The HPV 9-10 Trial: Early Initiation of HPV Vaccination

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Statistical Analysis Plan

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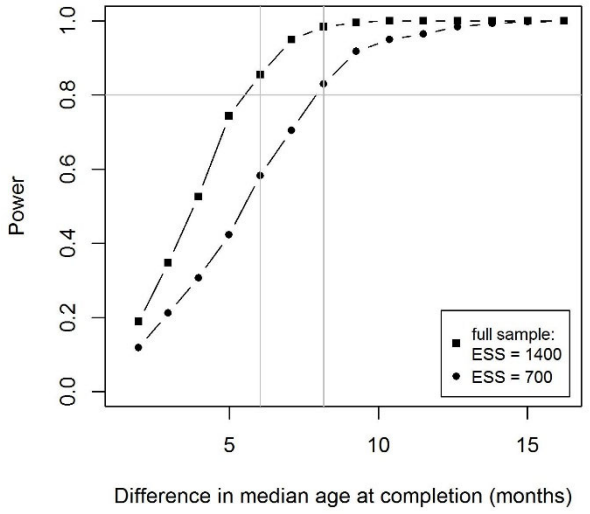
<u>Aim 2:</u> Conduct a cluster-randomized pragmatic trial comparing HPV9-10yrs vs HPV11-12yrs and, using the RE-AIM framework, assess the following effectiveness outcomes:

a. <u>Primary outcome</u>: Age at HPV series completion
Hyp 2a: Patients in HPV9-10 practices will have earlier age at vaccine completion than those in HPV11-12.
b. <u>Secondary outcome</u>: HPV completion by age 13
Hyp 2b: Patients in HPV9-10 practices will have higher proportions completing HPV series by age 13 than those in HPV11-12.
c. <u>Secondary outcome</u>: Age at HPV series initiation
Hyp 2c: Patients in HPV9-10 practices will have earlier age at vaccine initiation (i.e., age at first dose) than those in HPV11-12.

<u>Overall Strategy:</u> Descriptive statistics will be computed for patient and practice characteristics, initially reporting on differences between: (1) different treatment arms and (2) patient dropouts vs. non-dropouts. Covariates to be adjusted for in multivariable models at the patient level include age, gender, and type of insurance. The primary analysis will employ the intent-to-treat principle. We will follow patients prospectively for 4 years, assessing series completion status for each patient at the end of follow-up; patients not seen by the practice at follow-up will be assumed not to have completed vaccination by end of study and will be treated as censored. We will explore, using interaction effects in regression models, whether practice type, payer mix (mostly commercial or Medicaid), patient socio-demographics, and number of providers in a practice impacts intervention effectiveness. Goodness-of-fit statistics and model fitting diagnostics will be used to assess for influential points, outliers and to evaluate alternative model specifications. Hypothesis tests will be two-sided with $\alpha = .05$ and p-values will be reported. We will follow recent guidelines for statistical analysis plans of randomized trials and the CONSORT statement to report cluster-randomized trials. All statistical analyses will be performed using R or SAS version 9.4 (SAS Institute Inc., Cary, N.C.).

a. **Primary Outcome: Age at HPV series completion**
To test the primary study hypothesis that eligible patients ages 9-10 in the HPV9-10 practices will have earlier HPV series completion rates relative to those in HPV11-12 practices, we will use a Cox proportional hazards regression model to compare age at vaccination between study arms. Patients not experiencing the event of interest will be administratively censored at end of study. The model will include a practice-level treatment group indicator, along with covariates as listed above. Comparison between groups will be performed by testing whether the hazard ratio between the 11-12 arm and the 9-10 arm is different from 1; clustering of patients within practices will be accounted for using robust covariance estimators. We estimated power based on the log-rank test for equality of survival curves using Monte Carlo simulations in R based on 1000 datasets. Because there will likely be few or no individuals completing vaccination by age 11 in the control arm, we have assumed that the hazard in the control arm is 0 between 9 and 11 years of age, and that the hazard in the treatment arm starts to increase from age 9. Assuming an intraclass correlation coefficient (ICC) within practices of 0.01 and 14 practices per treatment arm with 100 patients per practice, with 3.5 years of follow-up we will have 85.5% power (alpha=0.05) to detect a 6.0-month difference in median age at completion between treatment arms (corresponding to a difference in proportion completing by age 13 of 6%). Even with a 50% reduction in our effective sample size (ESS), we will have 83.0% power to detect an 8.2-month difference in medians between treatment arms. Holding all else constant, this reduction in ESS is consistent with (a) an ICC of 0.03; (b) 7 practices per arm (c) 34 patients per practice (see Figure).



