A Prospective Observational Study to Evaluate the Safety of COVID-19 Vaccination in Pregnant Women

Short Title: Observational Maternal COVID-19 Vaccination Study

Centers for Disease Control and Prevention
Clinical Immunization Safety Assessment (CISA) Project

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STATEMENT OF COMPLIANCE

- This trial will be conducted in compliance with the protocol, the International Conference on Harmonization (ICH) Guideline E6-Good Clinical Practice (GCP), and the applicable guidelines and regulatory requirements from the United States (US) Code of Federal Regulations (CFR), 45 CFR Part 46.
- All study personnel with subject contact have completed Human Subjects Protection Training.

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PROTOCOL SUMMARY

Title:	A Prospective Observational Study to Evaluate the Safety of COVID-19 Vaccination in Pregnant Women
Phase:	N/A
Population:	350 adult pregnant women aged 18–45 years at <34 weeks gestation who are either receiving their booster dose of a COVID-19 vaccine or are receiving their first dose of the primary COVID-19 vaccine series during the current pregnancy in accordance with the Advisory Committee on Immunization Practices (ACIP) and American College of Obstetricians & Gynecologists (ACOG) national recommendations.
Clinical Sites:	Three: Duke University (Lead); Cincinnati Children's Hospital Medical Center (Contributor); Boston Medical Center (Contributor)
Study Duration:	36 months (approximately 12 months to recruit/enroll, maximum of 9 months to follow, 15 months to perform analysis and laboratory assays)
Participant Duration:	Up to 12 months depending upon gestational age at enrollment and delivery. Will be followed for 90 days postpartum.
Description of Study Procedures:	This is a prospective, observational study. During the study, pregnant women will be followed post COVID-19 vaccination. Injection-site (local) and systemic reaction data will be assessed on vaccination day and daily during the 7 days following vaccination (including both doses if the woman receives a 2-dose vaccine) using either identical web-based or paper diaries, depending on study participant preference. Maternal serum samples will be collected for antibody titers relevant to COVID-19 at time points that include prior to vaccination, ~28 days post vaccination completion, and at delivery or end of pregnancy. At Duke University, maternal and infant cord blood will be collected at delivery and analyzed for the same antibody titers. At other clinical sites, these delivery samples will only be collected if feasible. Pregnant women will be followed through 90 days postpartum or 6 weeks postvaccination if pregnancy ends early, with comprehensive obstetric and neonatal outcomes obtained from medical record review.

Objectives:	Primary Objective: • To assess adverse pregnancy outcomes in pregnant women vaccinated with COVID-19 vaccine Secondary Objectives: • To assess preterm births occurring in pregnant women vaccinated with COVID-19 vaccine • To assess combined fetal and neonatal deaths after COVID-19 vaccination • To assess spontaneous abortions after COVID-19 vaccination • To assess solicited local and systemic reactogenicity events in pregnant women vaccinated with COVID-19 vaccine Exploratory Objectives: • To assess serious adverse events (SAE) in pregnant women vaccinated with COVID-19 vaccine • To assess health outcomes through 3 months of age in infants born to women vaccinated with COVID-19 vaccine • To assess safety profiles in pregnant women vaccinated with COVID-19 vaccine by baseline COVID-19 serostatus (positive versus negative) • To assess safety profiles in pregnant women vaccinated with COVID-19 vaccine by history of infection (any positive COVID-19 tests, self-reported COVID-19 disease history) • To assess maternal immune responses to SARS-CoV-2 antigens after COVID-19 vaccine* • To assess cord blood antibody levels to SARS-CoV-2 antigens*
Outcome Measures:	Primary Outcome Measure: • Proportions of a composite of adverse pregnancy outcomes in pregnant women vaccinated with COVID-19 vaccine Secondary Outcome Measures: • Proportions of preterm birth • Proportions of combined fetal and neonatal death • Proportions of spontaneous abortion • Proportions of pregnant women with moderate/severe solicited reactogenicity events (local and/or systemic) within 7 days after each dose of COVID-19 vaccine

	• Proportion of women with ≥1 severe local and/or systemic reactogenicity event Exploratory Outcome Measures: • Proportion of women with SAEs • Proportion of infants with medically attended adverse events through 90 days of life after maternal COVID-19 vaccination • Proportion of infants with SAEs through 90 days of life • Primary, secondary, exploratory outcome measure (EOM)1, and EOM2 by maternal baseline COVID-19 serostatus (positive versus negative) • Primary, secondary, EOM1, and EOM2 by history of COVID-19 disease (positive COVID-19 tests or self-reported history vs. negative tests/history) • *Exploratory outcome measures regarding maternal and cord blood antibody analyses will be included in a future protocol amendment
Estimated Time to Complete Enrollment:	Approximately 12 months for enrollment

1. BACKGROUND

1.1 Background

The novel coronavirus, SARS-CoV-2, also known as COVID-19, has emerged as a deadly global pandemic. Since its identification in December 2019 in China, almost 240 million cases with almost 4.9 million deaths have been identified worldwide.[1] As of October 11, 2021, there were ~44 million cases and over 715,000 deaths associated with COVID-19 in the United States.[2] While many individuals have asymptomatic or mild to moderate respiratory illness that is self-limiting, significant morbidity and mortality are markedly increased in older individuals or those have underlying chronic illness such as cardiovascular and pulmonary diseases and diabetes. Treatment relies primarily on supportive therapy with the addition of remdesivir and monoclonal antibodies approved under emergency use authorization and dexamethasone in hospitalized patients.[3]

Research on strategies to treat or prevent the disease have focused on nonpregnant adults, leaving pregnant women and their obstetric providers without the knowledge or tools needed to adequately care for them, their fetuses, and their soon-to-be born infants. Initial reports from China did not suggest an increase in maternal or infant mortality. However, several publications since suggest that pregnant women are at higher risk for severe disease including hospitalization, ICU admission, and mechanical ventilation.[4] Additionally, racial and ethnic disparities of COVID-19 cases in the United States are similar to the general population, with non-Hispanic black and Hispanic pregnant women having a higher risk of COVID-19 disease.[5] In addition, the high incidence of known risk factors for disease severity during pregnancy (hypertension, diabetes, and obesity) add to the risk of COVID-19 in pregnant women in the United States. Currently remdesivir and dexamethasone are used for hospitalized pregnant women with severe COVID-19 infection, though pregnant women remain systematically excluded from all other investigational treatment trials.

