Centers for Disease Control and Prevention

Clinical Immunization Safety Assessment (CISA) Project

A Prospective, Randomized, Clinical Trial to Compare Adverse Birth Outcomes in Pregnant Women Receiving Quadrivalent Recombinant Influenza Vaccine (RIV4) versus Quadrivalent Inactivated Influenza Vaccine (IIV4)

Short Title: Safety of RIV4 versus IIV4 in Pregnant Women

Statistical Analysis Plan

Version 2.0

August 19, 2022

1 INTRODUCTION

This document describes the statistical procedures that will be utilized for the CISA protocol Safety and Immunogenicity of Pregnant Women Receiving Quadrivalent Recombinant Influenza Vaccine (RIV4) versus Quadrivalent Inactivated Influenza Vaccine (IIV4) that was approved on August 10, 2020. This statistical analysis plan (SAP) describes the methods of statistical analysis. The initial draft SAP (Version 0.1) was developed prior to any data being analyzed in order to avoid bias. Any subsequent changes that occur to the study protocol and requires changes to the analysis procedures will be documented in the SAP (both draft versions (0.X) and the final version (X.0)). Table 1 below will be used for tracking of changes to the SAP. In this study adult pregnant women ≥ 18 years at ≤ 34 weeks gestation are randomized 1:1 to receive either RIV4 (Flublok® quadrivalent recombinant influenza vaccine) or IIV4 (quadrivalent inactivated influenza vaccine) using a permuted block randomization scheme stratified by study site (Duke, Cincinnati, Boston).

Table 1. Statistical Analysis Plan Versions

Version	Date of Approval	Major Changes from Prior Version
0.1	TBD	NA
0.2	TBD	Removed language regarding stratification by gestational age because an error in setting up REDCap lead to drawing from only the <20 weeks randomization block in the 2019-20 influenza season.

2 PROTOCOL OBJECTIVES

2.1 Primary

a) PO1: To compare the proportions of adverse birth outcomes in pregnant women vaccinated with RIV4 versus IIV4.
Research hypothesis: The proportion of pregnant women with adverse birth outcomes will be noninferior (not higher) after receipt of RIV4 compared to IIV4.

2.2 Secondary

a) SO1: To compare proportions of preterm birth after RIV4 versus IIV4 vaccination.

b) SO2: To compare proportions of combined fetal and neonatal death after RIV4 versus IIV4 vaccination.

c) SO3: To compare proportions of spontaneous abortion after RIV4 versus IIV4 vaccination.

d) SO4: To compare proportions of moderate/severe solicited reactogenicity events in pregnant women vaccinated with RIV4 versus IIV4.

2.3 Exploratory

a) EO1: To compare and describe serious adverse events (SAE) in pregnant women vaccinated with RIV4 versus IIV4.

b) EO2: To compare proportions of adverse pregnancy and birth outcomes of clinical interest after RIV4 versus IIV4 vaccination.

c) EO3: To compare and describe health outcomes through 90 days of life in infants born to women after RIV4 versus IIV4 vaccination.

d) EO4: To compare maternal immune responses to influenza antigens after RIV4 versus IIV4 vaccination.

e) EO5: To compare cord blood antibody levels for influenza antigens after RIV4 versus IIV4 vaccination.

3 STUDY ENDPOINTS

3.1 Primary

a) POM1: Proportions of adverse birth outcomes in pregnant women vaccinated with RIV4 versus IIV4.
Adverse birth outcome is a composite of occurrence of at least one of the following: preterm birth, spontaneous abortion, fetal death, or neonatal death.

3.2 Secondary

a) SOM1: Proportions of preterm birth after RIV4 versus IIV4 vaccination.

b) SOM2: Proportions of combined fetal and neonatal death after RIV4 versus IIV4 vaccination.

c) SOM3: Proportions of spontaneous abortion after RIV4 versus IIV4 vaccination.

d) SOM4: Proportions of pregnant women with moderate/severe solicited reactogenicity events (local and systemic) within 8 days after vaccination with RIV4 versus IIV4.

