NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry
Protocol number	C4591022
Protocol version identifier	4.0
Date	09 May 2022
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	COVID-19 mRNA Vaccine is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)
Research question and objectives	Is the risk of pregnancy and infant safety outcomes increased among pregnant women in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry who were vaccinated with the Pfizer-BioNTech COVID-19 vaccine during pregnancy compared with those who did not receive any COVID-19 vaccine during pregnancy? Study Objective

	• To assess whether pregnant women who received the Pfizer-BioNTech COVID-19 vaccine during pregnancy experienced increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, elective termination/abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth at one year of age, relative to pregnant women who received no COVID-19 vaccines during pregnancy.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	Coronavirus disease 2019
EUA	Emergency Use Authorization
EU PAS	European Union Post Authorization Study
FDA	Food and Drug Administration
HCP	health care provider
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IEC	independent ethics committee
IRB	Institutional Review Board
IPTW	inverse probability of treatment weighting
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MI	multiple imputation
MICE	multivariate imputation by chained equations
mRNA	messenger ribonucleic acid
NCHS	National Center for Health Statistics
OTIS	Organization of Teratology Information Specialists

Abbreviation	Definition
PASS	Post-Authorization Safety Study
PDA	patent ductus arteriosus
PFO	patent foramen ovale
PMC	postmarketing commitment
RR	risk ratio
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOP	standard operating procedure
Tdap	tetanus, diphtheria, and acellular pertussis
UCSD	University of California San Diego
US	United States
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry

Main author: Christina Chambers, University of California San Diego (UCSD) and the Organization of Teratology Information Specialists (OTIS)

Rationale and background: In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was first identified by public health officials in China. The World Health Organization (WHO) declared the SARS-CoV-2 outbreak and associated disease (Coronavirus disease 2019 [COVID-19] a global pandemic in March 2020. Despite public health efforts, the incidence of COVID-19 has continued to rise, largely affecting middle-aged persons with worsening clinical sequelae linked to increasing age and comorbid conditions (e.g., cardiovascular disease, diabetes and chronic lung disease). As of 17 May 2021, over 32.9 million COVID-19 cases and 586,330 deaths have been reported in the United States (US) alone (The Center for Systems Science and Engineering at Johns Hopkins University, 2021). The Food and Drug Administration (FDA) initially granted Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine two-dose primary series on 11 December 2020 in individuals 16 years of age and older, and approved the vaccine for this population on 23 August 2021 (FDA, 2021a; FDA, 2021b). FDA expanded the EUA on 10 May 2021 to include children 12-15 years of age, and on 29 October 2021 to include lower-dose vaccine administration for children 5-11 years of age (FDA, 2021c; FDA, 2021d). The EUA was further amended on 12 August 2021 to include the administration of a third primary series dose in certain immunocompromised individuals 12 years of age and older, and on 22 September 2021 to allow for use of a single booster dose at least six months after completion of the primary series in certain populations (FDA, 2021e).

Available data suggest that pregnant women who become infected with COVID-19 may be more likely to be hospitalized and may be at increased risk of preterm delivery (MMWR, 2020). Pfizer is conducting a Phase 2/3 clinical trial of the safety and immunogenicity of the Pfizer-BioNTech COVID-19 vaccine in pregnant women. Interim analyses of Pfizer's Phase 3 clinical trial for vaccine candidate BNT162b2 were reported in December 2020 and showed that the two-dose regimen had 95% efficacy in the prevention of COVID-19 among individuals without evidence of prior SARS-CoV-2 infection. While the current product labeling communicates that data are insufficient, the Pfizer-BioNTech COVID-19 vaccine may be received by pregnant women when they and their healthcare providers believe that risk/benefit considerations favor its use. As of 25 October 2021, more than 169,000 women reported to the Centers for Disease Control and Prevention's (CDC) V-safe surveillance system that they were vaccinated during pregnancy (CDC, 2021a). Therefore, information regarding the real-world safety of vaccination during pregnancy is essential from a public health perspective.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a postmarketing commitment (PMC) to the FDA.

Research question and objectives: Is the risk of pregnancy and infant safety outcomes increased among pregnant women in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry (OTIS Pregnancy Registry) who were vaccinated with the Pfizer-BioNTech COVID-19 vaccine during pregnancy compared with those who did not receive any COVID-19 vaccine during pregnancy?

Study Objective

- To assess whether pregnant women who received the Pfizer-BioNTech COVID-19 vaccine during pregnancy experienced increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, elective termination/abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth at one year of age, relative to pregnant women who received no COVID-19 vaccines during pregnancy.

Study design: This proposed study is a prospective, observational cohort study of pregnancy and infant safety outcomes in pregnant women with exposure to the Pfizer-BioNTech COVID-19 vaccine using data from the OTIS Pregnancy Registry. The birth prevalence/incidence rates of pregnancy outcomes and incidence proportion of the infant outcome for women exposed to any dose of the Pfizer-BioNTech COVID-19 within one month prior to the first day of the last menstrual period (LMP) to end of pregnancy will be compared to those observed in a comparator cohort unexposed to any COVID-19 vaccine during this period.

Population: The study population includes pregnant women of all ages participating in the OTIS Pregnancy Registry on or after 11 December 2020 (i.e., date FDA granted EUA for the Pfizer-BioNTech COVID-19 vaccine). The OTIS Pregnancy Registry includes women who reside in the US or Canada. Women with a known pregnancy outcome at the time of study enrollment (e.g., positive prenatal diagnostic test results for a major congenital malformation prior to study entry), exposure to known human teratogens during pregnancy, or receipt of any vaccine during pregnancy other than the Pfizer-BioNTech COVID-19 vaccine, influenza vaccine, or Tdap vaccine are not eligible for study entry.

Variables: Exposure will be defined as receipt of the Pfizer-BioNTech COVID-19 vaccine obtained by maternal report and/or medical record, with information on the gestational timing and date(s) of vaccination captured. A copy of the COVID-19 vaccine record is requested to supplement maternal report of vaccination. Pregnancy outcomes of interest include major congenital malformations, spontaneous abortion, elective termination/abortion for any reason, stillbirth, preterm delivery, and small for gestational age. The infant outcome of interest is small for age postnatal growth of live born infants at one year of age. Each pregnancy and infant outcome will be analyzed separately, and the following exposed cohort and unexposed cohort will be defined for each outcome analysis (depending on a

participant's timing of vaccination/study enrollment as it relates to the at-risk period for an outcome):

- **Pfizer-BioNTech COVID-19 Vaccine-Exposed**
  - Pregnant women with exposure to at least one dose of the Pfizer-BioNTech COVID-19 vaccine within one month before the first day of LMP up to and including end of pregnancy
- **COVID-19 Vaccine-Unexposed (Comparator)**
  - Pregnant women with no exposure to any COVID-19 vaccine within one month before the first day of LMP up to and including end of pregnancy.

Information on study outcomes will be obtained by maternal report and/or medical record review. Potential confounders or covariates to be collected include maternal age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication use, vaccine exposures (including COVID-19 vaccination prior to and during pregnancy), vitamin/mineral exposures, and prenatal tests. For women who received the Pfizer-BioNTech COVID-19 vaccine, information will also be collected on the specific doses (i.e., 1st, 2nd, 3rd, and booster) of the vaccine received.

Data source: This study will use data collected as part of the OTIS Pregnancy Registry from maternal interviews, medical records (obstetric, delivery hospital, pediatric, vaccine provider, and/or other specialty provider if applicable), and pregnancy exposure diary.

