Title: Mixed-Methods approach to evaluate a mHealth intervention to increase adherence to triage of HPV+ women who have performed self-collection

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a. Significance

Cervical cancer is a disease of health and gender inequalities, and is primarily a cancer of poor, socially vulnerable women. **Even though it is almost entirely preventable, in Latin America it is the leading cause of cancer death among women**.[1] In Argentina, it is the second cause of female cancer death: every year 5,000 women are diagnosed with cervical cancer and more than 1,800 die from the disease.[1] In Argentina, and generally across Latin America, high mortality is related to problems in the continuity of the prevention process, including low screening coverage and loss to follow-up, diagnosis, and treatment.[6,15]

New screening tests detect the presence of high-risk types of HPV which causes cervical cancer. HPV tests have important advantages over the Pap as a primary screening test, including higher sensitivity (over 90%)[2] and a high negative predictive value,[16] which allow reduced screening frequencies. The HPV test is objective and is not operator-dependent. Very importantly, through self-collection strategies, HPV testing can reduce barriers to screening and increase coverage.[17] HPV self-collection is highly accurate,[3] and is acceptable among women in different countries.[14,18-20] However, HPV is common so screening identifies women who are HPV+ (around 10%), but only a portion of them will have a precancerous lesion requiring further evaluation.

Triage tests for HPV+ women determine those who need additional diagnostic procedures. **While several triage methods are available for detecting precancerous lesions, including cytology and colposcopy,[5] all methods require HPV+ women to attend health centers for triage to determine appropriate follow-up**. This includes reflex cytology because the method, as reflex test on HPV+ specimens is rather inaccurate in self-collected samples.[21] In Argentina, cytology is used as triage. During a screening visit at a health center, providers perform both HPV and Pap tests, but cytology is only read from the Pap if the HPV test is positive.[11] Women who are HPV+ and have an abnormal Pap (Atypical Squamous Cells of Undetermined Significance -ASC-US-, Atypical Squamous Cells cannot exclude High grade lesions -ASC-H-, High-grade lesions or cancer) are referred for colposcopy/biopsy and treatment if needed. However, it is not possible to do both the HPV test and Pap when women self-collect samples at home: therefore HPV+ women are referred for triage at the health center after self-collection.

Although triage and follow-up steps following initial screening are essential to prevention, most of the programmatic efforts have been devoted to increasing screening coverage, access to diagnosis and treatment of cervical precancerous lesions is a much less studied problem. However, a study in Colombia showed that appropriate follow-up and treatment can have a 20% greater impact on reducing mortality than high screening coverage.[22] Despite this, most screening programs face important problems to assure follow-up and treatment of precancerous lesions, which is a major obstacle for screening effectiveness.[6]

From 2012-2013 the EMA study (Self-collection Modality trial, initials EMA in Spanish) a cluster randomized controlled trial, assessed screening uptake of HPV self-collection offered by Community Health Workers (CHWs) during home visits. The intervention resulted in a four-fold increase in screening uptake (from 20% to 86%), demonstrating that offering HPV self-collection at home visits through CHWs is an effective strategy to improve cervical screening coverage.[14] Furthermore, these results showed that self-collection facilitated screening access in women who do not regularly attend health centers. **However, adherence to triage during the programmatic scaling-up of HPV test self-collection has been low.** Only 30% of HPV+ women successfully followed-up within 120 days after screening.[7] Two additional studies analyzed why screen+ women failed to complete follow-up and found that health system, individual patient, and interpersonal/family factors affected adherence. Delays in result delivery or not receiving results was the most commonly reported problem.[9-10] In addition, 30% of the women reported subjective reasons, including fear, denial regarding the disease, or not considering it necessary to continue with the health care process. Other social and contextual

factors, including work and domestic organization, and problems with transportation, were also reported.[9-10] **There is a critical need for comprehensive interventions to improve delivery of results, to provide personal counseling in response to subjective barriers, and to help address social/interpersonal barriers to adherence to follow-up.**

Patient navigation programs have been proposed for women with abnormal Pap smears (ASCUS+) who have not received follow-up care.[23] However, the navigation strategy is much more difficult to implement to assure triage of HPV+ women as this represents around 10% of all screened women.[11] For example, in 2012, in Jujuy, 21,283 women were screened, 2,861 were HPV+, and 807 were HPV+ and had abnormal Pap smears (4 of total screened women).[11] **It would be too costly for health systems to provide intensive support through patient navigation for all HPV+ women. Thus, there is a critical need to implement innovative solutions that do not depend on extensive use of human resources to solve the problem of the low adherence to triage.**

Numerous studies have evaluated the effectiveness of mHealth tools in increasing adherence to medication, medical tests, or visits.[12,24-29] Mobile phone text messages (SMS messages) are useful to remind patients about medication adherence, such as antiretroviral therapy and asthma treatment,[12,24,25] and in reducing non-attendance rates to preventive health care centers and outpatient clinics in many low- and middle-income countries (LMIC).[26-30] Similarly, mHealth tools targeted at providers, such as SMS reminders for CHWs, have been shown to improve the quality of service they provide to the population, most prominently through decision support, and alert and reminder tools.[31-34] SMS messages have advantages over other reminder systems, including that they can be sent to patients simultaneously and require less staff.[12,29] SMS reminders are easy to use and useful for patients.[12,29,35,36] For example, a study in Argentina showed that 92% of pregnant women stated that SMS messages sent by the Tucumán province Maternity Hospital were useful to confirm a post-partum home visit, and 60% reported they would have forgotten the appointment without the reminder.[35] Similarly a qualitative study in South Africa also reported SMS messages being acceptable, relevant, and useful.[36] In addition, studies in LMIC suggest that mHealth interventions dependent on mobile phone ownership are feasible and may reach the majority of patients in key subgroups, such as those who have low education and poor access to the health system.[29-30] Thus, **SMS reminder messages may help triage adherence for HPV+ women.**

