interventions

We aim to organize each session including team members with different and complementing backgrounds (medical – social/community – background knowledge specific to the organization). More particularly, we aim that each session is attended by at least 3 team members corresponding with one of each of the following profiles:

1) *A researcher with a medical background.* The interventions will be guided by the main researcher in charge of the acceptability study in each study country. The main researcher will take the lead during the educational sessions (arm 2 and 3), give the instructions about self-sampling (arm 3) and will be responsible for the management of the samples (arm 3). The main researcher will be assisted by fellow researchers involved in ELEVATE, including medical students (in the broad sense, including students studying medicine, health promotion, biomedical sciences, etc.). We expect that it will not be feasible for this main researcher to conduct all sessions. Therefore, the main researcher might be replaced by another health care professional (e.g. nurse, physician, medical assistant) or one of the medical students, after they were properly trained and followed some other sessions.

2) *Community-based researchers* will mainly include social workers and community (health) workers. They might not have a medical background but are experienced with working with hard-to-reach women. Community-based researchers will be involved in all stages of this study; however, their core responsibilities will be participant recruitment, assisting during the educational sessions, assisting during self-sampling and (post) counselling, and data collection (questionnaires). They will also be invited to participate in evaluation components of the pilot study *(Obj 6)*. Community-based researchers can also help determine which wording will be used for recruitment and data collection.

   It is estimated that 3-5 community-based researchers will be required in total.

   The general criteria for the selection of community-based researchers include:
   - Community and/or social workers experienced in working with socio-economically vulnerable women
   - Ages between 21 and 60 (preferably 21-35 years old)
   - Speak fluidly the local language
   - Extra asset: Speak another language spoken by the target group
   - Have communication, research and leadership skills
   - Have a good relation with the community
   - Have the willingness and the time to collaborate
   - Extra asset: female

3) *People that are working or volunteering in the organizations* participating in the acceptability study. These will have a similar profile as the previous group, but additionally they are active in the organization and possibly have a professional relationship with the women. During the focus group discussions, it was reported that trust will be an important facilitator during the information sessions and to encourage women to take a self-sample. Therefore, we aim to invite a familiar face to the information sessions as much as possible. Due to the workload of the organizations, this might not always be possible. However, we will ask if they could express their assent about study participation to women visiting their organization and if possible promote the sessions in their specific working groups or group activities. In addition, we will ask for the organization's support to ensure that all sessions are adapted to the specific target group (culturally sensitive and comprehensible).

4.3. Recruitment of participants

In agreement with the participating organizations, the research team (including the community-based researchers) will hand out invitations (leaflets) to invite women to informative sessions on cervical cancer screening. While handing the invitation, the researcher will shortly describe the goal of the session, emphasizing the benefits for the women. If women are invited for arm 3, they will also be told that they will be offered a self-screening test during the session. Women will receive a leaflet stating the time and place they are expected. Women will be asked to invite other women as well.

We aim to link the sessions to group activities where women are already gathered such as sport activities, integration programs and meals in social restaurants. Therefore, we will work closely with the social

workers and volunteers active in the organizations and will ask for their support to invite women. However, we expect that their contribution will be limited due to their day-to-day workload and tasks.

We will explore with the respective organizations what the best approach is in their context with regard to the timeframe between the invitation and the information session. We learned during the focus group discussions that for many socio-economically vulnerable women it is difficult to commit to show up on another day, for various reasons. Therefore, we aim to organize the educational sessions directly following their group activity, integration class or meal in the restaurant (i.e. the moment they will be invited). In some subgroups of women, such as young mothers, it seems advisable to inform them that they will need to stay a bit longer so they can organize this.

All participants will be offered a small incentive for study participation, such as a voucher.

