Multilevel HPV Self-Testing Intervention for the Increase of Cervical Cancer Screening among Women in Appalachia

NCT04411849

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1. Introduction / Overview

The overall P01 program titled "Take CARE: Improving Uptake of Cervical Cancer Prevention Services in Appalachia" is a series of three projects that will be implemented within health systems across four states in Appalachia. All three are designed to work in tandem and are focused on reducing the cancer burden in Appalachia through health system-based interventions, but each has a specific focus. Project 1 focuses on reducing cigarette smoking in adult female smokers who are considering quitting through counseling and nicotine replacement therapy. Project 2 is designed to improve HPV vaccination rates among 11-12 year olds and 13-26 year olds through educational and promotional materials and Electronic Health Record reminders. Project 3 seeks to improve cervical cancer screening rates. Project 3 will be described in detail in this protocol.

Most cases of cervical cancer occur among unscreened and underscreened women.[1,2] Current screening guidelines from the United States (US) Preventive Services Task Force and other organizations recommend women ages 30-65 should receive a combination of cytology (i.e., Pap test) and a clinic-based HPV test every 5 years, a clinic-based HPV test alone every 5 years, or cytology alone every 3 years.[3] However, nearly 20% of age-eligible women in the US are not within guidelines.[4] Strategies to increase screening among these women, including HPV self-testing, have therefore been identified as the most important cervical cancer screening research priority.[5]

HPV self-testing involves women using a device to collect their own cervicovaginal sample for HPV testing. International work has shown that up to about 40% of unscreened and underscreened women who are sent an HPV self-test in the mail will use the test at home and return it by mail (i.e., mail-based HPV self-testing).[6-15] As a result, multiple countries (e.g., the Netherlands and Australia) recently integrated mail-based HPV self-testing into their national screening programs.[16,17] In the US, focus group and survey studies have shown that most women would be willing to use an HPV self-test (i.e., high acceptability), and recent pilot studies, including our own work, have established the feasibility of mail-based HPV self-testing programs.[18-24]

Given the emergence of HPV self-testing, there is a need to examine the effectiveness and implementation of large mail-based HPV self-testing programs in the US. In doing so, it is critical to identify strategies that may increase women's return of a mailed HPV self-test and receipt of follow-up care, if needed. One promising strategy is patient navigation (PN). PN is a patient-centered healthcare delivery model that provides education and support to help people overcome concerns and barriers to care.[25] In past research, PN has repeatedly increased cancer screening behaviors, including cervical cancer screening, and receipt of follow-up care.[26-29] Thus, it is important that PN be examined for helping women use/return an HPV self-test and receive follow-up care, if needed. Many of the most common concerns and barriers reported by women about using an HPV self-test are modifiable and include: concerns about using the test incorrectly; uncertainty about test accuracy; and worry about returning a test by mail.[9,22,30,31] However, very little is known about PN in the context of HPV self-testing.

The proposed project will evaluate a multilevel cervical cancer screening intervention centered around HPV self-testing via a delayed intervention trial. The intervention will include mail-based HPV self-testing (patient-level), healthcare provider education sessions about HPV self-testing (provider-level), and PN for women who do not initially return their HPV self-test or who subsequently test positive for a high-risk (i.e., oncogenic) HPV infection (system-level). The intervention will be part of a P01 cervical cancer prevention program implemented in clinics within health systems in Appalachia, a geographic region with cervical cancer disparities.

2. Specific Aims

Specific aims will address each outcome type (service, implementation, and client outcomes) recommended for implementation research:[32]

Aim 1 (service outcomes): Determine the effectiveness of the intervention in increasing cervical cancer screening (primary outcome). Hypothesis 1a: The intervention will increase screening among unscreened and underscreened Appalachian women who are ages 30-64. Further, PN will increase HPV self-test return among

women who are initially non-returners. Screening will be defined as: a) return of an HPV self-test and negative for a high-risk HPV infection; b) return of an HPV self-test, positive for a high-risk HPV infection, and attendance at a follow-up appointment; or c) receipt of a clinic-based test (e.g., Pap test). Hypothesis 1b: The increase in screening will be similar across patient characteristics.

Aim 2 (implementation outcomes): Assess the fidelity, sustainability, and cost-effectiveness of the intervention. Hypothesis 2a: We hypothesize that the intervention will be implemented with high fidelity and sustained by the clinics/health systems. Hypothesis 2b: We also hypothesize that the intervention will be a cost-effective strategy for increasing cervical cancer screening.

Aim 3 (client outcomes): Determine satisfaction with the intervention at the patient- and provider-levels. Hypothesis 3a: Women will report high levels of satisfaction with HPV self-testing (if HPV self-test is returned) and PN (if received). Hypothesis 3b: Healthcare providers will report high levels of satisfaction with the provider education sessions and have improved knowledge, attitudes, and beliefs about HPV self-testing.