A characteristic of home-based self-collection is that the screened women are not active patients of a health center, as the screening occurs outside the medical facility. Thus, in this situation, the link between the health center/health professional and the patient is tenuous, increasing the risk of non-adherence to follow-up steps. Additionally, adherence to diagnosis and treatment requires the patient to receive results, and understand the meaning of positive and/or abnormal results, and take action on that information to continue along the screening process. **mHealth interventions can enhance the link between patients and health services and have been shown to increase adherence in primary care and gynecology care settings via reminders, counseling, or by addressing patient apprehensions.**[12,26-29]

The general aim of our application is to evaluate the implementation of a multi-component mHealth intervention targeted to women and health providers to increase adherence to triage among women with HPV-positive self-collected tests. The mHealth intervention will include SMS messages sent to HPV+ women to inform them when results are available, and subsequent SMS messages as reminders. In addition, for those HPV+ women who did not had a triage cytology result within 60 days of the HPV test result, CHWs will receive an e-mail and SMS message so they can contact these women for a personal visit to their homes for specific counseling and support. This study will evaluate the effectiveness of the intervention and also identify and understand the processes and factors that are associated with its success (or lack of). **Results of this project will provide evidence to increase the number of HPV+ women who adhere to triage, but its significance will not be limited to this specific line of care.** If the approach is proved successful, it could be adapted to increase compliance of other important steps of the cervical prevention process, such as

colposcopy/biopsy and treatment. In addition, it might be also adapted for implementation in other cancer prevention programs, such as colon and breast cancer control programs.

b. Innovation

The proposed study is innovative in two ways: (a) by combining mHealth technologies with a personal contact with CHWs to increase adherence to triage of HPV+ women, and (b) by proposing an evaluation of the strategy using Implementation Science tools and frameworks.

a. The majority of the developments in the mHealth field have been related to health problems such as hypertension, diabetes, tuberculosis or HIV-AIDS. Specifically regarding cervical cancer, no previous use of these technologies in HPV self-collection screening programs has been published. There is increasing recognition that progress in complex health problems will come from integration of technological advances and social innovations.[37] The EMA study showed that an integrated approach with synergy between two innovations, HPV self-collection and CHW work reorganization, can result in a real difference in cervical cancer control.[14] In the EMA study, women mentioned that the form and content of the messages transmitted by CHWs and the prior trust they had in them favored acceptance of self-collection.[38] Similarly, **we expect that a multi-component intervention combining mHealth technologies with CHWs work will improve adherence to follow-up care, increase the effectiveness of the self-collection intervention, and accelerate reduction of disease burden**. This will be possible because the intervention will be rooted in the existing health system, carried out in programmatic conditions with existing human resources, and will not imply a complex reorganization of the cervical prevention program already in place. Combining a mHealth technology with CHW work for cervical cancer prevention is highly innovative, as it presents a model for integration of mHealth technologies that has a twofold potential. **First, using an automated system for communicating results immediately is a novel approach to inform HPV+ women about results, reduce the delay in result delivery, and reinforce trust in the health system.** Reminders will minimize forgetfulness, especially when patients are busy with work or are away from home.[39-40] Further, the proposed mHealth intervention will reinforce the privileged link that CHWs have with their communities. Despite being automated, these interventions are perceived to provide social support and reflect the concern of the health care providers.[40] Thus, **mHealth technologies can facilitate and strengthen the relationship between CHWs and community women**, creating a health promoting environment because they are trusted members of their communities and can reinforce health messages and behaviors. Additionally by sending SMS messages to CHWs to prompt visits for counseling and support for HPV+ women who do not respond to reminders, this intervention will provide a tailored component of social support to address barriers, adding to the novelty of evaluating a comprehensive multi-component mHealth intervention.

b. Despite the fact that failure of cervical cancer prevention programs in the Region has been mainly due to problems with how screening has been implemented, **implementation research in Latin America is lacking**. In effect, cytology-based screening at a population-level has proven effective for reducing cervical cancer mortality in developed countries.[41] However, cytology-based screening has been available in most Latin American countries for more than 50 years, yet prevention programs have not experience similar reductions in cervical cancer incidence and mortality. Challenges related to low-coverage, lack of quality controls, lack of provider adherence to protocols and recommendations, low patient adherence to diagnosis and follow-up, and lack of information systems persist. This history of Regional cytology-based screening is an example of how implementation problems can prevent successful integration of effective interventions into existing health care delivery systems. **HPV DNA testing opens a window of opportunity[42] for changing the history of cervical cancer prevention** and has important advantages over cytology. Experts acknowledge HPV testing as an effective technological solution, and there is increasing recognition of the need for a policy change.[42] However, changing the technology by itself has not eliminated some implementation factors, such as low adherence to follow-up, which also challenged cytology-based screening. Thus, applying implementation science tools and frameworks can enhance the way HPV-based

interventions in cervical cancer prevention are planned, fielded, and evaluated. Thus, **the study is innovative as its design and approach can serve as a model of work, constituting an important advance in the use of Implementation Science in the Region and for cervical cancer prevention.** It will show how an intervention can be planned, fielded and evaluated using frameworks and tools used by Implementation Science. The intervention has great potential for cervical cancer prevention, with a concrete possibility of saving thousands of lives in Latin America, LMIC, underserved women from US, and even in settings where HPV self-collection is not available because this integration can be applied to diagnosis and treatment of precancerous lesions in cytology-based screening or with other screening methods such as VIA.

c. Approach

Overview and Design: The study design will follow the structure of an **effectiveness-implementation hybrid type I trial[43]** and will use **mixed-methods approach**. We will use a Hybrid type I design as proposed by Curran and colleagues [43] to galvanize the translation of efficacious treatments to enhance their public health impact. This hybrid design is appropriate for the proposed intervention because it has strong face validity that will support applicability to a new setting or population, there is at least indirect evidence for the intervention that will support applicability to a new setting or population, and there is minimal risk associated with the intervention.[43]

