Title
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Permalink
https://escholarship.org/uc/item/2989q4s0

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Publication Date
2019-09-01

DOI
10.1016/j.conctc.2019.100413

Peer reviewed
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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ARTICLE INFO

Keywords:
- Pragmatic clinical trial
- Delivery system science
- Health care delivery research
- Clinical effectiveness research
- Dissemination
- Implementation

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

### 1. Generalizability

**Outcome**
- Generalizability Limited to overdue women who persisted being overdue for ≥5 months

**Comparison**
- Pragmatic design
  - Ideal design

### 2. Embedding trials into clinical workflows

- **Pragmatic design**
  - Embedded pragmatic trials are integrated into healthcare system workflows. This design includes clinical champions, including pragmatic study population, recruitment plan, and clinical workflows, as well as funding receipt, during which time we experienced changes in stakeholders and trialists.
- **Ideal design**
  - Embedding trials into clinical workflows requires strong, continued engagement of clinical and operational champions. Like many others, we experienced > 15 months between submission and trial initiation.

### 3. Negotiating study population

- We also had to navigate and alter our pragmatic trial design around 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, identifying strategies for engaging this high-risk population is essential.

### 4. Documenting delivery system support for the trial

- After navigating trial design with the delivery system, we had to compete for extramural funding and convince peer reviewers that our outreach is effective in activating overdue women (25,26). To ensure generalizability, focusing on this hard-to-reach population was viewed as feasible, patient-centered, and a high priority by the healthcare system. This proved more challenging than anticipated.

### 5. Implications of lengthy timeline from submission to funding

- The timeline from grant submission to funding is lengthy, which has strong, continued implications for embedded research due to the required strong, continued engagement of clinical and operational champions like many others, we experienced > 15 months between submission and trial initiation.

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**Table 1**

| Description | Pragmatic design vs. desired design for the HOME pragmatic trial testing home HPV testing vs. in-clinic Pap screening. |
|-------------|---------------------------------------------------------------------------------------------------------------|
| **Outcomes**| **Comparison**                                                                                                    |
| Screening  | The timeline from grant submission to funding is lengthy, which has strong, continued implications for embedded research due to the required strong, continued engagement of clinical and operational champions like many others, we experienced > 15 months between submission and trial initiation. |
| 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, identifying strategies for engaging this high-risk population is essential. |

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**Figure 1**

In the optimal pragmatic trial design, we wanted to include all age-eligible women as fast as feasible, patient-centered, and a high priority by the healthcare system.
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.

Funding

This work was supported by the National Cancer Institute of the National Institutes of Health [grant number R01 CA168598, ClinicalTrials.gov: NCT02005510]. The National Cancer Institute had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