3.3 Exploratory

a)

1. EOM1.1: Frequency and descriptions of serious adverse events in pregnant women vaccinated with RIV4 versus IIV4 during the 42 days after vaccination.

2. EOM1.2: Frequency and descriptions of serious adverse events in pregnant women vaccinated with RIV4 versus IIV4 during the study

b)

1. EOM2.1. Proportions of infants born small-for-gestational age after RIV4 versus IIV4 vaccination.

2. EOM2.2: Proportion of pregnant women with clinical chorioamnionitis after RIV4 versus IIV4 vaccination.

3. EOM2.3: Proportion of women with preeclampsia or eclampsia after RIV4 versus IIV4 vaccination.

c)

1. EOM3.1: Proportion of infants with medically-attended events through 90 days of life after maternal RIV4 versus IIV4 vaccination.

2. EOM3.2: Frequency and description of SAEs in infants through 90 days of life after maternal RIV4 versus IIV4 vaccination.

3. EOM3.3 Proportion of infants with neonatal death after maternal RIV4 versus IIV4 vaccination.

d)

1. EOM4.1: Proportion of pregnant women achieving seroconversion at day 29 after RIV4 versus IIV4 vaccination [a Hemagglutination Inhibition Assay (HAI) titer $\geq$ 1:40 at day 29 if the baseline titer is < 1:10 or a minimum four-fold rise in HAI titer if the baseline titer is $\geq$ 1:10) for each influenza vaccine antigen].

2. EOM4.2: Proportion of pregnant women with a seroprotective HAI titer (≥ 1:40) post-vaccination at day 29 after RIV4 versus IIV4 vaccination for each influenza vaccine antigen.

3. EOM4.3: The maternal geometric mean HAI titer (GMT) pre and post-vaccination at day 29 after RIV4 versus IIV4 for each influenza vaccine antigen and the post/pre-vaccination ratio.

e)

1. EOM5.1: Proportion of infants with cord blood seroprotective HAI titer (≥ 1:40) for each influenza vaccine antigen after maternal RIV4 versus IIV4 vaccination.

2. EOM5.2: Infant cord blood geometric mean HAI titer (GMT) for each influenza vaccine antigen after maternal RIV4 versus IIV4 vaccination.

3. EOM5.3: Ratio of cord blood to maternal influenza antibody titers at time of delivery for each influenza vaccine antigen after maternal RIV4 versus IIV4 vaccination.

4 STUDY DESIGN

4.1 Study Description

This study is a prospective, randomized clinical trial of approximately 430 pregnant women enrolled at Duke University Medical Center (Lead Contractor), Cincinnati Children's Hospital Medical Center (Contributing Contractor), and Boston Medical Center (Contributing Contractor). Pregnant women ≥ 18 years of age at ≤ 34 weeks gestation, will be enrolled and randomized 1:1 to receive either quadrivalent recombinant influenza vaccine (RIV4) or quadrivalent inactivated influenza vaccine (IIV4). The designated vaccine brands for this study are Flublok® quadrivalent (Sanofi) and quadrivalent Flulaval® (GSK) (comparator

IIV4). However, the choice of IIV4 vaccine administered will be based on availability from manufacturers prior to the 2019-2020 and 2020-2021 influenza seasons.

After vaccination, participants and their infants will be followed to assess adverse pregnancy and birth outcomes, maternal vaccine reactogenicity, immunogenicity, serious adverse events, and short-term infant outcomes. Maternal and infant outcomes will be collected by medical record review from enrollment through 90 days postpartum.

4.2 Laboratory

Serologic studies – We will evaluate pre- and post-vaccination serologic responses in both IIV4 and RIV4 groups. IgG levels will be measured for the specific viral strains included in the 2019-2020 and 2020-2021 quadrivalent influenza vaccines using hemagglutination inhibition assays at the Duke Regional Biocontainment Laboratory (RBL) Virology Unit. Venous blood (approximately 15 mL of blood) will be collected from each participant before and 29 (-7 to +14) days after vaccination. At Duke, maternal and infant cord blood (approximately 15mL of blood each) collection will be performed at delivery for serological analysis in both RIV4 and IIV4 vaccination groups. At the other sites, these samples (maternal and cord blood) will be collected during delivery only if feasible for similar serological analysis. An assessment of placental antibody transfer (maternal:cord antibody ratio) will be determined.