We combine a **cluster randomized trial** to evaluate the effectiveness of a multi-component mHealth intervention with a **mixed methods approach involving quantitative and qualitative evaluations of the implementation using the RE-AIM[44] and** Consolidated Framework for Implementation Research (**CFIR)[45] frameworks.** The RE-AIM framework is particularly appropriate to assess the public health impact of the intervention as a function of 5 factors that are considered necessary for success.[44] The Reach, Effectiveness, Adoption, Implementation, and Maintenance. The CFIR is particularly helpful to systematically assess contextual factors that influence implementation and adoption.[45] These models will be integrated in all stages of the research process, including conceptualization (e.g., selecting implementation processes on which to focus), data collection (e.g., using components of the conceptual models as interview questions and scripts), and analysis. Mixed methods designs have been increasingly utilized to develop a science base for identifying and overcoming barriers to implementation,[46,47] as qualitative methods allow a deep understanding about the reasons for success or failure of a strategy, while quantitative methods allow for measurement of intervention outcomes.[48] In this study, we will integrate quantitative and qualitative methods in multiple ways and follow Greene's typology of **mixed-methods for convergence and complementarity**.[49] We will carry out formative research with women to be used in developing the framing and content of SMS messages (**qualitative secondary method)**. Then we will carry out a **pragmatic cluster randomized trial** to measure the effectiveness of the multi-component mHealth intervention in improving triage adherence among HPV+ women (**quantitative primary method** for Specific Aim 1). Finally, during the post-intervention phase (Implementation evaluation for Specific Aim 2), we will carry out a **quantitative survey** to measure acceptability of the strategy by CHWs (**quantitative secondary method**), and **semi-structured interviews (qualitative secondary methods)** to health authorities and health professionals,[50] to give them an opportunity to express their own perspectives, values and opinions about the intervention.[47] We will also interview HPV+ women using a **structured questionnaire (quantitative secondary method)** to collect information about acceptability of the intervention, reasons for triage adherence/non-adherence, and their views about the strategy.

Setting: The research will take place in the province of Jujuy, located in Northwest Argentina (Map 1). Eighty-five percent of Jujuy's population lives in urban areas and the rate of mobile phone penetration was 82% of urban households in 2011, though this percentage has probably increased.[51] Jujuy has a high cervical cancer mortality rate (10.6 per 100.000 women during 2012-2014). The public health sector in Argentina includes a network of public

Map 1. Jujuy province

hospitals and primary health care centers which provide care to the poor and the population not covered by the social security sector (workers of the informal economy and their families). For the uninsured, health services are provided free of cost. The Jujuy public health system includes a main hospital and 300 primary health care centers. **The Primary Health Care System (PHC) integrates approximately 700 paid full-time CHWs who twice yearly visit approximately 110,000 households for health-related tasks such as immunization and promoting maternal and child health.** In 2015, the provincial Ministry of Health provided all of them with personal laptops for work support (communicate with health services and providers through e-mails, access online educational materials, among others). In Jujuy, HPV testing was introduced in 2012 through the Jujuy Demonstration Project[11]. Since then it is the primary screening test, and is available to all women aged 30 and over at public health centers. The provincial program on cervical cancer prevention uses SITAM, the national screening information system.[52] SITAM registers all screening, diagnosis, and treatment events for the public health system. It works as an online medical record, and therefore, upon processing of HPV tests and Pap smears, results are immediately registered in SITAM to generate a diagnosis form, which is instantly available at public health establishments with an online terminal (around 80% of them; the Ministry of Health is at present working to have 100% of them by the end of 2017). **HPV self-collection is offered during the routine CHW home visits, those women who accept the offer perform self-collection at home.** CHWs take self-collected samples to health care centers, where all samples are stored and sent to the provincial laboratory for processing. In 2014 and 2015, approximately 38% of total women aged 30 years and over, screened at the public health sector did it through self-collection.[53] Women who opt for self-collection are instructed to go the health center in 30 days to pick up results. The information from the HPV test form is entered into SITAM by the administrative staff in the laboratory.

SPECIFIC AIM 1. **To evaluate the effectiveness of a multi-component mHealth intervention to increase adherence to triage among women with HPV+ self-collected tests compared to usual care.**

Formative research. Four **focus group discussions** (FGD) will be carried out **to explore women's opinions about how to frame SMS messages and their content**. We will also explore barriers women face in accessing triage, which will be used to develop strategies CHWs can use to overcome them during the intervention. FGD are a well-established technique to allow in-depth exploration of participants' views and allow respondents to react and build upon responses of other group members, which may result in the production of data or ideas that might not have been uncovered in individual interviews.[54-55] Each FGD will have 8-10 women and will be carried with the following stratification criteria: Two FGD with women aged 30-50 years (urban/rural); Two with women aged 51+ years (urban/rural). Participants will be recruited by CHWs during routine health rounds, a recruitment strategy which we have used and found effective.[38] FGD data will be collected in Spanish, facilitated by well-trained research staff. Data analysis will be conducted following the content analysis methodology[54] (See *Qualitative data analysis section*), Transcriptions and observation notes will be read multiple times, coded, and analyzed to identify content and themes. We will operationalize perspectives and reactions to SMS messages to identify which ones can be used as cues to action following the Health Belief Model (HBM)[56-57] (see Figure 2). Analysts will develop an initial codebook upon reading the transcripts and add new codes as they emerge. To ensure coding reliability, two researchers will independently code and perform consistency checks throughout analysis. We will use Atlas.ti to organize, code, and summarize patterns. Data will be systematically analyzed and responses compared across groups. Drawing from FGD results, we will develop **SMS messages which will be validated and pilot tested** using a validation protocol that has already been used in Argentina.[58] Around 5 women aged 30+ will evaluate the proposed SMS messages using a validated 7-item questionnaire with open and closed-ended questions.[58] Trained interviewers will administer the questionnaires in face to face interactions and will document participants' responses in writing. During the validation, two main areas will to be prioritized: SMS

message understanding and appeal. This process will lead to the elimination of some SMS messages and to improvements in their wording. Validation recruitment will take place in urban and rural PHCs around the capital city of Jujuy.