The US Department of Health and Human Services announced the framework for Operation Warp Speed (OWS) on May 15, 2020, with the goal of delivering safe and efficacious vaccine to prevent COVID-19 by January 2021. Vaccines were developed and tested in clinical trials at a historic pace and in December 2020 and February 2021 FDA authorized three COVID-19 vaccines under Emergency Use Authorizations (EUAs).[6] Two are mRNA vaccines: Pfizer-BioNTech mRNA vaccine, for use in persons aged ≥16 years and Moderna for use in persons aged ≥18 years.[7, 8] The third Janssen COVID-19 vaccine uses a replication-deficient adenovirus (Ad26) vector and is authorized for persons aged ≥18 years.[9] Following the EUAs, these vaccines were recommended by the Advisory Committee on Immunization Practices.[10]

Pregnant women were excluded from the clinical trials supporting these EUAs. None of the currently authorized COVID-19 vaccines are live virus vaccines, and the EUAs do not contraindicate vaccination in pregnant women. CDC's Interim Clinical Considerations state the following: "Any of the currently authorized COVID-19 vaccines can be administered to pregnant or lactating people; ACIP does not state a product preference. Pregnant people may choose to receive a COVID-19 vaccine."[11]

Limited data on the safety of COVID-19 vaccine in pregnant women has left experts in obstetrics, infectious disease, and infection control and prevention questioning the risk or appropriateness for pregnant women to continue to work in the healthcare setting.[12]

As of September 27, 2021, there have been over 161,000 pregnancies reported in CDC's v-safe post-vaccination health checker. Data collected from v-safe through February 2021 has not indicated any safety concerns based on reactogenicity or adverse events observed in pregnant women. Side effects in pregnant and nonpregnant populations were similar. Additionally, no differences in adverse pregnancy outcomes appear when comparing pregnant women participating in the v-safe pregnancy registry with the background rate. Spontaneous abortion rate appears to be consistent between women receiving COVID-19 vaccination during pregnancy and background rate.[13]

Overall, 65% of the US healthcare workforce are women, with nearly 80% of being between the ages of 16–54 years.[14] Additionally, 28.5% of women have at least one comorbid condition associated with COVID-19 hospitalization (obesity, hypertension, and diabetes).[15] Given all that we know about the disease course and treatments thus far, a preventive vaccine would be a far better public health intervention by reducing or eliminating COVID-19 related morbidity and mortality as well as significantly reduce healthcare resource utilization.

1.2 Summary & Rationale

In clinical practice, the FDA approved the Pfizer-BioNTech COVID-19 vaccine in August 2021 and granted an Emergency Use Authorization for Moderna COVID-19 vaccine in December 2020 and Janssen COVID-19 vaccine in February 2021. As the COVID-19 pandemic continues there is a need to comprehensively monitor the safety of COVID-19 vaccines in pregnant women. Efforts currently underway include a study of the Pfizer-BioNTech vaccine for women 24 0/7 to 34 0/7 weeks' gestation (NCT04754594).[16] Additionally, CDC is conducting several studies and activities to monitor the safety of COVID-19 in pregnant women.[17] This Clinical Immunization Safety Assessment (CISA) Project prospective observational study in pregnant women will provide detailed reactogenicity information and clinical outcomes data and will complement other research and surveillance efforts to better understand the safety of COVID-19 vaccine in pregnant women. CISA has experience in observational and randomized clinical trials of vaccines administered during pregnancy.

2. STUDY OBJECTIVES

Primary Objective (PO):

- PO1: To assess adverse pregnancy outcomes in pregnant women vaccinated with COVID-19 vaccine.
  Adverse birth outcomes is a composite of occurrence of at least one of the following: preterm birth, spontaneous abortion, fetal death, or neonatal death.

Secondary Objectives (SO):

- SO1: To assess preterm births occurring in pregnant women vaccinated with COVID-19 vaccine
- SO2: To assess combined fetal and neonatal deaths after COVID-19 vaccination
- SO3: To assess spontaneous abortions after COVID-19 vaccination
- SO4: To assess solicited local and systemic reactogenicity events in pregnant women vaccinated with COVID-19 vaccine

Exploratory Objectives (EO):

- EO1: To assess serious adverse events (SAE) in pregnant women vaccinated with COVID-19 vaccine
- EO2: To assess health outcomes through 3 months of age in infants born to women vaccinated with COVID-19 vaccine
- EO3: To assess safety profiles in pregnant women vaccinated with COVID-19 vaccine by baseline COVID-19 serostatus (positive versus negative)
- EO4: To assess safety profiles in pregnant women vaccinated with COVID-19 vaccine by history of infection (any positive COVID-19 tests, self-reported COVID-19 disease history)
- EO5: To assess maternal immune responses to SARS-CoV-2 antigens after COVID-19 vaccine*
- EO6: To assess cord blood antibody levels to SARS-CoV-2 antigens*

2.1 Study Outcome Measures

2.1.1 Primary Outcome Measure (POM):

POM1: Proportions of adverse pregnancy outcomes in pregnant women vaccinated with COVID-19 vaccine

Adverse birth outcome is a composite of occurrence of at least one of the following: preterm birth, spontaneous abortion, fetal death, or neonatal death.

