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Improving the promise of embedded pragmatic trials: Surmountable barriers encountered in an evaluation of home-based HPV self-sampling to increase cervical cancer screening in overdue women

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ABSTRACT

Despite increased attention on how to conduct pragmatic trials and their importance, there remains an under-appreciation for the reality of what they take to design, compete and secure funding and execute. Many barriers are surmountable through increased exposure to experiences from completed trials. This report summarizes our experience in designing, securing funding and implementing the Home-Based Options to Make screening Easier (HOME) pragmatic trial, which was designed to evaluate home human papillomavirus testing for cervical cancer screening in underscreened women (women who had not received a cervical cancer screening test in ≥3.5 years). This report highlights factors at the level of research teams, organizations seeking to conduct embedded research, reviewers and funding agencies that challenge pragmatic trial design and execution. There is an urgent need to train on peer-reviewers how to evaluate embedded trial grant proposals, for agencies to pursue more rapid and innovative funding strategies, and to consider strategies for reviewers and funders to evaluate stakeholder buy-in (beyond letters of support). These factors together are needed to realize the promise of pragmatic trials to more efficiently and effectively generate critical data that inform changes in health care delivery and benefit patients.

The promise of pragmatic trials that include head-to-head comparisons of interventions in health systems with patients and providers who represent the end users of the evidence is enormous [1]. Timely, well-designed, patient- and stakeholder-informed studies embedded in clinical care are needed to speed research translation into practice adoption. Despite increased attention [1–6], there remains an under-appreciation for the reality of what pragmatic trials require to design, compete and secure funding and execute. We believe these trials are critical for achieving high-quality healthcare [7,8] and that many barriers are surmountable through increased exposure to experiences from completed trials. This report highlights factors at the level of research teams, reviewers and funding agencies that challenge pragmatic trial design and execution.

1. Background

To frame our experience, some content background is needed. Papanicolaou (Pap) screening has reduced cervical cancer incidence and mortality by > 50% over the last 40 years [9]. However, U.S. cervical cancer screening adherence has declined from a high of 82% in 2003 to 74% in 2016 [10,11]. Several European population-based trials have demonstrated mailing human papillomavirus (HPV) self-sampling kits improves screening participation in hard-to-reach women [12–14]. Home-based HPV screening with in-clinic follow-up of HPV-positive women can address important screening barriers (e.g., logistical, financial, geographic and personal [15–20]) and could eliminate clinic visits for most women, since nearly 90% will be HPV-negative and not require additional testing.

Briefly, we conducted the Home-Based Options to Make screening Easier (HOME) pragmatic trial to evaluate home-HPV testing for cervical cancer screening in women at Kaiser Permanente Washington (KPWA)aged 30–65 who were underscreened (had not received a cervical cancer screening test in ≥3.5 years) (ClinicalTrials.gov, NCT02005510) [21]. When the HOME trial was designed, primary HPV screening (via clinician- or self-collection) was not an accepted cervical

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cancer screening approach, and at the time of this writing, did not count towards Healthcare Effectiveness Data and Information Set (HEDIS) screening quality metrics [10].

2. Embedding trials into clinical workflows

Embedded pragmatic trials are integrated into healthcare system workflows. This design requires multi-level stakeholder buy-in from clinical and operational champions, including negotiating study populations, recruitment plan, and clinical workflow protocols. HOME stakeholder negotiations took ~18 months before grant submission and required an embedded investigator with long-standing collaborative relationships to negotiate with clinical and operational leaders to evaluate an innovative, not yet approved, alternative to Pap screening, and agree on the target population, recruitment timing and integration.

In our optimal pragmatic trial design, we wanted to include all age-eligible women to compare the effectiveness of HPV self-sampling versus usual care reminders and outreach for Pap screening on two outcomes—screening uptake and early detection/treatment of cervical neoplasia (Table 1). Pap screening is a HEDIS quality measure [10], which translates to market reputation (based on quality metrics) and financial incentives for health plans. Therefore, negotiations with stakeholders led to limiting our study population to underscreened women. Since 25% of U.S. age-eligible women are underscreened [10] and > 50% of cervical cancers are diagnosed in underscreened women [22–24], identifying strategies for engaging this high-risk population is a priority; however, these women are hard-to-reach [22–24] and trial results may not generalize to screening-adherent women. Regardless of generalizability, focusing on this hard-to-reach population was viewed as feasible, patient-centered, and a high priority by the healthcare system.

3. Negotiating study population

We also had to negotiate and alter our pragmatic trial design around recruitment timing. We wanted to mailing kits when women were reminded they were overdue. However, KPWA provides annual preventive services outreach around a woman's birthday noting all upcoming recommended preventive services and their due dates; this outreach is effective in activating overdue women [25,26]. To ensure we did not interfere with this overdue reminder, we negotiated to wait 5 months following the birthday letter before mailing kits. This timing of recruitment further limited our sample and generalizability to more screening-elusive women and those with longer-term health plan enrollment.

