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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

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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.

Keywords

pragmatic clinical trial; human papillomavirus; self-sampling; cervical cancer; screening

1. Introduction

Although widespread adoption of routine Papanicolaou (Pap) screening has reduced cervical cancer incidence and mortality in the U.S. by more than 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. 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) toward 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 Figure 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 more than 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.

2.4 Integration of the trial into the clinical delivery system

Kaiser Permanente Washington clinical and system-level collaborators were consulted throughout trial design and implementation to facilitate integration of trial elements into standard care and to ensure the trial tested strategies that could be used for implementation. One of the negotiated elements of the trial was to ensure our recruitment did not intervene with standard strategies for getting overdue women to attend Pap screening. As such, we allowed 5 months (0.4 years) after women received their annual preventive care birthday letter reminders to ensure traditional outreach strategies had an opportunity to activate women to receive their recommended screening. Informational materials included with hrHPV self-sampling kits and results messaging about recommended follow-up of hrHPV

self-sampling results were developed in collaboration with clinical delivery system partners. Because Pap screening remains a HEDIS quality indicator, kit informational materials included the recommendation to continue routine Pap screening regardless of hrHPV self-screening results. This amounts to a hybrid screening strategy, in which the intervention could have activated women to either: a) complete the kit (with or without appropriate triage based on results), b) attend Pap screening only, c) complete the kit after attending Pap screening, or d) do nothing. This strategy differs from other international strategies that offer hrHPV self-sampling either as a sole screening strategy, or, as an alternative to Pap screening but with in-clinic follow-up only for those with hrHPV-positive results.

Trial information was disseminated to primary care teams using the existing infrastructure for provider education, including clinical update emails sent to all Kaiser Permanente Washington providers and staff immediately before implementation (February 2014), and again mid-trial (March 2015). The updates and electronic results text (see section 2.6.2.5, “Results text and follow-up”) included instructions on how to notify women of their hrHPV self-sampling results and how to manage the results. The text of the updates and contact information for the study team and clinical leads was accessible to staff at all times through an internet link on the cervical cancer screening guideline clinical webpage. During the trial, study staff and clinical investigators fielded clinical and logistical questions from primary care teams or women via a toll-free telephone number. Questions from primary care teams were also managed by study staff and clinicians using email and electronic staff messages.

2.5 Eligibility and randomization

Waivers of consent and Health Insurance Portability and Accountability Act (HIPAA) authorization were granted to identify eligible women through electronic medical record (EMR) data. Eligibility was assessed weekly from February 2014 through August 2016. To reduce participation bias, all eligible women were enrolled into the trial under a waiver of consent. Participants were randomly allocated to either the intervention arm or the control arm with a 1:1 ratio. One-year post-randomization, control arm participants were re-assessed for eligibility and re-randomization.

Women became eligible 5 months after receiving a birthday letter reminder indicating they were due or overdue for their Pap. Women were eligible to be randomized if they met the following inclusion criteria: 1) were between the ages of 30 and 64 years; 2) had not had a hysterectomy; 3) had a primary care provider within the integrated delivery system; 4) had been continuously enrolled for at least 3.4 years; and 5) had not had a Pap within 3.4 years. The rationale for assessing eligibility 5 months (0.4 years) after a birthday letter was to: a) ensure that our recruitment did not interfere with usual care Pap screening outreach strategies (discussed above in section 2.4, “Integration of the trial into the clinical delivery system”), b) target hard-to-reach women who were not activated by traditional Pap screening outreach strategies, and c) ensure that the 6-month time frame for assessing screening uptake ended before the next year’s birthday letter was sent (i.e., avoid contamination by traditional outreach). We identified 63,789 women who met the first four eligibility criteria. Of these women, 17,256 (27.1%) had not had a Pap within 3.4 years. Of those 17,256 women, 666 were excluded per exclusion criteria, i.e. they had previously indicated they did not want to

be contacted for research studies, had a pregnancy-related procedure or diagnosis code in their EMR within the prior 3 months, or had an “interpreter needed” flag in their EMR (because kit materials were in English only) (Figure 1).

2.6 Interventions

2.6.1 Usual care—Kaiser Permanente promotes preventive health services through integrated services at the patient, provider, clinic, and systems levels. Enhanced telephone contact, a patient Web portal, EMR, clinical decision support applications and other healthcare information and communication technologies are all used to support patient care [40–43]. In addition to the birthday letter, women overdue for preventive services also receive telephone outreach from their primary care team (timed approximately one month after the birthday letter). The EMR also has provider-targeted automatic alerts for overdue women that persist until a Pap is ordered or the alert is overridden; however, these are not standardized across clinics or providers.

Women randomized to the usual care arm did not receive any study-related interventions or contact from the study team.

2.6.2 Mailed hrHPV self-sampling kit

2.6.2.1 Overview: In addition to usual care, women allocated to the intervention arm were mailed hrHPV self-sampling kits with a pre-paid envelope to return samples directly to the central clinical laboratory. Results were documented in the EMR and women’s primary care teams managed results communication and follow-up care. Standardized protocols were developed to educate primary care teams on recommended follow-up (see section 2.4 above, “Integration of the trial into the clinical delivery system”) .

