NIH PRAGMATIC TRIALS COLLABORATORY

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NIH Collaboratory Ethics and Regulatory Core: Initial Consultation
Self-Testing for Cervical Cancer in Priority Populations (STEP-2)
February 21, 2025; 4:00-5:00 pm ET (via Zoom)

Attendees:

- Core, Coordinating Center, and NIH: Joe Ali (Johns Hopkins University), David Magnus (Stanford University), Kevin McBryde (National Center for Complementary and Integrative Health), Stephanie Morain (Johns Hopkins University), Pearl O'Rourke (retired), Caleigh Propes (Johns Hopkins University), Tammy Reece (Duke University), Damon Seils (Duke University), Jeremy Sugarman (Johns Hopkins University), Dave Wendler (NIH Clinical Center)
- Study team: Anna Edelmann (Kaiser Permanente Center for Health Research), John Lin (University of Washington), Jenny Maki (University of Washington), Jasmin Tiro (University of Chicago)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
Overview of the trial	Meeting attendees received the trial's project summary and data management and sharing plan with the agenda (see supplementary material attached). Pearl O'Rourke facilitated introductions, and Jeremy Sugarman welcomed the study team and described the purpose of the consultation. The STEP-2 team members present were Jasmin Tiro (principal investigator, University of Chicago, with Rachel Winer and Amanda Petrik [not present]), Anna Edelmann (project manager, Kaiser Permanente Center for Health Research), John Lin (lead project manager, University of Washington), and Jenny Maki (IRB reliance administrator, University of Washington). **Project overview**: Jasmin gave an overview of the project, which is supported by the National Cancer Institute through a UG3/UH3 award mechanism. The goal of STEP-2 is to test the comparative effectiveness of in-clinic distribution of human papillomavirus (HPV) self-sampling kits vs in-clinic plus mailed self-sampling kits or usual care, in order to improve cervical cancer screening rates. The project is currently in the UG3 planning phase. **Research team**: University of Washington, University of Chicago, Kaiser Permanente (Northwest) Center for Health Research, Kaiser Permanente Washington Health Research Institute.		

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	Healthcare system and Medicaid health plan partners: Virginia Garcia Memorial Health Center (Oregon), HealthPoint Community Health Center (Washington), CareOregon, Molina Healthcare, Community Health Plan of Washington. **NIH Institute Providing Support/Oversight**: National Cancer Institute (NCI). **Study design**: The study team plans to conduct a cluster randomized trial in federally qualified health centers (FQHCs) and Medicaid health plans in Oregon and Washington to evaluate the comparative effectiveness and cost-effectiveness of in-clinic distribution of HPV self-sampling kits and in-clinic plus mailed distribution of HPV self-sampling kits vs usual care in an attempt to improve rates of cervical cancer screening among eligible patients who are due or overdue for routine screening. In the 2-year UG3 planning phase, the study team is pilot testing the interventions in 2 FQHCs and 3 health plans. Enrollment in the 3-month pilot test will begin in August 2025. The study team has also conducted 2 Boot Camp Translation Sessions (1 in English, 1 in Spanish) with a total of 15 patient participants to develop patient-facing materials that motivate and instruct patients on how to use the HPV self-sampling kit. The study's stakeholder advisory board has met 3 times so far to provide feedback on 3 of the implementation strategies (clinic readiness tool, practice facilitation guide, and clinician and clinical staff webinars). In the UH3 implementation phase, the study team plans to conduct a cluster randomized trial in 42 FQHC clinics to evaluate the comparative effectiveness and cost-effectiveness of the interventions. Clinics will be randomly assigned to usual care, in-clinic distribution of HPV self-sampling kits, or in-clinic plus mailed distribution of HPV self-sampling kits. In the in-clinic distribution arm, clinics will offer self-sampling kits at both in-person and telehealth encounters. In the in-clinic plus mailed distribution arm, mailing of the kits will be administered by 3 Medicaid health plans. Jasmin highlighted an unanticipated challenge the study team has encountered in the mailed distribution arm: how to reach unestablished patients (that is, patients who are enrolled in Medicaid but have not yet had a clinic visit and do not have a medical record number).		