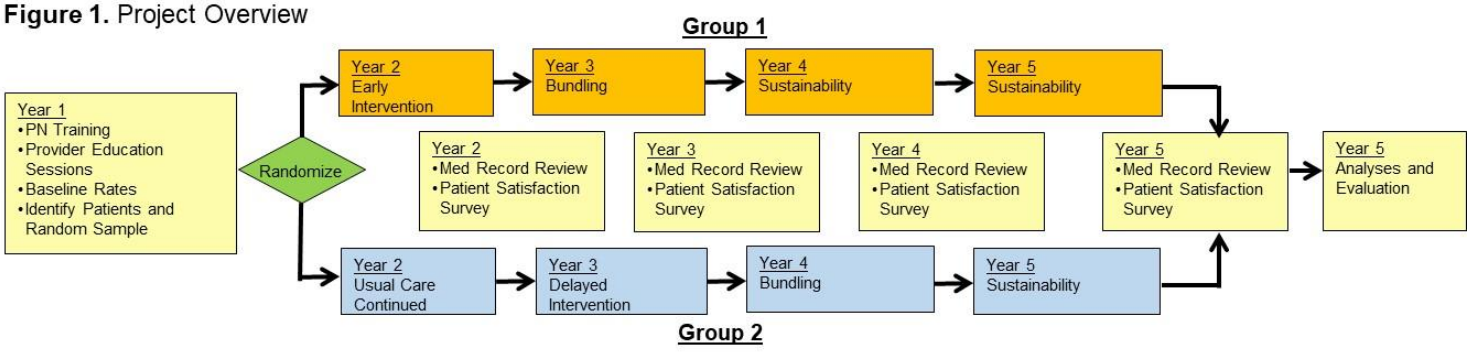
3. Methods

Overview

We will examine the effectiveness and implementation of the multilevel intervention using a delayed intervention trial (Figure 1). The methodology for this study will draw heavily upon our recently completed pilot study of a mail-based HPV self-testing program (IRB# 2015C0036).[24] Further, this study will build upon the formative work currently being done for this P01 program under IRB# 2019C0169. The study described in this protocol will involve a Group Randomized Trial (GRT). In GRTs, identifiable groups are randomized to a treatment condition with measurements taken on members from those groups to assess the impact of the intervention. In this project, health systems will be randomized to one of two study arms (Group 1 will be the Early Intervention and Group 2 will be the Usual Care Continued/Delayed Intervention). Please note that similar to IRB# 2015C0036, the intervention will be referred to as "The HOME (Health Outcomes through Motivation and Education) Project" or simply as the "HOME Project".

Note. Some of the materials included as appendices with this submission will be further refined by the study team. Upon completion, final versions will be submitted for IRB review and approval in a future amendment. IRB approval will be obtained prior to the use of the final versions in the study.

Figure 1. Project Overview



Health Systems and Clinics

The P01 program will involve a total of 10 health systems in four states. A letter of support from each system has been included. Several of the health systems include multiple clinics. Similar to the other projects in this P01 program, all activities and participants will stem from these health systems/clinics (as described below).

Year 1 Preliminary Activities

During Year 1, we will conduct two necessary preliminary activities outside of the GRT portion of the study: training of patient navigators and provider education sessions.

Training of Patient Navigators

PN will be provided during the randomized trial to help women both: a) use/return their HPV self-test (if they do not initially return their device); and b) attend an in-clinic follow-up visit if their returned self-test is positive for high-risk HPV infection. Patient navigators (PNs) will perform the following activities during the trial: a) provide information about HPV, cervical cancer, and screening; b) address patients' concerns/barriers about HPV self-testing and attending a follow-up visit (if needed); c) help set goals and plans for achieving these outcomes; and d) provide social support. These activities are key components of behavior change technique[33] and were used in our past PN work.[34] The PNs will be health system/clinic staff that have agreed to serve as PNs for this project.

To prepare PNs for the GRT, members of the project team will lead PN training activities. Modeled after our past PN work,[34] training may include both a review of general PN principles and project-specific training. General PN principles may include training on keeping relationships professional with patients, potential ethical issues (e.g., confidentiality), and how to work as a link between patients and the clinic. Project-specific training may include detailed information about the project and how to: a) provide information in an understandable format about HPV, cervical cancer, and screening (including self-testing); b) interpret HPV testing results and discuss the results; c) address patients' likely concerns, barriers, and questions; d) help patients set goals and plans for screening; e) provide social support; f) compile a list of potential local resources (e.g., transportation systems); and g) complete project forms.

Specific training activities may include case studies, content reading, role-playing, and mock interactions with patients. During training, we will stress how to: provide information about HPV, cervical cancer, and screening, with a focus on Appalachian disparities; describe the effectiveness of HPV self-testing; and address women's concerns/barriers. For social support, PNs will be trained to provide support that is informational (i.e. trusted source of information), emotional (e.g., supportive listening, expressing concern, etc.), and instrumental (e.g., help with transportation, etc.). PNs will apply these skills when interacting with patients during the randomized trial (as described below). However, during training, there will be no interaction with actual patients or human subject involvement of any kind.

Provider Education Sessions

To ensure providers and staff at participating health systems/clinics are knowledgeable about HPV self-testing, we will conduct education sessions as the provider-level component of the multilevel intervention. Eligibility criteria will include: a) employee at a clinic of a participating health system; b) age 18 or older; and c) involved with the cervical cancer screening process (e.g., physicians, nurses, physician assistants, staff that assist with scheduling screening tests). Providers and staff will attend one session each (about 60 minutes long). We will conduct a session with each clinic within a health system, with a members of the project team leading each session. Attendees will view a standardized automated PowerPoint presentation patterned heavily after a presentation used for provider education sessions in our past work on HPV self-testing (IRB# 2015C0036).[35] The presentation (see Appendices for presentation slides and script) will provide information about HPV and cervical cancer, screening recommendations, HPV self-testing and how to talk with patients about testing results, our project, and how this project fits into the integrated cervical cancer prevention program. Education session content will be the same for all clinics. All attendees will provide written consent or consent online (see Appendices) at the beginning of their session. We will work with each health center to determine if it would be preferable to conduct their session in-person (written consent will be used) or virtually (online consent will be used). The two versions of the consent

form are nearly identical, with only minor differences to account for mode of administration (written vs. online). Virtual sessions will be conducted either synchronously (i.e., at a specified day/time for all providers to attend) or asynchronously (i.e., providers will complete the session at their convenience), depending on each health center's preference. Synchronous sessions will be recorded (using Zoom or equivalent) for any healthcare providers that cannot attend during the specified session time.

Based on our pilot study,[24] we estimate about 80% attendance at the sessions among health system employees. To maximize attendance, we will work with clinics to find a convenient session time (e.g., at an existing meeting). Each attendee will complete a brief pre- and post-test survey (see Appendices). Using items based on those from our pilot study,[24] surveys will assess: demographics (pre- survey only); knowledge, attitudes, and beliefs about cervical cancer and HPV self-testing (pre- and post-surveys); and satisfaction with the session (post- survey only). The resulting survey data will be used in evaluation. Surveys will be either written (for in-person sessions) or online (for virtual sessions), with survey items being identical for the two modes of administration. For online surveys, an introduction email (see Appendix) will be sent to healthcare providers to link them to their surveys.

