Centers for Disease Control and Prevention (CDC)

Clinical Immunization Safety Assessment (CISA) Project SAE

A Prospective, Randomized, Open-label Clinical Trial to Assess Apnea Following Administration of 13-valent Conjugate Pneumococcal Vaccine, Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccine, Inactivated Polio Vaccine, Hepatitis B Vaccine, and *Haemophilus influenzae* Type B Vaccine in Preterm Infants

Short Title:

Apnea in Preterm Infants Following the Administration of Routine Childhood Vaccines

Statistical Analysis Plan

Version 4.0

October 14, 2022

1 INTRODUCTION

This document describes the statistical procedures that will be utilized for the CISA protocol Apnea in Preterm Infants Following the Administration of Routine Childhood Vaccines. This statistical analysis plan (SAP) describes the methods of statistical analysis. The SAP version 1.0 was written prior to any data being analyzed in order to avoid bias. Any subsequent changes that occur to the study protocol warranting changes to the analysis procedures will be documented in the SAP. **Table 1** below will be used for tracking changes to the SAP (both draft versions (0.X) and the final version (X.0).

Table 1. Statistical Analysis Plan Versions

Version	Date of Approval	Major Changes from Prior Version
0.1	NA	Minor edits from Rachel Greenberg
0.2	NA	Minor edits from Rachel Greenberg
1.0	November 14, 2019	Not applicable
2.0	February 10, 2020	• 6.4 Analysis population: Deleted analyzing secondary endpoints with ITT population • 7.1: Presentation of baseline data: added postnatal age on the day of randomization and postmenstrual age on the day of randomization • XXXX • 8.4: Postmenstrual age evaluation (new section) • Other minor edits
3.0	August 27, 2021	• 9.0 Sensitivity Analysis: 1. Apneic events that cannot be adjudicated will be counted as non-apneic events
4.0	October 14, 2022	• Change relative risk to odds ratio • 8.4 Updated the PMA analysis to be performed by PMA group (PMA <37 weeks / ≥37 weeks)

2 PROTOCOL OBJECTIVES

2.1 Primary

a) PO 1: To compare proportions of preterm infants with apnea in a 48-hour monitoring period after vaccination in the "vaccinated" group versus a 48-hour monitoring period after randomization in the "unvaccinated" group.
The primary hypothesis is that the proportion of infants with apnea will be higher in the "vaccinated" group compared to the "unvaccinated" group.

2.2 Secondary

a) SO 1: To compare the clinical importance of apneic events in a 48-hour monitoring period after vaccination in the "vaccinated" group versus a 48-hour monitoring period after randomization in the "unvaccinated" group.

b) SO 2: To compare proportions of preterm infants with severe cardiorespiratory events in a 48-hour monitoring period after vaccination in the “vaccinated” group versus a 48-hour monitoring period after randomization in the “unvaccinated” group.

2.3 Exploratory

a) EO 1: To compare proportions of preterm infants with temperature instability in a 48-hour monitoring period after vaccination in the “vaccinated” group versus a 48-hour monitoring period after randomization in the “unvaccinated” group.

b) EO 2: To compare proportions of preterm infants with other clinically important adverse events in a 48-hour monitoring period after vaccination in the “vaccinated” group versus a 48-hour monitoring period after randomization in the “unvaccinated” group.

c) EO 3: To compare clinically important adverse events occurring between 48 hours and 14 days after vaccination among infants in the vaccinated group who do, and do not have apnea in a 48-hour monitoring period after vaccination.