2.1.2 Secondary Outcome Measures (SOM):

- SOM1: Proportions of preterm birth
- SOM2: Proportions of combined fetal and neonatal death
- SOM3: Proportions of spontaneous abortion
- SOM4: Proportions of pregnant women with moderate/severe solicited reactogenicity events (local or systemic) within 7 days after each dose of COVID-19 vaccine
- SOM4.1: Proportion of women with ≥1 severe local or systemic reactogenicity event

2.1.3 Exploratory Outcome Measures (EOM):

- EOM1: Proportions of women with SAEs
- EOM2.1: Proportion of infants with medically attended adverse events through 90 days of life after maternal COVID-19 vaccination
- EOM2.2: Proportion of infant with SAEs through 90 days of life
- EOM3: Compare primary, secondary, EOM1, and EOM2 by maternal baseline COVID-19 serostatus (positive vs. negative)
- EOM4: Compare primary, secondary, EOM1, and EOM2 by history of COVID-19 disease (positive COVID-19 tests or self-reported history vs. negative tests/history)
- *EOM 5 and 6: Exploratory outcome measures regarding maternal and cord blood antibody analyses will be included in a future protocol amendment

3. STUDY DESIGN

3.1 Main study design

This study is a prospective, observational study to evaluate the safety of COVID-19 vaccine(s) in 350 pregnant women who are either receiving their booster dose of a COVID-19 vaccine or are receiving the first dose of their primary COVID-19 vaccine series.. Duke will serve as the Lead Contractor in conjunction with Cincinnati Children's Hospital Medical Center and Boston Medical Center. With Day 1 serving as the day of vaccination, participants will be followed through Day 7 (total 7 days) for symptoms of reactogenicity; if two doses are administered reactogenicity data will be collected after each dose. For the PO, we will assess adverse birth outcomes as the primary study endpoint. SOs will individually assess adverse birth outcomes such as preterm birth, spontaneous abortion, fetal death and neonatal death as well as solicited reactogenicity events and overall maternal SAEs following vaccination.

3.2 Laboratory studies

3.2.1 Serologic studies – We will evaluate pre- and post-vaccination serologic responses in women vaccinated against COVID-19. Prevaccination blood samples will be analyzed qualitatively for COVID-19 (SARS-CoV-2) antibody status (positive or negative) at Cincinnati Children's Hospital Medical Center in a CLIA-certified lab. Postvaccination geometric mean titers (GMTs) for each SARS-CoV-2 antigen will be calculated. Venous blood (approximately 12 mL of blood) will be collected from each participant in close proximity to the first vaccination (up to 3 days before or after vaccination) and approximately 28 days after the last dose of vaccine received. For participants receiving two doses of vaccine, an optional blood collection will occur at approximately 21 days after first vaccination and up to 2 days prior to second vaccination. Those receiving a booster dose of a COVID-19 vaccine will have blood draws on Day 1 (before vaccination) and Day 21. At Duke, maternal and cord blood (approximately 12 mL of blood each) collection will be performed at delivery for serological analysis. At the other sites, these samples (maternal and cord blood) will be collected during delivery only if feasible for similar serological analysis.

3.2.2 Future studies – In addition to the specified analyses described thus far, there might be other tests or assays that have yet to be identified that might be important for interpreting our study findings or of relevance to maternal-infant health outcomes. Therefore, participants will be offered, through an opt-in strategy, to allow for the storage of any remaining blood (serum/plasma) after all specified analyses have been completed. Additional laboratory assays may test for antibodies against other bacteria or viruses, markers of inflammation, or used in research on the health of mothers and infants. Specimens banked for use in other studies will be linked to information (including identifying information) that participants provided to the study. Because it is unknown if future testing will be of any utility, results of future testing will not be provided. In addition, participants will be offered, again through an opt-in strategy, to allow study staff to contact them in the future to take part in other research studies.

4 STUDY ENROLLMENT AND WITHDRAWALS

4.1 Participant Inclusion Criteria

Participants who meet all of the following criteria will be eligible to participate in this interventional study:

1. Pregnant women 18–45 years of age at the time of consent, inclusive

2. Intention of receiving or within 1 day following receipt of the first dose or only dose of COVID-19 vaccine or persons receiving a booster dose of a COVID-19 vaccine based on ACIP and ACOG guidelines in response to the FDA EUA or approval and in conjunction with federal and local vaccination campaign distribution plans
3. Willing to provide informed consent in a written or electronic format
4. Gestational age at time of consent <34 weeks 0 days based on reconciliation of last menstrual period and ultrasound dating. Estimated due date (EDD) and gestational age (GA-EDD) will be based on reconciliation of "sure" first day of the last menstrual period (LMP) and earliest dating ultrasound. If the LMP is uncertain, then the earliest dating ultrasound will be used to determine EDD and GA. If the ultrasound derived-EDD is in agreement with sure-LMP derived EDD (**Table 1**), then the LMP-derived EDD is used to determine GA. If the ultrasound derived EDD is not in agreement with the LMP-derived EDD, the ultrasound-derived EDD is used to determine GA.

Table 1. Ultrasound Parameters for Using Sure LMP to Determine Gestational Age

Gestational age at first ultrasound by LMP	Ultrasound agreement with LMP
8 6/7 wk or less	± 5 days
9 0/7 wk to 13 6/7 wk	± 7 days
14 0/7 wk to 15 6/7 wk	± 7 days
16 0/7 wk to 21 6/7 wk	± 10 days
22 0/7 wk to 27 6/7 wk	± 14 days
28 0/7 wk and beyond	± 21 days

5. Intention of being available for entire study period and complete all relevant study procedures, including follow-up phone calls and collection of delivery information.
6. English or Spanish literate.

4.2 Participant Exclusion Criteria

Participants who meet any of the following criteria will not be eligible to participate in this study:

1. Has immunosuppression as a result of an underlying illness or medications, such as antirejection/transplant regiments or immunomodulatory agents. Stable HIV disease is permitted per the following parameters:
    a. Confirmed stable HIV disease defined as document viral load <50 copies/mL and CD4 count >200 within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months
2. Has known hepatitis B (HBV) or hepatitis C (HBC). Stable HBV or HBC are permitted per the following parameters:
    a. If known HBV: confirmed inactive chronic HBV infection: HBsAg present for ≥6 months and HBeAg negative, anti-HBe positive; serum HBV DNA <2000 IU/mL; persistently normal ALT or AST levels; in those who had liver biopsy, findings that confirm absence of significant necroinflammation
    b. If known HCV: evidence of sustained virological response for ≥12 weeks after treatment or without evidence of HCV RNA viremia (undetectable HCV RNA)
3. Use of oral, parenteral, or high-dose inhaled glucocorticoids
4. Has an active neoplastic disease (excluding nonmelanoma skin cancer), including those who used anticancer chemotherapy or radiation therapy during the current pregnancy

5. Signs or symptoms of active preterm labor, defined as regular uterine contractions with cervical change (dilation/effacement)
6. Known fetal congenital anomaly, e.g., genetic abnormality or major congenital malformation based on antenatal ultrasound
7. Anyone who is already enrolled or plans to enroll in another randomized clinical trial with any drug, vaccine or medical device. Coenrollment in behavioral or other observational intervention studies are allowed at any time.
8. Any condition which, in the opinion of the investigators, might pose a health risk to the subject or interfere with the evaluation of the study objectives.
9. Anyone who is a relative of any research study personnel or is an employee supervised by study staff.