4.3 Sample Size and Power

Allowing for a 5% drop out rate and given an initial N=430, there should be approximately 408 pregnant women participants for evaluation. We assume that 15% of pregnant women will have adverse birth outcomes after vaccination with RIV4 or IIV4, based on national and CISA site estimates of preterm birth rates. We have selected a clinically meaningful noninferiority margin of 10%. Statistical calculations show that with a one-sided alpha of 0.025 and 204 subjects in each group across all study sites, there is approximately 81% power to reject the null hypothesis that RIV4 is inferior to IIV4 in the proportion of adverse birth outcomes.

4.4 Randomization

Participants will be randomized (1:1) to receive either RIV4 (Flublok® quadrivalent recombinant influenza vaccine) or IIV4 (quadrivalent inactivated influenza vaccine) using a permuted block randomization scheme stratified by study site (Duke, Cincinnati, Boston). The project statistician will generate permuted block randomization schemes which will be uploaded to REDCap. 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 during Visit 1, participant randomization will be through REDCap with treatment allocation recorded on the case report form (CRF).

In the event that REDCap is unavailable, manual randomization will occur through the use of envelopes. The project statistician will prepare 20 envelopes per gestational age group per site (total of 40 per site) that will use the same randomization strategy as the primary scheme embedded in REDCap. When an unblinded team member is informed of the gestational age group, he/she 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 unblinded personnel to add the assignment. A log will need to be kept at the site capturing these instances.

We had planned to have gestational age as a stratification factor for randomization (<20 weeks, ≥ 20 weeks). Unfortunately, the setup in REDCap only drew from the <20 weeks randomization block. The benefits for randomization have been maintained, and we will evaluate secondary outcomes by site and gestational age to determine if specified analyses can adjust for this factor. The cell counts need to be 5 or greater to have reasonable results.

4.5 Blinding

This study is double-blinded, therefore study staff and participants will be blinded to randomization assignments. Trained, licensed staff will serve as unblinded vaccinators to administer either RIV4 or IIV4. All other study personnel involved in collection of memory aids, follow-up phone calls, and data collection, will be blinded to randomization arm. Laboratory staff will be blinded to randomization arm assignment.

The participant will receive documentation of receipt of influenza vaccine without specification of whether it was RIV4 or IIV4 vaccine to preserve blinding. In the event of individual participant clinical safety issues or overall study safety concerns, then blinding may be broken.

5 PARAMETERS OF ANALYSIS

5.1 Data Collection and Storage

Data will be handled according to the Duke Vaccine and Trials Unit Standard Operation Procedure (SOP) (DVTU M010). Data will be captured on paper case report forms (CRFs) and entered into the REDCap database. Memory aid data may be entered directly into REDCap by the participant, if the participant chooses to use this method.

5.2 Analytic Issues

There are three study sites participating in the study and analysis of the primary objective will be stratified by site (Duke, Boston, Cincinnati) to account for this unit of randomization. All objectives will be stratified by site when applicable. There is one primary objective being evaluated, using a noninferiority hypothesis at the one-sided alpha 0.025 level. Otherwise, the alpha level will be set at two-sided alpha 0.05 for the secondary objectives and all exploratory objectives.

6 ANALYSIS POPULATIONS

6.1 Modified Intent-to-Treat (mITT):

The mITT Population includes any participant that was enrolled, randomized into the study, and received study vaccine.

6.2 Per Protocol (PP):

The PP Population is a subset of the mITT Population excluding those participants with major protocol violations as determined by the study investigators (Appendix 1).

6.3 Maternal Immunogenicity Population

The Maternal Immunogenicity Population is a subset of the mITT Population that includes only pregnant women participants who received study vaccine, provide baseline and post-vaccination Visit 4 blood draws available for analysis within the protocol-defined time frame,

and with no major protocol violations affecting immunogenicity as determined by the study investigators.