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	Outcomes: The primary outcome of the clinical trial is the proportion of eligible patients who complete screening. The primary comparisons will be between (1) usual care and in-clinic distribution among those who have an encounter (regardless of insurance type) and (2) in-clinic distribution and in-clinic plus mailed distribution among Medicaid enrollees. A cost-effectiveness analysis will compare in-clinic distribution vs usual care and in-clinic plus mail distribution vs in-clinic distribution alone. **Discussion**: David Magnus asked why the study team is using cluster randomization. Jasmin replied that randomization must be done at the clinic level, not the individual level, because of the risk of contamination. She added that the study team is considering how to address the potential for contamination across clinics within the same healthcare system. Jasmin and John Lin further explained that, akin to some quality improvement initiatives and implementation science, the study will test the impact of a suite of implementation strategies to aid clinics in integrating HPV self-sampling into their clinical workflow—a clinic readiness tool; a facilitation guide for practice facilitators selected by the clinic; patient-centered materials; and clinician and clinic staff webinars. The last implementation strategy is an implementation toolkit for mailed self-sampling kits, intended to assist health plans and clinics working together in mailing HPV self-sampling kits to Medicaid enrollees. The trial will not test the effectiveness of HPV self-sampling. For information and appropriate framing, Jeremy shared the following reference on the distinctions between research and quality improvement: • Finkelstein JA, Brickman AL, Capron A, et al. Oversight on the borderline: Quality improvement and pragmatic research. *Clin Trials*. 2015 Oct;12(5):457-66. doi: 10.1177/1740774515597682. PMID: 26374685; PMCID: PMC4699562. https://pubmed.ncbi.nlm.nih.gov/26374685/ Dave Wendler asked about reasons for the low baseline cervical cancer screening rates. Jasmin replied that screening was limited to clinician-collected modalities prior to Food and Drug Administration (FDA) approval of HPV self-sampling. Most FQHCs used HPV/Pap cotesting rather than primary HPV testing, due to lab preference. Clinician-collected screening tends to only be offered during wellness visits because		

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	of the required clinic setup; it cannot be easily offered during urgent care or specialty care visits, even though a patient may be due for screening, because it slows down dwell times. (Dwell time can be calculated as the length of visit from check-in to discharge [or a subcomponent of the visit]. FQHCs often have target metrics to decrease dwell times, and adding an unplanned pelvic exam with HPV/Pap test often increases the dwell time because of room setup.) FQHC clinic populations tend to use healthcare services urgently or access care for chronic conditions rather than attend wellness visits. In the STEP-2 trial, clinicians can offer self-collection at any visit. Thus, the study team anticipates greater reach and higher rates of screening. Jeremy asked whether there is equipoise between the usual care arm and the intervention arms. Jasmin responded that any clinic today could add HPV self-testing to its clinic processes, as the kits are FDA-approved, and the STEP-2 trial will not prohibit clinics from doing that. There are many reasons clinics are not adding the modality, largely because of lack of laboratory capacity. Also, a new CPT code and claims code have led to an increase in the price of the tests. The STEP-2 trial will test implementation strategies to help clinics understand how to integrate the self-sampling kits into clinic processes and how their workflows will change. Pearl asked whether, in the in-clinic distribution arm, the study team will stratify patients by whether they pick up the self-sampling kit during a visit or must come to the clinic to pick up the kit after a telehealth visit. Jasmin responded that they are not currently planning to stratify patients in this way but would be interested in adding this as a secondary analysis. Pearl asked whether patient education materials are specific to the self-sampling kit itself and/or promote the importance of HPV testing. She asked whether patients in the usual care arm would receive any materials. Jasmin responded that currently the patient-facing materials developed through the Bootcamp Translation process will be focused on how to use the HPV self-sampling kit. While the study team did not plan to develop and offer any specific patient educational materials promoting cervical cancer screening to clinics assigned to the usual care arm, they are considering referring clinics to materials commonly used across the country. She noted that clinics can change their “usual practice” at any time during the trial.		