4.3 Recruitment

This study will include pregnant women who have received or are planning to receive a COVID-19 vaccine. Pregnant women at <34 weeks, 18–45 years old, who are planning to receive or recently received (within previous 1 day) COVID-19 vaccine (either receiving their booster dose of a COVID-19 vaccine or are receiving the first dose of their primary COVID-19 vaccine series) will be recruited at Duke University Hospital (Duke), University of Cincinnati Medical Center (Cincinnati), or Boston Medical Center (Boston). Pregnant women will be recruited from prenatal clinics and COVID-19 vaccination clinics affiliated with these sites. Medical records will be reviewed to identify, contact, and offer study enrollment to potentially eligible pregnant women. IRB-approved informational flyers/advertisements will be used to recruit pregnant women receiving vaccination through public COVID-19 vaccination sites or clinics (prenatal, primary care, or other clinic administering vaccine). Potential participants will be screened for eligibility and consented for study participation (if eligible) in-person (during routine prenatal care) or virtually (telephone or televisit). Medical and obstetric history, including vaccine history and COVID-19 disease history, will be obtained via participant self-report with verification by chart review whenever feasible (including medical records, employee health records, immunization registry records, and pharmacy records).

4.4 Reasons for and Handling of Withdrawals

The following may be reason for study withdrawal:

- As deemed necessary by the principal investigator (PI)
- Participant withdrawal of consent
- Loss to follow-up
- Termination of the study by the sponsor

Participants who enroll in the study but do not receive any COVID-19 vaccine will be considered a screen-failure. Participants may withdraw their consent for study participation at any time and for any reason, without penalty. Participants who withdraw from the study after receiving at least one dose of vaccine will be considered lost to follow-up. Every attempt should be made to collect all data specified by the protocol, including collection of pregnancy outcome/safety data via medical record review for participants who request withdrawal from study interventions/procedures.

4.5 Termination of Study

This study may be terminated for safety concerns of the principal investigators from the Lead or Contributing sites, CDC, or participating IRBs.

5 STUDY SCHEDULE, PROCEDURES, & EVALUATIONS

5.1 Schedule of events

Pregnant women meeting the proposed eligibility criteria will be recruited. Informed consent (written or electronic) will be obtained from study participants prior to conducting any study procedures. **Table 2** describes the proposed schedule of study visits with further details below.

Table 2. Study Visit Schedule

Procedure	Screening Visit	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4[6]	Visit 5[6]	SAE Visit	Visit 6	Visit 7	Unscheduled Visit
Type of contact	Chart Abstraction/ Clinic/Phone	Clinic/ Phone	Clinic	Phone/Text /Email/Data Review	Clinic	Phone/Text/ Email/Data Review	Clinic	Phone/Text/ Email/Data Review	Hospital/ Chart Abstraction	Phone/Text/ Email/Chart Abstraction	Clinic
Informed consent & Medical Release of Information	X										
Review Eligibility Criteria	X										
Demographic, Medical, and obstetric history	X										
Vaccination History	X	X									
Positive COVID-19 test history	X	X			X		X		X		X
Vital signs (temperature, blood pressure, and heart rate)		X	X		X						X
Blood sample collection		X	X[1]		X[2]		X		X[3]		
Vaccination[4]		X[5]			X[6]						
Obtain immediate adverse event information		X			X						
Dispense memory aid		X									
Dispense study supplies		X									
Complete memory aid form (REDCap or paper)		X		X	X	X					
Concomitant medications/vaccinations	X	X		X	X	X	X	X	X	X	X
Obtain solicited and unsolicited adverse events				X	X						X
Obtain serious adverse event information				X	X	X	X	X	X	X	X
Infant data collection										X	

[1] This blood collection may occur up to 3 days prior to or 3 days after first vaccination. If not done at Visit 1a, this should be collected at Visit 1b.
[2] Blood draw at Visit 3 is optional unless only one-dose vaccine or booster dose (given as standard of care) was received.
[3] Cord blood and maternal blood collection at Visit 6 will be collected when feasible by the site.
[4] Vaccination is not considered a study procedure but is included in this table as reference for when study visits should occur.
[5] This visit can occur up to one day before or one day after vaccination.
[6] Will only occur if vaccine received is a two-dose vaccine.

Screening Visit, −30 to +1 day of vaccination (Chart Abstraction & Clinic Visit – may occur simultaneously with Visit 1)

- Obtain informed consent (written or electronic) and release of medical record information
- Review and confirm study eligibility
- Obtain information on preferred method of contact for follow-up (telephone, email reminder or text reminder)
- Obtain demographic data and vaccination history and COVID-19 disease history
- Obtain medical history (e.g., chronic hypertension, diabetes, autoimmune disorder), obstetric history (e.g., parity, prior preterm birth, low birthweight, small for gestational age), and current pregnancy status (e.g., gestational diabetes, gestational hypertension, placenta previa, EDD)
- Obtain concomitant medication/vaccination use

Visit 1a, ±1 day within first dose or booster dose (Screening and Enrollment – Phone or Clinic Visit)

- If Screening Visit occurred prior to Visit 1, review and confirm eligibility and all data collected during Screening Visit.
- Confirm preferred method of contact for follow-up (telephone, email, or text reminder)
- Confirm date of next scheduled study visit (attempt to coincide with regularly scheduled prenatal visit as feasible)

Visit 1b, ±3 days within first dose or booster dose (Clinic Visit)

- If not collected at Visit 1a, obtain 12 mL (~2 tubes) blood sample for serologic analysis
- Obtain vital signs, including oral temperature, at this visit
- Dispense oral thermometer, ruler (in order to standardize measurements) and memory aid. Review instructions for use of thermometer, ruler, and memory aid completion. Participants will be given the choice of completing the memory aid electronically or on paper. Participants who select the electronic method will enter their data into a REDCap web-based system.