References

[1] K.P. Weinfurt, A.F. Hernandez, G.D. Coronado, L.L. DeBar, L.M. Dember, B.B. Green, et al., Pragmatic clinical trials embedded in healthcare systems: generalizable lessons from the NIH Collaborative, BMC Med. Res. Methodol. 17 (2017) 144, https://doi.org/10.1186/s12874-017-0420-7.
[2] R.M. Califf, J. Sugarman, Exploring the ethical and regulatory issues in pragmatic clinical trials, Clin Trials 12 (2015) 436–441, https://doi.org/10.1177/1740744515596334.
[3] J.A. Finkelstein, A.L. Brickman, A. Capron, D.E. Ford, A. Gombos, S.M. Greene, et al., Oversight on the borderline: quality improvement and pragmatic research, Clin Trials 12 (2015) 457–466, https://doi.org/10.1177/1740744515597562.
[4] R.E. McKinney Jr., L.M. Beskow, D.E. Ford, J.D. Lantos, J. McColl, B. Patriak-Lake, et al., Use of altered informed consent in pragmatic clinical research, Clin Trials 12 (2015) 494–502, https://doi.org/10.1177/1740744515597688.
[5] R.L. Richesson, B.B. Green, R. Laws, J. Puro, M.G. Kahn, A. Bauck, et al., Pragmatic (trial) informatics: a perspective from the NIH health care systems research collaboratory, J. Am. Med. Inform. Assoc. 24 (2017) 966–1001, https://doi.org/10.1093/jamia/occ316.
[6] E.B. Larson, C. Tachibana, E. Thompson, G.D. Coronado, L. Debar, L.M. Dember, et al., Trials without tribulations: minimizing the burden of pragmatic research on healthcare systems, Healthcare 4 (2016) 138–141, https://doi.org/10.1016/j.hsjdi.2015.07.005.
[7] Institute of Medicine, Crossing the Quality Chasm: A New Health System for the 21st Century, (2001) Washington (DC).
[8] J.E. Berkowitz, O.M. Gatewood, L.E. Goldblum, B.W. Gayler, Hormonal replacement therapy: mammographic manifestations, Radiology 174 (1990) 199–201.
[9] A. Noone, N. Howlader, M. Krapcho, M. Akinlotan, J.N. Bolin, J. Helduser, C. Ojinnaka, A. Lichorad, D. McClellan, Understanding barriers to cervical cancer screening in women with access to care, behavioral risk factor surveillance system, 2014, Prev. Chronic Dis. 2016 (2017) 74–77, https://doi.org/10.1016/s12874-017-0316-9.
[10] C. Tachibana, E. Thompson, G.D. Coronado, L. DeBar, L.M. Dember, et al., Pragmatic clinical trials, Clin. Trials 12 (2015) 485–493, https://doi.org/10.1177/174074451559832.
[11] A. White, T.D. Thompson, M.C. White, S.A. Sabatino, J. de Moor, P.V. Doria-Rose, et al., Cancer screening test use - United States, 2015, MMWR Mortal. Wkly. Rep. 66 (2017) 201–206, https://doi.org/10.15585/mmwr.mm6608a1.
[12] M. Arbyn, P.E. Castle, Offering self-sampling kits for HPV testing to reach women who do not attend in the regular cervical cancer screening program, Cancer Epidemiol. Biomark. Prev. 24 (2015) 769–772, https://doi.org/10.1158/1535-7163-EB-15-0417.
[13] F. Verdoorn, M. Jentschke, P. Hillelmanns, C.S. Racey, P.J. Snijders, M. Arbyn, Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials, Eur. J. Cancer 51 (2015) 2375–2385, https://doi.org/10.1016/j.ejca.2015.06.055-3382.
[14] A. Crawford, V. Benard, J. King, C.C. Thomas, Understanding barriers to cervical cancer screening in women with access to care, behavioral risk factor surveillance system, 2014, Prev. Chronic Dis. 13 (2016) E154, https://doi.org/10.5888/pcd13.160225.
[15] M. Akinlotan, J.N. Bolin, J. Helduser, C. Ojinnaka, A. Lichorad, D. McClellan, Cervical cancer screening barriers and risk factor knowledge among uninsured women, J. Community Health 42 (2017) 770–777, https://doi.org/10.1007/s10900-017-0316-9.
[16] D. Sadow, D. Solomon, H.W. Lawson, M. Killackey, S.L. Kulasegaram, J. Cairn, et al., American cancer society, American society for colposcopy and cervical pathology, and American society for clinical pathology screening guidelines for the prevention and early detection of cervical cancer, Am. J. Clin. Pathol. 137 (2012) 516–542, https://doi.org/10.1093/ajcp/aqz099.
[17] J. Zapka, S.H. Taplin, R.A. Price, C. Cranos, R. Madigan, G. Bliss, Factors in quality care–the challenge of follow-up to abnormal cancer screening tests–problems in the steps and interfaces of care, J. Natl. Cancer Inst. Monogr. (2010) 58–71 [pii]10.1093/jncimonographs/lgp009.
[18] J. Zapka, J. King, R.A. Price, R.H. Martin, M.D. Rosenthal, Predictors of cervical cancer screening adherence in a United States: a systematic review, J. Adv. Pract. Oncol. 5 (2014) 31–41.
[19] J. Zapka, S.H. Taplin, R.A. Price, C. Cranos, R. Yabroff, Factors in quality care–the challenge of follow-up to abnormal cancer screening tests–problems in the steps and interfaces of care, J. Natl. Cancer Inst. Monogr. (2010) 58–71 [pii]10.1093/jncimonographs/lgp009.
[20] L. DeBar, L.M. Dember, et al., 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.

Funding

This work was supported by the National Cancer Institute of the National Institutes of Health [grant number R01 CA168598, ClinicalTrials.gov: NCT02005510]. The National Cancer Institute had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

References
[29] The Donaghue Foundation, Greater value portfolio, http://donaghue.org/grant-opportunities/greater-value-portfolio/, (2019), Accessed date: 20 June 2019.

[30] National Institutes of Health Office of Extramural Research, Department of health and human services, USA government. HEAL initiative: translational devices to treat pain (UGI/UHS clinical trial optional), https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-19-016.html, (2019), Accessed date: 20 June 2019.

[31] U. S. Preventive Services Task Force, S.J. Curry, A.H. Krist, D.K. Owens, M.J. Barry, A.B. Caughey, et al., Screening for cervical cancer: US preventive services Task Force recommendation statement, J. Am. Med. Assoc. 320 (2018) 674–686, https://doi.org/10.1001/jama.2018.10897.