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	Pearl asked what happens with patients who are not Medicaid beneficiaries but are in the in-clinic plus mailed distribution arm (considering that the mailed distribution will be administered by the Medicaid health plans). Jasmin responded that patients not covered by Medicaid in those clinics will not receive a mailed kit; this is pragmatic because some clinics do not have financial resources (postage or staff time) to mail kits to uninsured patients. The primary comparison for the in-clinic distribution arm vs the in-clinic plus mailed distribution arm will be cervical cancer screening completion among Medicaid enrollees only. However, all patients assigned to these 2 arms who have an encounter (in person or telehealth) may be offered an HPV self-sampling kit by a clinician. Stephanie Morain asked whether the study team is concerned about self-sampling kits being lost in the mail. Jasmin responded that they will address this concern somewhat by mailing an introductory letter to patients in the in-clinic plus mailed distribution arm, which will both allow the patient to opt out of the study and help the study team determine if mail is deliverable at the patient's address. Pearl asked whether the study team is concerned about patients who obtain a self-sampling kit in person not being able to return the kit by mail. Jasmin Tiro responded that, in general, the clinics will encourage use of the kits during the clinic visit; patients may take it home and bring back later if they choose; clinics do not have the resources to pay for postage paid return. Pearl asked about FDA approval for the self-sampling kits. John replied that the kits are FDA-approved for in-clinic distribution but not mailed distribution. Therefore, the study team will help clinics establish a contract with the University of Washington reference laboratory to access the lab's existing Clinical Laboratory Improvement Amendments (CLIA) lab-developed test (LDT) mailed kit offering. Jasmin and John explained that the FDA allows use of the CLIA LDT approval mechanism as an alternate regulatory pathway for clinical use of non–FDA approved tests. The study team will send more information to the NIH Collaboratory Coordinating Center about its use of the CLIA LDT approval pathway in this study and a previous study. The Core will review these materials to better understand the study team's planned approach and will follow up as needed.	Send information about the CLIA LDT approval pathway to be used in this study to Tammy Reece at the Coordinating Center Review details about the CLIA LDT approval pathway	**Study team** **Core**

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Status of IRB approval	The study team received IRB approval for the pilot test and the qualitative work described above as part of the UG3 planning phase. Approval of the clinical trial in the UH3 implementation phase will be contingent on the results of the pilot study. The University of Washington is the single IRB of record.		
Risk (Does the project meet regulatory criteria for being considered minimal risk?); and consent (planned processes for relevant subjects)	The pilot study was determined to meet the criteria for being considered minimal risk, and the study team received a waiver of consent for the distribution of the HPV self-sampling kits. Consent will be obtained for the patient interviews. For patients assigned to the in-clinic distribution arm or the in-clinic plus mail arm, patients will be invited by mail to participate in the interview, then they will be contacted by phone to assess their interest and offered an opportunity to opt out. Interviews will be conducted over the phone either immediately after consent or at a time convenient for the patient. Physicians will also be treated as consented subjects for the physician survey component of the study.		
Privacy (including HIPAA)	The study received a waiver of HIPAA authorization. The mailed self-sampling kits will not have information on the box stating that they contain an HPV test. The study team has advised the health plans to use nondescript packaging. All study data will go to a single site (Kaiser Permanente Northwest), and all mailings will be sent from the health plans. Patients may return mailed kits by using postage paid return to the clinics or dropping off at the clinic (if they do not trust the mail). Thus, the study team will not collect addresses, subscriber numbers, or other protected information. There will be a certificate of confidentiality for the study.		
Monitoring and oversight	The study will not use a DSMB but instead will use a data and safety monitoring plan. There will be yearly reports on data and safety monitoring, including overall protocol	Double-check with NCI project officer	**Study team**

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	adherence, protocol adherence to the data management plan (extraction/collection and analysis), informed consent protocol adherence, adverse events and unanticipated problem review/reporting, and maintenance of study subject privacy and confidentiality. Jeremy encouraged the study team to double-check with the NCI project officer that their approach is consistent with NCI's expectations for data monitoring. Jasmin noted this method of monitoring via a data safety monitoring plan was used for the HOME and STEP pragmatic trials that were funded by NCI. John further noted that there is precedent for NCI approval of a data safety monitoring plan instead of a DSMB for minimal risk trials, including the prior HOME and STEP trials, and also the University of Minnesota Isbaar HPV self-collect project in FQHC clinics. Jasmin will check with Cindy Vinson, the project officer, about monitoring requirements.	that the approach to data monitoring meets NCI requirements	
Issues beyond this project (regulatory and ethics concerns raised by the project, if any)	Jeremy asked whether anything in the project will be used for any other indication. John replied that the study team will not provide any data to any FDA applications or receive HPV self-sampling kits from manufacturers.		