Visit 2, 7 + 3 days post first dose or booster dose (Phone/Text/Email/Online Memory Aid review)

- Participants will complete their memory aid via paper or electronic entry from Day 1–7.
- Participants using paper diary:
    - Study staff will contact participants using paper memory aid to collect and record memory aid data including AEs (solicited and unsolicited), SAEs, pregnancy status, and concomitant medications
    - Participants will be:
        - Asked to notify the study staff if they are hospitalized or have a severe adverse event
        - Follow up with their healthcare if they have symptoms they find concerning
        - Reminded that their next visit will be within 2 days of their second dose for Visit 3 (unless received single dose vaccine)
- Participants using REDCap web-based system:

  - Study staff will review REDCap system to confirm data capture and assess for any AEs, SAEs, pregnancy status, and concomitant medications.
  - The study team will contact participants if they have any missing information. The study team may also contact participants if more information is needed to better describe AEs [including SAEs and severe (Grade 2) events] reported in the REDCap web-based system.
  - All participants using the REDCap web-based system will be:
    - Asked to notify the study staff if they are hospitalized or have a severe adverse event
    - Follow up with their healthcare provider if they have symptoms they find concerning
- Study staff will also approach participants at follow-up prenatal appointments which should be within 2–4 weeks from vaccination visit based on routine prenatal care guidelines. In the instances where this is not possible, the study team will schedule a study visit for the participant to return to the research unit to complete the study visit.

Visit 3, two-dose regimen, −2 days through day of second dose (Clinic Visit)

- The timing of this visit will occur based on the schedule per EUA.
- Obtain vital signs, including oral temperature, at this visit.
- Record any AEs, SAEs, and concomitant medications.
- Confirm preferred method of contact for follow-up (telephone, email, or text reminder).
- Ensure participant has received the second dose of COVID-19 vaccine if the vaccine administered is a two dose vaccine.
- Instruct participant to complete memory aid starting on the day of the second dose of vaccine for 7 days.
- **Optional: Obtain 12 mL (~2 tubes) blood sample for serologic analysis.*

Visit 3, one dose received, one-dose regimen, or booster dose, 21 + 3 days post-vaccination (Clinic Visit)

- Obtain vital signs, including oral temperature, at this visit.
- Record any AEs, SAEs, and concomitant medications.
- Confirm preferred method of contact for follow-up (telephone, email, or text reminder).
- Obtain 12 mL (~2 tubes) blood sample for serologic analysis.

Visit 4, 7 + 3 days post second dose (Phone/Text/Email)

- Subjects will complete their memory aid via paper or electronic entry, study staff will review subject entered data within the database or by contacting them by phone. If any missing values or Grade 2 or greater events occurred (online memory aid), the study staff will contact them by phone to gather more information.
- <u>This visit will not occur for subjects that only receive one dose of the vaccine or a booster dose of the vaccine</u>.

Visit 5, window 28–35 days post second dose (Clinic Visit)

- Obtain 12 mL (~2 tubes) blood sample for serologic analysis***.***
- Record any AEs, SAEs, and concomitant medications.

- Confirm preferred method of contact for follow-up (telephone, email, or text reminder).
- This visit will not occur for subjects that only receive one dose of the vaccine or a booster dose of the vaccine.

SAE Visit, 6 weeks ± 7 days post last dose (Phone/Text/Email)

- Record any SAEs the subject had since their last dose of any COVID-19 vaccine, primary or booster.

Visit 6, Birth Outcomes Visit, Medical Record Review/Phone Call/ Hospital

Electronic medical records will be comprehensively reviewed for detailed information about maternal health events during pregnancy and maternal and infant outcomes as defined by the American College of Obstetrics & Gynecology's reVITALize and Obstetric Data Definitions.[18] Concomitant medications during delivery hospitalization will be limited to those that are relevant to pregnancy outcomes of interest, e.g., antenatal corticosteroids, or tocolytics in the setting of preterm labor/preterm birth, magnesium in the setting of preeclampsia, antibiotics in the setting of Group B *Streptococcus* (GBS) prophylaxis or chorioamnionitis, etc. Maternal blood and infant cord blood will be collected at this visit, if feasible.

In order to capture and follow all participants, as a separate plan of follow up, study participants who are not identified via medical record review at delivery will be contacted by phone approximately 2 weeks after their EDD to determine if delivery occurred elsewhere. If so, maternal and infant medical records will be requested from the delivery hospital for data collection.

Visit 7, Postnatal Day 90 (window Postnatal Days 90–97) Phone Call/Text/Email Follow-Up/Chart Abstraction

Study staff will contact study participants to record any maternal or infant SAEs, including neonatal/infant death and re-hospitalization, and concomitant medications. Information will also be collected on maternal or infant emergency room visits and unanticipated visits to the primary care pediatrician or a specialist. Data will be verified via review of medical records. Sites will have subjects sign medical records release forms for both themselves and their infants at the time of informed consent. This is done so that in the event subjects and/or their infants are seen outside of the site's medical coverages, that medical records regarding their emergency room or unanticipated visits can be requested. For neonatal deaths identified by the study team prior to Visit 7, study participants will contact participants only if more information is needed for data collection.

***Unscheduled Visits**

- Obtain vital signs including oral temperature for the pregnant women.
- Record any solicited and unsolicited AEs through Day 7, maternal and infant SAEs through 90 days after delivery, and concomitant medications.
- Confirm preferred method of contact for follow-up (telephone, email, or text reminder).

5.2 Reactogenicity and Safety Assessments

Frequency and occurrence of local and systemic reactogenicity, unsolicited AEs, SAEs, concomitant medication use, and unscheduled medical care will be assessed through 7 days post-vaccination (after each dose of vaccine) using a standard memory aid. At the

time of study enrollment, participants receiving their booster dose of a COVID-19 vaccine or are receiving the first dose of their primary COVID-19 vaccine series will be given a thermometer and instructed on using the memory aid to document oral temperatures and postvaccination symptoms. Beginning on the evening of Study Visit 1 (Day 1) following COVID-19 vaccination, these participants will record their oral temperature using the study-supplied thermometer for the next 7 days (Day 1–7) and, if applicable, again for 7 days following the second dose of the vaccine. Temperature will be recorded at roughly the same time each day or when a participant feels feverish. If a temperature ≥100.4°F (38°C) is recorded, a second measurement will be taken. If more than one temperature is taken on the same day, the highest temperature should be recorded. Fever will be defined as a measured temperature ≥ 100.4°F (38°C). Participants will classify local and other systemic reactogenicity events as mild, moderate, or severe as described in **Tables 3 and 4**.