Year 1 Randomized Trial Activities

Baseline Screening Rates and Patient Identification

We will work with the health systems to use their EHR systems to obtain baseline cervical cancer screening rates and identify potentially eligible women. Participation will be limited to one woman per household. Eligibility criteria will include:

a) female;
b) ages 30-64 (64 will be the upper age limit instead of 65 so women do not age out of the cervical cancer screening guidelines);
c) not within recommended cervical cancer screening guidelines for women in this age range (i.e., no Pap test in last 3 years or clinic-based HPV test in last 5 years);
d) resident of an Appalachian county or patient at a health system in an Appalachian county;
e) not currently pregnant;
f) intact cervix;
g) no history of invasive cervical cancer;
h) seen in a participating clinic/health system in last 2 years (i.e., active patient); and
i) have a working telephone.

During this process involving EHRs, members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about participants will involve only ID numbers. All identified women will be entered into a database by clinic staff (see Appendix).

Cervical Cancer Screening Reminder Letter

We will next mail all identified potentially eligible women a standard reminder letter to get a clinic-based cervical cancer screening test (e.g., Pap test) (see Appendix). The letter will indicate that, according to EHR, they are due for a clinic-based cervical cancer screening test and encourage them to contact their clinic to schedule a test (contact information for the clinic will be provided). All letters will appear on clinic/health system letterhead and be signed by a clinic representative. Many health systems have utilized this type of reminder letter for cervical cancer screening,[36] so it can be considered "usual care." We think it is important that all potentially eligible women receive this letter that encourages clinic-based cervical cancer screening test before any HPV self-tests are sent. The clinics will mail all of the reminder letters to women. Members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about patients will involve only ID numbers.

We will allow about 4-5 months for women who are sent a reminder letter to receive a clinic-based cervical cancer screening test. At the end of the this time period, we will work with the clinics/health systems and use EHR to

identify women who received a clinic-based cervical cancer screening test since the reminder letters were sent. Any woman who has received a test will not continue in the project, as they are no longer unscreened/underscreened. Based on the mean effect size of past studies of mailed cervical cancer screening reminder letters, we anticipate that only about 5% of women who are sent a reminder letter will receive a clinic-based test during the 4-5 month period.[36]

Randomization

Health systems will be randomized to one of two treatment groups (Group 1 or Group 2) for the cervical cancer prevention program (Figure 1). A 1:1 allocation scheme stratified by state will be used (i.e., five systems per treatment group). Health system will be the unit of randomization. All clinics in a health system will be in the same treatment group.

Year 2 Randomized Trial Activities

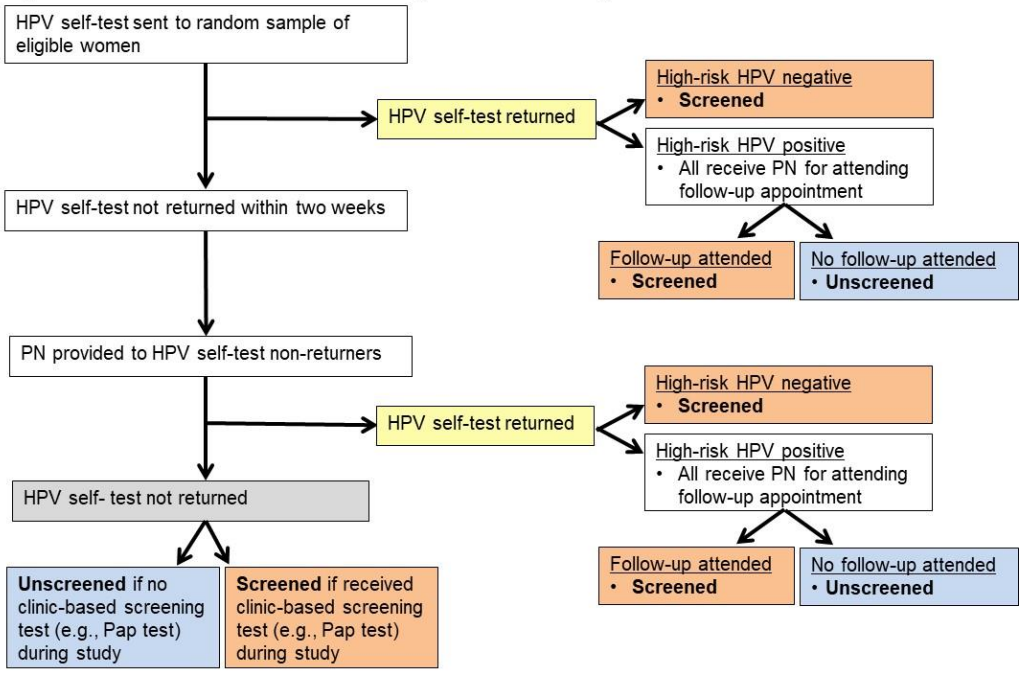
Group 1: Early Intervention

Group 1 clinics/health systems will receive Early Intervention during Year 1, including HPV self-test devices sent to women (patient-level component) and PN (system-level component). Figure 2 provides an overview of these components.

HPV Self-Test Distribution and Return

Women in Group 1 clinics/health systems who did not get a clinic-based cervical cancer screening test in the 4-5 months after the reminder letter will be on a sampling frame to receive an HPV self-test. We will randomly sample from this list, stratified by clinic. We will sample a total of 600 women across Group 1 health systems. Sampled women will first be sent a letter (see Appendix) asking them to confirm their eligibility criteria (as defined above). If women meet any criteria that would make them ineligible, they will be asked to indicate this information and return the letter in a provided postage-paid return envelope. Return of a letter will be considered consent for providing this information. Women who return their letter and are found to be ineligible will not continue in the project, and a potential replacement will be randomly sampled from the remaining list (who will then be sent a letter to confirm eligibility). Women who do not return a letter will be considered as confirmed eligible since only women who meet criteria making them ineligible will be asked to return their letter. The clinics will mail all of the reminder letters to women. Members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about patients will involve only ID numbers.