4. Documenting delivery system support for the trial

After negotiating trial design with the delivery system, we had to compete for extramural funding and convince peer reviewers that our embedded design was sound and feasible. Throughout stakeholder negotiations, we worked with clinical and information technology (IT) partners to ensure seamless integration with our laboratory, patients, providers and health plan. We designed our home HPV mailing strategies to directly mirror KPWAs other preventive clinical care strategies. We carefully considered how to best notify providers and patients about test findings, requiring significant IT investment to send notifications via electronic health records and patient web portals. Clinical stakeholders and trialists developed a plan to train all clinical teams (clinician, nurse, lab staff) on each team member's role and responsibility for clinical care activity after a positive home HPV result. Although this plan was detailed in the grant application, including accompanying letters of support, some-reviewers criticized our approach, e.g. “I have serious and grave concerns about the trial design involving an unknown number of clinicians having to follow-up with patients in an experimental trial for a not currently approved screening test … You do both the patients and the clinicians a disservice in expecting clinicians to deal with patient questions and concerns-there may also be medico-legal considerations.” It is unclear what and where else we could have assured reviewers that all key stakeholders co-designed and bought-in on all study aspects.

Additionally, reviewers were concerned about obtaining a waiver of consent for > 18,000 women to identify and randomize eligible women and to collect individual level data on responders and non-responders. Without one, participation bias could have compromised trial evaluation. This proved more challenging and time consuming than anticipated despite extensive discussions with our IRB before grant submission. We were required to include an information sheet for intervention-arm women explaining we were testing a screening innovation and recommended all women still receive a Pap test regardless of whether they completed the home-test, limiting our ability to evaluate what home-testing uptake might have been without this recommendation. There were additional negotiations with IRB on data access for outcomes in women who actively refused vs. Passively (did not return the kit, but no active refusal via phone/mail) refused the intervention [27,28].

5. Implications of lengthy timeline from submission to funding

The timeline from grant submission to funding is lengthy, which has significant implications for embedded research due to the required strong, continued engagement of clinical and operational champions. Like many others, we experienced > 18 months between submission and funding receipt, during which time we experienced changes in clinical champions (left the organization) and HPV-testing assays used in our cytopathology laboratory. Laboratory changes necessitated additional alterations to patient triage algorithms and a pre-trial validation study comparing self-vs. Provider-collected HPV samples; neither were planned nor budgeted within the grant and delayed our trial launch. Fortunately, cervical cancer underscreening remained a

Table 1
Comparison of pragmatic design vs. desired design for the HOME pragmatic trial testing home HPV testing vs. in-clinic Pap screening.

	Pragmatic design	Ideal design
Population	Women overdue for cervical cancer screening	All women due for cervical cancer screening
Intervention & comparators	Mailed home HPV kit with instructions and cover letter from clinical champions (indicating the need to receive a routine Pap test, even if the home HPV test result is negative) vs. standard of care. Timing: 5 months after annual preventive services reminder letter mailed indicating women were overdue for cervical cancer screening.	Mailed home HPV kit with instructions and cover letter from personal primary care provider (indicating that women with negative home HPV test results do not need to come into the clinic for additional screening) vs. standard of care. Timing: Proximal to due date, or at time of annual preventive services reminder letter for overdue women.
Outcomes	• Cervical intraepithelial neoplasia grade 2 or higher detection and treatment • Women's experience	
Generalizability	Limited to overdue women who persisted being overdue for ≥5 months following annual reminder letter	All women due for cervical cancer screening timed to their due date

priority; thus, we were able to engage new clinical champions to support our funded trial and address operational obstacles that arose during implementation. Contingency planning is needed, as clinical champion and technology changes are constant issues. Additionally, we hope funding agencies will continue to pursue innovative strategies to improve time from submission to funding and to encourage applications that allow rapid learning and modifications based on early findings [29,30].

6. Pragmatic design impacts generalizability of findings, which may not keep up with evolving evidence

In 2018, as our trial was ending, the United States Preventive Services Task Force updated cervical cancer screening recommendation to include primary HPV testing alone in women ages 30–65 years, allowing the possibility of self-collection [31]. Our trial results are being adjudicated and will answer questions about home testing effectiveness in a very hard-to-reach population of persistently overdue women and who were recommended to undergo Pap screening regardless of their decision to complete a home-HPV test. However, our results do not provide information on screening uptake for the broader population of women now eligible for primary HPV testing with the new guidelines.

7. Summary

Embedded pragmatic trials are challenging to design, obtain multi-stakeholder buy in, and embed within standard workflows of delivery systems; however, they are well-worth the effort. Clinical champion co-investigators are needed with real effort to ensure trial compatibility with clinical guidelines, plan for contingencies, and facilitate test result reporting to providers via electronic health records and to patients via web portals. There is an urgent need to train peer-reviewers how to evaluate these proposals, for agencies to pursue more rapid and innovative funding strategies, and to consider strategies for reviewers and funders to evaluate stakeholder buy-in (beyond letters of support). These factors together are needed to realize the promise of pragmatic trials to more efficiently and effectively generate critical data that inform changes in health care delivery and benefit patients.

Declaration of interest

None.

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