During Visits 2, 3, and 4 information reported by participants will be reviewed for accuracy and completion. Participants who report moderate or severe solicited AEs or express any concern about symptoms/unsolicited events will be encouraged to follow up with their obstetrician or primary care provider. Study staff will assist with coordination of referral appointments as necessary. Medical records will be obtained and reviewed for any unscheduled medical appointment through post-vaccination Day 43 following the last dose of the vaccine.

Table 3: 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 or 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
Axillary swelling/Tenderness	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity or resulted in medical visit or absenteeism

Table 4: 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 or resulted in medical visit or absenteeism
Myalgia (Body aches/muscle pain)	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity or 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 or 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 or 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 or resulted in medical visit or absenteeism

Table 4: System Reactogenicity			
Systemic	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Diarrhea	Noticeable but does not interfere with activity	Interferes with activity but did not necessitate medical visit or absenteeism	Prevents daily activity or 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 or 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 or resulted in medical visit or absenteeism

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

COVID-19 vaccine administration will follow site-specific vaccine campaign administration guidelines in accordance with current recommendations from the US Food and Drug Administration and the Advisory Committee on Immunization Practices (ACIP). There are no previously published randomized controlled COVID-19 vaccine trials that have been conducted in pregnant women; however, we do not foresee having a significant issue with SAEs given published observational studies and post-market surveillance data.[12, 19, 20] We will monitor study participants for SAEs during the protocol-defined surveillance period [i.e., from enrollment through 90 days postpartum].

An SAE is defined as an AE that meets one of the following conditions:

- Results in death (including spontaneous abortion [SAB] and fetal death) during the period of protocol-defined surveillance
- Is life-threatening (defined as immediate risk of death at the time of the event)
- Requires inpatient hospitalization or prolonged hospitalization during the period of protocol-defined surveillance (other than routine hospital admission such as for labor and delivery)
- Results in congenital anomaly or birth defect
- Results in a persistent or significant maternal or infant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event might jeopardize the participant and might require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Reporting Adverse Events

SAEs and unanticipated problems will be reported to the CDC and all participating IRBs according to institutional requirements. AEs that occur in a recipient following COVID-19 vaccination should be reported to CDC's Vaccine Adverse Event Reporting System (VAERS) by their vaccination site, primary care or obstetric provider, or by study staff. VAERS reporting will be shared with participants. Study site investigators will assess relatedness to vaccine or study procedures (related, possibly related, unlikely related, or not related) for SAEs. The study investigators will use their clinical judgement to make causality assessments and the final causality assessment decision is the responsibility of the site principal investigator where the subject was enrolled.

5.3 Biospecimens Collection & Handling

5.3.1 Serum

Maternal blood specimens and infant cord blood will be collected during study visits as described in **Table 2**. All blood samples (12 mL) will be collected into serum separator tubes and processed as follows:

- Gently mix the tube by inverting 5 times. Allow blood to clot at room temperature for at least 30 minutes.
- Centrifuge tube within 1-2 hours of collection at 2,000 relative centrifugal force (RCF) (g) for 10 minutes.
- Gently remove the blood specimen tube stopper avoiding serum contamination with red blood cells. Using a single-use pipette, transfer 0.5 mL aliquots of serum (top layer) into 1.0mL or 1.8 mL cryovials. Up to 5 cryovials are expected.
- Attach the study-specific barcode labels to the cryovial aliquots. Numbers should be placed lengthwise on the tube.
- Freeze the cryovials at −80°C in the temperature-monitored research center freezer for future shipment.

Serum aliquots will be stored until shipment to Cincinnati Children's Hospital Medical Center for planned laboratory analyses.

6 LABORATORY ANALYSES

6.1 COVID-19 Laboratory Analysis

Serum samples will be analyzed by the use of a qualitative enzyme-linked immunosorbent assay (ELISA) which measures IgG antibody to the SARS-CoV-2 Spike protein. Recombinant full length Spike protein is used to coat ELISA plates and serum samples that have an Optical Density (OD) value above the established cut off are considered positive for antibody. The assay was qualified for use in the Laboratory for Specialized Clinical Services at Cincinnati Children's Hospital Medical Center (CCHMC), a laboratory that is certified by the Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologist (CAP) under US FDA Emergency Use Authorization.

Qualitative serologic testing will be completed in periodic batches throughout the course of the study and will therefore not be available in real-time or for use in clinical decision-making. CCHMC will share participant results with each study site as permitted by FDA and CDC. Study sites may share results with participants as permitted by FDA, CDC, and local site regulations.

7 STATISTICAL CONSIDERATIONS

In collaboration with Boston Medical Center, Cincinnati Children's Hospital Medical Center, and CDC, the research team at Duke will oversee the statistical analysis. Data will reside on a secure Duke server maintained by Duke Health Technology Solutions (DHTS). For the study, a database will be developed and a dataset for the study without personal identifiers will be made available to the CDC upon request. Duke statisticians will develop a comprehensive statistical analysis plan. The summary points of the analysis plan are presented below.

7.1 Definitions

Pregnancy and birth outcomes in this study will be defined by the American College of Obstetrics and Gynecology's REVITALIZE Obstetric Data Definitions[21], CDC national Vital Statistic System[22] or World Health Organization[23] if available. 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
- 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

7.2 Sample Size and Power Estimation

Because this is an observational study with no randomization of subjects into treatment groups, there will be no formal statistical power or sample size calculation.

7.3 Analysis Plan

7.3.1 Study Populations **–** There will be one study population named the Study Cohort. The Study Cohort includes any participant that was enrolled and received at least one dose of a COVID-19 vaccine.

7.3.2 Primary Objective – To assess adverse birth outcomes in pregnant women vaccinated with COVID-19 vaccine. Tables will be produced that summarize adverse birth outcomes (see definition above) with the number, percentage and 95% confidence interval. These tables will be broken down by each site and across all sites. A listing of all adverse birth outcomes will also be presented.

7.3.3 Secondary Objective 1 – To assess preterm births occurring in pregnant women vaccinated with COVID-19 vaccine. Tables will be produced that summarize preterm births with the number, percentage and 95% confidence interval. These tables will be broken down by each site and across all sites.