Study size: The target sample size for the study is 2000 pregnant women: 1100 pregnant women in the Pfizer-BioNTech COVID-19 vaccine exposure cohort and 900 pregnant women in the COVID-19 vaccine-unexposed comparator cohort.

Data analysis: The distributions of demographic and baseline characteristics will be summarized within the exposure and comparator cohort. The following measures will be calculated for the pregnancy and infant outcomes: birth prevalence of major congenital malformations; incidence rates of spontaneous abortion, elective termination/abortion, stillbirth, and preterm delivery; and incidence proportions of small for gestational age and small for age postnatal growth at one year of age. For each outcome, risk estimates will be described separately for the Pfizer-BioNTech COVID-19 vaccine exposure cohort and the comparator cohort. The outcomes will be compared between the Pfizer-BioNTech COVID-19 vaccine-exposed and vaccine-unexposed cohorts. Where feasible, comparisons will also be made using methods to control potential confounding and to evaluate outcomes following receipt of specific doses (i.e., 1st, 2nd, 3rd, booster) in pregnancy.

Milestones: Pregnant women participating in the OTIS Pregnancy Registry on or after 11 December 2020 (date of EUA for the Pfizer-BioNTech COVID-19 vaccine) are eligible for study enrollment. The start of data collection (defined as start date of data extraction for the first interim report) will be 01 October 2021. Four annual interim reports will be submitted. The final study report and analysis is projected for December 2024.

5. AMENDMENTS AND UPDATES

Amendment Number	Date	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1	20 August 2021	6	Changed the date for "Final study report" from 01 December 2025 to 31 December 2025.	Information Request from Center for Biologics Evaluation and Research (CBER) received on 27 July 2021; CBER follow-up request on 19 August 2021.
		6	Changed the date for "End of data collection" from 01 August 2025 to 30 June 2025.	Allows for a 6-month period after end of data collection to conduct analyses and prepare final study report.
		9.3.1, 9.4.3, Table 1	Added clarification that a participant is classified as exposed if she reports in the maternal interviews that she received the Pfizer-BioNTech COVID-19 vaccine *or* if there is supporting documentation in the medical record for receipt of the Pfizer-BioNTech COVID-19 vaccine.	To clarify the use of maternal interviews and medical records in the classification of Pfizer-BioNTech COVID-19 vaccine exposure status.
		9.3.2.1	Added information on the expert dysmorphologist who reviews and classifies major congenital malformations including the qualifications and rationale for selection of the reviewer.	Information Request from Center for Biologics Evaluation and Research (CBER) received on 27 July 2021.
		Table 2, 9.4.2	Added clarifications on data elements that are collected as part of existing registry procedures.	Information Request from CBER received on 27 July 2021.
		9.4.1	Provided additional information on patient-initiated recruitment efforts and retention plans, including recruitment and retention strategies for diverse populations.	Information Request from CBER received on 27 July 2021.
		9.5	Added rationale for the target sample size.	Information Request from CBER received on 27 July 2021.
		Table 4	Added sample size and power calculations for the infant outcome of small for age postnatal growth at one year of age;	Information Request from CBER received on 27 July 2021.

Amendment Number	Date	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
			Added details on how the exposed and comparator sample sizes for each of the study endpoints were derived.	
			Corrected sample sizes for comparator cohort Ns in Table 4.	Error was made in transferring sample size estimates of comparator cohort to Table 4 in the previously submitted protocol.
2	29 November 2021	4, 6, 7	Updated milestones.	To reflect current recruitment timelines.
		7	Updated Rationale and Background.	1) To reflect the current approval and authorization status of the Pfizer-BioNTech COVID-19 vaccine in the United States, and 2) to update the number of women who reported to the Centers for Disease Control and Prevention V-safe surveillance system that they received the vaccine during pregnancy.
		9.1, 9.5, 9.7.3.1, Table 2, Table 4, Table 5	Increased sample size to allow for increased capture of women receiving a booster dose of the Pfizer-BioNTech COVID-19 vaccine during pregnancy; added 3rd and booster doses to the variable for specific dose of Pfizer-BioNTech COVID-19 vaccine; added subgroup analysis to include 3rd and booster doses.	To add safety assessment of 3rd and booster doses after authorization.
		9.3.1	Added clarification based on ACOG guidelines how gestational weeks are defined if first day of LMP is unclear or if ultrasound dates differ from LMP - derived dates.	To clarify how gestational weeks are calculated.
3	09 May 2022	4, 9.2.1, Table 2	Removed inclusion criteria of maternal age 18 or older	To allow for enrollment of individuals who are <18 years of age as per CBER request given vaccine authorization/approval in younger ages.
		Table 2	Change definition of gestational age at vaccination/study enrollment from <13,	To align with the SAP and definitions used for the study

Amendment Number	Date	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
			13-19.9, ≥20 weeks gestation to ≤13, 13.1-19.9, ≥20	

6. MILESTONES

Milestone	Planned Date
Registration in the EU PAS register	29 September 2021
Start of data collection	01 October 2021[1]
Interim Annual Reports[1]	31 January 2022 31 January 2023 31 January 2024
End of data collection	30 June 2024[2]
Final study report	31 December 2024

1 Pregnant women participating in the OTIS Pregnancy Registry on or after 11 December 2020 after EUA for the Pfizer-BioNTech COVID-19 vaccine are eligible for study inclusion. The start of data collection is defined as the planned date for starting data extraction for the first interim report.

2 The end of data collection is defined as the planned date on which the analytic dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

7. RATIONALE AND BACKGROUND

In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was first identified by public health officials in China. The World Health Organization (WHO) declared the SARS-CoV-2 outbreak and associated disease (Coronavirus disease 2019 [COVID-19] a global pandemic in March 2020. Despite public health efforts, the incidence of COVID-19 has continued to rise, largely affecting middle-aged persons with worsening clinical sequelae linked to increasing age and comorbid conditions (e.g., cardiovascular disease, diabetes and chronic lung disease). As of 17 May 2021, over 32.9 million COVID-19 cases and 586,330 deaths have been reported in the United States (US) alone (The Center for Systems Science and Engineering at Johns Hopkins University, 2021).

Pfizer and BioNTech have partnered to develop a novel (messenger ribonucleic acid) mRNA vaccine against SARS-CoV-2 for the prevention of COVID-19 (Candidate BNT162b2). Pfizer is conducting a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study among healthy individuals (NCT04368728). Interim analyses of Pfizer's Phase 3 clinical trial for vaccine candidate BNT162b2 were reported in December 2020 and showed that the two-dose regimen had 95% efficacy in the prevention of COVID-19 among individuals without evidence of prior SARS-CoV-2 infection. Based on the safety and efficacy data, as well as a review of manufacturing information regarding product quality and consistency, the Food and Drug Administration (FDA) determined that the known and potential benefits of the vaccine outweighed the known and potential risks for the prevention of COVID-19 in individuals 16 years of age and older (FDA, 2021a). The FDA initially granted Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine two-dose primary series on 11 December 2020 in individuals 16 years of age and older, and approved the vaccine for this population on 23 August 2021 (FDA, 2021a; FDA, 2021b). FDA expanded the EUA on 10 May 2021 to include children 12-15 years of age, and on 29 October 2021 to include lower-dose vaccine administration for children 5-11 years of age (FDA, 2021c; FDA, 2021d). The EUA was further amended on 12 August 2021 to include the administration of a third primary series dose in certain immunocompromised individuals 12 years of age and older, and on 22 September 2021 to allow for use of a single booster dose at least six months after completion of the primary series in certain populations (FDA, 2021e).