Development of Automated Messaging system: We will develop an **Automated System (AS) to send SMS messages and e-mails based on data from SITAM.** This Automated system will send SMS messages and e-mails and will work in an asynchronous manner. E-mails sent to CHWs will not include personal information about women, but a secure link to registries of women to be viewed in SITAM. SMS messages and E-mails will comply with security procedures.

Intervention: cluster-randomized trial. Approximately 200 CHWs from the PHC system of Jujuy will be randomized into two groups: 1) ***mHealth Intervention (MH) Group***: Women with positive self-collected tests will receive a **multi-component intervention** (Figure 1). HPV+ women will receive a weekly SMS message during the first month after self-collection result notifying them that test results are available, and they should go to the health center. In addition, CHWs will receive an e-mail and SMS message to visit those HPV+ women who, at 60 days since the HPV result have not attended triage. 2) ***Usual Care (UC) Group***: Women with positive self-collected tests will receive usual care as described in Settings.

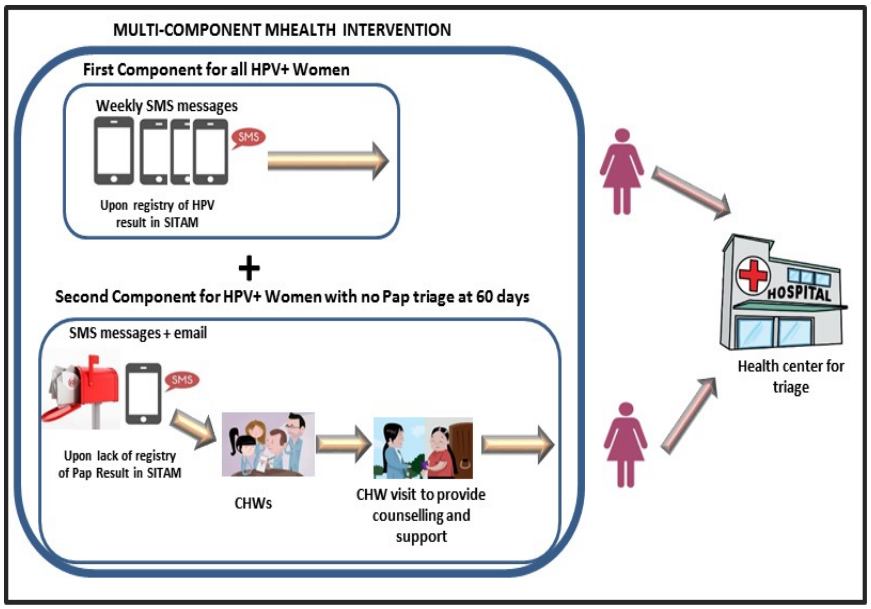


Figure 1. The multi-component mHealth Intervention

Hypothesis: **Adherence to triage will be higher in the MH intervention group compared to women receiving UC.** Following the HBM,[56-57] we assume that women are more likely to undertake a health behaviour (attend health center and complete triage) depending on the perceived severity, perceived threat of the disease, and perceived benefits of the recommended actions, concepts that account for the readiness to action. In addition, specific cues to action will activate that readiness and stimulate behavior. Using the HBM in this study is particularly appropriate because in the proposed intervention, the SMS messages serve as a cue to action, which will increase adherence (Figure 2). Also, the CHW visit to HPV+ women who have not responded to SMS reminders will be an additional cue to action, as well as an opportunity to provide counseling and support which will change women's perceived benefits and barriers of screening as well as perceived threat of cervical cancer.

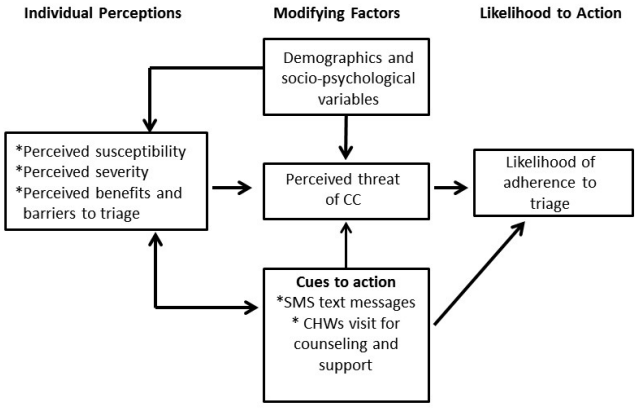
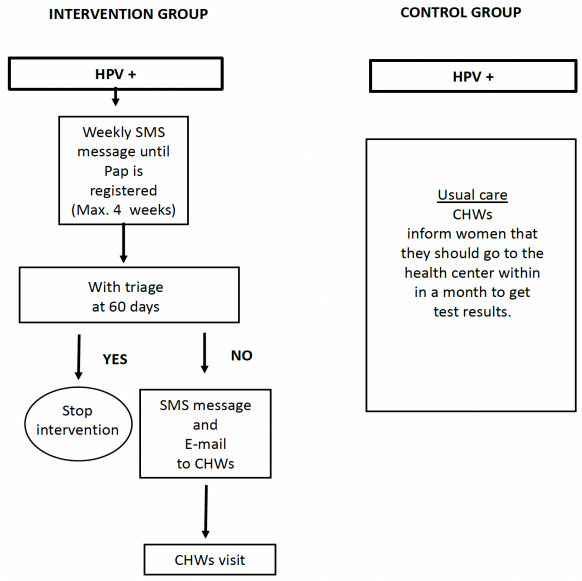


Figure 2. Health Belief Model, adapted from Janz and Becker 1984[57]

Outcomes: Primary outcome: **The percentage of women with triage smears at 120 days after HPV results are registered in SITAM**. This will allow measurement of the overall effect of the multi-component intervention including two periods: a) the 60 day period between the Test results and the SMS message and e-mail sent to CHWs (days 1-59); and b) the 60 day period between the SMS message and e-mail sent to CHWs and triage measurement (days 60-120). Secondary outcome:

The percentage of women with triage smears at 60 days after Test Results, when the first SMS message is sent (days 1-59). This outcome will allow us to measure the individual effect of the SMS messages sent to women (before CHWs receive prompts to contact non-compliant HPV+ women).