7.3.4 Secondary Objective 2 – To assess combined fetal and neonatal deaths after COVID-19 vaccination. Tables will be produced that summarize combined fetal and neonatal deaths with the number, percentage and 95% confidence interval. These tables will be broken down by each site and across all sites.

7.3.5 Secondary Objective 3 – To assess spontaneous abortions after COVID-19 vaccination. Tables will be produced that summarize SABs with the number, percentage and 95% confidence interval. These tables will be broken down by each site and across all sites. This will be a subgroup analysis of only those participants vaccinated at <20 weeks gestational age.

7.3.6 Secondary Objective 4 – To assess solicited local and systemic reactogenicity events in pregnant women vaccinated with COVID-19 vaccine. Tables will be produced that summarize each solicited local and systemic reactogenicity event by classification (none, mild, moderate, and severe), as well as by moderate or severe. These tables will have the number and percentage for each classification and will be for each site and across all sites. The number and proportion of women with one or more severe local or systemic reaction will be presented along with a 95% confidence interval. These severe reactions will also be provided in a listing.

7.3.7 Exploratory Objective 1 – To assess SAEs in pregnant women vaccinated with COVID-19 vaccine. Tables will be produced that summarize SAEs with the number, percentage and 95% confidence interval. These tables will be broken down by each site and across all sites. A listing of all SAEs will also be presented.

7.3.8 Exploratory Objective 2 – To assess health outcomes through 3 months of age in infants born to women vaccinated with COVID-19 vaccine. Tables will be produced that summarize infants with medically attended adverse events through 90 days of life after maternal COVID-19 vaccination with the number, percentage and 95% confidence interval. Similar tables will also be made for the proportion of SAEs in infants through 90 days of life. A listing of the medically attended adverse events and SAEs will also be presented. The aforementioned tables for medically-attended adverse events and SAEs will also be presented by the trimester of vaccination.

7.3.9 Exploratory Objective 3 – To assess safety profiles in pregnant women vaccinated with COVID-19 vaccine by baseline COVID-19 serostatus (positive versus negative). The tables described for the primary objective, secondary objectives, and exploratory objectives 1 and 2 will be presented by baseline COVID-19 serostatus grouping (positive or negative) instead of by site. The proportions by COVID-19 serostatus for the primary and secondary objectives will be descriptively assessed using an exact Mantel-Haenszel statistic (calculated in Proc Logistic in SAS) at the two-sided alpha=0.05 level. These descriptive analyses might be adjusted by site or other covariates depending on the number of outcomes at each site (need at least n=5 for each category breakdown) by COVID-19 serostatus.

7.3.10 Exploratory Objective 4 – To assess safety profiles in pregnant women vaccinated with COVID-19 vaccine by history of infection (positive COVID-19 tests, self-reported COVID-19 disease history). Analyses will follow same strategy as described above for Exploratory Objective 3.

If multiple COVID-19 vaccines (e.g., Pfizer, Moderna, Janssen, or others that may be approved in the future) or booster doses are administered to participants, then tables and comparisons as described for Exploratory Objective 3 will be presented stratified by vaccine and dose.

7.3.11 Interim Safety Data Review

An interim safety data review of all SAEs will be performed with the goal of identifying unexpected safety concerns of clinical importance. The interim safety data review will be performed by a panel with relevant expertise who are not investigators on the study. The safety review panel will assess the clinical narratives of SAEs for all participants who were vaccinated. Additional data reviews will be generated if the CDC and study investigators determine they are needed. There are no statistical analyses planned for this safety data review.

Public Health Reporting

The outcomes described above will be presented by demographic or other characteristics when deemed necessary by the CDC, in conjunction with study investigators.

7.4 Data Management Plan

The amount of data that will be collected for the proposed project will be substantial and will require a sophisticated, practical and flexible system that can accommodate different modes of data collection and several separate linked surveys. The novel Vanderbilt-designed resource developed specifically for online collection of research information, the Research Electronic Data Capture (REDCap) platform, will be used to design study forms, including the reaction forms and short customized questionnaires to collect information from study participants. This system will be used by Duke for data management. All electronic linkages will fulfill regulations for protection of human participants and requirements to minimize the risk of breach of confidentiality. After initial set-up, the work load required for electronic data collection will be substantially reduced (description of REDCap resources below). Duke investigators have previously used the REDCap system for collection and analysis of large quantities of data. Participants will be given the option to fill out their memory aid either directly in the REDCap system or on paper. All study-related documents containing protected health information, e.g., enrollment logs, case report forms, memory aids completed by study participants, will be maintained in secure research offices at Duke, which are accessible to research staff only.

7.4.1 Research Electronic Data Capture (REDCap)

Investigators within the NIH-funded Clinical and Translational Research Unit at Vanderbilt have developed REDCap (http://project-redcap.org/), to collect and manage data for diverse clinical and translational research studies. REDCap was designed around the concept of giving research teams an easy method to specify project needs and rapidly develop secure, web-based applications for collection, management and sharing of research data. REDCap accomplishes these key functions through use of a single study metadata table referenced by presentation-level operational modules. Based on this abstracted programming model, databases are developed in an efficient manner with little resource investment beyond the creation of a single data dictionary. The concept of metadata-driven application development is well established, and the critical factor for successful data collection lies in creating a simple workflow methodology allowing research teams to autonomously develop study-related metadata in an efficient manner. Of particular interest for this project, a subcomponent of REDCap, the REDCap Survey is designed for studies where data are collected directly from the research participant. This will be used with the web-based reaction forms that will be

completed by the study participants. Both products include secure institutional data hosting and include full audit-trails in compliance with HIPAA security requirements. The REDCap Consortium is comprised of 647 active institutional, including CCHMC. The REDCap currently supports 68,000 projects with over 89,000 users spanning numerous research focus areas across the consortium. The current project will use this software application for the design of electronic forms to collect information from study participants, to link the baseline data, sample collection date, and laboratory results in an automated database family, to perform data cleaning and data quality assurance efficiently, and to design an analytical dataset for the analysis of the project data.