Studies in women with COVID-19 infection are limited. The available data suggest that pregnant women who become infected with COVID-19 may be more likely to be hospitalized and may be at increased risk of preterm delivery (MMWR, 2020). The COVID-19 vaccine is likely to be utilized by pregnant women when they and their healthcare providers believe that risk/benefit considerations favor its use. Also, given the frequency of unplanned pregnancies, information regarding the safety of the COVID-19 vaccine in human pregnancy is essential from a public health perspective. As of 25 October 2021, more than 169,000 women reported to the Centers for Disease Control and Prevention (CDC) V-safe surveillance system that they were vaccinated during pregnancy (CDC, 2021a). Therefore, information regarding the real-world safety of vaccination during pregnancy is essential from a public health perspective.

The current Pfizer-BioNTech COVID-19 vaccine product label for healthcare providers specifies that safety data are insufficient or not available to assess vaccine-associated risks in pregnant or lactating women. However, Pfizer is conducting an ongoing Phase 2/3 clinical trial of the safety and immunogenicity of the vaccine in pregnant women. In addition, this protocol proposes an observational study to evaluate pregnancy and infant safety outcomes among pregnant women enrolled in an established North American pregnancy registry who were exposed to the Pfizer-BioNTech COVID-19 vaccine.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a postmarketing commitment (PMC) to the FDA.

8. RESEARCH QUESTION AND OBJECTIVES

Is the risk of pregnancy and infant safety outcomes increased among pregnant women in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry (OTIS Pregnancy Registry) who were vaccinated with the Pfizer-BioNTech COVID-19 vaccine during pregnancy compared with those who did not receive any COVID-19 vaccine during pregnancy?

Study Objective

- To assess whether pregnant women who received the Pfizer-BioNTech COVID-19 vaccine during pregnancy experienced increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, elective termination/abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth at one year of age, relative to pregnant women who received no COVID-19 vaccines during pregnancy.

9. RESEARCH METHODS

9.1. Study Design

This proposed study is a prospective, observational cohort study of pregnancy and infant safety outcomes in pregnant women of all ages in the OTIS Pregnancy Registry who received the Pfizer-BioNTech COVID-19 vaccine any time from one month before the first day of the last menstrual period (LMP) to the end of pregnancy. The comparator cohort includes pregnant women who received no COVID-19 vaccines within one month before the first day of LMP to end of pregnancy. The pregnancy outcomes are major congenital malformations, spontaneous abortion, elective termination/abortion, stillbirth, preterm delivery, and small for gestational age; the infant outcome is small for age postnatal growth at one year of age. The target sample size for the study is 2000 pregnant women: 1100 pregnant women in the Pfizer-BioNTech COVID-19 vaccine exposure cohort and 900 pregnant women in the COVID-19 vaccine-unexposed comparator cohort. The main measures of effect are unadjusted and adjusted risk ratios (RRs) and 95% confidence intervals (CIs) comparing the Pfizer-BioNTech COVID-19 vaccine exposed cohort to the comparator cohort for the outcomes of major congenital malformations, small for gestational age, and postnatal growth; and unadjusted and adjusted hazard ratios (HRs) and 95% CIs comparing the Pfizer-

BioNTech COVID-19 vaccine exposed cohort to the comparator cohort for the outcomes of spontaneous abortion, elective termination/abortion, stillbirth, and preterm delivery.

9.2. Setting

This study will use data that are collected as part of the existing OTIS Pregnancy Registry (described further in Section 9.4 Data Source) and converted to a structured database for analysis. The registry includes pregnant women who reside in the US or Canada and allows for direct capture of information from participants through various health interviews. To obtain information provided by the treating physicians, data are collected from medical records for pregnant women and their infants.

When pregnant women are in contact with the OTIS Research Center, enrollment in the OTIS Pregnancy Registry is voluntary and requires informed consent of the pregnant woman. The study encourages enrollment as early as possible in the pregnancy before any prenatal testing results are known. This is accomplished by encouraging clinicians to refer patients, and patients who contact an OTIS service or who self-refer, to enroll upon first positive pregnancy test. These efforts reduce possible bias based on prior knowledge of a normal or abnormal ultrasound and allow for better estimation of risk of spontaneous abortion.

9.2.1. Inclusion Criteria

Individuals must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Residence in the US or Canada
- Enrolled in the OTIS Pregnancy Registry and currently pregnant on or after 11 December 2020 (i.e., date of EUA for the Pfizer-BioNTech COVID-19 vaccine)

9.2.2. Exclusion Criteria

Individuals meeting any of the following criteria will not be included in the study:

- Previous entry into this study for a prior pregnancy
- Receipt of any vaccine other than the Pfizer-BioNTech COVID-19 vaccine, influenza vaccine, or Tdap vaccine (e.g., Moderna or Johnson & Johnson COVID-19 vaccines, human papillomavirus vaccine, hepatitis B vaccine, etc.) from one month before the first day of LMP up to and including end of pregnancy
- Exposure to known human teratogens during pregnancy within one month before the first day of LMP up to and including end of pregnancy
- Known pregnancy outcome at time of study enrollment (e.g., positive prenatal diagnostic test results for a major congenital malformation prior to study entry)

9.2.3. Follow-Up

Pregnant women are entered in a cohort at the time of enrollment into the OTIS Pregnancy Registry. Information is collected on their pregnancy to date and they are then followed for the duration of their pregnancy. In addition, infants will be followed for potential safety events through their first year of life. Follow-up will end at the earliest of the following events:

- Lost to follow-up, i.e., an enrolled individual who withdraws or who fails to complete the outcome interview despite a standard number of telephone attempts and attempt to contact by mail as per study procedure manual within one year of the participant's estimated due date.
- Receipt of any vaccine other than the Pfizer-BioNTech COVID-19 vaccine, influenza vaccine, or Tdap vaccine (e.g., Moderna or Johnson & Johnson COVID-19 vaccines, human papillomavirus vaccine, hepatitis B vaccine, etc.) during pregnancy
- Occurrence of spontaneous abortion, elective termination/abortion, or stillbirth
- End of follow-up (i.e., one-year post-partum)
- End of study period
- Infant death
- Maternal death during pregnancy.

9.3. Variables

Variables for the exposures, outcomes, demographics, and clinical characteristics of interest are included below. Data on these variables will be collected via maternal interview and medical record review per standard process described in the OTIS Pregnancy Registry protocol. Detailed operational definitions will be provided in the Statistical Analysis Plan (SAP).

9.3.1. Identification of Exposure and Comparator

Vaccine exposure data are obtained by maternal report and/or medical record to classify Pfizer-BioNTech COVID-19 vaccine exposure status. The two sources of information are used in order to minimize misclassification of exposure status. Detailed information regarding vaccine exposure status of participants is obtained through the maternal interviews including at enrollment, at interim timepoints during pregnancy, and at pregnancy outcome interview (0 to 6 weeks after the expected due date or end of pregnancy). Participants are directly queried about the specific vaccines they received, including information on the gestational timing, dates of exposure, and brand. Vaccine exposures are coded using the Slone Drug Dictionary. Maternal report that a COVID-19 vaccine was received is complemented by requesting a copy of the COVID-19 vaccine record. In addition, medical

records from the obstetric provider, hospital of delivery, and any specialty provider are reviewed (when available) for all participants.