***Participant inclusion criteria**:* Women aged 30+ that have performed HPV self-collection offered by CHWs during routine home visits. Participants must be competent to understand the consent form, able to communicate with study staff, and provide a working mobile phone number capable of receiving calls and SMS messages.

Study procedures. CHWs from both groups will identify eligible women and invite them to participate in the study during their routine home visits. Once women have performed HPV-self collection, CHWs will screen for eligibility criteria, including use of mobile phones. CHWs will ask women whether they would provide a working mobile phone number capable of receiving calls and SMS messages. Those women who would provide such telephone number will be explained the study objectives and will be invited to participate in the study. Women accepting to participate will be asked to provide the telephone number. Based on a mHealth study in Northern Argentina among women with Chagas disease,[35] and a mHealth study in Buenos Aires among poor population with high blood pressure,[60] we expect approximately 85% of women will provide a telephone number; with 70% providing their own personal mobile phone.

MH Group: CHWs will carefully explain participants the sequence of SMS messages to be received depending on the Test results, and how they should proceed after reception of the SMS messages. If the woman does not have a personal phone, she will be asked if she is willing to be contacted and receive the proposed SMS messages on a shared phone. CHWs will inform women about the nature and content of the SMS messages to be received. They will also explain that they might come back for a personal visit if they have not performed triage 60 days after the test results. Therefore, consent to participate also means women agreement to be contacted and receiving SMS messages, even if phones are shared by several family members.

Women with positive self-collected tests will receive a multi-component intervention (Figure 1). Upon registration in SITAM of the HPV result at the laboratory, they will receive a weekly SMS message for four weeks, notifying them that the test results are available, and they should go to the health center. Messages will be stopped if a Pap result is registered in SITAM.

Sixty days after the date of the Test result, CHWs will receive an e-mail and SMS message informing them that there are HPV+ women who have not had Pap triage (if this is the case). The e-mail will also contain a secure link to the list of HPV+ women to be visited, as explained above. CHWs will be asked to confirm receipt of the e-mail for monitoring project processes. CHWs will visit these HPV+ women within 15 days of being notified, for an in-person reminder and counseling about the importance of attending health centers and have triage performed. The script for this visit will be developed based on the results of the FGD using HBM concepts to address issues of perceived susceptibility, perceived severity, and benefits of triage. If possible, CHWs will also provide support to address barriers (e.g., connecting women with transport available in some municipalities). We will track CHW visit information on the Trial form, including visit attempts, date of visit and issues addressed during counseling. The subgroup of HPV+ women visited by CHWs are given 30 days to

get screened as we consider that they are probably women facing specific obstacles (i.e. lack of transportation) and might need additional time to solve them. This timeline is in agreement with programmatic organization of the cervical cancer prevention process.

UC care group: Once women have agreed to participate in the project, CHWs will provide UC counseling using specific routine programmatic materials[61] and information using standard provincial protocol and materials. They will inform women that they should go to the health center within in a month to get their test results.

CHWs from both groups will use a specific questionnaire (Trial form) to collect basic data about women socio-demographic characteristics, inclusion/exclusion criteria, and tasks performed by the CHWs. Eligible women who do not agree to participate will be asked basic socio-demographic data (age, health insurance, education level, and reason for refusal) to allow comparison of enrolled and non-enrolled women. In the MH group, the Trial form will include a section to be completed by CHWs for those HPV+ women who are on the non-compliant list because they did not complete triage before 60 days after the screening result was available. CHWs will register data about the in-person visit (women's availability, reasons for non-adherence to triage and support needs and action taken, if applicable).

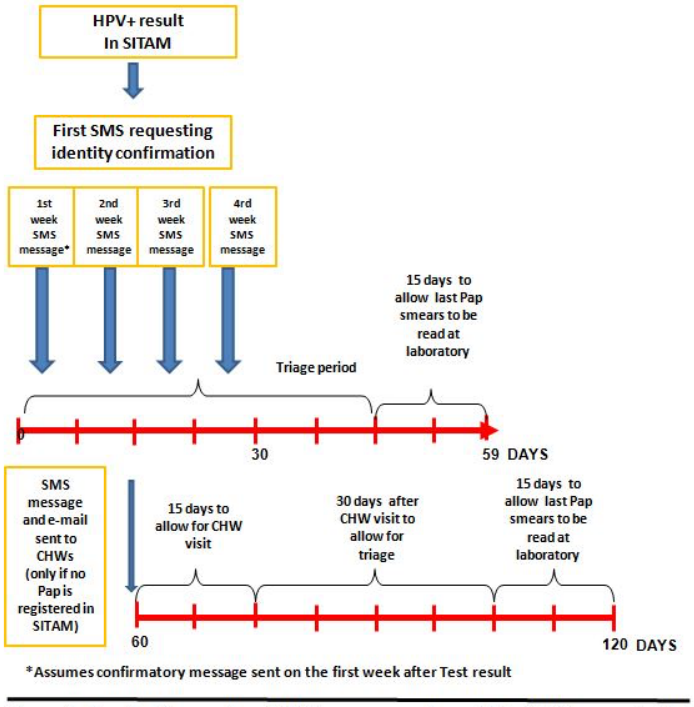


Figure 4. Timeline for sending of SMS messages and e-mails to HPV+ women in the Intervention Group

All Pap smears will be read at the provincial Cytology Laboratory (mean time 15 days between smear collection and report[53]) and results input into SITAM.

Training: Project staff will train CHWs about research methods including ethical considerations, study protocol, and informed consent. CHWs from the MH group will also be trained on how to provide counseling to women who have defaulted triage, using programmatic materials[61-62] as well as those developed specifically for this study. In total, two series of one-day workshops for CHWs from both trial groups will be held, led by Project team members. Participation of CHWs in training will be documented on the Attendance List at each training workshop.

