NCT03599583

Improving HPV Vaccination Delivery in Pediatric Primary Care: The STOP-HPV Trial 1. Comparison of Communication Skills and Standard of Care for Uptake of the HPV Vaccine.

Statistical Analysis Protocol

UCLA IRB Approval Date 1/9/2018 (IRB#17-001772)

Protocol and Analyses

Study Title: Impact of a Communication Intervention for Clinicians on Missed Opportunities for HPV Vaccination: A Randomized Controlled Trial from the American Academy of Pediatrics Pediatric Research in Office Settings (PROS) Network

Clinical Trials Registration: NCT03599557

Brief Summary:

This trial, part of a multi-year comprehensive intervention, is located in pediatric practices and health systems within the American Academy of Pediatrics Pediatric Research in Office Settings (PROS) Network. Most adolescents who receive human papillomavirus (HPV) vaccine are vaccinated in pediatric practices, yet missed opportunities (MOs) for HPV vaccination occur often and lead to low HPV vaccination rates. This cluster randomized clinical trial (RCT) will test the effectiveness (and cost-effectiveness) of training providers on HPV vaccine communication to reduce MOs and increase HPV vaccination rates.

Methods and Procedures

For this first part of the intervention, there are 2 study periods. We will randomize by practice (not provider) to avoid contamination. We will assess missed opportunities (MOs) and HPV vaccine rates using monthly and period-aggregate data, excluding the periods of ramping up of each intervention.

Period 0: This is the 12-month baseline period.

Period 1: Arm-1 practices will receive communication skills training. Arm-2 control practices will receive standard of care. The duration of the communication intervention period will be 6 months.

All analyses will be stratified by visit type (well or sick) and dose (initial vs subsequent). We consider MOs by visit type and dose separately as we hypothesized that MOs for different visit types and doses are driven by different factors. For the test of this communication intervention, we hypothesized that since almost all HPV vaccinations (and nearly 100% of initial doses) are provided during well-child care visits, an intervention focused upon communication may be potentially effective especially during well-child care visits.

Future interventions that focus upon changing practice procedures (e.g., providing feedback to providers with suggestions for utilizing sick/chronic visits, or prompts to remind providers to to consider HPV vaccinations) may have more of an impact at sick/chronic visits and for subsequent doses.

Study Design

Study Type: Interventional (Clinical Trial)

Actual Enrollment: 48 participants, where each participant is a pediatric primary care practice, to include all eligible patients at the practices during the two periods.

Allocation: Randomized

Intervention Model: Parallel Assignment

Intervention Model Description: This study will use a cluster RCT study design to test the impact of the communication intervention to reduce missed opportunities (MOs) and raise HPV vaccine rates.

Arms and Interventions:

- Arm 1 will receive the STOP-HPV communication intervention
- Arm 2 will receive standard of care

Inclusion and Exclusion criteria

Practice Inclusion Criteria:

- The practice provides HPV vaccination services to adolescents.
- The practice is part of Physician's Computer Company (PCC), Office Practicum (OP) or (a) yet-to-be selected health system(s).
- The practice has had the same EHR system in place for a year or more (with special consideration on a case by case basis if they are close to but not do not reach a year).
- The practice agrees to not participate in other HPV-related QI projects or research interventions during the study period (with special consideration on a case by case basis).

Practice Exclusion Criteria:

- The practice plans to change EHR systems in the next three years.
- The practice participated in the last year, is currently engaged in, or plans to participate in an office-based HPV-related quality improvement (QI) project or research intervention during the study period (with special consideration on a case by case basis).
- Estimated 20% or more of adolescents at the practice receive HPV vaccinations at schools or health department clinics (given standard practice and published data, the investigators expect that few to no practices will need to be excluded based on this restriction).

Patient inclusion criteria:

- All patients of participating practices (intervention and comparison) aged 11-17 years who have at least 1 visit to the practice within the past two years.