A participant is classified as unexposed if she reports that she did not receive any COVID-19 vaccine and her medical record (when available) shows no indication that she received any COVID-19 vaccine. A participant is classified as exposed if she reports in the maternal interviews that she received the Pfizer-BioNTech COVID-19 vaccine or if there is supporting documentation in the medical record for receipt of the Pfizer-BioNTech COVID-19 vaccine. If maternal report indicates no receipt of a COVID-19 vaccine but the medical record indicates discordance such that the Pfizer-BioNTech COVID-19 vaccine was administered, the medical record would supersede maternal report and the participant would be classified as Pfizer-BioNTech COVID-19 vaccine-exposed. Moreover, where maternal report indicates that the Pfizer-BioNTech COVID-19 vaccine was received but documentation in the medical record is discordant (i.e., no indication in medical record that COVID-19 vaccine was administered), the maternal report would supersede medical record for classification as exposed.

The estimated gestational weeks to qualify participants for the study for exposure and to classify outcomes is based on weeks from the first day of LMP which is counted as day 0. In circumstances where the date of LMP is not available or uncertain, or when a prenatal ultrasound estimates a gestational week that is discrepant according to obstetric guidelines, gestational week of pregnancy will be assigned based on the earliest available ultrasound (ACOG, 2017).

Table 1 below provides a description of variables for exposures to be included in this study. Each pregnancy and infant outcome will be analyzed separately, and the following exposure and comparator cohorts will be defined separately for each outcome analysis (depending on a participant's timing of vaccination/study enrollment as it relates to the at-risk period for an outcome):

- **Pfizer-BioNTech COVID-19 Vaccine (Exposure)**
  - Receipt of at least one dose of the Pfizer-BioNTech COVID-19 vaccine during the study period at any time from one month before the first day of LMP up to and including end of pregnancy
- **COVID-19 Vaccine-Unexposed (Comparator)**
  - Receipt of no COVID-19 vaccines during the study period within one month before the first day of LMP up to and including end of pregnancy

9.3.2. Classification of Pregnancy and Infant Outcomes

The following pregnancy and infant outcome variables (refer to Table 1) are obtained by maternal report and/or medical record review (when available) as part of existing procedures for the pregnancy registry.

9.3.2.1. Major Congenital Malformations

The method for classifying major congenital malformations for purpose of analysis has been described by the study investigators and the OTIS Research Group (CDC, 2000; Olsen et al., 2010) and has been used in previous studies conducted by OTIS.

A major congenital malformation is defined as a defect that has either cosmetic or functional significance to the child (e.g., a cleft lip). Major congenital malformations diagnosed during pregnancy and up to 1 year of age are reported by participants or the healthcare provider, or are identified through medical record review. Independent confirmation of certain defects is required via medical record review. For example, a heart murmur thought to represent a ventricular septal defect prior to 1 year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 noted will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies.

Classification of major defects is performed uniformly across cohorts according to the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) coding criteria (CDC, 2017).

- Some major congenital malformations are known consequences of pregnancy events, such as preterm delivery, and are therefore not directly due to vaccine exposure. For example, isolated patent ductus arteriosus or isolated inguinal hernia in an infant delivered before 36 weeks' gestation are considered consequences of prematurity, and therefore, using CDC coding criteria, none of these defects are counted as major congenital malformations. Other structural defects, such as club foot or cranial synostosis, could be due to position of the infant in the uterus or could be primary defects initiated earlier in pregnancy. In most cases, it is not possible to know the true onset or etiology of the defect. Therefore, using CDC coding criteria, these anomalies are counted as major congenital malformations uniformly across all cohorts.

- One exception to using the CDC coding criteria is that chromosomal anomalies will not be counted as major congenital malformations as it is unlikely that a vaccine exposure could cause a chromosomal defect.

The uniform coding reduces differences in outcome definitions between studies for a better interpretation of results in the event they are compared. It is anticipated that the occurrence of defects that are unrelated to vaccine exposure in the proposed study population will be nondifferential across cohorts. Therefore, their inclusion, when indicated, represents part of the baseline risk for major congenital malformations in each cohort. This should not impact the risk estimates and measures of association.

Major congenital malformations identified by prenatal ultrasound or examination of the products of conception following elective termination/abortion or spontaneous abortion will not be included in the primary analysis due to potential bias involved in non-uniform use of prenatal diagnosis and pathology evaluation for all abortuses.

As per recommendations in the FDA draft Guidance for Industry *Postapproval Pregnancy Safety Studies* (May 2019), an expert dysmorphologist and co-investigator for OTIS Pregnancy Registry studies, Dr. Kenneth Lyons Jones, reviews all the medical records and reports of major congenital malformations. The review is done blinded to exposure status and performed in the same manner for exposed and comparator cohorts. Dr. Jones is a pediatrician and the leading authority on environmental causes of congenital anomalies. He is the author of the main textbook in this field titled Smith's Recognizable Patterns of Malformation, 8th Edition (Jones et al., 2021).

9.3.2.2. Spontaneous abortion

Defined as non-deliberate fetal death which occurs prior to 20 weeks from the first day of LMP.

9.3.2.3. Elective termination/abortion

Defined as deliberate termination of pregnancy at any time in gestation. Reasons for elective termination/abortion are captured and are classified as due to medical reasons or social reasons.

9.3.2.4. Stillbirth

Defined as non-deliberate fetal death any time in gestation at or after 20 weeks from the first day of LMP.

9.3.2.5. Preterm delivery

Defined as live birth prior to 37 weeks' gestation as counted from the first day of LMP.

9.3.2.6. Small for gestational age at birth

Defined separately for weight, length, and head circumference (binary endpoints) as birth size less than or equal to the 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants (CDC, 2000; Olsen et al., 2010).

9.3.2.7. Small for age postnatal growth at one year of age

Defined separately for weight, length, and head circumference (binary endpoints) as postnatal size less than or equal to the 10th centile for sex and age using National Center for Health Statistics (NCHS) pediatric growth curves, and adjusted postnatal age for preterm infants if the postnatal measurement is obtained at less than 1 year of age (CDC, 2000).

Table 1. Exposure, Comparator, Exclusion, and Outcome Variables

Variable	Role	Data Source(s)	Operational Definition
Exposure to the Pfizer-BioNTech	Exposure	Maternal report	Maternal report of exposure to the Pfizer-BioNTech COVID-19 vaccine of at least one dose any time from one month prior to the first day of LMP to end of pregnancy

Table 1. Exposure, Comparator, Exclusion, and Outcome Variables

Variable	Role	Data Source(s)	Operational Definition
COVID-19 vaccine		Vaccine record (e.g., COVID-19 vaccine or yellow card) Medical record	
Gestational timing of the Pfizer-BioNTech COVID-19 vaccine use	Exposure	Maternal report Vaccine record (e.g., COVID-19 vaccine or yellow card) Medical record	Dates of the Pfizer-BioNTech COVID-19 vaccine administration one month prior to the first day of LMP up to and including end of pregnancy
No vaccine exposure during pregnancy	Comparator	Maternal report Medical record	Maternal report of no exposure to any vaccines at any time from one month prior to the first day of LMP to end of pregnancy
Exposure to non-study vaccines during the pregnancy window up to study enrollment	Exclusion criterion	Maternal report Vaccine record (e.g., COVID-19 vaccine or yellow card) Medical record	Maternal report of exposure to any vaccine other than the Pfizer-BioNTech COVID-19 vaccine, influenza vaccine, or Tdap vaccine (e.g., Moderna or Johnson & Johnson COVID-19 vaccines, human papillomavirus vaccine, hepatitis B vaccine, etc.)
Maternal pregnancy exposure to a known human teratogen	Exclusion criterion	Maternal report Medical record	Maternal pregnancy exposure to a known human teratogen (e.g., Type I Diabetes)
Major congenital malformation	Pregnancy outcome	Maternal report Medical record OTIS investigator review	A major structural or chromosomal defect that has either cosmetic or functional significance to the child (e.g., a cleft lip). Classified using the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) coding criteria (CDC, 2017) • According to the CDC MACDP guidelines, the following do not qualify as major congenital malformations: o Those findings that are present in infants with outcomes at <36 weeks gestational