The mITT Population is the primary analysis population for the safety and health outcomes analyses, with the PP Population as a confirmatory analysis population. The Immunogenicity Population is the primary analysis population for maternal immunogenicity outcomes (Exploratory Objectives 5); otherwise the mITT Population will be used for the Exploratory Objectives.

7 BASELINE DATA AND FLOW CHART

7.1 Presentation of Baseline Data

The following baseline information will be presented by treatment group, age, ethnicity, race and tobacco, marijuana or other substance use, gestational age at vaccination, study enrollment site, and influenza season of enrollment. Summary statistics (e.g., mean, standard deviation, median) will be presented for continuous variables. Categorical variables will be described with frequencies and percentages. Specific medical issues (i.e., hypertension, diabetes, and prior preterm birth) will also be presented.

7.2 Flow Chart

The number of enrolled participants will be presented in a flow chart by treatment group. The number of visits completed and missed will be presented, along with a breakdown of the three analysis populations.

8 ANALYSIS OF STUDY OBJECTIVES

8.1 Primary Objective

1. To compare the proportions of adverse birth outcomes in pregnant women vaccinated with RIV4 versus IIV4.
   - *Research hypothesis: The proportion of pregnant women with adverse birth outcomes will be noninferior (not higher – based on the noninferiority margin) after receipt of RIV4 compared to IIV4.*

     This objective will be assessed using a one-sided noninferiority test with the alpha level set at 0.025 (1-sided) and a noninferiority margin of 10%.

     The null hypothesis assumes that RIV4 is inferior to IIV4 in regards to the proportion of pregnant women with adverse birth outcomes.

     $$H_o: RIV4 - IIV4 \geq 0.10 \ (10\%)$$

     The alternative hypothesis states that RIV4 is noninferior to IIV4 in regards to the proportion of pregnant women with adverse birth outcomes.

     $$H_a: RIV4 - IIV4 < 0.10 \ (10\%)$$

     The upper bound of a stratified (by study site) Newcombe binomial confidence interval (Yan and Su 2010) with Cochran-Mantel-Haenszel (CMH) weighting of the difference will be used to make this assessment.

A composite outcome for adverse birth outcome [defined by the occurrence of at least one of the following events: preterm birth, spontaneous abortion, fetal death or neonatal death] will be used as the primary study endpoint.

Definitions for the component of the primary outcome measures are as follows:

- Preterm birth- born alive at less than 37 weeks and 0 days gestation
- Spontaneous abortion (SAB)- pregnancy loss prior to 20 weeks 0 days
- Fetal death- intrauterine death of fetus at or after 20 weeks 0 days
- Neonatal death- infant death within first 28 days of life.

8.2 Secondary Objectives

1. SO1: To compare proportions of preterm birth after RIV4 versus IIV4 vaccination.

   This proportion will be compared between the RIV4 group and the IIV4 group using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. The site adjusted odds ratio and corresponding 95% confidence interval for the proportion of preterm birth will also be calculated.

2. SO2: To compare proportions of combined fetal death and neonatal death after RIV4 versus IIV4 vaccination.

   These proportions will be compared between the RIV4 group and the IIV4 group using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. The site adjusted odds ratio and corresponding 95% confidence interval for the proportions of combined fetal death and neonatal death will also be calculated.

3. SO3: To compare proportions of spontaneous abortion after RIV4 versus IIV4 vaccination.

   This proportion will be compared between the RIV4 group and the IIV4 group using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. The site adjusted odds ratio and corresponding 95% confidence interval for the proportion of spontaneous abortion after vaccination will also be calculated. This will be a subgroup analysis of only those participants vaccinated at less than 20 weeks gestational age.

4. SO4: To compare proportions of moderate/severe solicited reactogenicity events in pregnant women vaccinated with RIV4 versus IIV4 (tables 2 and 3 below).

Reactogenicity will be assessed for 8 days following the vaccination at Visit 1. These proportions will be presented by treatment group, symptom, and grade level (moderate/severe) for women with injection site reactogenicity within 8 days post-vaccination. These proportions will be compared between the RIV4 group and the IIV4 group, within symptom, using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. Systemic reactogenicity will be presented in a similar fashion. There will be 14 comparisons performed.