PROJECT SUMMARY/ABSTRACT

The 29.3 million patients receiving care in US Federally Qualified Health Centers (FQHCs) have much lower cervical cancer screening rates than national averages: Only 53% of eligible patients were up-to-date in 2021 and the COVID-19 pandemic exacerbated these disparities. Self-sampling for human papillomavirus (HPV) is an evidence-based cervical cancer screening method with high potential to reduce screening barriers. Self-sampling kits can be distributed at clinics or mailed to patients' homes. Despite widespread international adoption, HPV self-sampling is nascent in the US. Little data is available to inform implementing this preventive service in low-resource settings such as FQHCs. Our two-phase pilot and pragmatic trial will adapt and evaluate two programs to integrate HPV self-sampling into FQHCs. Our trial accounts for the context, capacity and resources of FQHCs, and leverages FQHC-Medicaid partnerships to promote this preventive care service. Phase 1 will be a milestone-driven planning phase. We will use community-engaged research and interest-holder input to adapt and pilot-test 2 multilevel interventions in 2 FQHCs for distributing HPV self-sampling kits: in clinic distribution and in clinic plus mailed distribution. Phase 2 will be a cluster-randomized pragmatic trial in 42 Oregon and Washington FQHC clinics to evaluate the comparative effectiveness and cost-effectiveness of the interventions. Clinics will be randomized to Usual Care (*UC*), in-clinic distribution (*Clinic Only*), or in-clinic plus mailed distribution (*Clinic + Mail*). For in-clinic distribution, providers will offer self-sampling at in-person or telehealth encounters. The mailed component will be administered by Medicaid health plans. The primary outcome is the proportion of eligible patients (30-64 years, due/overdue for routine screening) who complete screening. Two primary comparisons are (1) *UC* vs *Clinic Only* and (2) *Clinic Only* vs *Clinic + Mail*. To minimize bias, each comparison includes distinct but overlapping patient populations. Comparison 1a includes all patients (Medicaid and non-Medicaid) with a clinic encounter during the 12-month study period. Comparison 1b is restricted to Medicaid patients who are enrolled with the clinic, but does not require a clinic encounter during the 12-month study period. Cost-effectiveness will compare the *Clinic Only* HPV self-sampling intervention relative to *UC*, and *Clinic + Mail* relative to *Clinic Only.* We will use the RE-AIM framework and PRISM to evaluate the implementation strategies through mixed methods. Our pragmatic trial will be the first in the US to determine the effectiveness and cost-effectiveness of HPV self-sampling for increasing cervical cancer screening in FQHC settings. Results from our comparisons and evaluation of implementation strategies will inform broad-scale implementation of HPV self-sampling across FQHCs and other safety-net clinics in the US to reduce cervical cancer screening disparities.

DATA MANAGEMENT AND SHARING PLAN

Element 1: Data Type

A. Types and amount of scientific data expected to be generated in the project:

1. Type of Scientific Data. The scientific data to be generated and/or collected will include clinical data on patients who are ages 30–64 years and patients at Federally Qualified Health Centers (FQHCs), as well as qualitative data from patients, clinicians, and health plan staff, and survey data from clinicians.
2. Estimated Amount of Scientific Data. We estimate data will include clinical data from patients who receive care at FQHCs (Pilot n=600, Full Trial n=15,525); Boot Camp Translation (n=22) and qualitative data from patients (n=50), clinicians (n=72), health plan staff (n=8) and survey data from clinicians (n=300).
3. Scientific Data Source. The scientific data generated under this project will be collected/generated from claims and clinical datasets from the FQHCs, which will be obtained under a waiver of informed consent. We will also collect qualitative interview and survey data. Interview and survey data will be obtained with informed consent.
4. Scientific Data Format. Data will be individual level limited data sets transferred through a secure file transfer system.

B. Scientific data that will be preserved and shared, and the rationale for doing so:

1. Scientific Data to be Shared: UW anticipates the preservation and sharing of the following scientific data: Transcribed qualitative interview data, survey data, and deidentified or limited clinical data. Data will be stored within a secure computing environment. Identifiable individual level data will not be shared. All direct participant identifiers (e.g., names, clinic names, addresses) will be removed and maintained in a secure file. All other scientific data (interview data, survey data, and clinical data) will be both preserved and shared with unique identifiers. Participant identifiers will not be shared.
2. Rationale: The scientific data anticipated to be preserved and shared under this project represents the maximum level of sharing appropriate, based on the following factors:
   Waiver of Informed Consent*: A waiver of informed consent will be requested for this project for clinical data. Any restriction imposed by the IRB will be reflected or updated in this document upon approval.*
   Informed Consent*: Informed consent is anticipated to be required for participation in survey and qualitative project components.*
   Applicable Laws*: The data being shared under this plan is covered under HIPAA. Other laws may also apply and restrict UW's ability to share certain scientific data.*
   Participant Privacy and Safety Concerns: *The following privacy and safety concerns may restrict UW's ability to share certain scientific data: content in the qualitative interviews that identifies patients, clinicians or health plan staff, and puts them at risk for re-identification or suffering harm.*
   Restrictions imposed by existing or anticipated agreements: *UW anticipates the following agreement(s), which may restrict UW's ability to share certain scientific data: agreements with collaborators or external data sources which may restrict disclosure of data by UW.*

C. Metadata, other relevant data, and associated documentation:

Documentation to be made publicly available to the research community includes data dictionaries, final versions of interview guides, survey instruments, and study-level metadata. Each variable in the data dictionary will include a brief description of the item, variable label, value labels, and standard codes for missing values. We will also include qualitative interview guides and codebooks describing themes or other codes that were used for analysis.