Table 1. Exposure, Comparator, Exclusion, and Outcome Variables

Variable	Role	Data Source(s)	Operational Definition
			age or if gestational age is unavailable, weighing <2500 grams, and are attributed to prematurity alone, such as patent ductus arteriosus (PDA), patent foramen ovale (PFO), and inguinal hernias o Infants with only transient or infectious conditions, or biochemical abnormalities, are classified as being without major congenital malformations unless there is a possibility that the condition reflects an unrecognized major congenital malformation
Spontaneous abortion	Pregnancy outcome	Maternal report Medical record	Non-deliberate embryonic or fetal death that occurs prior to 20 weeks' gestation (CDC, 2021b)
Stillbirth	Pregnancy outcome	Maternal report Medical record	A non-deliberate fetal death that occurs at or after 20 weeks' gestation but prior to delivery (Prager S et al., 2021)
Preterm delivery	Pregnancy outcome	Maternal report Medical record	A spontaneous or induced delivery at <37 gestational weeks (as counted from the first day of LMP) (CDC, 2021c)
Small for gestational age	Infant outcome	Maternal report Medical record	Birth size (weight, length, or head circumference) $\leq 10^{th}$ percentile for sex and gestational age using NCHS pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants are used for preterm infants (Olsen et al., 2010; Schlaudecker EP et al., 2017)
Small for age postnatal growth at one year of age	Infant outcome	Medical record	Postnatal size (weight, length or head circumference) $\leq 10^{th}$ percentile for sex and age using NCHS pediatric growth curves and adjusted postnatal age for preterm infants

Abbreviations: CDC, Centers for Disease Control and Prevention; LMP, last menstrual period; MACDP, Metropolitan Atlanta Congenital Defects Program; NCHS, National Center for Health Statistics

9.3.3. Demographic and Clinical Characteristics

Potential confounders and other covariates to be collected include maternal age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, and prenatal tests. Table 2 provides a description of corresponding variables to be included in this study. The SAP will provide greater detail on covariable definitions, such as a listing of known human teratogens.

Table 2. Demographic and Clinical Variables

Variable	Role	Data Source(s)	Operational Definition
Age	Confounder	Maternal report	Maternal age (years) at due date, continuous and categorical (<18, 18-25, 25-29, 30-34, >34)
Race	Confounder	Maternal report	Maternal/Paternal race (Caucasian/White, Black, Asian/Pacific Islander, Native American, Other)
Ethnicity	Confounder	Maternal report	Maternal/Paternal ethnicity (Hispanic, Non-Hispanic)
Education	Confounder	Maternal report	Maternal Educational Category (years of completed education <12, 12-15, >15)
Socioeconomic category	Confounder	Maternal report	Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (1-5) (Hollingshead A, 1975)
Geographic area of residence	Confounder	Maternal report	Geographic area of residence (e.g., US, Canada)
Referral source	Confounder	Maternal report	Source options: Sponsor, OTIS service, health care provider (HCP), Internet, Other, UC Rely
Gestational age at vaccination/study enrollment	Confounder	Maternal report Medical record	Weeks of pregnancy at time of enrollment, continuous and categorical (≤13, 13.1-19.9, ≥20): gestational age is calculated from the first date of LMP
Trimester of vaccination/study enrollment	Confounder	Maternal report Medical record	1st, 2nd, or 3rd trimester categorization based on gestational age at vaccination/study enrollment
Height	Confounder	Maternal report	Maternal height (cm)
Pre-pregnancy body weight	Confounder	Maternal report Medical record	Maternal pre-pregnancy body weight (kg)
Pre-pregnancy body mass index (BMI)	Confounder	Maternal report	Maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25-29.9, ≥30)
Number of prior pregnancies	Confounder	Maternal report Medical record	Number of times ever pregnant (1, 2-3, 4-5, ≥6)
Number of previous live birth or stillbirth deliveries	Confounder	Maternal report Medical record	Number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, ≥5)
Previous pregnancies with a major congenital malformation	Confounder	Maternal report	≥1 previous pregnancy with a major structural or chromosomal defect diagnosed in utero or post-partum – Yes/No

Table 2. Demographic and Clinical Variables

Variable	Role	Data Source(s)	Operational Definition
Type of major congenital malformation in previous pregnancies	Confounder	Maternal report	A major structural or chromosomal defect that has either cosmetic or functional significance to the child (e.g., a cleft lip) classified using CDC coding criteria
Number of previous pregnancies ending in spontaneous abortion	Confounder	Maternal report Medical record	Number of previous pregnancies ending in spontaneous abortion (0, 1, 2, ≥3)
Number of previous pregnancies ending in elective termination/abortion	Confounder	Maternal report Medical record	Number of previous pregnancies ending in elective termination/abortion (0, 1, 2, ≥3)
Previous pregnancies ending in preterm delivery	Confounder	Maternal report	≥1 previous pregnancy ending in preterm delivery – Yes/No
Previous pregnancies ending in fetal growth restriction	Confounder	Maternal report	≥1 previous pregnancy ending in fetal growth restriction – Yes/No
Number of previous ectopic pregnancies	Confounder	Maternal report Medical record	Number of previous pregnancies ending in ectopic pregnancy (0, 1, 2, ≥3); ectopic pregnancy is defined as a pregnancy in which the fetus develops outside the uterus, typically in a fallopian tube.
Family history of genetic disorders and major congenital malformations	Confounder	Maternal report	Any family history of a major structural or chromosomal defect that has either cosmetic or functional significance to the child as defined using the CDC coding criteria – Yes/No
Prenatal vitamin, multivitamin, or folic acid use in pregnancy	Confounder	Maternal report	Prenatal, Multivitamin or Folic Acid supplement use by timing (began prior to conception, post-conception only, not taken at all)
Alcohol use in pregnancy	Confounder	Maternal report	Yes/No; dose and frequency are captured
Tobacco use in pregnancy	Confounder	Maternal report	Yes/No
Prenatal diagnostic tests prior to enrollment	Confounder	Maternal report Medical record	Tests performed prior to enrollment (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis)
Prenatal diagnostic tests any time during pregnancy	Confounder	Maternal report Medical record	Tests performed any time in pregnancy (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis)

Table 2. Demographic and Clinical Variables

Variable	Role	Data Source(s)	Operational Definition
Pregnancy complications	Confounder	Maternal report Medical record	Pregnancy induced hypertension Preeclampsia Gestational diabetes
Comorbid maternal medical history	Confounder	Maternal report Medical record	Comorbid maternal medical history (e.g., chronic hypertension, asthma)
Current medication use	Confounder	Maternal report	Prescription and over-the-counter medications are captured for the period of time from the first day of LMP through the end of pregnancy. Dose, frequency, duration, and indication including stop and start dates are collected
Exposure to the influenza or Tdap vaccine	Confounder	Maternal report Medical record	Maternal report of exposure to an influenza or Tdap vaccine any time from one month prior to the first day of LMP up to and including end of pregnancy
Pfizer-BioNTech COVID-19 vaccine dose	Covariate	Maternal report Medical record	Maternal report of the specific doses (1st, 2nd, 3rd, booster) of the Pfizer-BioNTech COVID-19 vaccine any time from one month prior to the first day of LMP up to and including the end of pregnancy
COVID-19 vaccine prior to pregnancy	Confounder	Maternal report Medical record	Maternal report of exposure to at least one dose of any COVID-19 vaccine any time prior to one month before the first day of LMP
COVID-19 infection symptoms and/or positive test during pregnancy	Confounder	Maternal report Medical record	Symptom inventory from maternal interviews; test results from maternal report and medical record
COVID-19 infection positive test prior to pregnancy	Confounder	Maternal report Medical record	Test results from maternal report and medical record

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; cm, centimeters; kg, kilograms; HCP, health care provider; LMP, last menstrual period; OTIS, Organization of Teratology Information Specialists.