Figure 2. Overview of the HPV Self-Testing and Patient Navigation Processes



Each woman who is confirmed eligible will next be mailed an HPV self-test. Self-tests will be sent by mail by the clinics, as members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about participants will involve only ID numbers. Women will be sent the HPV self-test free of charge, and the subsequent HPV testing will also be free of charge to women.

The HPV self-test device will be a device developed by Preventive Oncology International (POI) (see Appendix). The device is 20 cm in length, which is similar to a regular-sized tampon. This device is easy for women to use. A woman inserts the brush end of the device into her vagina until she feels slight resistance, exposing the brush to the cervix. The participant then holds the handle end of the device and rotates a few times to collect the sample. She then withdraws the brush from her vagina. Once the brush is fully removed, the participant breaks the brush end of the device into the plastic return tube. HPV testing can be effectively performed on this single sample. Step-by-step instructions for using this device clearly indicated on its packaging (see Appendix).

This device has been widely used in research studies,[37-41] and it has been found to be just as sensitive as a physician-performed test for detecting HPV and, in some instances, cervical dysplasia.[40,41] Importantly, this device is highly similar in terms of usability and safety to self-test devices that were used successfully in our past HPV self-test work (IRB# 2015C0036).

We will send additional materials along with the self-test device and its packaging: an introductory booklet (see Appendix), an information booklet about cervical cancer (see Appendix), and a postage-paid return box. The introductory booklet will explain the self-test's purpose and answer common questions about the self-test. To ensure women are knowledgeable about cervical cancer, we will include an information booklet about cervical cancer (based on an information sheet created by the Centers for Disease Control and Prevention (CDC)) (see Appendix). To return the self-test, women will place the plastic return tube (containing the used brush end of the device) in the return box. We will provide an instruction card that explains the return process (see Appendix). The return box will be pre-addressed. Return of an HPV self-test will be considered consent for the self-test.

Patient Navigation for HPV Self-Test Device Return

Women who have not returned their HPV self-test within two weeks of the device being sent will receive PN for self-test return. PNs will attempt to contact these initial non-returners by text message and/or telephone, making up to 10 attempts at different times and on different days, including weekends. If no contact is made after the final attempt, PNs will send women a letter asking them to contact the PNs (see Appendix). Using a similar approach, PNs contacted almost 90% of participants in our past work.[34] During interactions with participants, PNs will apply their training to provide information about HPV and self-testing, address women's concerns and barriers to using/returning their self-test, help women set goals and plans for using/returning their self-test, and provide social support. PNs will also ask women if they need a replacement device sent. To ensure consistency in the process, PNs will use developed guides/scripts during calls and text messages (see Appendices). If a woman has already returned her self-test by the time of contact, the PN will ask if she had any questions. Members of the study team will not have direct contact with any of the participants, only the PNs (who are employees of the clinics) will contact participants or have access to participants' contact information.

PNs will contact each of these initial non-returners at least once about using/returning their self-test, with additional contacts as needed (e.g., if PNs need to locate further information after the first contact). This will allow PNs flexibility that is tailored to each woman's needs. Following completion of PN (or final contact attempt without success and a letter sent), we will give women two additional weeks to return their HPV self-test. All women who do not return their self-test following this additional time will be classified as having not returned their HPV self-test.

HPV Testing

All returned HPV self-tests will be sent to a laboratory at Atila BioSystems (Mountain View, CA) for HPV testing. The laboratory has expertise in HPV testing and has performed this type of testing extensively in the past. Testing will use the Atila AmpFire HPV test, which produces one of the following outcomes for each sample: (a) positive for high-risk HPV type 16 or 18; (b) positive for a high-risk HPV type other than type 16 or 18 (i.e., type 31, 33, 35,

39, 45, 51, 52, 53, 56, 58, 59, 66 or 68); (c) negative for high-risk HPV types; or (d) inadequate sample. The detectable high-risk HPV types cause almost all cervical cancers. We do not expect "inadequate sample" to occur often since all women in our pilot study collected adequate samples,[24] but will send a replacement device for resampling if it does occur. The laboratory will send HPV testing results to the project team via secure email and using only participant ID numbers. Results will be available within about a month after a sample is sent to the laboratory. All HPV testing results will be entered into a database by the project team (see Appendix).

Notification of Results to Clinics

Upon receipt of HPV testing results, we will notify a designated person at each clinic (e.g., the PN) of the results for each participant (using only participant ID numbers). This notification will occur via secure email. The notification email (see Appendix) will be patterned after a similar communication in our past HPV self-test work (IRB# 2015C0036) and contain: a) HPV testing results for participants; b) an interpretation of the results; and c) contact information for the project team in case there are any questions.

Notification of Results to Women

The clinics will then mail a notification letter to each participant (see Appendix). The notification letter will include HPV testing results and an interpretation of the results. The letter will indicate appropriate next steps based on the HPV testing results. For women who test negative for high-risk HPV types, the letter will indicate that no follow-up care is needed at this time. For women who test positive for high-risk HPV types, the letter will indicate that someone from their clinic (e.g., PN) will contact them in the next few days to help schedule a follow-up appointment. Contact information for the clinic will be provided in this letter.