Element 2: Related Tools, Software and/or Code

Quantitative scientific data will be processed and analyzed with SAS, STATA or R; and codes for analysis in papers will be shared. We will remove local path names and macros for local computing.

Element 3: Standards

To facilitate data use, the study will identify a single data safety monitoring plan (DSMP) Manager, who will use standard processing and documentation protocols for data formats and dictionaries as well as for variable names, descriptions, and labels. Metadata will include, at minimum, mandatory properties recommended by the latest DataCite metadata schema. Data dictionaries will be provided in text (.csv) format. Study-level metadata will also be provided in text (.txt) format. Survey questionnaires, interview guides, and the qualitative codebook will be provided in portable document format (PDF).

Element 4: Data Preservation, Access, and Associated Timelines

A. Repository where scientific data and metadata will be archived:

The scientific data anticipated to be shared under this project, as described in Element 1 of this Plan, will be deposited and maintained at the UW Data Repository (Dryad open-access). Public-use and restricted-access study data and associated documentation will be made available to the research community free of charge.

B. How scientific data will be findable and identifiable:

The scientific data anticipated to be shared under this project, as described in Element 1 of this Plan, will be assigned a persistent unique identifier when submitted to the UW Data Repository. Instructions for requesting data access will be provided in published articles and presentations.

C. When and how long the scientific data will be made available:

The scientific data anticipated to be shared under this project, as described in Element 1 of this Plan, will be deposited in the repository specified above as soon as possible, but no later than the time of associated manuscript publication or completion of the funded project period for the parent award, whichever is earlier. Data will be made available for 5 years.

Element 5: Access, Distribution, or Reuse Considerations

A. Factors affecting subsequent access, distribution, or reuse of scientific data:

UW is committed to providing the maximum level of reuse appropriate for the scientific data being preserved and shared under this project. The limitations affecting subsequent access, distribution, or reuse of scientific data for this project are as follows:

Informed Consent: The informed consent for this project is anticipated to include describing future uses of the data through a deidentified data repository.

Applicable Laws: No laws are expected to restrict subsequent access, distribution, or reuse of scientific data being preserved and shared under this project.

Participant Privacy and Safety Concerns: No privacy and safety concerns are expected to restrict subsequent access, distribution, or reuse of scientific data being preserved and shared under this project.

Restrictions imposed by existing or anticipated agreements: UW does not anticipate entering into any agreements which may restrict access, distribution, or reuse of scientific data being preserved and shared under this project.

B. Whether access to scientific data will be controlled:

The repository described in Element 4 of this Plan has been **established specifically for projects conducted at UW**. Access to qualified researchers will be provided through the following UW Data Repository policies and procedures:

1. Public Use Data: All deidentified study data that are not designated as restricted use will be made available as public use data to the research community via the UW Data Repository. Users of the public use data must register with RDAC and agree to the Terms of Use, which are designed to protect study participants by limiting data use to scientific research and aggregate statistical reporting, prohibiting attempts to identify study participants, and requiring immediate reporting of any disclosure of study participant identity. Data users also agree not to share or redistribute any data downloads.
2. Restricted Access Data: Data that are determined to be potentially identifying through indirect or deductive disclosure will be provided under restricted access and under a data contract to users who demonstrate a valid research need and meet conditions of use. Access to restricted study data is available via an application to the UW Data Repository.

C. Protections for privacy, rights, and confidentiality of human research participants:

The scientific data derived from humans under this project and shared as described in this Plan will be protected through processes developed at UW. Once the data collection for this study has concluded, all direct respondent identifiers (e.g., names and addresses) will be removed and maintained in a separate control file.

Element 6: Oversight of Data Management and Sharing:

Monitoring of and compliance with this Data Management and Sharing Plan will be the responsibility of the project's Principal Investigators, Dr. Winer, Dr. Petrik, and Dr. Tiro. The plan will be implemented and managed by the project staff working under the direction of Dr. Winer. Dr. Winer will meet with the project director and research staff weekly. They will also ensure that the research datasets are uploaded to the UW Data Repository as agreed upon in this Data Management and Sharing Plan.