Evaluating the Impact of Optimizing the Use of HPV Vaccine Standing Orders in Primary Care Clinics

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Analysis plan

Our cluster randomized clinical trial evaluates the impact of standing orders support on HPV vaccine communication and uptake. This trial randomly assigns primary care clinics to receive HPV vaccine standing orders support with communication training or communication training alone. Results of the trial will inform an implementation guide for healthcare systems looking to optimize their use of HPV vaccine standing orders.

Hypotheses

Our first hypothesis is that standing orders support with HPV vaccine communication training leads to higher HPV vaccination rates than communication training alone. We predict that standing orders support will lead to higher HPV vaccine initiation at 12 months among children ages 9-12 years (primary trial outcome). We also predict that standing orders support will lead to higher HPV vaccine initiation at 24 months and higher HPV vaccine completion at 12 and 24 months (secondary trial outcomes).

Our second hypothesis is that standing orders support with HPV vaccine communication training leads to better communication with families about HPV vaccine than communication training alone (secondary trial outcomes). **Our third hypothesis is that standing orders support with HPV vaccine communication training leads to better implementation** of HPV vaccine standing orders (secondary trial outcomes).

Sample

This trial will enroll 34 primary care clinics from healthcare systems that serve around 15,000 patients ages 9-12 years who have not received any doses of HPV vaccine. We estimated sample size for our 2-arm trial using the following inputs: intervention effect of 6 to 7.5 percentage point increase in HPV vaccine initiation only in the treatment arm (based on observed effect sizes in previous standing orders trials), secular trend of 7.5 to 12 percentage point increase in HPV vaccine initiation in both the control and intervention arms (based on NIS-Teen vaccination data for the US), 400 unvaccinated patients per clinic, intraclass correlation range from 0.03 to 0.04 (based on analyses of previous similar datasets), 80% power, and α of .05. Using these inputs yielded a low-end value of 15 clinics per trial arm and a high-end value of 17 clinics (30-34 clinics in total across the two arms).

Randomization

A biostatistician will receive anonymized IDs for clinics once they enroll. The biostatistician will create pairs of clinics and randomly assign one of the clinics to the intervention arm and the other clinic to the control arm. If the number of clinics in trial arms becomes imbalanced, the biostatistician will adjust randomization probabilities. For clinics with at least 25% overlap in providers, randomization will assign them to the same arm.

Edit 5/1/24: Because clinics in a system enroll at the same time, randomization will be blocked within system.

Measures

Trial outcomes are described in Table 1. For vaccination outcomes, healthcare systems will provide HPV vaccination data for eligible patients in each enrolled clinic: HPV vaccine series initiation (1+ doses) between 1 and 12 months and between 13 and 24 months; and HPV vaccine series completion (2 doses) between 1 and 12 months and between 13 and 24 months. For communication and implementation

outcomes, data will come from surveys of communication training attendees. HPV vaccine communication and standing order implementation outcomes will be measured as continuous variables. Edit 5/1/24: In place of collecting clinic-level data, we will now obtain data on individual patients. As planned, the follow-up periods (12 and 24 months) will begin on the date of randomization to trial arm. Rurality will be defined for each clinic as having 40% or more patients with RUCA codes 4-10.

Table 1. Trial outcomes and values

Primary trial outcome

HPV vaccination, from clinic EHR

HPV vaccine series initiation at 12 months (dichotomous, 0 or 1)

Secondary trial outcomes

HPV vaccination, from clinic EHR

HPV vaccine series initiation at 24 months (dichotomous, 0 or 1)
HPV vaccine series completion at 12 months (dichotomous, 0 or 1)
HPV vaccine series completion at 24 months (dichotomous, 0 or 1)

HPV vaccine communication, reported by communication training attendees

Recommendation behaviors for ages 9-10 years (continuous, 1-5)
Recommendation behaviors for ages 11-12 years (continuous, 1-5)
Recommendation attitudes (continuous, 1-5)
Recommendation efficacy (continuous, 1-5)
Recommendation norms (continuous, 1-5)
Recommendation intentions (continuous, 1-5)
Recommendation time spent (continuous, 0-99 minutes)

HPV vaccine standing orders implementation, reported by communication training attendees

Standing orders attitudes (continuous, 1-5)
Standing orders norms (continuous, 1-5)
Standing orders efficacy (continuous, 1-5)
Standing orders behavior adoption (continuous, 1-5)
Standing orders acceptability (continuous, 1-5)
Standing orders appropriateness (continuous, 1-5)
Standing orders role understanding (continuous, 1-5)
Standing orders feasibility (continuous, 1-5)
Standing orders sustainability (continuous, 1-5)

Analytic Plan

Analyses of trial outcomes will be intent-to-treat. If a clinic withdraws from the trial, merges, or closes permanently, we will use data that are available at follow-up and drop the clinic if no data are available. (We do this because the cohorts are defined at follow-up.) Statistical analyses will be conducted in SAS and R The critical alpha will be .05 and tests will be two-tailed.

Primary trial outcome: HPV vaccine initiation by 12-month follow-up

Analyses of the primary HPV vaccination outcome will use generalized estimating equations (GEE) using a log link. The predictor will be trial arm (control vs. intervention, dichotomous) and the outcome will be HPV vaccination (not received vs. received, dichotomous).

Edit 5/1/24: Updated text to reflect patient-level data (no longer using patient counts per clinic or clinic offset). Trial arm will be the primary fixed effect as a two-level, categorical variable. To take into account the randomization approach, healthcare system will be a categorical covariate. The GEE model will cluster patients within clinics. For HPV vaccine initiation, the analysis cohort will be patients with no HPV vaccine doses 12 months previously. For HPV vaccine completion, the analysis cohort will be patients with no or one HPV vaccine doses 12 months previously.

Additional exploratory analyses will examine moderation of the intervention's impact on HPV vaccine initiation by the following variables:

- Patient characteristics: age (9-10 years vs. 11-12 years) and gender (male vs. female); and
- Clinic characteristics: baseline HPV vaccine initiation rate, rurality, proportion Black patients, proportion Hispanic patients, specialty (pediatrics or other), and timing of HPV vaccine standing orders adoption (1-12 months before trial enrollment vs. 13+ months before trial enrollment).

Exploratory analyses will use GEE, as described above, rerunning the models and adding the main effect and interactions with trial arm for each potential moderator variable. For statistically significant interactions, we will stratify the analyses by each level of categorical moderator variable (dichotomizing continuous moderators as needed).

Secondary trial outcomes

Analyses of the secondary HPV vaccination outcomes will use GEE as described above. Analyses of the communication and implementation outcomes will use general linear models with trial arm as the dichotomous predictor.