Randomization and sample size calculations: All CHWs (clusters) (approximately 700) of the Jujuy province offer self-collection and will be eligible to participate in the study. After classifying them into four groups according to gender and urban/rural setting, a stratified sample of 240 CHWs will be randomly selected with allocation proportional to strata. Selected CHWs will be invited to participate in the study following the order defined by the random list until 200 are enrolled. Enrolled CHWs will be randomly allocated to the MH or the UC group (3:2 ratio). The statistician will produce computer-generated random number lists for the CHW selection and the intervention allocation. Allocation concealment is guaranteed because all CHW will be assigned to the trial arms at the same time. Blinding of intervention and outcome assessments is not feasible due to the characteristics of the study. The number of CHWs was defined based on pragmatic considerations. From our experience[14,] this is a feasible number of CHWs that can be enrolled in the trial and trained in programmatic, routine conditions. We decided to allocate a larger number of CHWs to the MH group to be able to detect changes in the time series trend associated with the second component of the intervention

(see Analysis Plan below). In addition, a larger number of CHWs in the intervention group will benefit the assessment of the implementation outcomes. Based on PHC records and previous experience[14] we estimate that each CHW will enroll an average of 20 eligible women in a 10-month period. We assumed an attrition rate of 20% due to problems with mobile phones (i.e. non-identified number, unpaid phone bill, lack of signal, etc.), SMS messages not delivered and/or other issues. Under a 13% prevalence of HPV+ in this population,[11] we estimate that each CWH will contribute with an average of 2 HPV+ women. Primary outcome: The target sample size (120 CHWs in the MH group and 80 CHWs in the UC group, each one providing 2 HPV+ women) will have 97% power to detect a 20% triage difference between the two groups when the control group has a 30% triage in a 120-days period (two-sided test, alpha=0.05). Correlation induced by the CHWs was included in power calculations assuming an intra-class correlation coefficient of 0.10. Secondary outcome: Under the same assumptions, the proposed sample size will have 90% power to detect a difference of 10% in triage between groups when the control group has a 15% triage by day 60.

A specifically built database will be used (RCT database), combining information from the Trial Form, the AS Monitoring Registry, and SITAM, the national screening information system.[52] The Trial Form will register information about the randomization group, agreement to participate in the study, women's socio-demographic data, and tasks performed by the CHWs (contact after reminder and reasons of no contact). Data on HPV testing, triage, diagnosis and treatment will be uploaded importing data from SITAM, linking the records through each woman's national identification number. The AS Monitoring Registry will include data from the Automated System regarding receipt of confirmatory SMS messages and e-mails, and valid phone numbers and e-mails. Data entry will be done through specific software that will include range and inter-item consistency checks. Data will be stored in files compatible for analysis with statistical packages (Stata).

Analysis plan: All analysis will be conducted on an intention-to-treat (ITT) basis; the effect of the multi-component mHealth intervention on the primary outcome will be assessed using a generalized estimating equations approach. The model (logit link, and binomial distribution) will include trial group as fixed effect and CHWs as the clustering variable. Potential effect modification due to rural/urban location of the woman and CHW gender will be evaluated. Baseline socio-demographic characteristics of the women will be compared between groups using the same model with link and distribution selected depending on the variable. Factors showing clear unbalance between arms will be included in the model proposed above to adjust for potential confounding. The same approach will be used to estimate the intervention effect on the secondary outcome. Analyses will be conducted using STATA 14.0 or SAS v.9.4. The trial will follow the CONSORT extension for cluster randomized trials reporting guidelines.[63]

Potential problems and limitations: One of the potential limitations of randomization of CHWs is the **risk for contamination** due to CHWs assigned to different study groups, but working in neighboring areas, which could activate CHWs and women in the UC group. However, our prior work using CHW cluster randomization[14] suggests that this risk is low and the effect of contamination is minimal. If such effect occurs, we expect them to be moderate because meaningful improvements in adherence to triage require a systematic effort to address problems related to follow-up adherence which are unlikely to occur in the absence of a specific intervention. Also, **it is not possible to blind CHWs (clusters) or women in this study**. However, laboratory personnel processing the HPV-test and personnel entering data in SITAM, the national screening information system, will be blind. Moreover, the assessment of primary and secondary outcomes will be objective, as data on triage is extracted from SITAM. Nevertheless we will compare demographics characteristics and screening history of women enrolled in the two study groups and will control in the analysis for any variable showing unbalance between study groups. Other problems that might affect the RCT are those related to **poor cell phone network coverage or reception or gaps in service due to unpaid telephone bills**. However, the sample size calculations accounted for this type of attrition, as described above. Finally, **if women do not confirm their identity within one week of initial SMS**

message reception, it will affect the delivery of the intervention (number of SMS messages the woman will receive). To minimize this potential problem, CHWs will emphasize the importance and ease of confirming identity as soon as possible, ideally within 24 hours, not exceeding 7 days.

We **evaluated and ruled out alternative designs** such as having a three group trial (comparing SMS messages to women vs. SMS messages to women + SMS message and e-mail to CHWs vs. UC) because the main aim of the trial is to assess the effect of the multi-component intervention, not each component separately. In addition, such a trial should include a larger number of CHWs, which would attempt against feasibility of a study that will take place in a real-world, programmatic context. Instead, we propose a time series approach to explore the differential impact of each component of the intervention.

Safety and monitoring

All SMS messages and e-mails will comply with security procedures according to NIH Human Protection Subject Guidelines [47]. The PI will be responsible for monitoring of adverse events and data quality and safety, as this is a low-risk investigation. The Plan for monitoring of data quality and accuracy will include the following: Data entry from the CRT will be done through specific software that will include range and inter-item consistency checks. Entries out of the expected range will not be permitted. Re-entry of 20% of questionnaires will be done for quality control. The data cleaning process will actively search for errors in a planned way.

SPECIFIC AIM 2: To evaluate the implementation strategy and identify barriers and facilitators to implementation of the multi-component mHealth intervention.