Patient Navigation for Follow-Up Appointment

All women who test positive for a high-risk HPV type will receive PN for scheduling/attending a follow-up appointment (i.e., for a Pap test or other follow-up care [e.g., colposcopy] as deemed appropriate by the health system). We think it is important to provide PN to all of these women given their HPV infection and lack of screening prior to this project. PNs will attempt to contact women by text message and/or telephone starting about a week after women's notification letters are mailed (to allow time for letter delivery). PNs will make up to 10 attempts at different times and on different days, including weekends. If no contact is made after the final attempt, PNs will send women a letter asking them to contact the PNs (see Appendix). PN activities will be similar to those described above for HPV self-test use/return. Using developed guides/scripts (see Appendices), this interaction will focus on women's HPV testing results and the importance of scheduling/attending a follow-up appointment. PNs will be aware of HPV testing results prior to the calls and/or text messages. PNs will contact these women at least once about scheduling/attending a follow-up appointment, with additional contacts as needed.

Group 2: Usual Care Continued / Delayed Intervention

Women in Group 2 clinics/health systems who did not get a clinic-based cervical cancer screening test in the 4-5 month period following the reminder letter being sent will be on a sampling frame to continue with usual care. We will randomly sample from this list, stratified by clinic. We will sample a total of 600 women across all Group 2 health systems. Similar to sampled women in Group 1, sampled women in Group 2 will first be sent a letter (see Appendix) asking them to confirm their eligibility criteria (as defined above). If women meet any criteria that would make them ineligible, they will be asked to indicate this information and return the letter in a provided postage-paid return envelope. Return of a letter will be considered consent for providing this information. Women who return their letter and are found to be ineligible will not continue in the project, and a potential replacement will be randomly sampled from the remaining list (who will then be sent a letter to confirm eligibility). Women who do not return a letter will be considered as confirmed eligible since only women who meet criteria making them ineligible will be asked to return their letter. The clinics will mail all of the reminder letters to women. Members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about patients will involve only ID numbers.

Each woman who is confirmed eligible will next be mailed an additional reminder letter to get a clinic-based cervical cancer screening test (i.e., usual care continued; see Appendix) and an information sheet about cervical cancer (the same information sheet that will be sent to Group 1; see Appendix). These materials will be sent by the clinics,

as members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about participants will involve only ID numbers.

Data Collection for Year 2

There will be two data collection activities at during Year 2: a medical record review and a patient satisfaction survey.

Medical Record Review

We will work with the each health system to gather data from EHR. For women in Groups 1 and 2, we will confirm whether any received a clinic-based cervical cancer screening test during Year 2. For women in Group 1 who tested positive for a high-risk HPV type based on their self-test, we will also confirm: a) any follow-up appointment attended; b) any follow-up care received (e.g., Pap test, colposcopy, etc.); and c) any cervical abnormalities (precancerous and cancerous) found during this follow-up. During this process involving EHRs, members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about participants will involve only ID numbers. This information will be entered into a database by clinic staff (see Appendix).

Patient Satisfaction Survey

All women who were sent an HPV self-test during Year 2 (i.e., Group 1) will be sent a patient satisfaction survey about HPV self-testing (see Appendix) and an introductory letter about the survey (see Appendix). The survey will be sent to both self-test returners and non-returners. The clinics will mail all of the surveys to participants, with each survey containing the participant's unique ID number. Members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about participants will involve only ID numbers.

The survey will examine women's decisions/experiences with their self-test and PN (if applicable), as this information will be valuable in evaluating the intervention. The survey will assess reasons for returning or not returning the self-test, satisfaction with the self-test (appearance, usability, etc.) and its instructions (appearance, readability, etc.). For women who received PN, the survey will assess their satisfaction with PN. Women will be provided with a postage-paid return envelope, and survey return will be considered consent. Women will be sent a $25 gift card for returning the survey (see Appendix for letter that will be sent with the gift card).

Year 3 Randomized Trial Activities

Group 1: Bundling

The Bundling phase will occur in Group 1 clinics/health systems during Year 3. Implementation will mirror the Early Intervention phase, with the large difference being that all three projects in the P01 program will be occurring simultaneously during all of this project year (whereas the start of projects will be staggered during the Early Intervention phase).

In this phase, 100 eligible women across Group 1 health system who are unscreened/underscreened will be randomly sampled from the sampling frame and sent an HPV self-test. The methodology during the Bundling phase will mirror the methodology of the Active Intervention phase during Year 2.

Group 2: Delayed Intervention

Group 2 clinics/health systems will receive delayed intervention during Year 3. The methodology of this phase will be identical to the Group 1 Active Intervention during Year 2. In this phase, 100 eligible women across Group 2

health systems who are unscreened/underscreened will be randomly sampled from the sampling frame and sent a self-test.

Data Collection for Year 3

Similar to data collection during Year 2, data collection during Year 3 will include a medical record review and a patient satisfaction survey. As described for Year 2, members of the project team will not have access to any identifying information (including contact information) of the patients. All communication between the project team and clinics about participants will involve only ID numbers.

Medical Record Review

For all women in Groups 1 and 2, we will confirm whether women received a clinic-based cervical cancer screening test during Year 3. For women in Groups 1 and 2 who tested positive for a high-risk HPV type based on their self-test, we will confirm: a) any follow-up appointment attended; b) any follow-up care received; and c) any cervical abnormalities (precancerous and cancerous) found during this follow-up care.

Patient Satisfaction Survey

The survey and methodology will be identical to those described previously. We will send a survey to all women in Groups 1 and 2 who were sent an HPV self-test during Year 3.

Year 4 Randomized Trial Activities

Group 1: Sustainability

Group 1 clinics/health systems will move to the Sustainability phase during Year 4. During this phase, the project team will step back and allow the clinics/health systems to fully lead intervention implementation, including all PN activities. The project team will only be consulted if issues arise that the clinics/health systems cannot resolve. This phase will allow us to examine intervention sustainability in real world settings. In this phase, 100 eligible women across Group 1 health systems who remain unscreened/underscreened will be randomly sampled from the sampling frame and sent an HPV self-test. Starting in Year 4, we will ask patients to confirm their eligibility criteria by returning a completed eligibility confirmation form (see Appendix). Return of a completed form will be considered consent for providing this information. Any women found to be ineligible will be sent a letter indicating that they are not eligible for this project (see Appendix) and will not continue in the project (as in previous project years). Women who are confirmed eligible will continue in the project in the same manner as previous project years.