4.4. Educational sessions (arm 2 & 3)

Participants included will attend an information session. The information session will take place in the space where the group activities take place (provided by the organizations), the classroom of the integration course or a private room nearby the social restaurants. Sessions will be organized following the group activities (e.g. after sport activity, integration course or meal in social restaurant), with an approximate duration of 20 minutes (excluding sample taking). The sessions will be organized both during weekdays and weekends, depending on the activities they are linked to and according to the preferences of the organizations and women. The content of the session will cover sexual health, cervical cancer and screening services off-site. In the last part of the information session, participants in:

- **arm 2** - will be provided information on how to be screened for cervical cancer and where they can obtain these services off-site.
- **arm 3** - will be provided information on how to be screened for cervical cancer, and where they can obtain these services off-site. In addition, they will receive information on self-sampling and will be offered a self-sampling kit and asked to take a sample on-site and return it.

4.5. Cervical cancer screening through self-sampling (arm 3)

4.5.1. Self-collection

Women in arm 3 will receive information regarding the self-sampling test and they will be invited to collect a self-sample at the same moment. Contact information (i.e. a telephone number) will be collected in order to inform the women about their test result in case they test positive for HPV.

Each kit will include a self-sampling device (i. e. The Evalyn Brush (Rovers, The Netherlands)), an instruction leaflet and a recipient to store the sample. The self-sample can be taken on-site - after the information session -, in a private, comfortable and safe space where it is comfortable for them to do so.

All the samples collected will be returned to the researcher. The researcher will then directly label the samples (cfr section 4.5.2).

4.5.2. Sample management and storage

Samples will be collected, the Evalyn brush will be rinsed in a recipient filled with preservative medium (i.e. ThinPrep or Roch Cell Collection medium) and the recipient will be labelled using a unique identification code corresponding to the participant and labelled using a unique identification code corresponding to the participant. Also, the date, location of collection and study country will be added. Before analysis and after homogenization, the sample will be divided in 2: 1 part of the sample will be used for the HPV analysis, the second half will be stored to be used in other components of the study (e.g. during the validation phase of the cartridges of the new ELEVATE screening tool) and/or for future research regarding sexual and reproductive health.

Each of the samples will be labeled with a unique identifier code that will be composed out of 21 digits:
X-X-XX.XX.XXXX-XXX-XX.XX.XXXX

- The 1st referring to the country it was collected:
    - 1: Belgium
    - 2: Brazil
    - 3: Ecuador
    - 4: Portugal
- The 2nd referring to the health/community centre where it was collected: all centres/organizations that will collaborate will be given 1-digit number
- 8 digits referring to the birth date of the patient: dd-mm-yyyy
- 3 digits referring to the number of included/sampled patients, starting in each centre with 001.
- 8 digits referring to the day of sample taking

We will color-mark the label to make clear which sample will go for HPV-analysis and which will be stored.

This unique identifier code will also be used to link the samples with the socio-demographic information of the woman (see section 5.2.2) and to ensure pseudonymization of the data and samples (see section 7).
Besides mentioning the code, the label of the sample should also state the HPV status (once the result is known).

After the end of the study (December 2023), the samples will be stored up to 5 years, only and if only the participant has given permission to use her samples in future research. Other samples will be destroyed.

4.5.3. Sample analysis

One half of the sample will be analysed in each study country. Analysis is expected to take a maximum of 2 weeks. After the result is known, the HPV status will be indicated on the sample.

The other half of the sample will be send to Ghent University, Belgium, and stored for further use in other components of the study (e.g. the validation of the cartridges in a later stage of the project) and/or for future research regarding sexual and reproductive health.

4.5.4. Communication of results

Women who tested positive for HPV will receive their result by phone, by email or in a one-on-one counselling with a researcher with medical background or community/social worker who is trained to answer related questions and refer to a physician if the questions are more complex and/or out of the scope of screening. After sample-taking, we will ask the participant how and when she prefers to be contacted. We will already explain to them that they will only receive a phone call in case of a positive test result. If they tested negative for HPV we won't call them to communicate their results (concept of 'no news = good news'). We will only call them 3 months later for the follow-up call.

All women who tested HPV-positive will be guided to a referral centre (by making an appointment for them, giving them directions and coordinates) for follow-up, following the local clinical guidelines.

4.6. Follow-up of participants

All participants of arm 3 who took the self-sample and tested positive will be contacted by phone 2-3 weeks after their participation to inform them on their test result.

