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Rationale and design of the HOME trial: A pragmatic randomized controlled trial of home-based human papillomavirus (HPV) self-sampling for increasing cervical cancer screening uptake and effectiveness in a U.S. healthcare system

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ABSTRACT

Women who delay or do not attend Papanicolaou (Pap) screening are at increased risk for cervical cancer. Trials in countries with organized screening programs have demonstrated that mailing high-risk (hr) human papillomavirus (HPV) self-sampling kits to under-screened women increases participation, but U.S. data are lacking. HOME is a pragmatic randomized controlled trial set within a U.S. integrated healthcare delivery system to compare two programmatic approaches for increasing cervical cancer screening uptake and effectiveness in under-screened women (≥ 3.4 years since last Pap) aged 30–64 years: 1) usual care (annual patient reminders and ad hoc outreach by clinics) and 2) usual care plus mailed hrHPV self-screening kits. Over 2.5 years, eligible women were identified through electronic medical record (EMR) data and randomized 1:1 to the intervention or control arm. Women in the intervention arm were mailed kits with pre-paid envelopes to return samples to the central clinical laboratory for hrHPV testing. Results were documented in the EMR to notify women's primary care providers of appropriate follow-up. Primary outcomes are detection and treatment of cervical neoplasia. Secondary outcomes are cervical cancer screening uptake, abnormal screening results, and women's experiences and attitudes towards hrHPV self-sampling and follow-up of hrHPV-positive results (measured through surveys and interviews). The trial was designed to evaluate whether a programmatic strategy incorporating hrHPV self-sampling is effective in promoting adherence to the complete screening process (including follow-up of abnormal screening results and treatment). The objective of this report is to describe the rationale and design of this pragmatic trial.

1. Introduction

Although widespread adoption of routine Papanicolaou (Pap) screening has reduced cervical cancer incidence and mortality in the U.S. by > 50% over the past forty years [1], 20%–30% of U.S. women attend screening less frequently than recommended by current guidelines or not at all [2–4]. Of the 12,000 cervical cancers diagnosed annually in the U.S. [5], over half are in unscreened or under-screened women [6–8]. To increase timely participation in routine screening, innovative strategies targeting hard-to-reach women are needed.

Abbreviations: ASCCP, American Society for Colposcopy and Cervical Pathology; ACS, American Cancer Society; AE, adverse event; AGS, atypical glandular cells; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells, cannot rule out a high-grade lesion; ASC-US, atypical squamous cells of undetermined significance; CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2+, cervical intraepithelial neoplasia grade 2 or higher; CIS, carcinoma in situ; FDA, Food and Drug Administration; HEDIS, Healthcare Effectiveness Data and Information Set; HIPAA, Health Insurance Portability and Accountability Act; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial lesion; PCP, primary care provider; RCT, randomized controlled trial; UW, University of Washington

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Strategies that move screening out of clinical settings could effectively address common barriers related to logistics (e.g. inconvenience, difficulty finding childcare or taking time off work, lack of transportation, or not living in close proximity to a clinic) or negative emotions (e.g., fear or embarrassment related to pelvic exams or negative experiences with medical care) [8–13]. Internationally, there is growing interest in a primary screening strategy of home-based self-sampling for high-risk (hr) human papillomavirus (HPV) – the etiologic agent of cervical cancer – to increase screening participation. By triaging only women with hrHPV-positive results to follow-up, the need for in-clinic screening could be eliminated for a majority of women. Studies across varying populations consistently demonstrate that hrHPV self-sampling is feasible and acceptable to women [14,15] and has comparable sensitivity to clinician-collected samples for detecting hrHPV infections and cervical pre-cancers [14,16–18]. Furthermore, population-based randomized controlled trials (RCTs) in countries with organized screening programs have demonstrated that mailing hrHPV self-sampling kits to hard-to-reach women increases screening participation compared to traditional invitations to attend clinic-based screening [19–30]. Importantly, women with hrHPV positive results were highly compliant with attending diagnostic follow-up [19,20,25,26,28–32], yielding increased detection of cervical pre-cancers [19,20,30]. Several of these countries, including the Netherlands and Australia, have subsequently implemented or plan to implement home-based hrHPV self-screening as an option for overdue women as part of their national cervical cancer screening programs [33].