9.4. Data Source

The OTIS Pregnancy Registry was established in 1999 for addressing questions regarding drug and vaccine safety in pregnancy among other research objectives. It is conducted by the OTIS Research Group, a network of university and health department-based telephone information centers serving pregnant women and healthcare providers throughout the US and

Canada (Leen-Mitchell et al, 2000). These services receive over 70,000 spontaneous inquiries per year from women and healthcare providers about the safety or risk associated with environmental exposures in pregnancy, including medications and vaccines. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and healthcare provider callers free of charge.

These services also provide a basis for collaborative research. Pregnant women who call are recruited for the OTIS Pregnancy Registry, and the healthcare providers are requested to contact the OTIS Pregnancy Registry to provide patient referrals. Active recruitment strategies are also used, e.g., direct mailings to healthcare providers, website, and professional meetings. Enrollment in the OTIS Pregnancy Registry is voluntary and requires informed consent by the pregnant woman. The OTIS Research Center is responsible for verifying the participant selection criteria, enrolling each participant and securing informed consent, oral and written (when available or applicable), providing all pregnancy (intake/enrollment and interim I and II) and post-partum follow-up interviews and medical record review, recording and storage of all data, and subsequent data analysis and interpretation.

As part of the OTIS Pregnancy Registry protocol, data are collected using maternal interview(s), medical record review (obstetric, delivery hospital, pediatric, vaccine provider, and/or other specialty provider if applicable), and the pregnancy exposure diary (see Table 3).

Table 3. Timing of Cohort Enrollment, Interviews, Examinations, and Medical Records

	Any Time In Pregnancy	20-22 Weeks' Gestation[b]	32-34 Weeks' Gestation[c]	0-6 Weeks Post-Delivery	0-12 Months Post-Delivery	1 Year Post-Delivery
Referral[a]	√					
Enrollment and Consent[a]	√					
Enrollment Interview[a]	√					
Interim Interview I		√				
Interim Interview II			√			
Pregnancy Outcome Interview and Request for Medical Records				√		
Medical Record Acquisition and Review					√	
Pediatric 1-Year Medical Records Request and Review						√

a. Participants may enroll in the study any time during pregnancy.
b. If participant is enrolled and Intake Interview is conducted after 18 weeks' gestation, only one interim interview is conducted during pregnancy at 32-34 weeks gestation.

Table 3. Timing of Cohort Enrollment, Interviews, Examinations, and Medical Records

	Any Time In Pregnancy	20-22 Weeks' Gestation[b]	32-34 Weeks' Gestation[c]	0-6 Weeks Post-Delivery	0-12 Months Post-Delivery	1 Year Post-Delivery

c. If participant is enrolled and Intake Interview is conducted at 30 weeks' gestation or after, no Interim Interview is collected.

Medication or vaccine exposures entered into the database are coded using the Slone Drug Dictionary. Major congenital malformations are coded using the MACDP coding list. Data are recorded on hard copies of forms and these records are retained by OTIS at the OTIS Research Center. These forms are considered the primary data sources for studies and can be adapted to add new data elements. Data from these forms are extracted and entered into a customized OTIS study database located in the Research Center.

9.4.1. Modalities of Recruitment

All exposed and comparison individuals will be recruited through spontaneous callers to participating OTIS member services in locations throughout North America and through active recruitment strategies, e.g., direct mailings to healthcare providers, website, and professional meetings, in alignment with the OTIS Pregnancy Registry Protocol. Each OTIS service will provide exposure counseling in the routine manner for all exposed and unexposed women who initially make contact with the service with questions regarding a current pregnancy. Subsequently, each OTIS service will request permission to refer the participant to the Research Center at the University of California, San Diego. Potential participants who agree to be referred will contact the Research Center or be contacted if they prefer. Women can self-refer via the OTIS Pregnancy Registry website, telephone, email, text, or chat. Healthcare providers can also contact the OTIS Pregnancy Registry and refer patients; however, in all cases the participant is the individual who provides informed consent for participation and completes the interview-based data collection.

To reach a broad population and raise awareness about the study, OTIS Pregnancy Registry studies use direct to consumer social media. OTIS also has partnerships with healthcare provider systems such as Kaiser Permanente, agencies such as CDC, and professional societies including the Society for Maternal Fetal Medicine, the American Academy of Pediatrics, and the American Academy of Allergy Asthma and Immunology. Partners promote the OTIS Pregnancy Registry network and studies on their websites and through presentations and exhibits at professional meetings. These strategies have resulted in cohort recruitment of a diverse sample including representation of women from each of the major race/ethnicity groups as well as across the range of socioeconomic status.

Once the target sample size is met for this Pfizer-BioNTech COVID-19 vaccine study (see Section 9.5 Study Size), recruitment efforts for the study will cease, and study enrollment will be closed. However, the OTIS Pregnancy Registry will remain open for enrollment for its other ongoing studies unrelated to the Pfizer-BioNTech COVID-19 vaccine study.

Retention of participants in the OTIS Pregnancy Registry is supported by frequent contact with the enrolled participant, building and maintaining a relationship between the study interviewer and the mother herself, and by ensuring the multiple alternative contact numbers/addresses are obtained and updated. Retention rates in OTIS Pregnancy Registry studies are typically extremely high at 95% or better.

9.4.2. Maternal Interviews

Below is a detailed description of each interview as conducted under the OTIS Pregnancy Registry protocol:

- **Intake/Enrollment Interview**: A structured maternal intake telephone interview is conducted at enrollment by a trained Research Associate from the OTIS Research Center. This interview includes questions on the following: pregnancy history, including major congenital malformations, genetic disorders, number of live births, and multiple gestations; current health history; pre-pregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education and ethnicity; income category; current medication use, both prescription and over the counter; other environmental or occupational exposures, alcohol, tobacco, caffeine and illicit drug use, vaccine exposure prior to and during pregnancy; current pregnancy complications including illnesses; family history of adverse pregnancy outcomes, including major congenital malformations and genetic disorders; names and addresses of health care providers; and vaccine use from one month prior to LMP and throughout pregnancy. To supplement future interviews and improve recall, participants are given a pregnancy exposure diary to record any additional exposures (medications, vaccinations, vitamins, etc.) or events as the pregnancy progresses. Each woman is also sent the informed consent document and the US Health Insurance Portability and Accountability Act (HIPAA) Authorization Addendum (when applicable) via electronic signature or paper, and a research HIPAA compliant obstetric medical record release form.

- **Interim Interviews I and II**: Telephone interviews are conducted at 20-22 and 32-34 weeks' gestation (if enrolled at those times) by a trained Research Associate from the OTIS Research Center. Women who have enrolled prior to 18 weeks post-LMP will be interviewed by telephone at 20-22 weeks post-LMP, 32-34 weeks post-LMP and within 2 to 6 weeks after the expected due date. Women who have enrolled between 19 and 20 weeks post-LMP will be interviewed at 32-34 weeks post-LMP (See Table 2 Schedule of Follow-up). These interviews are intended to update records of pregnancy exposures (medications, vaccinations, vitamins, etc.), results of prenatal tests, events of interest since last interview (including if the pregnancy has ended prior to the expected due date), and contact info.