3 STUDY ENDPOINTS

3.1 Primary

a)

POM 1.1: Proportion of infants with ≥ 1 apneic event in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

3.2 Secondary

a)

1. SOM 1.1: Average number of apneic episodes in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

2. SOM 1.2: Average duration of apneic episodes in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

3. SOM 1.3: Proportion of infants requiring any increase in respiratory support in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

b)

1. SOM 2.1: Proportion of infants with ≥1 severe cardiorespiratory event in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

2. SOM 2.2: Proportion of infants requiring positive pressure ventilation in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

3.3 Exploratory

a)

1. EOM 1.1: Proportion of infants with fever in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

2. EOM 1.2: Proportion of infants with hypothermia in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

b)

1. EOM 2.1: Average number of oxygen desaturation events in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

2. EOM 2.2: Average number of bradycardia events in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

3. EOM 2.3: Proportion of infants requiring blood culture for and/or antibiotics (intravenously or intramuscularly) in the setting of blood culture for sepsis evaluation in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

4. EOM 2.4: Proportion of infants with a serious adverse event in a 48-hour monitoring period after vaccination in the “vaccinated” group and a 48-hour monitoring period after randomization in the “unvaccinated” group.

c)

1. EOM 3.1: Proportion of hospitalized infants with ≥ 1 episode of clinical apnea between 48 hours and 14 days after vaccination.

2. EOM 3.2: Proportion of hospitalized infants requiring any increase in respiratory support between 48 hours and 14 days after vaccination.

3. EOM 3.3. Proportion of hospitalized infants requiring blood culture and/or antibiotics (intravenously or intramuscularly) in the setting of blood culture for sepsis evaluation in between 48 hours and 14 days after vaccination.

4. EOM 3.4. Proportion of hospitalized infants requiring positive pressure ventilation in between 48 hours and 14 days after vaccination.

5. EOM 3.5. Proportion of discharged infants readmitted to the hospital within 14 days of vaccination.

4 STUDY DESIGN

4.1 Study Description

This study is a prospective, randomized, open-label clinical trial to assess apnea in the 48 hours after randomization ("unvaccinated" group) versus 48 hours after vaccination ("vaccinated" group). The study population consist of premature infants <33 weeks and 0 days gestation at birth who have been hospitalized since birth and eligible to receive 2-month vaccines per the Advisory Committee on Immunization Practices (ACIP) schedule. Infants randomized to the "vaccinated group" will receive three vaccines:

(1) 13-valent Conjugate Pneumococcal Vaccine (PCV13);
(2) Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccine (DTaP), Inactivated Polio Vaccine (IPV)], Hepatitis B vaccine (HBV); and
(3) *Haemophilus influenzae* Type B Vaccine (Hib).

At least 300 infants will be enrolled over a period of 28 months at Duke University (Duke), University of North Carolina at Chapel Hill (UNC) and Cincinnati Children's Hospital Medical Center (CCHMC). The first 12 infants (Duke: 4, UNC: 4, CCHMC: 4) will be enrolled in a pilot study to assess the feasibility of the protocol and study instruments. The remaining 288 will be enrolled after the pilot study; 86 infants at Duke, 86 infants at UNC and 116 infants at CCHMC.

On day 1, eligible infants will be randomized 1:1 to a "vaccinated" or "unvaccinated" group. Infants in the "vaccinated" group will be observed on cardiorespiratory and pulse oximetry monitoring and PCV13, DTaP-IPV-HBV, and Hib vaccines will be given within 6 hours of randomization per Advisory Committee on Immunization Practices (ACIP) recommendations. Infants in the "unvaccinated" group will be continued on cardiorespiratory and pulse oximetry monitoring and no vaccines will be administered. Continuous cardiorespiratory and pulse oximetry monitoring are standard of care procedures for infants hospitalized in NICU. The study will collect data from the continuous cardiorespiratory and pulse oximetry monitors from randomization to 48 hours after randomization for infants in the unvaccinated group, and from randomization to 48 hours after vaccination for infants in the vaccinated group. Blinded analyst(s) at Duke University and Cincinnati Children's will evaluate data recorded by the cardiorespiratory and pulse oximeter monitors during this time period to determine the occurrence of apnea, bradycardia, and desaturation. In addition, information will be collected on increased respiratory support, sepsis evaluation and serious adverse events.

For infants in the "vaccinated" group, the study will also collect adverse events of clinical interest and serious adverse events occurring between the end of the 48-hour monitoring period and 14 days after vaccination. This information will be collected through parental report and review of medical records.