2.6.2.2 hrHPV self-sampling kits: Kits included an invitation letter, research information sheet, and materials for self-collecting and returning a sample. The letter invited women to try the kit as part of a research study evaluating new ways to screen women for cervical cancer. The letter included Kaiser Permanente Washington’s cervical cancer screening recommendations to receive Pap testing every 3 years, or on a different schedule if recommended by their health care provider. Because home hrHPV self-screening is not standard of care in the U.S., the letter also advised women to receive routine Pap tests, regardless of their hrHPV self-sampling results. The letter was signed by the trial’s two co-investigators with clinical leadership roles in primary care and women’s health.

The research information sheet described study procedures, potential risks and benefits, measures to protect privacy and confidentiality, and HIPAA compliance. Women were informed participation was voluntary and provided with a telephone number to call with questions or to “opt-out” of having their individual-level medical record data used for research.

The kit was developed and tested in our previous studies of hrHPV self-sampling [44], and contained two individually wrapped Dacron-tipped swabs, one capped tube (labeled with the woman’s individual health record number and the name of her primary care provider), one set of non-latex gloves, one plastic bag, one biohazard bag, illustrated instructions for

collecting and return-mailing a sample (see supplementary appendix), and one padded mailing envelope addressed to the central laboratory with pre-paid postage.

2.6.2.3 Outreach to promote kit uptake: The study programmer checked the EMR daily for received kits. A protocol to promote kit uptake was developed to mirror standard outreach protocols for preventive care. If the kit was not returned within three weeks of the mailing date, study staff made up to three calls to inquire whether the kit had been received and answer any questions about the kit or the study. If the participant indicated the kit was lost or not received, she was offered a replacement kit.

2.6.2.4 Laboratory testing for hrHPV: Samples were tested with the FDA-approved Cobas® 4800 HPV Test (Roche Diagnostics) – the same assay used for standard care hrHPV testing on clinician-collected samples. The Cobas® test concurrently detects HPV16 and HPV18 (the two hrHPV types found in up to 70% of cervical cancers [45]) and a pool of 12 other hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) in three separate channels. A fourth channel includes an internal beta-globin control to reduce false-negative results. Before commencing the trial, the laboratory validated the Cobas® test on self-collected vaginal samples by demonstrating agreement above a pre-specified threshold (>80%) on 86 paired self-collected vaginal samples (collected in a tube with no transport media) and clinician-obtained liquid-based cervical cytology samples (collected in SurePath media) from 30 to 64 year old women attending screening in our clinics.

Upon lab receipt, the self-collected samples were suspended in 1.5 ml SurePath media and processed per the standard hrHPV protocol used for clinician-obtained cervical samples. Results were reported as positive for HPV16/18, positive for other (non-HPV16/18) hrHPV types, negative for hrHPV, or unsatisfactory (negative for the internal beta globin-control). If the laboratory determined a sample was non-viable, the sample was not tested and no result was entered into the EMR. The laboratory reported non-viable samples to research staff who notified the woman and offered a replacement kit. Any sample received more than 21 days after the collection date was considered non-viable per previous studies of maximum specimen stability [46–48].

hrHPV results were entered in the EMR, and reported out per usual care; specifically: 1) the woman's primary care provider was electronically notified per standard protocol; 2) women with negative results were immediately notified via the patient Web portal, while abnormal results were delayed 24–48 hours to give the primary care team time to call; and 3) providers were instructed to contact women not active on the portal to communicate results.

2.6.2.5 Results text and follow-up: Follow-up recommendations for home hrHPV test results were developed in conjunction with the clinical leaders and informed by ASCCP management guidelines [39]. Because home-based hrHPV screening is not standard of care in the U.S., does not count toward HEDIS screening rates, and because there were no U.S. guidelines for primary HPV screening available when the study launched, both the IRB and the delivery system required that women with hrHPV negative results still be advised to attend in-clinic screening (Pap or co-testing). Women with unsatisfactory results were also advised to attend in-clinic cervical cancer screening, and were not offered an opportunity to

redo the self-sample (mirroring expected screening protocols if home hrHPV screening were integrated into the Kaiser Permanente Washington clinical delivery system). Women testing positive for non-HPV16/18 types were advised to receive in-clinic co-testing. Messages to providers advised management based on the clinical co-testing result when home and in-clinic hrHPV results were discordant, given potential time delays between home-based and in-clinic screening (e.g., infection could have resolved causing 2nd result to be negative). Women positive for HPV16/18 were recommended for immediate colposcopy, based on ASCCP management guidelines recommending immediate colposcopy after an HPV16/18 positive result [39]. Electronic test results included a section visible to both the woman and her primary care provider, and a section for providers only which reminded them of management guidelines and the timing of patient notification via the portal. Results-specific text visible to both women and providers included one of the following messages:

> **hrHPV negative**:"No high-risk HPV strains were found in your sample. Although this is reassuring, it's important to make an appointment with your health care team for in-clinic cervical cancer screening, since the effectiveness of home HPV testing is still being evaluated." (Starting May 2015, the phrase "home HPV testing" was changed to "home cervical cancer screening" – see section 2.9 below, "Mid-trial modifications to the study design.").
>
> **hrHPV positive for types other than HPV16 or HPV18**:"High-risk HPV strains were found in your sample. This result requires follow-up in the clinic with a Pap and HPV test. Please make an appointment with your health care team. You and your health care team should use the test results from the clinic to decide what steps to take next."
>
> **HPV16 and/or HPV18 positive**:"High-risk types 16 and/or 18 were found in your sample. This result requires follow-up in the clinic. Please contact your health care team to schedule follow-up." In an effort to minimize confusion or anxiety, the recommended follow-up (immediate colposcopy) was communicated to providers only so that providers could convey the information directly to their patients.
>
> **Unsatisfactory**:"There was not enough material on the swab for us to complete the test. Please make an appointment with your health care team for in-clinic cervical cancer screening."