- **Pregnancy Outcome Interview**: A structured telephone interview are conducted by a trained Research Associate from the OTIS Research Center at 0 to 6 weeks after the expected due date, or at an interim interview point or earliest convenient time for the

participant if pregnancy has ended. This interview elicits information based on type of birth:

- For women with live born infants: date of delivery, hospital location and mode of delivery; sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including malformations; type and length of hospital stay for pregnant women and their infants; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview.

- For women with spontaneous abortions: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview.

- For women with stillborn infants: all of the above for women with spontaneous abortions, plus sex, delivery or birth complications including malformations, birth size and autopsy results if available.

9.4.3. Medical Records and General Pediatric Evaluation

Upon completion of the outcome interview, each woman is sent a packet electronically or by hard copy mail containing research HIPAA compliant medical records release forms for the delivery hospital, obstetrician, pediatrician, vaccine provider, and specialist if applicable. For women whose pregnancies have ended in spontaneous abortion, elective termination/abortion, or stillbirth, records release forms are mailed for the specialist's evaluation, if applicable, and if prenatal diagnosis, pathology or autopsy reports are available. Each eligible woman is asked to sign (electronically or wet signature) the medical records release forms, as well as UCSD HIPAA Authorization Addendum (if they or their infant receives medical care at UCSD/Rady Children's hospital) and to return them along with the pregnancy exposure diary form.

Upon receipt of the signed medical records release forms, a standard physical evaluation form is mailed to each pediatrician or other physician responsible for the care of each live born infant. This form includes information on infant size at the time of the latest examination and an open-ended question about postnatal complications and congenital anomalies.

At one year of age, another research HIPAA compliant medical records release form for the pediatrician, or health care provider caring for the child, is sent to the mother of the infant for signature electronically or by hard copy mail. The signed form with a standard physical evaluation form is sent to the health care provider to request updated information on growth, and major congenital malformations.

Medical records for pregnant women and their infants are also captured at birth and again for the infant at one year of age. Medical records are reviewed by trained abstractors to supplement information self-reported by the participant related to vaccine exposure, outcomes, prenatal tests, and medical history.

9.4.4. Scientific Advisory Board

An existing external Scientific Advisory Board under the Vaccines and Medication in Pregnancy Surveillance System (VAMPSS) provides oversight for the study and reviews study summary data on an annual basis. Members of the Board provide advice to the Registry investigators on interpretation of the data and provide advice on strategies for the dissemination of information regarding the study.

The VAMPSS Scientific Advisory Board is managed by the American Academy of Allergy Asthma and Immunology. The Scientific Advisory Board is comprised of membership representing specialization in maternal fetal medicine, biostatistics, vaccine epidemiology, and representation from the Centers for Disease Control, National Institutes of Health/Child Health Institute, the American Academy of Pediatrics, and a consumer representative. The Board is chaired by a designated member, and each member has one vote. A dedicated charter describes roles and responsibilities of the Board members, and members complete conflict of interest disclosures on an annual basis.

9.5. Study Size

Recruitment goals are set at 1100 participants in the Pfizer-BioNTech COVID-19 vaccine exposure cohort and 900 participants in the comparator cohort, for a total of 2000 participants enrolled in the study. The target sample size for the Pfizer-BioNTech COVID-19 vaccine exposure cohort was increased from an initial sample size of 900 to 1100 to allow for increased capture of women receiving a booster dose during pregnancy. The rationale for the target sample size of 1100 pregnant women in the exposed cohort and 900 pregnant women in the comparator cohort was based on several considerations for feasibility of enrollment. These considerations included early trends in referrals of COVID-19 vaccinated pregnant women to the OTIS Pregnancy Registry, inclusion of women exposed to a booster dose as well as a reasonable time period for recruitment of pregnant women and the necessary time to collect outcome data to one year postpartum. An additional consideration was reasonable statistical power to detect differences for each outcome of interest. Balance in the cohort numbers by trimester of exposure in the vaccine-exposed cohort and by trimester of enrollment in both cohorts will be monitored on a monthly basis, and overall balance addressed by adjusting recruitment activities as needed. It is not possible to predict if the recruitment rates will be equal in all years, and therefore, sample size is based on estimates that may require revision as the study progresses.

As women will be eligible to enroll at any time in pregnancy, the gestational age at enrollment is expected to vary from 2 weeks to 41 weeks. Based on the gestational week at enrollment, only the portion of the overall sample enrolled prior to 20 weeks' gestation will be eligible for the analysis of spontaneous abortion. We estimate based on prior experience that half the overall sample will enroll prior to 20 weeks. Similarly, only the subset of the

sample enrolled prior to 37 weeks' gestation will be eligible for the analysis of preterm birth. It is estimated that 95% of the overall sample will enroll before 37 weeks. For the outcome of major birth defects, the main subset eligible for this assessment will be restricted in the exposed cohort to women who received at least one dose of the Pfizer-BioNTech COVID-19 vaccine from one month prior to LMP to the end of the first trimester. Pregnant women who received the Pfizer-BioNTech COVID-19 vaccine only during their second or third trimester will be excluded from the analysis. Based on previous experience in OTIS studies, the estimated lost to follow-up rate is 5% (Chambers et al, 2016).

Based on these assumptions, for the outcome of major birth defects, it is estimated that 85% will result in live birth after exclusion of pregnancy losses (10%) in women enrolled in the first half of pregnancy, and lost-to-follow-up (5%). For spontaneous abortion, it is estimated that half of the overall sample will enroll prior to 20 weeks' gestation. For preterm delivery, it is estimated that 80% of the overall sample will enroll prior to 37 weeks' gestation and will end in a singleton live birth. For the outcome of small for gestational age, it is estimated that 85% of the overall sample will end in a singleton live birth.

Baseline birth prevalence, incidence rates, and incidence proportions of major congenital malformations, preterm delivery, and small for gestational age, respectively, are based on previous OTIS Pregnancy Registry studies and on general population data. Table 4 gives the power for various detectable relative risks (RRs)/hazard ratios (HRs) for two-sided alpha level of 0.05 in the comparisons of the exposed cohort to the comparator cohort for the range of background risks of the outcomes of interest.

Table 4. Sample Size and Power for a Specified Effect Size

Outcome	N in Exposed Cohort	N in Comparator Cohort	Birth Prevalence/ Incidence in Comparator Cohort	Detectable Relative Risk/ Hazard Ratio	Power[1]
Major congenital malformations[2]	311	765	3%[3]	2.1	65.8%
				2.5	86.7%
				2.7	92.6%
Spontaneous abortion	550	450	10%[4]	1.5	66.6%
				1.7	90.1%
				1.8	95.6%
Preterm delivery	880	720	10%[5]	1.4	69.1%
				1.5	85.6%
				1.6	94.7%
Small for gestational age	935	765	10%[6]	1.4	71.7%
				1.5	87.6%
				1.6	95.8%
Small for age postnatal growth at one year of age	935	765	10%[6]	1.4	71.7%
				1.5	87.6%
				1.6	95.8%

Table 4. Sample Size and Power for a Specified Effect Size

Outcome	N in Exposed Cohort	N in Comparator Cohort	Birth Prevalence/ Incidence in Comparator Cohort	Detectable Relative Risk/ Hazard Ratio	Power[1]

1. Arcsine transformation using pwr.2p.test() in R package 'pwr' to obtain effect size h, where $h = 2 * \sin^{-1}\sqrt{p_1} - 2 * \sin^{-1}\sqrt{p_2}$ and p_1 = event rate in the exposed cohort, p_2 = event rate in the comparison cohort, assuming 2 sided alpha = 0.05.
2. Among livebirths.
3. CDC, 2017.
4. Avalos et al., 2012.
5. Ferré et al., 2016.
6. CDC, 2017; Nellhaus, 1968; Olsen et al., 2010.