Group 2: Bundling

The Bundling phase will occur in Group 2 health systems during Year 4. This phase will be identical to the Bundling phase for Group 1 during Year 3, as described above. In this phase, 100 eligible women across Group 2 health systems who remain unscreened/underscreened will be randomly sampled from the sampling frame and sent an HPV self-test. Starting in Year 4, we will ask patients to confirm their eligibility criteria by returning a completed eligibility confirmation form (see Appendix). Return of a completed form will be considered consent for providing this information. Any women found to be ineligible will be sent a letter indicating that they are not eligible for this project (see Appendix) and will not continue in the project (as in previous project years). Women who are confirmed eligible will continue in the project in the same manner as previous project years.

Data Collection for Year 4

Data collection activities (Medical Record Review and Patient Satisfaction Survey) will be identical to those described for Year 3.

Year 5 Randomized Trial Activities

Groups 1 and 2: Sustainability

Group 1 clinics/health systems will continue with the Sustainability phase, as described above during Year 5. Group 2 clinics/health systems will also enter the Sustainability phase, as described above, during Year 5. In this phase, 100 women across Group 1 health systems and 100 women across Group 2 health systems who remain unscreened/underscreened will be randomly sampled from the sampling frame and sent an HPV self-test.

Data Collection for Year 5

Data collection activities (Medical Record Review and Patient Satisfaction Survey) will be identical to those described for Year 3.

Statistical Methods: Analyses and Evaluation

We will conduct analyses/evaluation of each outcome type recommended for implementation research:[32] implementation, service, and client outcomes.

Aim 1 (Service Outcomes)

Service outcomes will include intervention effectiveness, equitableness, and safety (Table 1). We hypothesize the intervention will increase cervical cancer screening and that PN will increase HPV self-test return among women who do not initially return their self-test (Hypothesis 1a). We think PN will increase HPV self-test return among these initial non-returners given PN's positive effect on health outcomes in past studies.[26-29] Lastly, we hypothesize the increase in screening will be similar across patient characteristics (i.e., equitableness)(Hypothesis 1b).

Table 1. Service Outcomes and Data Sources

Outcome	Measure	Level	Data Source
Effectiveness	Cervical cancer screening	Patient-level	HPV self-test data and medical records
Equitableness	Demographic and health-related characteristics	Patient-level	Medical records
Safety	Reported issues in using an HPV self-test	Patient-level	Patient satisfaction surveys

Measures

The patient-level effectiveness outcome and primary outcome for our project will be whether or not women get "screened" during the project. There are three ways a woman can be considered "screened." The first is to return their HPV self-test and test negative for high-risk HPV types. The second is to return their HPV self-test, test positive for high-risk HPV types, and then attend a follow-up appointment at their health system. We are requiring these women to attend a follow-up appointment to be considered "screened" given their HPV infection. The third way is to receive a clinic-based screening test (e.g., Pap test), regardless of HPV self-test return status. This will most likely apply to women in Group 2 health systems during the Usual Care Continued phase, but past studies have shown that some women will get a Pap test after receiving an HPV self-test in the mail (without using the self-test).[42] All women not meeting one of these three criteria will be considered "unscreened." To determine this outcome, we will examine HPV self-test return status, HPV testing results, and EHR data (follow-up appointment attendance, Pap testing, etc.) for each sampled woman.

Among women who return their HPV self-test, we will examine the timing of device return and categorize each as returned within two weeks of distribution (i.e., prior to any PN) or after two weeks of distribution (i.e., following PN). We will also examine HPV testing results (positive or negative for high-risk HPV types) and collect data from EHR on the number of normal and abnormal clinic-based cervical cancer screening tests received by each woman and any cervical abnormalities found (i.e., low-grade squamous intraepithelial lesion, etc.).

To assess if the intervention is equitable (Figure 4), we will examine patient characteristics via data from HER (e.g., age and when their most recent clinic-based cervical cancer screening test prior to project entry occurred [if

ever]). Lastly, to assess safety, we will examine data from the patient satisfaction survey to see if women report any issues about using their HPV self-test. We do not anticipate such reports to be common, as HPV self-test devices have been used safely and easily by women in several research studies.[6-15]

Sample Size

The project's total sample size will be 1800 women across Years 2-5 (900 women from Group 1 clinics/health systems and 900 from Group 2 clinics/health systems). These sample sizes are feasible given the expected sampling frame size (see Table 1) and will give us at least 90% power for the below analyses.[43] The power calculation assumed a two-sided alpha=0.05, an intraclass correlation coefficient<0.017 (based on our pilot study), and the below outcome occurrences.

Primary Analyses

Primary analyses will examine the proportion of women from Year 2 screened, as defined above, and use an intent-to-treat approach. To compare treatment groups (Group 1 vs. Group 2), we will use generalized linear mixed models (GLMMs) to account for the correlation between women from the same clinic,[44] though we expect cluster effects to be low (i.e., intraclass correlation coefficient<0.017 based on our pilot study). Since our outcome is binary, we will use a logit link to estimate odds ratios for the GLMMs. We expect that 30% of women from Group 1 clinics/health systems and 10% of women in Group 2 clinics/health systems will be categorized as screened. The primary model will be unadjusted, but we will conduct sensitivity analysis that include potential confounders due to imbalance from randomization (p<0.10 when comparing groups). Results will determine the effectiveness of the intervention in increasing cervical cancer screening compared to usual care.