Table 2: Injection-site Reactogenicity*			
Symptom	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Tenderness	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Induration/ Swelling	25 to ≤50 mm	51 to ≤100 mm	>100 mm
Erythema	25 to ≤50 mm	51 to ≤100 mm	>100 mm

**Injection-site criteria being used in the CISA Study on Safety of RIV4 versus IIV4 in Pregnant Women*

Table 3: System Reactogenicity*			
Systemic	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Fever **	≥100.4 to ≤101.1° F	≥101.2 to ≤102.0° F	≥102.1° F
Malaise (Fatigue)	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Myalgia (Body aches)	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Arthralgia (Joint pain)	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Nausea	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Vomiting	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Diarrhea	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Abdominal pain	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism

Headache	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism
Chills/shivering	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity and resulted in medical visit or absenteeism

*** Oral temperature, no recent hot/cold beverages or smoking*

8.3 Exploratory Objectives

1. EO1: To compare and describe serious adverse events (SAE) in pregnant women vaccinated with RIV4 and IIV4.

   The proportion and 95% exact binomial confidence interval of the number of participants with serious adverse events (SAEs), as well as the total number of events, will be presented by site, vaccine group, severity, and relatedness. Listings of these SAEs will also be presented. Non-overlapping confidence boundaries will be an indication of a statistical difference between the groups. These presentations and listings will be provided for the participant's study duration and for the first 42 days after vaccination. Note the study monitoring period for each participant is up to 90 days post-partum.

2. EO2: To compare proportions of adverse birth outcomes of clinical interest after RIV4 versus IIV4 vaccination.

   These proportions (i.e., infants born small-for-gestational age, pregnant women with clinical chorioamnionitis, and pregnant women with preeclampsia or eclampsia) will be compared between the RIV4 group and the IIV4 group using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level.

3. EO3: To compare proportions of severe local and/or solicited reactogenicity events in pregnant women vaccinated with RIV4 versus IIV4 and describe proportions of solicited reactogenicity events by severity grade in pregnant women vaccinated with RIV4 versus IIV4

   The proportion of pregnant women with one or more severe local and/or solicited reactogenicity event within 8 days after vaccination with RIV4 versus IIV4. The proportion of participants with ≥1 local, severe, and local or severe reaction will be compared between the RIV4 group and the IIV4 group using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level for the three comparisons.

   We will also describe the proportions of pregnant women with each reactogenicity events by severity grade after RIV4 and IIV4 vaccination. The severity grades are: any, mild, moderate and severe as noted above in Tables 2 and 3.

4. EO4: To compare and describe health outcomes through 90 days of life in infants born to women after RIV4 versus IIV4 vaccination.

The proportion of infants with medically-attended events through 90 days of life and the proportion of infants with neonatal death will be compared between the RIV4 group and the IIV4 group using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. The proportion and 95% exact binomial confidence interval of SAEs in infants through 90 days of life, as well as the total number of events, will be presented by site, vaccine group, severity, and relatedness. Listings of these SAEs will also be presented. Non-overlapping confidence boundaries will be an indication of a statistical difference between the groups.

5. EO5: To compare maternal immune responses to influenza antigens and calculate the post and pre-vaccination ratio after RIV4 versus IIV4 vaccination.

   The proportion of pregnant women achieving seroconversion at day 29 and the proportion pregnant women with a seroprotective HAI titer (≥ 1:40) pre- and post-immunization at day 29 will be compared using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. The geometric mean HAI titer (GMT) pre- and post-immunization at day 29 after RIV4 versus IIV4 vaccination for each influenza vaccine antigen will be compared (within vaccine arm pre versus post and within timeframe RIV4 versus IIV4) using a regression model with the log transformed titer value at the two-sided alpha 0.05 level. The proportion and 95% exact binomial confidence interval will also be presented in tabular format for each group. The Immunogenicity Population is the primary analysis population. The Maternal Immunogenicity Population is the primary analysis population.