All participants (arm 2 and 3) will be contacted by phone **3 months** after their participation:

- to gauge the **knowledge** on cervical cancer screening after the education session
- to verify whether they got a **pap smear** (all women in arm 2 and HPV-positive women of arm 3)
    - if not, why not
        - was an appointment made?
            - if not, why not

In case women do not have a phone, the community-based researcher can discuss with them the best way to schedule a day or set a temporary 'drop-in centre' for them to come in.

5. Data collection

5.1. Arm1

We will contact the respective instances in each study country to ask if more detailed data are available on screening coverage of the target group of socio-economically vulnerable women.

Outcome measures that will be examined for arm 1 are:

- Screening coverage at national level
- Screening coverage in the respective research area in each study country
- Follow-up rate among women who test positive (i.e. have a positive pap smear)

5.2. Arm 2 and arm 3

5.2.1. Participation registers

Participation registers will be used during the pilot to keep track of the participation rate (*obj 1*).

$$Participation\ rate = \frac{number\ of\ women\ who\ participate}{nimber\ of\ women\ who\ were\ invited}$$

The number of women who are invited will be defined by the number of leaflets (invitation letters handed out).

5.2.2. Questionnaires

5.2.2.1. Self-administered questionnaire: knowledge, willingness and uptake of conventional screening (arm 2 and arm 3)

A self-administered questionnaire will be applied to all participants at the start of each session to assess their current knowledge, willingness to get screened (conventionally) and uptake *(Obj 2).* Through this questionnaire, also socio-demographics, sexual behaviour and pregnancy history will be collected, as well as barriers of accessing cervical cancer screening.

Knowledge will be assessed through verifying whether the participant 1) has heard of cervical cancer, 2) knows the human papillomavirus (HPV) as primary cause, and 3) knows HPV is an STI.

Uptake of conventional screening will be assessed by asking participants' screening history, including 1) lifetime screening, 2) age at first screening and number of pap smears received, and 3) being screened in the last 3 years.

Participants will be asked to indicate their willingness to receive a pap smear and reasons for opting/not opting for conventional screening (reasons for interest/disinterest in continuation among those with previous pap smear uptake). Participants will also be asked to indicate acceptance of self-sampling. (See Appendix I: questionnaire 1)

5.2.2.2. Self-administered questionnaire: attitudes towards self-sampling (arm 3)

A self-administered questionnaire will be applied to all participants in arm 3 after the educational session, and before self-sample taking, to assess attitudes regarding self-sampling (pre-intervention) *(Obj 3).*

Attitudes will be assessed through asking participants to use 5-point Likert scale responses to indicate their perceptions of self-sampling and reasons for accepting or not-accepting the self-sample device. (See Appendix II: questionnaire 2)

5.2.2.3. Self-administered questionnaire: users' perspectives in self-sampling (arm 3)

A self-administered questionnaire will be applied to all participants in arm 3 who took a self-sample to assess users' experience regarding self-sampling (post-intervention) *(Obj 3).*

Users' perspectives will be assessed through asking participants to use 5-point Likert scale responses report their experience with the self-sampling brush. (See Appendix III: questionnaire 3)

5.2.2.4. Follow-up questionnaire: knowledge, willingness and uptake of conventional screening (arm 2 and arm 3)

A questionnaire will be applied during a follow-up phone call 3 months after the session to assess whether or not a screening appointment was made and participants got screened (=uptake), as well as to evaluate

knowledge after receiving the informative session *(Obj 2, Obj 4 and Obj 5). (See Appendix IV: questionnaire 4)*

Knowledge and willingness to get screened will be assessed by applying short, closed questions in order to quickly evaluate these outcomes by phone.

Women will be contacted through a message, phone call or e-mail (according to their preference) asking them when would be convenient for them to answer some questions. Women will be contacted up to 5 times maximum before considering them lost-to-follow.

Each participant will be attributed a unique identifier alpha-numeric code that will be used to link the respective questionnaires and to ensure pseudonymization of the data. The information that links the unique identifier code to the name and contacts of the participants will be registered. Only the community-based researcher (healthcare professional or community health worker) responsible for the data collection will have access to these personal data. No other member of the research team will have access to the name and contacts of the participants.