RE-AIM and CFIR frameworks will guide the implementation evaluation: as illustrated in Figure 5. The CFIR comprises 39 common constructs from published implementation frameworks and models and organizes them into five major domains.[45] In this study we will analyze the following domains: **Intervention Characteristic** (Relative advantage; adaptability; complexity and cost); **Outer Setting** (Patient needs and resources; external policies and incentives); **Inner Setting** (Structural characteristics; tension for change, relative priority and available resources; access to knowledge and information); and **Characteristics of Individuals** (Knowledge and beliefs about the intervention; perceived self-efficacy).[45] Proposed quantitative and qualitative measures based on RE-AIM and CFIR frameworks are presented in Table 1.

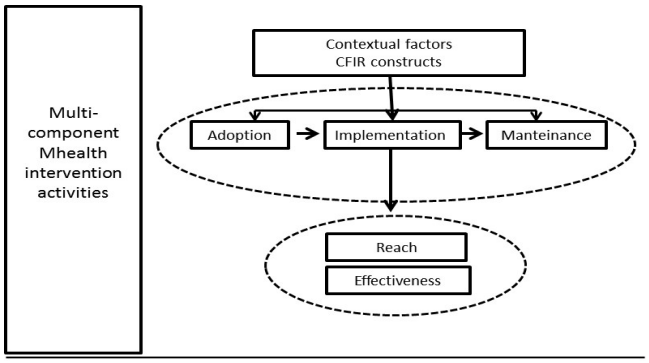


Figure 5. Implementation evaluation. Adapted from Damshroder et al., 2015. [64]

We will use data from the RCT database and will also conduct a self-administered semi-structured survey of CHWs, semi-structured interviews with key stakeholders, and a survey of HPV+ women. The CFIR will be used to develop surveys and interview guides and guide data collection and analysis. Eight weeks after the RCT (intervention and measurement of primary outcome) is finished we will hold a workshop as a closing activity to present preliminary results to CHWs and health authorities. During this workshop, CHWs will be asked to complete an anonymous, **self-administered semi-structured survey** to evaluate their perspectives and acceptability of the intervention (see outcomes and qualitative evaluation in Table 1), and about barriers and facilitators of the intervention, considering a subgroup of CFIR constructs. We will administer the survey during the closing activity to assure a high level of response. Project staff members will emphasize that participation in the survey is anonymous and voluntary; all participating CHWs will sign consent forms. Those CHWs who were not able to attend this closing activity will receive the survey by mail and will be requested to send it to project staff in a blind envelope. A specific database built for the Survey will be used for analysis, which is described in the **Quantitative data analysis Section.**

Qualitative data from open-ended questions will be transcribed, coded, and analyzed as described in the Qualitative data analysis Section.

In the third year of the project, we will conduct ***Semi-structured interviews with stakeholders*** to evaluate their acceptability of the intervention and perspectives on how to build and enhance project sustainability (See qualitative evaluation in Table 1). Stakeholder participants will include leaders and intermediate coordinators of PHC, HPV laboratory, and Women Health Department, the director of the provincial Program on Cervical Cancer Prevention, Minister and Secretaries of Health, and heads of gynecology services. In semi-structured interviews, "the interviewee has the possibility to talk freely about the issue in question without being held to the question asked".[65] Constructs to be considered in the script will include: Relative Advantage, Adaptability, Complexity and cost; Patient Needs and Resources, and External Policies and Incentives; Structural Characteristics; Tension for Change; Relative Priority; . These constructs will be measured at 8 weeks after the end of the trial period (implementation of the intervention + measurement of primary outcome). Interviews with health authorities will be carried out also include questions to evaluate the potential for programmatic incorporation of the multicomponent mHealth Intervention, as to measure the Maintenance dimension of RE-AIM. The sample size will be determined based on relevance and theoretical saturation.[65] We will select participants to ensure a wide range of responses are captured (i.e., we expect stakeholder with different interests, backgrounds, and involvement/interaction with intervention activities to have varied opinions) and to allow comparisons between them. To ensure we include enough stakeholders from relevant groups in the sample, we plan to conduct at least 20 interviews; however, we will recruit until we reach theoretical saturation and no longer find anything new about relevant dimensions, though this can depend on the complexity of the dimensions being analyzed.[66] Qualitative data will be recorded, transcribed, coded, and analyzed as described below (Section on Qualitative data analysis).

Table 1. Measurements and data sources proposed for Implementation Evaluation based on RE-AIM and CFIR

	Quantitative outcomes	Qualitative evaluation	Data source
Reach Representativeness of women reached by the intervention (quantitative data)	-% of eligible women who accepted to participate in the study -Socio-demographic information of participant/non-participant women		*RTC database (Trial Form)*
Effectiveness in increasing women's adherence to triage (quantitative and qualitative data)	-Primary outcome: percentage of women with triage smears 120 days after test results are registered in SITAM.	Reasons for adherence/non adherence to triage.	*RCT database (SITAM)* *HPV+ Women Survey*
*Adoption by CHWs of the strategy of visiting HPV+ women after receiving SMS messages and e-mails**	-% of CHWs that visited at least one HPV+ women after receiving the SMS message and e-mail.		*RCT database (Trial Form+Automated System Monitoring Registry)*
Acceptability of the intervention by adopters	-% of CHWs that agreed with programmatic incorporation of the mHealth intervention.	CFIR construct: Knowledge and beliefs about the intervention; perceived self-efficacy	*Self-administered semi-structured survey of CHWs*
Implementation of intervention activities according to protocol (quantitative data)	-% of randomized CHWs that participated in trainings. -% of SMS messages that reached a valid phone number. -% of HPV+ women who sent confirmatory SMS messages. -% of e-mails that reached a valid e-mail address. -% of CHWs who sent confirmatory e-mails.		*Automated System Monitoring Registry and Training Attendance List*
Acceptability of the intervention by women. (quantitative and qualitative data)	-% of women who accept and are satisfied with the intervention.	*Women level* Experience and perception of the intervention; acceptability of SMS messages, pertinence of frequency, reception time and content of SMS messages.	*HPV+ Women Survey*
Barriers and facilitators to implementing and administering the intervention (qualitative data)		*Stakeholder/CHWs level* **CFIR constructs:** Relative Advantage; Adaptability; complexity and cost. Patient Needs & Resources and External Policies & Incentives. Structural Characteristics; Tension for Change, Relative Priority and available Resources, Access to Knowledge & Information.	*Semi-structured interviews with stakeholders and Self-administered semi-structured survey of CHWs*
Maintenance		Intention to incorporate the strategy.	*Interview with Stakeholders*