4.2 Sample Size and Power

The study has approximately 84.3% power to reject the null hypothesis of no difference in the proportion of infants with apnea in the "vaccinated" group compared to the "unvaccinated" group based on a two-side alpha 0.05 chi-square test with N=135 per group. This assumes that the proportion of infants with apnea will be 15% in the "unvaccinated" group and 2-fold higher (30%) in the "vaccinated" group. This assumption is based on a review of the literature and expert opinion. The study allows for a 10% dropout rate to give a total sample of 300 infants.

4.3 Randomization

Participants will be randomized (1:1) to either vaccinated or unvaccinated groups using a permuted block randomization scheme stratified by gestational age (<28 weeks, ≥28 weeks) and study site (i.e. Duke University Medical Center, University of North Carolina at Chapel Hill Hospital, and Cincinnati Children's Hospital Medical Center). Infants randomized to the vaccinated group should receive vaccines within 6 hours but will be allowed to receive vaccines up to 12 hours post-randomization. The first 12 infants enrolled in the Pilot Phase I will be randomized in a separate permuted block by manual randomization (e.g., envelopes). The project statistician at Duke University will generate permuted block randomization schemes, which will be uploaded to REDCap for the full study. The randomization schedule will not be available to the study staff, so the next randomization allocation will not be known before randomization occurs. Following confirmation of study eligibility criteria, participant randomization will be through REDCap with treatment arm allocation recorded on the case report form. In the event that REDCap is unavailable, manual randomization will occur through the use of envelopes. The project statistician will prepare 20 envelopes per site that will use the same randomization strategy as the primary scheme embedded in REDCap. When manually randomizing, the team member will pull the next envelope in order. In order to capture the allocation per subject, a separate form in REDCap will be used by the personnel to add the assignment. A log will need to be kept at the site capturing these instances.

4.4 Blinding

This study will be open label and study staff, caregivers, and parent(s)/LAR(s) will not be blinded to treatment arm assignments. The output from the cardiorespiratory monitors will be read by analysts who are blinded to the treatment arm assignments.

5 PARAMETERS OF ANALYSIS

5.1 Data Collection and Storage

Data will be handled according to the Duke Vaccine and Trials Unit SOP (DVTU M010). Data will be captured on paper CRFs and entered into the REDCap database. Data will also be captured using the output from the monitors. These data files will be processed in SAS 9.4 to determine outcomes of interest related to apnea and cardiorespiratory events.

5.2 Analytic Issues

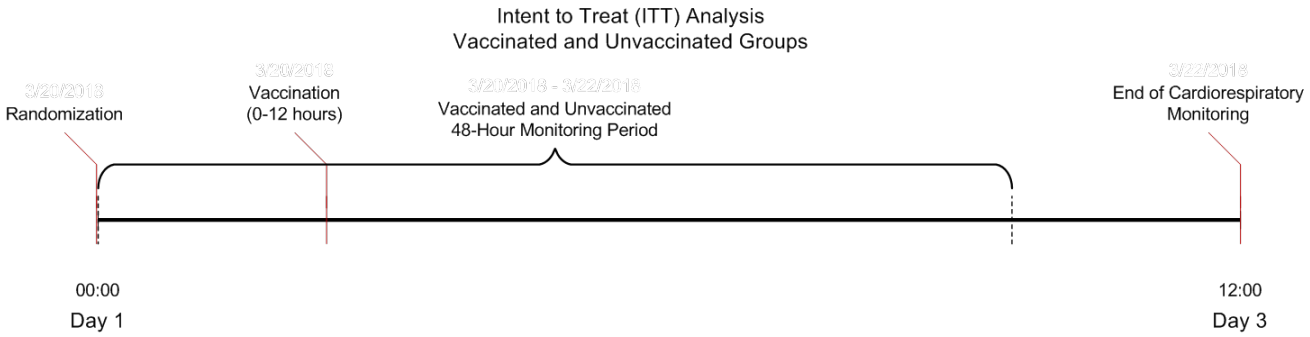
There are three sites participating in the study and analysis of the primary objective will be stratified by site to account for this unit of randomization. Secondary data objectives may be stratified by site when applicable. There is one primary objective evaluated at the two-sided alpha 0.05 level and no adjustments to the alpha level will be made for secondary and exploratory analyses.