5.3. Focus group discussions

FGDs will be conducted with community-based researchers to explore their beliefs and attitudes towards the HPV screening strategy (including self-sampling) and understand their acceptance of the HPV screening intervention *(Obj 6).* One FGD will focus on arm 2, i.e. the feasibility of the educational session, and another FGD will be organized to discuss the implementation of arm 3. (See Appendix V: Topic guide)

The Conceptual Framework of Rogers' Diffusion of Innovation Model (1995) will be used to explore the topics related to characteristics of innovation (relative advantage, compatibility, complexity, trialability, observability).

6. Data analysis – sample size calculation

6.1. Quantitative data

The primary endpoint is the participation in screening which is defined in Arm 1 as the proportion of women who had a PAP smear taken by a GP or gynaecologist within the national screening program, in Arm 2 as the proportion of women who go for PAP smear after attending the information session with targeted referrals for off-site screening and in Arm 3 as the proportion of women who accept to take an HPV self-test on site after the information session.

Two important measures of take-up will be estimated:

> **Take-up 1** - To compare the take-up of an on-site HPV screening intervention with the current national screening services accounting for self-selection of women who decide to attend clinics (arm 1 vs. arm 3).

Take-up 2 - To compare the take-up of an on-site HPV screening intervention with targeted referrals to off-site screening (population impact regardless of self-selection) (arm 2 vs. arm 3).

Sample calculation was defined according to an estimated increase in take-up compared with current screening coverage for each study country.

6.2. Qualitative data

Audio recordings of the interviews will be transcribed, and the transcripts will be analysed through content analysis. This technique allows the data to be systematized in key topics and organized in different categories and sub-categories. Simultaneously, written notes taken during the interviews will be also used to improve and complete the information if considered relevant.

7. Data management

All data will be entered in a Redcap. In total, the following information will be entered:

1) Participation registers
2) Self-administered questionnaire among all (KAP)
3) 2 self-adminstered questionaire in arm 3 (attitudes towards (=pre-intervention) and users' experience (=post-intervention))
4) Telephone questionnaire (=follow-up assessment)

The unique identifier code will be used to link all the questionnaires of the same participant and to ensure pseudonymization of the data.

Only members of the research team will have access to the pseudonymized data: the data will be saved on work computers of team members only, and a back-up will be saved on a protected server that can only be accessed with a username and password.

8. Training community-based researchers

Both researchers with a medical background and community-based researchers will be involved in all stages of the study. Researchers with a medical background and medical students (in the broad sense, including students studying medicine, health promotion, biomedical sciences, etc.) will assist during the educational sessions and possibly, after they followed some sessions provided by the main researcher (gynecologist), give the sessions themselves. Community-based researchers including social workers and community (health) workers will equally be involved in all stages of this study; however, their core responsibilities will be participant recruitment, assisting during the educational sessions, assisting during self-sampling and (post) counselling, and data collection (questionnaires).

Both groups of researchers will be provided training. The training will cover: HPV and cervical cancer, screening and diagnosis of cervical cancer, follow up of cervical lesion; research methods for the project and their specific tasks; interpersonal communication skills; appropriate responses to sensitive

information (i.e. how to react to women who share experiences of sexual violence, stigma, ill health, etc.); appropriate communication of results.

A standard training session will be prepared and adapted at each study site to their needs and context. Training materials will also be developed. The training will be carried out through role plays, video projections and pamphlets.

People who are working or volunteering in the organizations will be invited to this training session, however if they will not take an active role during the sessions, this is not mandatory. In case they will assist in recruiting women, they will receive a shorter training about the main goals and methods of the project.

9. Ethics

9.1. Protection of subjects

A patient safety plan was developed in order to ensure protection of (potential) participants, including a stigma reduction programme and strategies to tackle harms and emergencies. The stigma reduction programme provides details on ethics and communication training of the researchers involved in the study.