The 2012 U.S. consensus guidelines recommend Pap and hrHPV co-testing as the preferred strategy in women aged 30 to 65 years [34]; in 2015, the American Society for Colposcopy and Cervical Pathology (ASCCP) and American Cancer Society (ACS) released interim guidelines endorsing clinician-collected primary hrHPV screening as an alternative to co-testing or Pap alone [35]. Importantly, however, Healthcare Effectiveness Data and Information Set (HEDIS) only counts completed Pap test (with or without HPV co-testing) towards the quality outcome. Consequently, evaluating cervical cancer screening strategies that do not count towards quality measures for providers and health plans is challenging. However, with the potential of expanding hrHPV testing in clinical practice as a primary screening strategy, future U.S. screening strategies that incorporate *home-based self-sampling* for hrHPV testing are conceivable. U.S.-based data are needed to evaluate whether strategies incorporating home-based self-sampling for hrHPV could effectively increase screening participation and compliance in hard-to-reach women, and enhance detection and treatment of cervical pre-cancers. To this end, we designed a pragmatic RCT within a U.S. healthcare delivery system to compare two programmatic approaches for increasing cervical cancer screening uptake and effectiveness in under-screened women: 1) usual care (annual patient reminders and ad hoc outreach by clinics) and 2) usual care plus mailed hrHPV self-screening kits.

2. Methods

2.1. Trial design overview

The HOME (**H**ome-based **O**ptions to **M**ake cervical cancer screening **E**asy) trial is a pragmatic, parallel, single-blind, randomized controlled trial. The objective is to compare two programmatic strategies for improving uptake and effectiveness of cervical cancer screening in 30 to 64 year old women who are overdue for routine Pap screening, defined as not having had a Pap test within ≥ 3.4 years. The two strategies are usual care alone (control arm) versus usual care plus a mailed hrHPV self-sampling kit (intervention arm). The trial is fully embedded within the healthcare delivery system and designed to evaluate whether the intervention arm effectively promotes adherence to the complete screening process (screening, diagnostic follow-up, and treatment, if necessary). The trial design is summarized in Fig. 1.

The primary aims are to compare proportions of cervical pre-cancers detected and treated between arms. The secondary aims are to compare the following between arms: 1) cervical cancer screening uptake; 2) predictors of screening uptake; 3) proportions of abnormal screening tests; and 4) positive predictive value (PPV) of abnormal screening tests to detect pre-cancer. Additional secondary aims are to identify women's experiences and attitudes associated with using hrHPV self-screening kits and adhering to follow-up of hrHPV-positive test results through surveys and in-depth interviews in a subset of intervention-arm women. Compared to usual care alone, we hypothesized that mailing hrHPV self-sampling kits to underscreened women would increase detection and treatment of cervical pre-cancers and improve screening uptake among underscreened women.

2.2. Protocol approvals and registration

The trial was approved by the Institutional Review Boards of the University of Washington (UW) and Kaiser Permanente Washington (formerly Group Health), and is registered at ClinicalTrials.gov (NCT02005510). At the request of the Kaiser Permanente Washington Institutional Review Board, the investigators requested a risk determination from the U.S. Food and Drug Administration (FDA), which determined the trial to be a nonsignificant risk device study.

2.3. Study setting

The study is set within Kaiser Permanente Washington, an integrated mixed model health care delivery system providing health care or health insurance to > 650,000 individuals in Washington State. Throughout the study, Kaiser Permanente Washington's cervical cancer screening guidelines have followed the 2012 U.S. Preventive Services Task Force guidelines [36]. Routine Pap screening is recommended every three years for women 21 to 64 years of age. Pap/hrHPV co-testing was added as an optional strategy for women ≥ 30 years of age in August 2012, but was used infrequently before August 2013. Kaiser Permanente uses patient-, provider-, and systems-level services to promote screening adherence, including an annual “birthday letter” with Pap screening reminder if due [37]. Women who have a record of hysterectomy or have opted out of cervical cancer screening receive annual birthday letters that do not include a Pap reminder.

As standard clinical practice at Kaiser Permanente Washington, Pap results are classified according to the Bethesda system [38] as negative for intraepithelial lesion or malignancy (NILM), unsatisfactory, ASC-US (atypical squamous cells of undetermined significance), LSIL (low-grade squamous intraepithelial lesion), ASC-H (atypical squamous cells, cannot exclude high-grade lesion), HSIL (high-grade squamous intraepithelial lesion), AGC (atypical glandular cells), AIS (adenocarcinoma in situ) or cancer. Throughout the study, Kaiser Permanente Washington has followed the 2012 ASCCP Consensus Guidelines for management of abnormal results [39]. LSIL, ASC-H, AGC, or HSIL + (including AIS, carcinoma in situ [CIS], and cancer) warrant immediate referral for colposcopic examination. Reflex hrHPV testing of residual liquid-based Pap specimens is used to triage women with ASC-US results; women who are ASC-US/hrHPV + are referred for immediate colposcopy, whereas hrHPV negative women can return to a regular screening schedule. For co-tested women, testing positive for HPV16 and/or HPV18 warrants immediate colposcopy referral (even when the concurrent Pap test is normal). Repeat co-testing in 12 months is recommended for Pap-negative/other hrHPV-positive results. Women with cervical intraepithelial neoplasia grade 2 or higher (CIN 2 +) diagnosed on colposcopically-directed biopsy are referred for treatment. Loop electrosurgical excision procedure (LEEP) is the preferred treatment modality.