Additionally, all patient/provider results text included the following message: "If you have questions about this result, please contact your health care team. If you have questions about the research that they are not able to answer, please feel free to call study staff at (toll-free telephone number)." For patients with negative or unsatisfactory results, a link to an internal Kaiser Permanente Washington website with general information on cervical cancer screening was provided. Starting May 2015, results text for women with positive results included a link to a study-specific website with information on home-based hrHPV screening (see section 2.9 below, "Mid-trial modifications to the study design").

Text visible to providers only included : "Please see the comments above regarding the recommended clinical management of this research study test result. As with standard HPV results, normal results will be sent to the patient via [the patient Web portal] immediately,

and abnormal results will be sent after 24–48 hours. Results are not sent to the patient by mail, regardless of whether or not they are active on [the patient Web portal]. You are required to contact patients who are not active on [the patient Web portal], regardless of their test results. Please contact the patient as appropriate – note that the patient will NOT be contacted by study staff. **Patients who are HPV 16 and/or 18 positive are recommended for immediate colposcopy. We do NOT recommend that the patient get a Pap test first, or repeat the HPV test in the clinic.**"

2.7 Interviews

To understand women's attitudes, emotional responses, and information needs after receiving a positive hrHPV self-sampling result and correlates of completing recommended follow-up, a subset of intervention arm women were invited to complete a semi-structured telephone interview (Figure 1). Potential participants were identified 1 to 2 weeks after completing all recommended diagnostic follow-up or treatment, or after they were no longer being assessed for main trial outcomes if recommended follow-up was not completed. An invitation letter and information sheet was mailed with a telephone number to opt-out. If the potential participant did not opt-out, an interviewer called a few days later to conduct a 15–20 minute interview. After the interview was completed, a cash incentive was distributed (increased mid-enrollment from $25 to $50 to enhance participation). Interviews were conducted until the research team determined saturation had been reached. Interviews were conducted between August 2014 and March 2017. In total, interview invitations were mailed to 58 hrHPV positive women who completed recommended follow-up (34 completed interviews) and 16 hrHPV positive women who did not complete recommended follow-up (12 completed interviews).

2.8 Surveys

To identify women's experiences and attitudes associated with using hrHPV self-sampling kits, a subset of women randomized to the intervention arm were invited to complete an online survey. The survey measured woman-level characteristics that influence kit uptake, including: knowledge about HPV and its connection with cervical cancer, perceived risk of cervical cancer, beliefs about the efficacy of HPV testing, attitudes towards Pap screening, and trust in new health care technologies and the health care system [53–57]. Additional questions focused on kit-user experiences, barriers, and future cervical cancer screening intentions and preferences. Responders and non-responders to the kit were mailed invitation letters 6-months post-randomization. Letters contained a link to an online survey and a telephone number to request a paper version. Survey invitees were randomized to receive either a $5 pre-incentive only or a $2 pre-incentive and $10 post-incentive. To avoid interfering with main trial outcomes, participants were excluded from invitation if they were still under follow-up for diagnostic or treatment outcomes (Figure 2) or if they were invited for the semi-structured interview. Survey invitation mailings started in January 2015, and mailings to each group stopped after 100 surveys were completed. In total, survey invitations were mailed to 272 kit returners (118 completed surveys) and 1,055 kit non-returners (116 completed surveys).

2.9 Mid-trial modifications to the trial design

Based on interviews with trial participants with positive hrHPV results, minor modifications were made in May 2015 to the kit invitation letter, information sheet, and results text that emphasized the link between hrHPV and cervical cancer. To facilitate women's understanding of the kit's purpose, the phrase "home HPV testing" was changed to "home cervical cancer screening." At the time of results notification for women with positive hrHPV results, we included a study-specific website reiterating the purpose of hrHPV tests as well as explaining what hrHPV results mean and why in-clinic follow-up is recommended.

2.10 Outcome measures

Screening, diagnosis, and treatment outcome measurements and timing are depicted in Figure 2.

2.10.1 Primary outcomes—The two primary outcomes are histologically-diagnosed CIN 2+ and treated CIN 2+. These outcomes will be identified by a combination of programmatic extraction and manual review of the EMR. To count as an outcome, CIN 2+ must be preceded by an abnormal screening result within 6 months after randomization. Diagnosed CIN 2+ will be captured within 6 months after an abnormal screening result, and treated CIN 2+ will be captured within 6 months after a CIN 2+ diagnosis.