Patient exclusion criteria:

- None apart from age of patients (above).

Main Outcomes and Measures

Primary Outcome Measures:

1. Rate and change in the rate of missed vaccination opportunities among all clinicians [Time Frame: Monthly from months 0 (baseline) to month 6, and also aggregated over the 6-month period from month 0, where month 0 is site specific and depends on completion of site staff training and readiness to proceed.]

   Change in the rate of missed vaccination opportunities from baseline through the end of the communication intervention period among all clinicians.

2. Rate and change in the rate of missed vaccination opportunities among consenting clinicians [Time Frame: Monthly from months 0 (baseline) to month 6, and also aggregated over the 6-month period from month 0, where month 0 is site specific and depends on completion of site staff training and readiness to proceed.]

   Change in the rate of missed vaccination opportunities from baseline through the end of the communication intervention period among consenting clinicians.

Analysis

Primary Analysis

All analyses will be stratified by visit type (well or sick) and dose (initial vs subsequent). Visit-level analyses will implement marginal models (such as estimated with generalized estimating equations (GEE) (Fitzmaurice 2011) to estimate relative and absolute changes in rates between intervention and control practices, and over time. These methods facilitate estimation of standardized (for patient-level characteristics) (Korn and Graubard 1999) rates of MOs over time. Assumptions include a large number of practice sites (Hayes and Moulton 2017), an assumption that our study satisfies for comparisons of all 48 sites. With fewer than 40 clusters, however, some form of correction is warranted to correct confidence bounds. (Huang 2016).

GEE methods will use marginal mean models with a logit link (binary family) as is appropriate for binary outcomes for missed opportunities. The clustering level will be the practice site for all analyses. This approach will not consider clustering of clinicians within practice site. This approach will also not consider the repeated measures of visits within child. Children are not nested within clinician, as a child can be seen by more than one clinician.

GEE methods will produce robust standard errors and respective confidence bounds directly for odds ratios. Odds ratios, however, are not easy to interpret for even rates that are common. For that reason, we will transform log odds estimates and their ratios into risk ratios and risk differences, and then use the delta method to estimate robust confidence bounds on the risk difference scale. Secondary analyses will include standardization by visit and patient-level factors prior to transformation.

Survey methods provide a computational alternative to GEE methods, which can fail with large cluster sizes, and assume independence working correlation structures. Survey methods will be used to replace GEE algorithms if the GEE algorithms fail. Such failure can occur when clusters (practice sites) are large. SAS, Stata, and R all have survey algorithms for logit link model.

Confidence bounds, alternatively, will be generated using percentile-based, bootstrap resampling of the practices to account for correlation of visit-level measures within practices to verify the validity of robust standard errors output by standard GEE procedures (Davison 1997) at our sample size of practices. Confidence bounds based on resampling will protect against large-sample assumptions made by standard implementations of GEE(Goodman 1994).

Programs for resampling are well described in R (Cluster.Bootstrap (2018), Stata, and in SAS (PROC SURVEY SELECT). We will use whichever one is easiest.

Secondary Analysis

Person-level analyses (vaccination rates) will employ the same marginal model methods as visit-level analyses.

References

Davison AC, Hinkley DV. Bootstrap methods and their application. Cambridge ; New York, NY, USA: Cambridge University Press; 1997.

Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. 2nd ed. Hoboken, N.J.: Wiley; 2011.

Goodman, Steven N., and Jesse A. Berlin. "The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results." Annals of internal medicine 121.3 (1994): 200-206.

Hayes RJ, Moulton LH. Cluster randomised trials, second edition. CRC Press, 2017

Huang S, Fiero MH, Bell ML. Generalized estimating equations in cluster randomized trials with a small number of clusters: Review of practice and simulation study. Clin Trials. 2016; 13(4):445-9. [PMID: 27094487]

Korn EL, Graubard BI. Analysis of health surveys. New York: Wiley; 1999.

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