Data will be entered directly into the REDCap database by members of the study team, from Duke, Cincinnati, and Boston. Study investigators will be responsible for assuring that all paper records are securely stored according to the requirements of their IRBs. The study investigators will be responsible for assuring the accuracy of the data entered from the paper forms into REDCap, as appropriate. Only the assigned identifiers will be used in REDCap. Therefore, personal health identifiers will not appear in the REDCap database.

In order to perform data cleaning and data quality assurance efficiently, numerous built-in filters and checks for consistency of the data including range and limit checks, branching logic, and pull down menus to limit choices for categorical variables to a pre-specified list will be implemented and performed automatically to minimize data entry error. The data will be randomly sampled and checked against source records on a regular basis. The data and related analytical datasets will also be stored at the lead and contributing sites with secured password-protected computers. Coded data without personal identifiers will be made available to the CDC and transferred using a secure transfer method as described above.

7.4.2 Role of the CDC Investigators in the Project

This study is funded by a CDC contract with Duke University, Cincinnati Children's Hospital Medical Center and Boston University as Task Orders in the CISA Project Contract. CDC staff will collaborate with the sites to develop the protocol, conduct the study, ensure the study is aligned with US Department of Health and Human Services (CDC) public health priorities, and analyze the data and disseminate the results. CDC may receive access to coded data not containing any directly identifying information.

8 HUMAN PARTICIPANTS

8.1 Human Participants Involvement, Characteristics, and Design

Duke, Cincinnati, and Boston investigators will be responsible for submitting the protocol, informed consent, memory aids, recruitment materials and any written or verbally conveyed materials specific to this project to their institutional review boards. The CDC, as the funding agency, supports an exception to the sIRB mandate for the participating sites under the provision at 114(b)(2)(ii). CDC staff will be responsible for submitting materials to the CDC IRB for review and for obtaining reliance on Duke IRB.

To facilitate participant recruitment at the practices, we will request a waiver of consent and HIPAA authorization as per institutional requirements for ascertainment (identification, selection) or recruitment of potential participants while recording

identifiable private health information (PHI) prior to obtaining the participant's consent. This information will be obtained from review of the electronic scheduling and medical record systems in the clinics in order to determine eligibility for study enrollment. We will review only the minimum amount of information necessary to determine eligibility, i.e., date of birth, current pregnancy status, pregnancy history, medical and surgical history, ultrasounds pertaining to current pregnancy, and recent laboratory test results. The PHI collected prior to consent will be used to recruit and screen only. Use of PHI in this manner involves no more than minimal risk to participants and no information will leave the study sites. Informed consent will be sought in accordance with 45 CFR 46.116, prior to enrollment.

Continuing reviews will be submitted to the IRBs in accordance with the new Common Rule. Protocol deviations or concerns about study integrity will be reported promptly to the overseeing IRB in accordance with institutional requirements.

8.2 Sources of Material

Medical history and immunization history will be obtained from the medical record and from patient report. Demographic information will be obtained from the medical record and patient report. Participants will record solicited adverse reactogenicity events and any medical intervention sought on the day of and 7 days following both vaccinations on the memory aid. Memory aid information will be reported to the study team during a telephone call or in the web-based REDCap system. The research staff will assess one or more of the following: weight, height, temperature, blood pressure, and pulse.

8.3 Potential Risks and Benefits

Risks of blood drawing include pain, swelling, bleeding, or bruising at the site where the blood sample is collected. Subjects may also experience dizziness or fainting. There is a small risk of infection around the vein where the blood was collected. Each maternal participant will be asked to have at least 3 blood samplings with the total volume not to exceed 50 mL. An optional blood sampling of an additional 12 mL may occur during Visit 3. There is no risk to the participant or their newborn for collection of cord blood, as the cord blood is drawn from the umbilical cord/placenta after the baby is not attached to it.

There is also the potential risk of loss of confidentiality about information obtained as part of this study.

There is no direct benefit to the pregnant women participating in this study. However, there may be a benefit of learning more about the safety of COVID vaccines in pregnant women, which may inform vaccine recommendations for pregnant women.

8.4 Adequacy of Protection Against Risks

8.4.1 Protections against Risk

Participants will be followed closely during the first 7 days after each vaccine dose for assessment of local and systemic reactogenicity, solicited and unsolicited AEs, SAEs, concomitant medication use, and unscheduled medical care.

Every effort possible will be made to keep information about participants confidential. Computerized participant information will be kept in password-protected files on secured servers. Paper case report forms will be kept in locked files belonging to the study personnel. Any publications resulting from this work will not contain any identifiable participant information.

8.4.2 ClinicalTrials.gov Requirements

As requested by CDC, the project is registered on ClinicalTrials.gov (NCT04826640). It is the responsibility of the lead site for creating, maintaining, and uploading pertinent information regarding the study to ClinicalTrials.gov. The lead site will post their IRB-approved informed consent within the study's record on ClinicalTrials.gov. Contributing sites will be responsible for providing the lead site with any changes to their site's information as applicable.

9.0 Human Participants

In obtaining and documenting informed consent, the Investigator and study team will comply with the applicable regulatory requirements, Good Clinical Practices, and ethical principles. Informed consent form, either written or electronic, must be obtained per IRB-approved processes at each site prior to initiation of any study activities.

9.1.1 Vulnerable Subjects Research

Vulnerable subjects

This study proposes to include pregnant women and neonates.

Pregnant women

COVID-19 vaccines are provided under a FDA licensure or EUA and are recommended by CDC, ACIP and ACOG during pregnancy.

The specific procedures to be performed as part of this study are limited to minimal blood draw (≤50 mL over a 4-week period), and other noninvasive procedures that are commonly performed during routine physical exams and are considered safe for pregnant women. These procedures do not pose greater than minimal risk to the fetus.

This study will involve only those women who have given their free and informed consent in accordance with 45 CFR 46.116. The small amount of blood that will be drawn during the duration of pregnancy (up to 50 mL) are considered safe and are not expected to cause any harm to the baby. No inducement, monetary or otherwise, will be offered to terminate a pregnancy. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy, or in determining the viability of a neonate.

Infants

Identifiable private information will be collected about the infants at the time of delivery. Significant infant complications identified during the delivery visit will be followed up to 90 days of life.

Mothers will be informed about the infant data collection at the time they consent for the study, and thus, the consent form for pregnant women will also serve as the parental permission for including the infant as a participant after delivery.

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