2.10.2 Secondary outcomes—There are several secondary outcomes. Two will be obtained from the EMR: cervical cancer screening uptake and abnormal screening results. Uptake will be captured within 6 months after randomization and defined as any of the following:

- **a.** Receiving a Pap test or co-test;
- **b.** Self-sampling HPV16/18-positive (regardless of any subsequent in-clinic follow-up, because recommended management is to proceed directly to diagnostic evaluation);
- **c.** Self-sampling hrHPV-negative (regardless of any subsequent in-clinic follow-up, based on the expectation that programs implementing hrHPV self-sampling would not require in-clinic follow-up of a negative result); or
- **d.** Self-sampling hrHPV-positive for non-HPV16/18 types only or unsatisfactory, *and* receiving a Pap or co-test.

Abnormal screening results will be captured within 6 months after randomization, and are defined as a result that warrants repeat testing, surveillance, or immediate colposcopy before returning to a routine screening schedule.

In terms of woman-reported secondary outcomes, we used telephone interviews to explore experiences and attitudes after receiving a positive hrHPV self-sampling result (see section 2.7 above, "Interviews"). We used surveys to assess experiences and attitudes associated with uptake of home-based hrHPV self-sampling (see section 2.8 above, "Surveys").

2.11 Data management and analysis

2.11.1 Retroactive exclusions—We were unable to identify and exclude a small number of women who, prior to randomization, either attended Pap screening or disenrolled close to the randomization date. These women will be excluded post-randomization from both study arms before analysis.

2.11.2 Data management—Individual-level EMR data will be available for analysis for women randomized to the control arm (Figure 3). EMR access for intervention arm women will depend on classification as responders, non-responders, or refusers. Women who returned a kit and did not opt-out of medical record review will be classified as responders, and their individual-level data will be available for analysis. Women who did not return a kit and did not opt-out will be classified as non-responders, and their data will be available in aggregate for analysis. Women who opted out of EMR review (regardless of whether or not they returned a kit) will be classified as refusers, and their data will be available in aggregate for select variables only (including hrHPV tests results and screening, diagnosis, and treatment outcomes).

2.11.3 Statistical analysis—Data will be analyzed based on the intention-to-treat principle. Denominators for each arm will generally include all women randomized to that arm, minus the women identified post-randomization as ineligible. For detected and treated CIN 2+, abnormal screening results, and screening uptake, we will compare the proportion of outcomes detected in the intervention arm to the proportion detected in the usual care arm and estimate relative risks using log-binomial regression. Robust variances estimates will be used to account for within-subject correlation due to re-randomized subjects contributing more than one observation period. If differences are observed in the distribution of EMR-derived subject characteristics across arms despite randomization, we will adjust for the relevant covariates in the regression models. Subject characteristics of interest include age, race, ethnicity, length of health plan enrollment before randomization, time since last Pap, geocoded socioeconomic status, distance from primary care provider, insurance plan type, tobacco use, body mass index, Charlson comorbidity score [49], and primary care provider type and specialty.

To evaluate predictors of screening uptake, we will use log-binomial regression to estimate the effects of subject characteristics on the probability of screening uptake. To test for effect modification by randomization arm (i.e., to test if home HPV screening is more effective at increasing uptake than usual care for subgroups of women), we will test characteristic-by-randomization arm interaction terms using log-binomial regression comparing the relative risk of screening uptake in the intervention arm relative to the usual care arm by characteristics of interest.

In an exploratory analysis, PPV of an abnormal screening test for detecting CIN 2+ will be estimated within each arm. The denominator will include women who receive an abnormal screening result within 6 months of randomization that warrants referral to colposcopy, and the numerator will incude women with diagnosed CIN 2+. We will also calculate PPV

restricting the denominator to women who receive colposcopy within 6 months of the abnormal screening result.

2.12 Power calculations

The trial was powered on the primary outcomes of diagnosed and treated CIN 2+. Power calculations assumed a two-sided alpha of 0.05 and used assumptions based on the literature and preliminary data that were available as of 2012. We made the following assumptions:

1. 30% of women randomized to the intervention arm would return self-sampling kits [19, 20, 22, 31];
2. 89% of women with hrHPV-positive self-sampling results would attend in-clinic follow-up [20, 22, 31];
3. 9% of women in the usual care arm and 9% of women in intervention arm who did not return a self-sampling kit would attend in-clinic cervical cancer screening within 6 months of randomization (based on Kaiser Permanente Washington data from 2007 to 2011);
4. 92% of women with abnormal screening results warranting referral to colposcopy would attend colposcopy, and 94% of women with diagnosed CIN 2+ would receive treatment [50];
5. 7.5% of all hrHPV self-sampling tests would be positive [20, 22, 31, 51];
6. 36% of women with hrHPV-positive self-sampling results and 5% of screened women without self-sampling results (in either arm) would have a final screening result warranting referral to colposcopy [51, 52];
7. In women referred for colposcopy, the proportions of women with CIN 2+ would be 25% in those with hrHPV-positive test results, and 9% in those without hrHPV test results [51, 52];
8. 2.2% of enrollees would disenroll from Kaiser Permanente Washington in the 6 months following randomization, and an additional 4.8% would disenroll by 18 months. Our estimated numbers of outcomes account for this anticipated disenrollment, but the denominators include all randomized women (minus those retroactively excluded), based on the intention-to-treat principle.