b. **Secondary Outcome: proportion completing HPV series by age 13**
To estimate proportion completing the HPV series by age 13, estimates of the survival curve for age at HPV series completion will be computed for each treatment arm based on the Cox regression models fitted for the primary analysis, using the estimated baseline hazard function; the statistic of interest is the difference between these estimates at age 13. We use survival analysis methods here (rather than logistic regression) because the analysis needs take into account that patients may be followed for different lengths of time, and they may or may not experience the event of interest by the end of the study. Standard errors will be estimated using the cluster bootstrap: resampling will occur at the practice level. Using the same simulations as described above to estimate power for the primary outcome, we found that the study will have 86.4% power to detect a 9% difference in the proportion completing by age 13 between treatment arms. This effect size corresponds to a completion rate at age 13 of 30% among controls and 39% among treated subjects.

c. **Secondary Outcome: Age at HPV series initiation**
The methods for estimating differences between treatment arms for the secondary outcome of age at HPV series initiation will be identical to those for the primary outcome (age at completion). The event of interest is series initiation (i.e., age at first dose). To estimate power, we used the same simulation design described above, now basing control initiation survival curves on previous data suggesting an initiation rate of 50% at age 13. The simulation results indicate that we will have >90% power (alpha=0.05) to detect an effect size equivalent to a difference in median age at initiation of 4.4 months. With a 50% reduction in ESS, we will still have 80.6% power to detect a difference in median age at initiation of 5.2 months.

Subgroup analyses

Sex as a biological variable: Although HPV vaccination is effective in both genders, HPV infection presents differently and causes different types of cancers in males and females. The vaccine was also recommended later for males, which may also affect rates of uptake by sex. Therefore, it is important to assess outcomes by gender.

HPV vaccine completion and initiation by gender, insurance and state

As for the primary outcome, Cox regression with standard errors adjusted for correlation within practices will be used to evaluate differences in treatment effect on age at vaccine initiation and completion within specified subgroups. The statistical analysis will involve tests of interaction terms between treatment and subgroup variable (e.g. gender) in the regression model. We do not expect to have data on ethnicity and race from all practices, therefore we will only be able to examine racial or ethnic differences in a subset of our practices.

Receipt of other adolescent vaccines (Tdap, MenACWY)
As for the primary outcome, Cox regression with standard errors adjusted for correlation within practices will be used to evaluate whether the intervention has any effect on receipt of other vaccines. The outcome will be age at completion of other vaccine (series), and patients not receiving these vaccines by end of study will be treated as censored. The statistical analysis will involve tests of the indicator for treatment status of the practice.

Other considerations

There are other potential methodological complexities in the analysis of the outcomes of this study, including left truncation and non-proportional hazards. *Left truncation*. We do not anticipate that left truncation will be a major issue for our primary study outcome because we only intend to include patients aged 9-10 at baseline, and vaccination rates in this age group should be zero. However, this could be an issue for some secondary outcomes, such as age at receipt of other childhood vaccines. Therefore, age of the child at baseline will be accounted for using delayed entry, as failure to account for this issue could lead to biased inference. *Non-proportional hazards*. We will test the proportional hazards assumption to see if any deviation is statistically significant; if found to be violated, we will employ alternative modeling strategies (e.g., time-dependent covariates/interactions, additive hazards regression). We note that even if there is evidence of non-proportional

hazards, the log-rank test remains valid, so we have chosen to use this for our power calculations. We will also perform a sensitivity analysis using Kaplan-Meier curves to assess the validity of some of the assumptions made by the Cox model, including proportional hazards. The Cox model essentially compares treatment arms across the entirety of the survival curve, while comparison of Kaplan-Meier curves at age 13 allows us to obtain more direct estimates of the treatment's effect on this particular endpoint. *Losses to follow-up*. Because it is possible that patients will be lost to follow-up prior to the administrative censoring we will apply at the end of the study, we will employ sensitivity analyses to determine how different assumptions regarding losses to follow-up might affect our results.

Outcome	**Type**	**Number of subjects**	**Effect size**	**Power**	**Method**
age at HPV series completion	Primary	2800	6.0-month difference in median ages	86%	Cox regression with robust covariance estimator
HPV completion by age 13 years	Secondary	2800	9%	86%	KM estimates with cluster bootstrap for variance estimation
age at HPV series initiation	Secondary	2800	4.4-month difference in median ages	>90%	Cox regression with robust covariance estimator