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)

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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 (co–principal investigator, University of Chicago; the other co–principal investigators, Rachel Winer and Amanda Petrik, were 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 vs usual care, in order to improve cervical cancer screening rates. The project is currently in the UG3 planning phase.	Based on findings from the pilot study and reductions in the project's budget, there will not be outreach to unestablished patients. In addition, the baseline survey of clinicians and staff about knowledge, attitudes, and behaviors about cervical cancer screening and HPV self-testing will not be done, but the survey may still be deployed after the 12-month measurement period.

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	Research team: University of Washington, University of Chicago, Kaiser Permanente (Northwest) Center for Health Research, Kaiser Permanente Washington Health Research Institute. **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.	The 42 clinics are part of 3 healthcare systems that contract with 2 Medicaid health plans. Based on this structure, the study team is deploying some aspects of the intervention at the system level. For example, intake and processing of the mailed HPV self-collection kits is being handled by centralized staff, with clinics handling

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	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). **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/	the reporting of test results and the management of abnormal test results. The study team is adjusting their measurement of natural diffusion of HPV self-collection in usual care clinics. Each clinic assigned to usual care will receive a baseline survey about their screening practices at the same time the intervention clinics begin practice facilitation. The intervention clinics will be able to determine workflow for offering screening and HPV self-collection to patients attending telehealth visits. This workflow will be decided on during practice facilitation. The study team is not concerned about the possibility of contamination across clinics in the same healthcare system but is concerned about use of HPV self-sampling within clinics prior to the measurement period. Therefore, the time between training clinic staff and launching the implementation strategies will be shortened by 2 months.

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	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 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	

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	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. 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	The pilot study found that clinics using Breast and Cervical Cancer Services funds for the uninsured wanted that paperwork integrated into the HPV self-collection workflow. The study team now stresses the importance of identifying patients who are due for screening before the appointment and including a flag to the front desk staff so they can complete the paperwork before the patient is placed in a room. Following the February 2025 consultation, the Coordinating Center requested more information from the study team about how the CLIA LDT

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	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.	approval pathway was used in the STEP trial (the team's previous study). In response, the study team provided the following documents from the STEP trial: (1) the presubmission request to the FDA; (2) the FDA approval letter; (3) the protocol design paper (PMID: 36241145); and (4) the outcomes paper (PMID: 38015219). In a follow-up, the Core representatives recommended that the test kit be reviewed under FDA regulations and that the IRB make a determination of significant or nonsignificant risk. Subsequently, the Core representatives noted that a federal district court had vacated the FDA final rule on the CLIA LDT pathway and that there is significant uncertainty about the regulation, but that they continue to believe the best approach would be to review the test kit under FDA regulations and have it assessed for significant or nonsignificant risk. After sharing the Core's recommendation with the IRB, the IRB stood by its determination and provided a written explanation of its interpretation of FDA regulations in its consideration of the STEP-2 trial. The Core had no further questions and believes that the IRB's decision is

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		defensible, given the recent vacatur of the FDA rule regarding laboratory-developed tests. FDA approval of HPV assays continues to evolve. The Teal Wand (Teal Health) and the BD Onclarity HPV Assay (Becton, Dickinson and Company) have been approved for mailed distribution (that is, the patient can use the test unsupervised by clinic staff). In the 3 participating FQHC systems, none of the contracted labs (Quest, Lab Corp) offer the BD Onclarity HPV Assay, so the study team will continue to process the mailed kit through the University of Washington lab. In the pilot, the University of Washington lab results were faxed to the clinic. Medical assistants had to check for these results and upload them into the patient's electronic health record (EHR). This was cumbersome. The study team is working with the health IT team of the FQHC system to program result reporting directly into the EHR.
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.	IRB approval for all UH3 activities has been obtained.

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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.	The UH3 phase received similar determinations and approvals as the UG3 phase. Namely, the UH3 activities were determined to meet the criteria for being considered minimal risk; a waiver of consent for the distribution of HPV self-sampling kits was received; a waiver of documentation of consent for the patient interviews was received and oral consent will be obtained; a waiver of documentation of consent for the physician and clinical staff surveys was received and consent will be implied by the respondent clicking "next" or completing the survey.
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 adherence, protocol adherence to the data management plan (extraction/collection	There have been no changes to the plan for monitoring and oversight.

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	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.	The administrative program director at NCI confirmed that the data and safety monitoring plan described in the funded grant is consistent with NCI's expectations for data monitoring.
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.	
Additional follow-up information		None.