We applied our enrollment criteria to data from 2007–2011 and estimated that over 2.5 years, we would identify approximately 17,600 eligible women. With a sample size of 17,600, we estimated we would have 85% power to detect between-arm differences in proportions of women with diagnosed CIN 2+ (0.19% versus 0.04% in the intervention and control arms, respectively), and 81% power for treated CIN 2+ (0.17% versus 0.03% in the intervention and control arms, respectively). We estimated 100% power to detect differences in abnormal screening results (1.1% versus 0.4% in the intervention and control arms, respectively) and screening uptake (35.9% versus 8.8% in the intervention and control arms, respectively).

2.13 Data and safety monitoring

Plans for adverse event (AE) monitoring, monitoring compliance with the study protocol, and interim data analyses were pre-specified through a data safety monitoring plan. The trial was considered minimal risk by the reviewing IRBs, with potential AEs associated with the self-sampling intervention deemed comparable to those encountered by women undergoing clinic-based screening. Expected AEs from self-sampling were discomfort and light bleeding. AEs were captured through self-report to the study telephone number, regularly monitored by study staff. All AEs were documented on a reporting form. The intensity of an AE was graded per Common Terminology Criteria for Adverse Events version 3.0. All AEs were reported to the IRB.

Research staff regularly audited the EMR for laboratory compliance with hrHPV self-sampling results reporting protocols. If provider-specific text was missing from the original report or results were not released to women through the portal, research staff asked the laboratory to electronically re-release the results to women and/or providers. Research staff also performed regular audits of both EMR data and secure messages between providers and women for provider compliance with recommended management of non-negative hrHPV self-sampling results. Interventions by the research team were modeled after standard clinical practice for similar screening tests such as home fecal occult blood test and were designed to balance patient safety concerns with pragmatic trial fidelity. In cases where a provider did not communicate a follow-up plan to a woman after a non-negative hrHPV result, a research team clinician sent the provider an electronic staff message with a reminder of the recommended follow-up plan. For women testing positive for HPV16 or HPV18, research staff monitored for communication of the recommended follow-up plan (immediate colposcopy). If the recommended follow-up plan was not communicated, a staff message was sent to the provider. Staff messages were generally sent within 2 to 4 weeks of the result date.

Interim data activities necessary for study management, progress reporting, data quality control, and data analyses were pre-specified. An interim data look at the kit return rate in the intervention arm was assessed by limited study staff 6 weeks after reaching 50% of expected target accrual; a kit return rate of >10% was set as the threshold for continuing the trial because a lower return rate was thought to make the intervention not clinically viable. Study staff involved in interim data activities were not involved in any scientific decisions about modifications to the study protocol, but could consult with an external scientific advisory committee if review of study data raised any potential ethical concerns. Membership on the external scientific committee included a Kaiser Permanente Washington Health Research Institute biostatistician and a UW clinician. The scientific leadership committee, comprised of the principal investigator, project PhD biostatistician, and one additional co-investigator, was blinded to all primary and secondary outcomes analyses until 6 months after the last subject was enrolled.

3. Discussion

Reaching under-screened women is a key U.S. priority for reducing disparities in cervical cancer prevention [34]. The HOME trial addresses the need for U.S.-based data on home-

based hrHPV self-sampling strategies for increasing screening participation and compliance. We designed a pragmatic trial to streamline the translational research pipeline and inform healthcare system decision-making about implementation if the intervention is successful. Trial results also have potential to change screening delivery by making it more convenient for women and improving clinic efficiency and capacity. Program success will be measured not only in terms of ability to improve screening uptake, but most importantly in ability to enhance early detection and treatment of cervical neoplasia. Screening is effective only if women are successfully followed from screening through treatment [53]. Therefore, this trial was designed to evaluate whether a home hrHPV screening program is effective in promoting adherence to the complete continuum of screening, follow-up, and treatment.

Pragmatic trials that are fully integrated into clinical practice require significant investments on the part of researchers and delivery system partners. This trial is based on two prior successful pragmatic RCTs at Kaiser Permanente Washington [54, 55] demonstrating feasibility of integrating innovative interventions into primary care. In Figure 4, we highlight the pragmatic features of the HOME trial using the PRagmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2) tool [56]. PRECIS-2 uses 9 design feature domains focused on eligibility, recruitment, setting, delivery, adherence, follow-up, outcomes, and analysis to describe clinical trials on a pragmatic to explanatory continuum. To optimize inclusion of women who would be eligible for the intervention if it were adopted into practice, we worked closely with our IRBs to receive a waiver of consent to identify eligible women from EMR data (with minimal exclusion criteria) and randomize them. Women had the ability to opt-out of having their individual-level medical record data used in the research, but passive consent was allowed which will significantly enhance the generalizability of the findings. Our trial was strengthened by the integrated healthcare system setting and direct clinical integration of the intervention with existing protocols for provider education, laboratory processing, and results notification, with primary care teams (not the study team) managing results follow-up. Trial outcomes will be obtained by passive review and analyzed using an intention-to-treat approach.