6 ANALYSIS POPULATIONS

6.1 Intent-to-Treat (ITT) population (Figure 1)

a) Definition: The ITT population includes any infant that was enrolled and randomized in the study.
b) Analysis: For the ITT analysis, study outcomes in the 48-hour monitoring after randomization will be evaluated in both vaccinated and unvaccinated group. Infants will be analyzed in their assigned treatment arms irrespective of receipt of vaccine.

Figure 1. Intent-to-Treat (ITT) Analysis



6.2 Modified Intent-to-Treat (mITT) population (Figure 2)

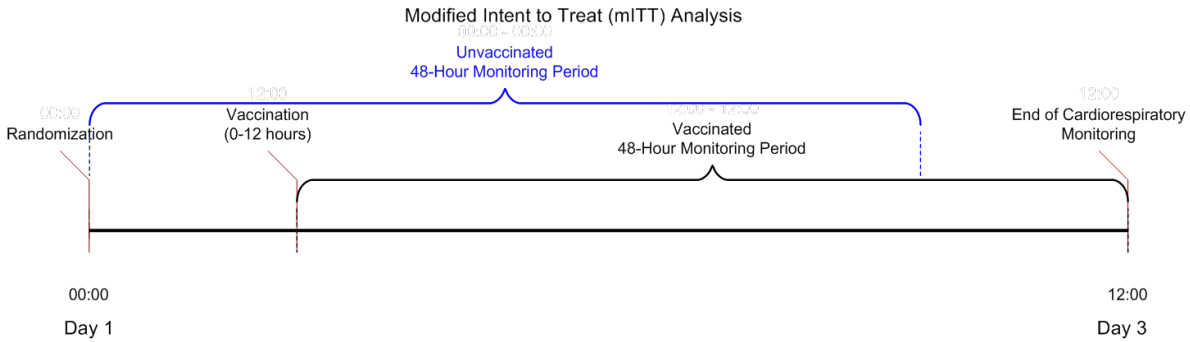
a) Definition: The definition is the same for the ITT and mITT. The mITT population includes any infant that was enrolled and randomized in the study.

b) Analysis: For the mITT analysis, infants will be analyzed in their assigned treatment arms irrespective of receipt of vaccine. Study outcomes will be included in the analysis as follows:

i) Vaccinated group: study outcomes in the 48-hour monitoring after vaccination. If vaccination does not occur by 12 hours after randomization, then study outcomes will be assessed between 12 and 60 hours after randomization.

ii) Unvaccinated group: study outcomes in the 48-hour monitoring period after randomization. This is the same for the IIT and the mITT populations.

Figure 2. Modified Intent-to-Treat (mITT) Analysis



6.3 Per Protocol (PP)

a) Definition: The PP population includes any infant that was enrolled, randomized and did not have any major protocol violations for analysis as determined by the study investigators. See Appendix 1.

b) Analysis: For the PP analysis, study outcomes will be included in the analysis as follows:

i) Vaccinated group: study outcomes in the 48-hour monitoring after vaccination. The analysis will exclude infants who do not receive vaccine by 12 hours.

ii) Unvaccinated group: study outcomes in the 48-hour monitoring period after randomization. The analysis will exclude infants who are vaccinated during the study period.

6.4 Analysis of populations

The mITT population will be the primary analysis population for all planned analyses for the study objectives. The ITT population will be analyzed for the primary objective. The PP population will be analyzed for all planned objectives as supporting analyses. For comparison, pre-specified secondary analyses will also be performed using the ITT and PP populations.