**Adoption of the Automated System will not be measured as it will be a unique centralized system linked to SITAM*

Finally, we will carry out a **Structured questionnaire among HPV+ women (Women Survey)** to evaluate their acceptability of the strategy, their perspectives about the implementation, and reasons for adherence and non-adherence to triage. We will survey all HPV+ women from the RCT intervention group (approximately 240 women), 5 months after the HPV test result (this is, one month after measurement of the primary outcome), irrespective of their triage status. The questionnaire will include open and closed questions with dimensions related with women's experiences and

perceptions, including acceptability and relevance of SMS message frequency, receipt time, and content; perceived effect of the multiple components of the intervention on their adherence, and reasons for adhering/not adhering to triage. The nominated list of these women and their contact details will be extracted from the RCT database. Trained interviewers will contact these women via telephone to make an appointment to visit them at their homes to administer the questionnaire. The training will be carried out by the project staff; it will include formal aspects regarding applying the questionnaire as well as skills for developing a connection with the interviewees. Interviewers will be provided with a list of women to interview with contact information.

Quantitative data analysis. This section refers to the analysis of data from the Women Survey and the Self-administered semi-structured survey of CHWs. A descriptive analysis of each study dimension will be carried out using simple frequencies and percentages for each of the variables under study. The association between the variables will be measured using the Chi square test of independence. Outcomes will be summarized as percentages and compared across women/CHWs socio-demographic characteristics using logistic regression. Results will be presented as estimates and 95% confidence intervals. Analysis will be conducted using STATA (version 13.0) and/or SAS (version 9.3).

Qualitative data analysis. We will use CFIR as an organizing and analytic framework for Aim 2. We will use an iterative approach to analyzing qualitative data, developing an initial codebook after reading the transcripts and responses and adding or revising thematic codes as they emerge from the data.[67] To ensure coding reliability, two researchers will independently code and perform consistency checks. They will hold regular discussions to resolve disagreements and reach consensus and will discuss uncertainties with a third team member. After coding, thematic and content analysis will be conducted. Content analysis methodology,[68] is defined as "a set of communication analysis techniques aimed at obtaining indicators that permit the inference of knowledge relative to the conditions of production/reception of messages, through a systematic and objective description of the message content".[68] We will use Atlas.ti to organize, analyze, and summarize data, generating a compilation sheet of the findings. Data from qualitative studies will be translated into English, for team work with the two co-investigators from the Dana-Farber Cancer Institute. Key documents will be back-translated.

STAKEHOLDER ENGAGEMENT TO CHANGE AND READINESS FOR CHANGE. Argentina has become a pioneer in the introduction of new technologies for HPV-based cervical cancer prevention. In 2011 the National Ministry of Health approved the incorporation of the test as a nation-wide screening method and between 2012-2014 the Jujuy Demonstration Project was carried out to implement and evaluate the programmatic components of an HPV-based screening strategy.[11] The province health authorities and professionals, actively participated in the design, implementation and evaluation of this project. They were also actively engaged in the above mentioned EMA project.[14] As a result of this, incorporation of HPV-self collection offered by CHWs began in 2014 as a programmatic, routine strategy. The need for a mHealth intervention to increase triage of HPV+ women was brought up by Jujuy health authorities in view of the low percentage (30%) of these women who have undergone cytology within 120 days since initial screening.[7] In addition, the Jujuy Minister of Health, Dr. Mario Fiad, has given high support to this project, as increasing adherence to triage is a high priority programmatic goal (see letter of support). This shows a real engagement of stakeholders for adoption and rolling out of the intervention if its effectiveness is confirmed.

DISSEMINATION PLAN. We will carry out active dialogue and meetings with health authorities at several moments of the project to present preliminary results and discuss implementation issues and future scaling-up. We will produce a video about the process of the intervention, with voices of women, CHWs and health authorities. Video producers will contact selected women, CHWs and health authorities after field work is finished. We also expect to publish at least three papers in high

impact international journals, and present results in several congresses including the Annual Conference on the Science of Implementation and Dissemination. Also, we will carry out several meetings with health authorities and heads of services to plan other dissemination activities in a participatory manner. Communication channels of the cervical cancer prevention programs (Twitter, Facebook, websites, meetings) will also be used to disseminate results.

FEASIBILITY OF THIS STUDY: The proposed study is led by the Center for the Study of State and Society, in association with Harvard University from the United States, and Deakin University from Australia, with support from the Argentinean National Cancer Institute and the Jujuy Ministry of Health. The need for a mHealth intervention to increase triage of HPV+ women was brought up by Jujuy health authorities in view of the low percentage of these women who have undergone cytology. The Head of the provincial cervical cancer prevention program has contributed to the study design. The Jujuy Province Ministry of Health has provided full support to the proposed project, as well as the Provincial Program on Cervical Cancer Prevention and the Director of the National Cancer Institute from Argentina, Dr. Roberto Pradier.

IMPACT AND FUTURE DIRECTIONS. Together, the results of both aims of this project will generate rich information on the effectiveness of a mHealth intervention on cervical cancer triage, the acceptability of mHealth interventions and CHW counseling, and the barriers and facilitators to implementing a multi-component intervention. These combined results will provide powerful evidence to scale-up a comprehensive multi-component mHealth intervention to the Argentina Ministry of Health that may have wide applicability in the Region, other LMICs, and even Latina populations in the US.

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