Secondary Analyses

We will conduct several secondary analyses for Aim 1. First, we will examine the proportion of HPV self-test returners who returned their self-test following receipt of PN. Results will provide valuable data on the added benefit of PN on HPV self-test return. Second, we will use GLMMs with a logit link to examine potential differences in the proportion of women screened across project years within each treatment group (i.e., comparing Years 2, 3, 4, and 5 for Group 1). Results will determine how screening rates changed over time, which will be key in assessing whether the intervention was maintained during the Bundling and Sustainability phases. Third, to assess if the intervention was equitable, we will use GLMMs with a logit link to examine if patient characteristics are associated with women being categorized as "screened". Fourth, to assess safety, we will descriptively examine women's reports of any issues experienced when using their HPV self-test. Lastly, we will descriptively examine the prevalence of high-risk HPV infection, abnormal clinic-based cervical cancer screening tests, and cervical abnormalities among women.

Aim 2 (Implementation Outcomes)

Implementation outcomes will examine the fidelity, sustainability, and cost-effectiveness of the intervention. We hypothesize that the intervention will be implemented with high fidelity and sustained by the clinics/health systems (Hypothesis 2a). We also hypothesize that the intervention will be a cost-effective strategy for increasing cervical cancer screening (Hypothesis 2b).

Fidelity

We will use several strategies to ensure and examine fidelity (i.e., the degree to which the intervention is conducted according to protocol). At the patient-level, we will develop an electronic tracking system to track all mailings (e.g., self-test distribution) and other data collection activities. At the provider level, we will conduct the provider education sessions using a standardized PowerPoint presentation. Data during the sessions will be collected using a checklist (for project team use only) that includes key observations related to fidelity (e.g. the presence of participants during entire session).

Sustainability

We will examine the screening rates during the Sustainability phase(s) for both Groups 1 and 2 to determine sustainability.

Cost-effectiveness

Cost-effectiveness analyses will be conducted from a payer perspective. We will first conduct a cost identification analysis. We will carefully consider all costs of the intervention, including those for HPV self-test devices, PN training/implementation, staff, mailing costs, and administrative costs. We will value the costs of each item using standard costs, and we will carefully distinguish costs related to scientific research from those of the interventions themselves. We will only include the intervention costs in our cost-effectiveness analyses. We will then aggregate the measures of costs and intervention effectiveness and calculate incremental cost-effectiveness ratios (ICER). The ICER measures the cost at which an added unit of outcome can be achieved by the intervention. Thus, the ICER will represent the marginal cost of an additional patient screened for cervical cancer due to the intervention. We will also conduct sensitivity analyses.

Aim 3 (Client Outcomes)

For client outcomes, we will determine the satisfaction with the multilevel intervention at the patient- and provider-levels (Table 2).

Table 2. Client Outcomes and Data Sources

Outcome	Measure	Level	Data Source
Satisfaction	Satisfaction with HPV self-testing and PN	Patient-level	Patient satisfaction survey
Satisfaction	Satisfaction with provider education sessions and change in knowledge, attitudes, and beliefs	Provider-level	Surveys from provider education sessions

Patient-Level

We hypothesize that women will report high levels of satisfaction with HPV self-testing (if HPV self-test is returned) and PN (if received) (Hypothesis 3a). Patient-level satisfaction data will come from the patient satisfaction surveys sent to women. We will examine satisfaction with both the HPV self-test device (appearance, usability, return process, etc.) and its instructions (appearance, readability, etc.). We will use items based on those from our pilot study to assess these constructs.[24] For women who received PN, we will also assess their satisfaction with PN using items from our past PN research.[34] All satisfaction items will use 5-point Likert response scales. We will consider means of 4.0 and greater to indicate high levels of satisfaction. We expect about 80% of women who were sent an HPV self-test to return a completed patient satisfaction survey (based on mailed survey return in our pilot study[24]).

Provider-Level

We hypothesize that healthcare providers and staff will report high levels of satisfaction with the provider education sessions and have improved knowledge, attitudes, and beliefs about HPV self-testing (Hypothesis 3b). Provider-level satisfaction data will come from the post-test surveys from provider education sessions. All satisfaction items will use 5-point Likert response scales. We will consider means of 4.0 and greater to indicate high satisfaction. We expect an estimated 503 attendees total at provider education sessions.

To examine changes in knowledge, attitudes, and beliefs about HPV self-testing, we will analyze pre- and post-test survey data from provider education sessions. Knowledge will be assessed with six true/false items. Attitude/belief items will assess constructs (perceived benefits of self-testing, self-efficacy to talk with patients about self-testing, etc.) using 5-point Likert response scales. Survey items will be based on items from our pilot study.[35] We will compare pre- and post- data using GLMMs with an identity link (i.e., a linear mixed model) to account for the correlation between providers at the same clinic,[44] though we expect an intraclass correlation coefficient<0.017 based on our pilot study. We expect the mean number of correct knowledge items will increase by about 1.2 items from pre- to post-test. Similarly, we expect means for attitude/belief items to increase by about 0.4 units (on a 5-point scale) from pre- to post-test.

Study Timeline

Table 3. Project Timeline				
Year 1	Q1	Q2	Q3	Q4
PN training / Provider Education	●	●		
Baseline Rates / Identify Patients			●	●
Screening Reminders / Randomize			●	●
Monthly Team Meetings	●	●	●	●
Year 2				
Group 1: Active Intervention	●	●	●	●
Group 2: Usual Care Continued	●	●	●	●
Data Collection and Management	●	●	●	●
Monthly Team Meetings	●	●	●	●
Year 3				
Group 1: Bundling	●	●	●	●
Group 2: Delayed Intervention	●	●	●	●
Data Collection and Management	●	●	●	●
Monthly Team Meetings	●	●	●	●
Year 4				
Group 1: Sustainability	●	●	●	●
Group 2: Bundling	●	●	●	●
Data Collection and Management	●	●	●	●
Monthly Team Meetings	●	●	●	●
Year 5				
Group 1: Sustainability	●	●	●	●
Group 2: Sustainability	●	●	●	●
Data Collection and Management	●	●	●	●
Analyses and Evaluation	●	●	●	●
Monthly Team Meetings	●	●	●	●

Human Subjects Information

Potential Risks and Benefits

Provider Education Sessions

We believe these education sessions will present minimal risk to participants. We do not anticipate harm to study participants. We do not anticipate any psychosocial harm, economic harm, legal jeopardy, or other side effects for these individuals. There is the small possibility that some participants may find some of the session topics or survey items embarrassing or worrisome. However, education sessions and surveys of this type are routinely conducted, with no ill effects to participants.