Although our trial mirrored current and expected clinical practice to the extent possible, there are certain research design features that should be considered when interpreting results. Perhaps the biggest difference in this pragmatic trial versus others evaluating home testing effectiveness in international settings is the hybrid screening strategy in the intervention arm that resulted from competing healthcare delivery system priorities for cervical cancer screening HEDIS scores. Our recruitment timing was driven by the need to ensure the delivery system had the opportunity to activate women who were overdue for screening and required we did not send any materials until 5 months after their most recent annual preventive care birthday letter. In addition, kit follow-up and guidance recommended Pap screening even for women with hrHPV-negative self-sampling results, which may have negatively impacted women’s decisions to self-sample. Finally, women’s decisions to self-sample may have been influenced (positively or negatively) by the fact that kits were mailed as part of a research study.

In summary, we designed a pragmatic trial that is timely and innovative in testing a novel and cost-effective [17, 18] programmatic approach to increasing cervical cancer screening

uptake and effectiveness. The trial was fully embedded within an integrated healthcare delivery system and is the first in the U.S. to evaluate whether a program incorporating mailed hrHPV self-sampling kits can enhance detection of cervical neoplasia and increase compliance with screening recommendations. The study targeted U.S. women who are at the highest risk for cervical cancer – under-screened women – and is thereby poised to reduce cervical cancer disparities stemming from preventive care services use. Additionally, results on health and demographic predictors of screening uptake and women's experiences and attitudes towards hrHPV self-sampling and follow-up of hrHPV-positive test results will inform dissemination to other healthcare systems and provide important information on sustainablility. Trial findings have the potential to provide a meaningful and sustained impact on the delivery of cervical cancer screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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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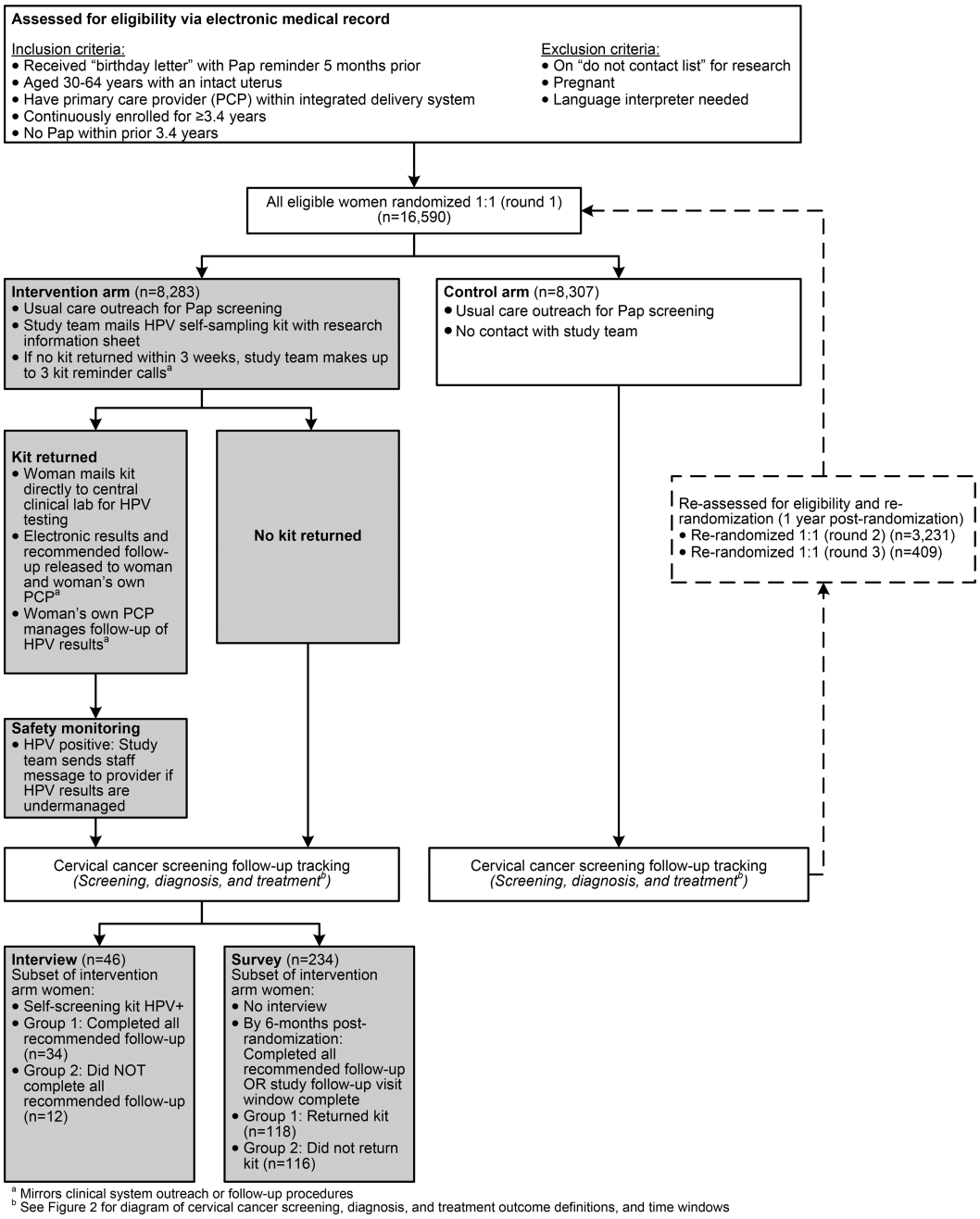

Figure 1.