7 BASELINE DATA AND FLOW CHART

7.1 Presentation of Baseline Data

The following baseline data will be presented by site and vaccination group: age, birthweight, sex, gestational age (median, range and number and percentages <28 weeks and ≥28 weeks gestational age), multiple gestation, reason for preterm delivery, insurance payer status, ethnicity, race, whether sibling currently enrolled or previously enrolled in this study, and medical conditions since birth (including intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia, seizures, and apnea of prematurity), postnatal age on the day of randomization, postmenstrual age on the day of randomization, respiratory support and supplemental oxygen use on the day of randomization, caffeine use on the day of randomization, and receipt of Synagis or other procedures during the study period. Summary statistics (e.g., mean, median, standard deviation, interquartile range) will be presented for continuous variables. Categorical variables will be described with frequencies and percentages.

7.2 Flow Chart

The number of enrolled participants will be presented in a flow chart by study site and vaccination group. The number of infants with complete cardiorespiratory monitoring data for the required length of monitoring will be presented, along with a breakdown of the analysis populations by arm.

8 ANALYSIS OF STUDY OBJECTIVES

For each objective below the analysis using the primary mITT population is described. Secondary analyses will also be done using the ITT and PP populations as described in Section 6.

8.1 Primary Objective

The primary objective (**PO-1**) of the study is to compare proportions of preterm infants with apnea in a 48-hour monitoring period after vaccination in the “vaccinated” group versus a 48-hour monitoring period after randomization in the “unvaccinated” group.

- *Research hypothesis: the proportion of infants with apnea will be higher in the “vaccinated” group compared to the “unvaccinated” group.*

The proportion of infants with ≥1 apneic event will be presented for each group and compared using a Mantel-Haenszel statistic in a stratified analysis by study site and gestational age to control for the randomization blocks at the two-sided alpha 0.05 level. The stratified odds ratio and corresponding 95% confidence interval for the occurrence of apnea will also be calculated.

Apnea will be defined as a pause in respirations of >20 seconds, or a pause in respirations of >15 seconds with associated bradycardia (heart rate <80 beats per minute), obtained from the cardiorespiratory monitor. Presence of ≥1 apneic event will be counted as positive (1) for this analysis and no apnea reported will be negative (0). Apneic events identified by the

cardiopulmonary monitor will be confirmed during manual blinded review via an agreed-upon review process. Apneic events determined by the monitor must also be confirmed by manual review to be counted as apnea for the primary analysis. If these events are NOT by manual review, then they are not counted as apnea for the primary analysis. However, events without supporting cardiorespiratory monitoring strips, that cannot be manually reviewed, will also be counted as apnea for the primary analysis.

No adjustments will be made to the alpha level (two-sided alpha=0.05) for the primary objective.

8.2 Secondary Objectives

There are two secondary objectives for this study.

a) The first secondary objective (**SO-1**) is to compare the clinical importance of apneic events in a 48-hour monitoring period after vaccination in the "vaccinated" group versus a 48-hour monitoring period after randomization in the "unvaccinated" group.

   There are 3 secondary outcome measures (SOM) for this objective. For SOM 1.1, the average number of apnea events in each group will be presented and the number of apnea events will be compared using a Poisson regression model with study site and gestational age as covariates to control for the randomization blocks. Summary statistics regarding the number of distinct apnea episodes and the duration of episodes, including mean, median, standard deviation, and range will be reported by group and site.
   For SOM 1.2, the average duration of apnea episodes between groups will be compared using a mixed effects model (Robinson 2007) with a random intercept for each infant with one or more events and study site and gestational age as covariates to control for the randomization blocks. Apneic events will be identified using the same criteria for primary objective.
   For SOM 1.3, the proportion of infants requiring an increase in respiratory support will be presented and compared using a Mantel-Haenszel statistic in a stratified analysis by site and gestational age to control for the randomization blocks at the two-sided alpha 0.05 level. The stratified odds ratio and corresponding 95% confidence interval for the occurrence will also be calculated. These tests will be performed at the alpha 0.05 level.

   Increase in mode of respiratory support will be defined as (a) progression from any lower level at baseline (at time of randomization in the unvaccinated group and vaccination in the vaccinated group) to any higher level, as well as (b) any increase in nasal cannula flow rate, or continuous positive airway pressure (CPAP).

b) The subsequent secondary objective (**SO-2**) is to compare proportions of preterm infants with severe cardiorespiratory events in a 48-hour monitoring period after vaccination in the "vaccinated" group versus a 48-hour monitoring period after randomization in the "unvaccinated" group.