6. EO6: To compare cord blood antibody levels for influenza antigens after RIV4 versus IIV4 vaccination.

   The proportion of infants with cord blood seroprotective HAI titer will be compared using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. Infant cord blood geometric mean HAI titer (GMT) for each influenza vaccine antigen will be compared using a regression model with the log transformed titer value at the two-sided alpha 0.05 level.

   The ratio and 95% confidence interval for cord blood to maternal influenza antibody titers at time of delivery for each influenza vaccine antigen after maternal RIV4 versus IIV4 vaccination will be presented. Non-overlapping confidence boundaries will be an indication of a statistical difference between the groups. The proportion and 95% exact binomial confidence interval will also be presented in tabular format for each group. The Immunogenicity Population is the primary analysis population.

9 SENSITIVITY ANALYSES

If there are any participants who receive the incorrect treatment (i.e., treatment other than what they were randomized to receive), then in the sensitivity analysis of the primary and secondary objectives, the participants will be analyzed based on the treatment the participant received not what the participant was randomized to receive. For example, if a participant was

randomized to RIV4 but inadvertently received IIV4, that participant would be reassigned to the IIV4 treatment group in the sensitivity analyses.

If more than 10% of the Maternal Immunogenicity Population have major protocol violations affecting immunogenicity as determined by the study investigators, then a sensitivity analysis will be performed for Exploratory Objective 6. No infant cord blood data will be analyzed from mothers with the major protocol violations affecting immunogenicity. These results will be compared with those using the mITT Population to make the best assessment of Exploratory Objective 6.

10 FURTHER ANALYSIS

If the error in stratification by gestational age results in an imbalance in gestational age between the treatment groups, evaluation of secondary outcomes by treatment group will be done using gestational age as a covariate if specified analyses can adjust for this factor. To have reasonable results, each cell count needs to be 5 or greater.

11 REFERENCES

Xin Yan & Xiao Gang Su (2010) Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions, Statistics in Biopharmaceutical Research, 2:3, 329-335, DOI: 10.1198/sbr.2009.0049

APPENDIX 1
Major Protocol Violations for Analysis

1. Major Protocol Violations for Exclusion from Per Protocol Populations:
   a. Age < 18 years of age at enrollment
   b. Gestational age >34 weeks at vaccination
   c. Did not provide written informed consent prior to vaccination
   d. End of participation in study (e.g. loss to follow-up, early termination/withdrawal) prior to end of pregnancy
   e. Receipt of the year's influenza vaccine (2019-20 or 2020-21) prior to study enrollment
   f. Study participation in both 2019-20 and 2020-21 influenza season
   g. Receipt of live vaccine while participating in this study or receipt of non-study vaccine within 7 days before or during the 8 days post-vaccination period.
   h. Receipt of experimental drugs or medical device while participating in this study
   i. Known multi-fetal gestation or fetal congenital anomaly at the time of enrollment, e.g. genetic abnormality or major congenital malformation based on antenatal ultrasound before randomization

2. Major Protocol Violations for Exclusion from Immunogenicity Populations:
   a. No vaccine received
   b. No pre- and/or post-vaccination blood draw
   c. Receipt of any other vaccine between the pre- and post-vaccination blood draws
   d. New immunosuppression disorders between the pre- and post-vaccination blood draws or receipt of immunosuppressive medication between the pre- and post-vaccination blood draws
   e. Subject who was inadvertently enrolled and randomized to the study, though they were later learned to have had met the following criteria for study exclusion that would have affected immunogenicity
   f. Influenza vaccine receipt during the current influenza season prior to study enrollment
   g. Use of oral, antenatal, or parenteral corticosteroids (≥ 20mg/day prednisone equivalent) or high-dose inhaled glucocorticoid for ≥ 14 consecutive days within the preceding 30 days
   h. Has an active neoplastic disease (excluding non-melanoma skin cancer), a history of any hematologic malignancy, current bleeding disorder, or taking anticoagulants (a daily aspirin is acceptable)
   i. Has a history of receiving immunoglobulin or other blood product (with exception of Rh immunoglobulin) within the 3 months prior to study vaccination