The **HOME** (**H**ome-based **O**ptions to **M**ake cervical cancer screening **E**asy) pragmatic randomized controlled trial design

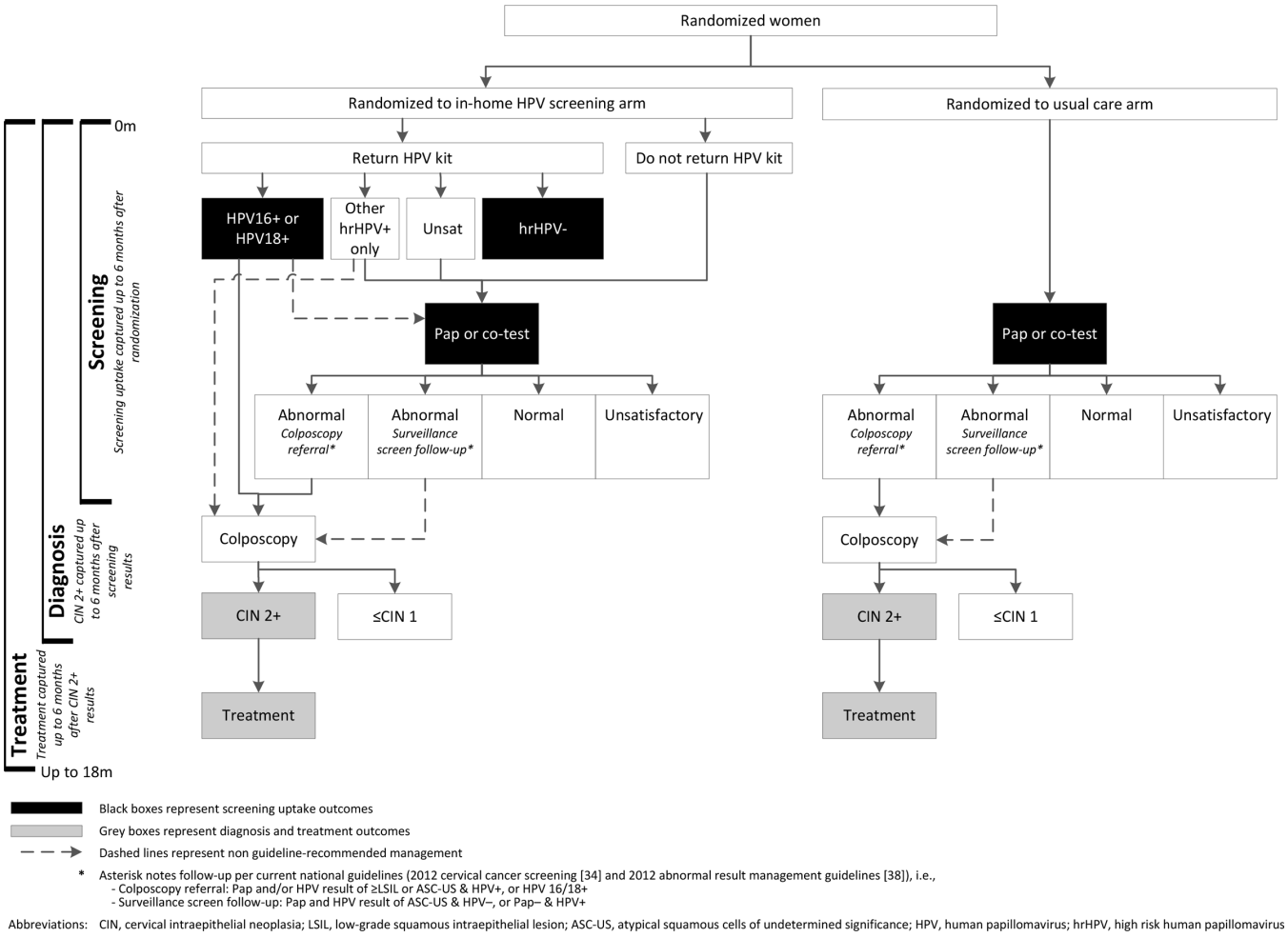

Figure 2.

Diagram of the HOME trial cervical cancer screening uptake, diagnosis, and treatment outcomes