   For this objective the proportion of infants in each group who experienced ≥1 severe cardiorespiratory event (SOM 2.1, as defined in **Section 5.4**) or received positive pressure ventilation (SOM 2.2) at least once during the 48 hours after

randomization/vaccination will be presented and these proportions will be compared using a Mantel-Haenszel statistic in a stratified analysis by study site and gestational age to control for the randomization blocks. The stratified odds ratio and corresponding 95% confidence interval for the occurrence of both measures will also be calculated.

Severe cardiorespiratory events will be defined according to the protocol. Events that meet the protocol-defined criteria due *only* to a respiratory pause of >30 seconds will be confirmed by manual review. Only events confirmed by manual review will be counted. However, events without supporting cardiorespiratory monitoring strips, that cannot be manually reviewed, will also be counted as apnea for this analysis.

No adjustments will be made to the alpha level (two-sided alpha=0.05) for these secondary objectives.

8.3 Exploratory Objectives

There are three exploratory objectives for this study.

a) The first exploratory objective (**EO-1**) is to compare proportions of preterm infants with temperature instability in a 48-hour monitoring period after vaccination in the "vaccinated" group versus a 48-hour monitoring period after randomization in the "unvaccinated" group.

   For this objective we will present the proportion of infants in each group experiencing fever (temperature ≥38°C) (EOM 1.1) and the proportion in each group experiencing hypothermia (temperature <36°C; as defined in **Section 5.4**) (EOM 1.2) at least once during the 48 hours after randomization/vaccination. These proportions (fever and hypothermia) will be compared using a Mantel-Haenszel statistic in a stratified analysis by study site and gestational age to control for the randomization blocks. The stratified odds ratio and corresponding 95% confidence interval for the occurrence of fever and hypothermia will also be calculated.

b) The second exploratory objective (**EO-2**) is to compare event counts and proportions of preterm infants with other clinically important adverse events in a 48-hour monitoring period after vaccination in the "vaccinated" group versus a 48-hour monitoring period after randomization in the "unvaccinated" group.

   For this objective the number of oxygen desaturation events (EOM 2.1) and the number of bradycardia events (EOM 2.2) will be presented using summary statistics regarding the number of distinct events and the duration of events, including mean, median, standard deviation, and range will be reported by group and site. The number of events for each outcome will be compared using a Poisson regression model with study site and gestational age as covariates to control for the randomization blocks.

   The proportion of infants in each group experiencing other clinically important adverse events (infants requiring blood culture and/or antibiotics (intravenously or intramuscularly) in the setting of blood culture for sepsis evaluation (EOM 2.3) and infants with a serious adverse event (SAE; EOM 2.4; protocol section 5.4) at least once during the 48 hours after randomization/vaccination will be presented. These

proportions will be compared using a Mantel-Haenszel statistic in a stratified analysis by study site and gestational age to control for the randomization blocks. The stratified odds ratio and corresponding 95% confidence interval for the occurrence of these outcome measures will also be calculated. We will provide a listing of SAE narratives and relatedness descriptions.

c) The third exploratory objective (**EO-3**) is to compare clinically important adverse events occurring between 48 hours and 14 days after vaccination among infants in the vaccinated group who do / do not have apnea in a 48-hour monitoring period after vaccination.

For this objective the proportion of infants in the vaccinated group with and without apnea in a 48-hour monitoring period who experience each of the clinically important adverse events listed below at least once between 48 hours and 14 days after vaccination will be presented.

- ≥ 1 episode of clinical apnea in hospitalized infants (EOM 3.1)
- any increase in respiratory support in hospitalized infants (EOM3.2)
- blood culture and/or antibiotics (intravenously or intramuscularly) in the setting of blood culture for sepsis evaluation in hospitalized infants (EOM 3.3)
- positive pressure ventilation in hospitalized infants (EOM 3.4)
- readmission to the hospital within 14 days of vaccination in discharged infants (EOM 3.5)

These subgroup comparisons will be made using a Mantel-Haenszel statistic in a stratified analysis by study site and gestational age to control for the randomization blocks at the two-sided alpha 0.05 level. The stratified odds ratio and corresponding 95% confidence interval for the occurrence of these outcome measures will also be calculated.