Importantly, the team will ensure that invitations, education sessions and self-sample taking will take place in a confidential environment that provides both visual and auditory privacy. The data collected will only be available to researchers and no third parties will have access to the data.

In addition, the team will ensure that no coercion can be exercised on (potential) participants, by ensuring that participation in the study is voluntary and that refusal to participate in the study will have no repercussion whatsoever. In addition, subjects will be informed that the confidentiality of the data collected in the phone calls and questionnaires is guaranteed.

9.2. Benefits for the participants

No payment will be offered in exchange for participation in the study, which eliminates the risk of coercion for poor subjects who may feel pressured to participate for financial gain. It will be explained to each participant that their information will help us to improve future cervical cancer screening programs.
The only benefit that participants may receive is information regarding cervical cancer and HPV screening, which will probably lead to increased knowledge and awareness. Such information will be provided during the information sessions and/or if participants have additional questions afterwards.

9.3. Confidentiality

To ensure confidentiality of data collected during the phone calls and through the questionnaires, the following steps will be taken:

- Only the person who is the community-based researcher (healthcare professional or community health worker) responsible for the data collection will have access to the information of the link between the unique identifier code and the name and contacts of the participants. Other members of the research team will never have access to any name or contact information of participants.

- Through all steps in the process of data gathering, data entry, data cleaning and data analysis, only research team members and the community-based researchers will have access to the data.
- The results of the study may be published for scientific purposes, but anonymity will be protected at all times and no result will be linked to specific individuals.

To ensure that all team members are aware about the latest data management guidelines, a separate document with details on data security, data storage, data sharing and data preservation will be provided to all partners.

9.4. General consent statement

A written consent form will be asked of all participants, in full compliance with the Declaration of Helsinki. The consent form will be written in simple language at a sixth-grade reading level. The language used in the consent form will be developed in collaboration with medical staff accustomed to share medical information with their patients.

The form will clearly state the objectives of the study and will also include a small screening section that will be used to verify whether or not the approached woman is eligible. When a woman is considered eligible, she will be explained in more detail what is expected from her, i.e. which procedures will take place if she decides to participate.

Only participants with decision-making capacity, that is, they are able to give consent, will be involved in the research. Language and literacy capabilities will be assessed. In case the participant cannot read or write herself, an impartial witness will be asked to join the reading of the consent form (authorized substitute decision maker). The witness will sign the consent form together with the participant. The participant will choose a witness so she can select someone she believes is appropriate and reliable (e.g. another woman from the community – without conflict of interest).

The following topics will be covered in the information sheet of the informed consent:

- Description of the study and its objectives
- To know that participation is voluntary
- To be able to withdraw themselves, their samples and their data from the project at any time
- To know that results can be shared with the participants
- Benefits and risks
- No costs for participants
- To receive assurances that appropriate insurance coverage is in place
- To have confidentiality and privacy protections clearly specified, following national legislations.
- To know of any potential commercial exploitation of the research.
- To know that students might participate in this study as research assistants.

Women will be asked if their data can be used in future research. If they agree, they will be asked to tick the box ‘I consent to have my data deposited in pseudonymised form in a trusted repository so it can be used for scientific purposes only’. If they don’t tick the box, their data will not be released for further use in other research.

Emergency contact information, as well as contact details of an independent person to direct complaints to, will be provided in the information sheet.