Randomized Controlled Trial

We believe the RCT will also present minimal risk to participants. We do not anticipate physical harm to study participants. We also do not anticipate any psychosocial harm, economic harm, legal jeopardy, or other side effects to participants. HPV self-tests have been used in numerous studies without causing physical or psychosocial harm,[6-15] and most women report low levels of discomfort and anxiety when using HPV self-tests. Instructions describing how to use the HPV self-test will be provided to all women along with their self-test device. Women will also be provided with contact information in case they have any questions or problems with the HPV self-test. There is the small possibility that some participants may experience anxiety after being notified of their HPV self-test results. Such effects are not common among women who receive negative HPV results, but could occur among women with positive results. In order to minimize this risk, women will be provided with contact information for the clinic and PN when they receive their HPV self-test results. Further, a PN will contact all women who test positive for a high-risk HPV type.

It is also not anticipated that the Patient Satisfaction Survey will cause any psychosocial harm, economic harm, legal jeopardy, or other side effects. Some women may find some of the survey questions embarrassing or

worrisome since this study focuses on HPV and cervical cancer prevention. However, surveys of this type are routinely conducted, with no ill effects to participants. Because all study surveys will be sent and returned via mail and completed by women in their homes with the option to skip any question they do not wish to answer, this is a minimal risk. We asked similar survey questions in our pilot study without any resulting problems.[24]

Protection Against Risk

Provider Education Sessions

All participants will provide informed consent before focus groups. The autonomy of participants will be protected by informing all participants of the purpose of the study and allowing them to opt out of participation without repercussion. Participants will be able to withdraw from the study at any time, and they will be able to refuse to answer any survey question.

Several precautions will be taken to avoid any breach of confidentiality. We will use identification numbers instead of the names of participants (or any other personal identifiers) on all session forms and in any database containing study data. The numbers and names will be linked in a separate study tracking database list that will be accessible only to the study team. All databases will be password protected behind the OSU firewall. All completed session forms (e.g., surveys) will be stored in locked file cabinets. Only members of the study team will have access to these hard copy documents.

We will use REDCap (Research Electronic Data Capture) to collect data online, as needed (e.g., provider education surveys). REDCap is a software toolset and workflow methodology for electronic collection and management of clinical and research data. The Ohio State Research Information Technology Electronic Data Capture will be used as a central location for data processing and management. REDCap provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of participant records, and variations of data exporting/importing. REDCap is hosted by OSUWMC IT in the Ackerman Datacenter (640 Ackerman Road; Room 345).

Randomized Controlled Trial

Every means will be taken to minimize the risk associated with participating in the RCT. The autonomy of participants will be protected by informing all participants of the purpose of the study and allowing them to opt out of participation without repercussion (i.e., women will not have to use the HPV self-test device or survey sent to them). For both the HPV self-test and Patient Satisfaction Survey, return of the device (or survey) will be considered consent. Participants will be able to withdraw from the study at any time, and they will be able to refuse to answer any survey question. Participants will be provided with contact information in case they have any questions or concerns or experience any negative outcomes.

Several precautions will be taken to avoid any breach of confidentiality. We will use identification numbers instead of the names of participants (or any other personal identifiers) on all study forms and in any database containing survey data. In fact, members of the study team will not have any direct access to personal identifiers. Only employees at the participating health systems/clinics will have access to this information. All study-related databases will be password protected behind the OSU firewall. All study records and completed study forms (e.g., surveys) will be stored in locked file cabinets. Only members of the study team will have access to these hard copy documents.

When sending HPV self-test specimens to Atila BioSystems (Mountain View, CA) for HPV testing and receiving the corresponding results from Atila BioSystems, only participants' identification numbers will be used. No names will be used in these processes. Atila BioSystems will send test results to the study team via email. Test results will only include participant ID numbers, participant names will not be included in the results sent from Atila BioSystems. Only members of the study team and employees at the participating health systems/clinics will have access to the HPV self-test specimens and the files containing test results from the Atila BioSystems.

Following HPV testing, the study team will send women's HPV self-test results to only a designated person at each clinic (e.g., the PN). This notification will occur via secure email. We will have multiple measures in place to

ensure patient confidentiality when sending HPV testing results to the health clinics. First, we will use secure email. Second, the email will include a statement regarding confidentiality. The clinics will then mail a notification letter to each participant. The notification letter will include HPV testing results and an interpretation of the results. The letter will indicate appropriate next steps based on the HPV testing results. For women who test negative for high-risk HPV types, the letter will indicate that no follow-up care is needed at this time and state when their next cervical cancer screening test should occur. For women who test positive for high-risk HPV types, the letter will indicate that they should contact their clinic to schedule a follow-up appointment and that a PN will contact them to help with this process. Contact information for the clinic and PN will be provided.

Potential Benefits

Provider Education Sessions

There may or may not be any direct benefits to participants in the education sessions. The study may improve participants' knowledge about HPV self-testing and cervical cancer screening. We believe these potential benefits of the study outweigh its minimal risks.

Randomized Controlled Trial

Women participating in the RCT will benefit by receiving a free HPV self-test. All women will be outside of recommended cervical cancer screening guidelines upon entry, so it is important that efforts like the proposed study are made to reach and screen these women. Women may also learn new information about cervical cancer by participating in this study.

Additionally, the intervention resulting from this study has the potential to improve cervical cancer screening and reduce current cervical cancer disparities among women from Appalachia. All participants and society in general will benefit from this study to the extent that the results will improve our understanding of an intervention promoting the use of HPV self-tests. These potential benefits of the study far outweigh its minimal risks.

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