No adjustments will be made to the alpha level (two-sided alpha=0.05) for these exploratory analyses.

8.4 Postmenstrual age (PMA) Evaluation

Study objectives PO1, SO1, SO2, EO2.1, EO2.2, EO3.1, and EO3.2 will be presented and evaluated between groups by postmenstrual age group (PMA <37 weeks / ≥37 weeks). PMA will be defined as the sum of gestational age plus postnatal age**.** PO1, SO2, and EO3 are categorical with either no event or 1 or more events, and will be presented and compared using a Mantel- Haenszel statistic by PMA group at the two-sided alpha 0.05 level. The stratified odds ratio and corresponding 95% confidence interval for the occurrence will also be calculated. SO1 and EO2 are count data and will be compared using a Poisson regression model with study site as covariates by PMA group. These tests will be performed at the alpha 0.05 level.

9 SENSITIVITY ANALYSES

The following sensitivity analyses are planned:

1) Apneic events that cannot be adjudicated will be counted as non-apneic events, and the PO-1 and SO-2 (severe cardiorespiratory events) will be reanalyzed.
2) All apneic events determined by the cardiorespiratory monitor will be counted as apneic events, regardless of manual review, and the PO-1 and SO-2 (severe cardiorespiratory events) will be reanalyzed.
3) The following infants will be excluded from analysis and all objectives re-analyzed:
    a. Infants with a major surgical procedure (including circumcision) during the study period.
    b. Receipt of any intramuscular injection, including Synagis or a vaccine other than DTaP, IPV, HBV, PCV13, or Hib during the study period.

10 INTERIM SAFETY DATA REVIEW

Given that this study involves administering U.S.-licensed vaccines recommended by the ACIP for preterm infants and included as part of routine clinical care, there will not be a designated data safety monitoring board for this study. However, due to the fragility of the study population and interventional design, one interim safety data review will be performed with the goal of identifying unexpected safety concerns of clinical importance. The safety data review will provide the study the opportunity to identified unexpected safety concerns and make changes to the protocol if needed. The interim safety data review will be done by a safety monitoring panel with relevant expertise, comprised of experts who are not co-investigators on this study. The safety population for the interim safety review will include infants who were enrolled and randomized. Infants who participated in the pilot study will also be included. The safety monitoring panel will review clinical narratives of SAEs. If the CDC and study investigators determine additional analyses or reviews are needed, efforts will be made to conducted additional analysis or reviews that will not include analyzing the primary endpoint as a first step. This is to avoid introducing bias or increasing sample size needs for statistical power.

Appendix 1

Major Protocol Violations for Analysis

1. Infant later found to have not met inclusion/exclusion criteria at the time of study entry.
    a. Infant will not be counted as a protocol violation for analysis if the only exclusion criterion met is that the child or parent/LAR is an immediate relative of study staff or an employee who is supervised by study staff.
2. Infant did not have cardiorespiratory monitoring data for the fully specified time period after vaccination/randomization
    a. Vaccinated group: No cardiopulmonary data for 48 or more hours after vaccination. Infants with <1 hour of absent cardiopulmonary data for this period will not be considered a violation for analysis.
    b. Unvaccinated group: No cardiopulmonary data for 48 or more hours after randomization. Infants with <1 hour of absent cardiopulmonary data for this period will not be considered a violation for analysis.
3. Infant did not receive all vaccines by 12 hours after randomization in the vaccinated group
4. Infant in the unvaccinated group received vaccines during the 48 hours after randomization.

References

Robinson, A. (2007). "Applied longitudinal analysis. Garrett M. Fitzmaurice, Nan M. Laird, James H. Ware, Wiley-Interscience, Hoboken, NJ, 2004. No. of pages: xix+506. Price: $105.00. ISBN 0-471-21487-6." Stat Med **26**(20): 3824-3825.