References

1. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: The size of the problem. Best Pract Res Clin Obstet Gynaecol. 20(2):207–25 (2006).
2. PDQ Screening and Prevention Editorial Board. Cervical Cancer Screening (PDQ®): Health Professional Version. PDQ Cancer Information Summaries (2002).
3. Sankaranarayanan, R., Budukh, A. M. & Rajkumar, R. Effective screening programmes for cervical cancer in low- and middle-income developing countries. Bull. World Health Organ. 79, 954–62 (2001).
4. Landy, R., Pesola, F., Castañón, A. & Sasieni, P. Impact of cervical screening on cervical cancer mortality: estimation using stage-specific results from a nested case–control study. Br. J. Cancer 115, 1140–1146 (2016).
5. Fobelets, M. & Pil, L. De kosteneffectiviteit van het bevolkingsonderzoek naar baarmoederhalskanker in Vlaanderen: gezondheidseconomische evaluatie. Een studie voor de Vlaamse Overheid. (Vrije Universiteit Brussel and Gent Universiteit, 2015).
6. Costa, A. R. et al. Cancer screening in Portugal: sex differences in prevalence, awareness of organized programmes and perception of benefits and adverse effects. Heal. Expect. 20, 211–220 (2017).
7. INCA. Diretrizes Brasileiras para o rastreamento Do Câncer Do Colo Do Útero. (2011).
8. Costa, R. F. A., Longatto-Filho, A., Pinheiro, C., Zeferino, L. C. & Fregnani, J. H. Historical Analysis of the Brazilian Cervical Cancer Screening Program from 2006 to 2013: A Time for Reflection. PLoS One 10, e0138945 (2015).
9. INEC: Instituto Nacional de Estadística y Censos (Statistics and Census National Institute).
10. Costa RFA, Longatto-Filho A, de Lima Vazquez F, Pinheiro C, Zeferino LC, Fregnani J. Trend analysis of the quality indicators for the Brazilian cervical cancer screening programme by region and state from 2006 to 2013. BMC Cancer. 2018;18(1):126.
11. Bruni, L. et al. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Brazil. Summary Report. (2017).
12. Bruni, L. et al. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Belgium. Summary Report. (2017).
13. OECD/EU. Health at a Glance: Europe 2018: State of Health in the EU Cycle, OECD Publishing, Paris (2018).
14. Vega, B. & Sacoto, C. Prevalencia de cáncer de cuello uterino en el Ecuador y estrategias para su reducción. Rev. la Fac. Ciencias Médicas, Univ. Cuenca 30, 46–51 (2012).
15. Arbyn, M., Fabri, V., Temmerman, M. & Simoens, C. Attendance at Cervical Cancer Screening and Use of Diagnostic and Therapeutic Procedures on the Uterine Cervix Assessed from Individual Health Insurance Data (Belgium, 2002-2006). PLoS One 9, e92615 (2014).
16. Costa, R. F. A. et al. Trend analysis of the quality indicators for the Brazilian cervical cancer screening programme by region and state from 2006 to 2013. BMC Cancer 18, 126 (2018).
17. Bruni, L, Albero, G., Serrano, B., Mena, M., Gomez, D., Muñoz, J., … de Sanjosé, S. (2019). Human Papillomavirus and Related Diseases Report BELGIUM. Retrieved from www.hpvcentre.net
18. Belgian Cancer Registry. (2018). Cancer factsheet Cervical Cancer Belgium 2018. Retrieved from https://kankerregister.org/media/docs/CancerFactSheets/2018/Cancer_Fact_Sheet_CervicalCancer_2018.pdf

19. Kellen, E., Benoy, I., Vanden Broeck, D., Martens, P., Bogers, J. P., Haelens, A., & Van Limbergen, E. (2018). A randomized, controlled trial of two strategies of offering the home-based HPV self-sampling test to non- participants in the Flemish cervical cancer screening program. International Journal of Cancer, 143(4), 861–868. https://doi.org/10.1002/ijc.31391
20. Centrum voor Kanker Opsporing. (2020). Jaarrapport 2020. Retrieved from https://baarmoederhalskanker.bevolkingsonderzoek.be/sites/default/files/atoms/files/Jaarrapport 2020_0.pdf
21. Arbyn, Marc, Fabri, V., Temmerman, M., & Simoens, C. (2014). Attendance at cervical cancer screening and use of diagnostic and therapeutic procedures on the uterine cervix assessed from individual health insurance data (Belgium, 2002-2006). PLoS ONE, 9(4), 2002–2006. https://doi.org/10.1371/journal.pone.0092615
22. Jolidon, V., De Prez, V., Willems, B., Bracke, P., Cullati, S., & Burton-Jeangros, C. (2020). Never and under cervical cancer screening in Switzerland and Belgium: Trends and inequalities. BMC Public Health, 20(1). https://doi.org/10.1186/s12889-020-09619-z