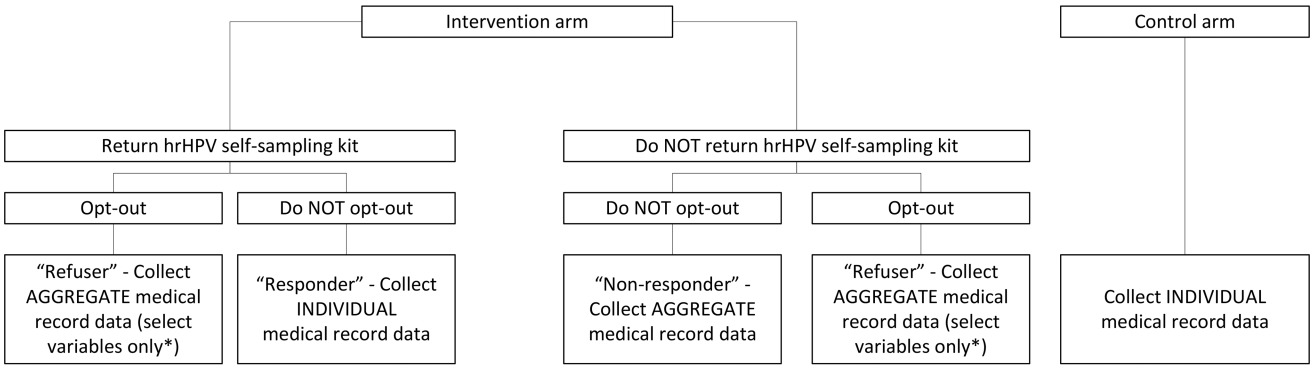

Figure 3.

Diagram of medical record access for collecting outcome and covariate data, based on randomization arm and level of participation.

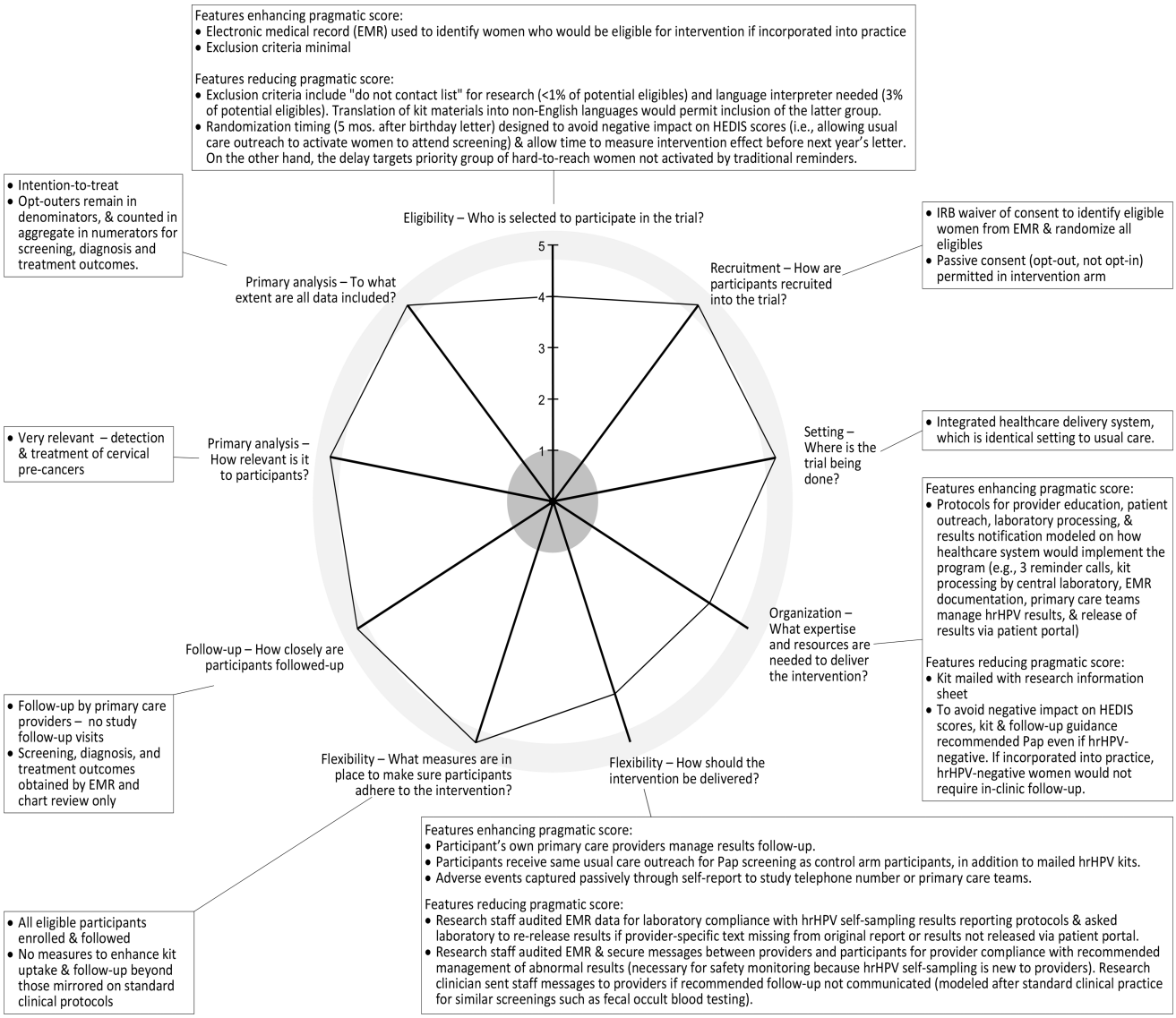

Figure 4.

The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel [56] applied to the HOME trial. Each domain was scored by the HOME trial investigators using a 5-point Likert scale, where 1=very explanatory; 2=rather explanatory; 3=equally pragmatic and explanatory; 4=rather pragmatic; and 5=very pragmatic.