NOTES

i. Major Congenital Malformations
   - N in exposed cohort for Major congenital malformations based on assumptions that 366 exposed to at least one dose from 1 month prior to LMP through the first trimester, and of these 10% will be lost to spontaneous abortion or stillbirth, and 5% lost to follow-up; 85% of the 366 enrolled will thus yield 311 eligible for the analysis.
   - N in comparator cohort = 900 enrolled x 85% resulting in at least one live birth = 765.

ii. Spontaneous Abortion
   - N in exposed cohort for spontaneous abortion based on estimate that ½ will be exposed and enroll in the first 20 weeks of gestation and thus be at risk of spontaneous abortion until 20 completed weeks; N of 1100 enrolled and exposed x 50% enrolled and exposed prior to 20 weeks = 550.
   - N in comparator cohort = 900 of which 50% will be enrolled prior to 20 weeks = 450.

iii. Preterm Delivery
   - N in exposed cohort based on 95% of the 1100 enrolled and exposed to at least one dose prior to 37 weeks, 10% pregnancy loss, and 5% lost to follow-up for an overall estimated 80% eligible for the analysis; 1100 enrolled x 80% = 880.
   - N in comparator cohort based on same assumptions; 900 enrolled x 80% = 720.

iv. Small for Gestational Age
   - N in exposed cohort based on 1100 enrolled and exposed to at least one dose from 1 month prior to LMP up through the end of pregnancy, 10% pregnancy loss, and 5% lost-to-follow-up; 1100 x 85% = 935.
   - N in comparator cohort based on same assumptions; 900 x 85% = 765.

v. Small for Age Postnatal Growth at One Year of Age
   - N in exposed cohort based on 1100 enrolled and exposed to at least one dose from 1 month prior to LMP up through the end of pregnancy; 10% pregnancy loss and 5% lost-to-follow-up; 1100 x 85% = 935.
   - N in comparator cohort based on same assumptions; 900 x 85% = 765.

9.6. Data Management

As per the OTIS Pregnancy Registry protocol, data are collected using maternal interview, medical record, and the pregnancy diary. Maternal interview data are recorded on hard copies of forms, and these forms will be retained by OTIS. These forms are considered the primary data sources for the registry. Medical records and medical record abstraction forms are hard copies or electronic copies and are retained on a secure server or in locked files. Data from maternal interview and medical record abstraction forms are extracted and entered into a customized OTIS registry database located in the Research Center and developed specifically for the OTIS Pregnancy Research Studies.

The database itself has built in range limits for key variables that prevent certain data entry errors. In addition, all data entry forms are reviewed for logical errors by the registry data manager on a bi-monthly basis, and 100% of key variables are double-checked for data entry accuracy. The registry statistician also conducts reviews of the cumulative data in the database for distributions and values that are illogical. The registry manager is responsible for working with the data manager and the supervisory staff to oversee the data validation procedures.

Access to the database is controlled by password, with different access privileges assigned to the managers, interviewers and data entry staff, and administrative staff; these privileges are outlined in detail in the OTIS Data Management Guide, Data Entry Standard Operating Procedure (SOP), and supplements to these guides. An audit log is built into the database to archive all such entry edits.

Hard copies of participant files and participant signed consent forms are kept in locked cabinets in locked file rooms, or electronically secured files, under the supervision of the study investigators.

9.7. Data Analysis

9.7.1. Statistical Methods

The distributions of demographic and baseline characteristics will be summarized within each exposure cohort. The following measures will be calculated for the pregnancy and infant outcomes: birth prevalence of major congenital malformations; incidence rates of spontaneous abortion, elective termination/abortion, stillbirth, and preterm delivery; and incidence proportions of small for gestational age and small for age postnatal growth at one year of age. For each outcome, risk estimates will be described separately for the Pfizer-BioNTech COVID-19 vaccine exposure cohort and each of the comparator cohorts. The outcomes will be compared between the Pfizer-BioNTech COVID-19 vaccine-exposed cohort and the comparator cohort. Where feasible, comparisons will also be made using methods to control potential confounding. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.2. Primary Analyses

The eligible populations and time periods for analyses may differ by pregnancy outcome depending on a participant's timing of vaccine exposure/study enrollment as it relates to the at-risk period for an outcome, in addition to type of birth (Table 5). For example, the analyses for major congenital malformations will be restricted to women exposed to at least one dose of the Pfizer-BioNTech COVID-19 vaccine during their first trimester (or enrolled in the study for COVID-19 unvaccinated comparator) whose pregnancies resulted in at least one live born infant. For preterm delivery, only those women exposed to at least one dose of the Pfizer-BioNTech COVID-19 vaccine (or enrolled in the study for unvaccinated comparator) prior to 37 weeks' gestation and whose pregnancies resulted in a live-born singleton are eligible for the analysis. The denominators for each exposure/comparator cohort and outcome analysis will include participants as follows:

Table 5. Denominators for Outcomes by Exposure/Comparator Cohort

Outcome	Pfizer-BioNTech COVID-19 Vaccine-Exposed (Exposure)	COVID-19 Vaccine-Unexposed (Comparator)
Major congenital malformations	Participants who received the Pfizer-BioNTech COVID-19 vaccine (1st, 2nd, 3rd, or booster dose) any time from one month before the first day of LMP through their first trimester and whose pregnancy resulted in ≥1 live birth	Participants who did not receive any COVID-19 vaccines any time from one month before the first day of LMP up to and including end of pregnancy and whose pregnancy resulted in ≥1 live birth
Spontaneous abortion	Participants who received the Pfizer-BioNTech COVID-19 vaccine (1st, 2nd, 3rd, or booster dose) any time from one month before the first day of LMP up to 20 weeks' gestation and were enrolled in the study prior to 20 weeks' gestation	Participants who did not receive any COVID-19 vaccines any time from one month before the first day of LMP up to and including end of pregnancy and were enrolled in the study prior to 20 weeks' gestation
Elective termination/abortion	Participants who received the Pfizer-BioNTech COVID-19 vaccine (1st, 2nd, 3rd, or booster dose) any time from one month before the first day of LMP up to and including end of pregnancy	Participants who did not receive any COVID-19 any time from one month before the first day of LMP up to and including end of pregnancy
Stillbirth	Participants who received the Pfizer-BioNTech COVID-19 vaccine (1st, 2nd, 3rd, or booster	Participants who did not receive any COVID-19 vaccines any

Table 5. Denominators for Outcomes by Exposure/Comparator Cohort

Outcome	Pfizer-BioNTech COVID-19 Vaccine-Exposed (Exposure)	COVID-19 Vaccine-Unexposed (Comparator)
	dose) any time from one month before the first day of LMP up to and including end of pregnancy, but must have follow-up at or after 20 weeks' gestation	time from one month before the first day of LMP up to and including end of pregnancy, but must have follow-up at or after 20 weeks' gestation
Preterm delivery	Participants who received the Pfizer-BioNTech COVID-19 vaccine (1st, 2nd, 3rd, or booster dose) any time from one month before the first day of LMP up to 37 weeks' gestation, were enrolled in the study prior to 37 weeks' gestation, and whose pregnancy resulted in a live-born singleton	Participants who did not receive any COVID-19 vaccines any time from one month before the first day of LMP up to and including end of pregnancy, were enrolled in the study prior to 37 weeks' gestation, and whose pregnancy resulted in a live-born singleton
Small for gestational age	Participants who received the Pfizer-BioNTech COVID-19 vaccine (1st, 2nd, 3rd, or booster dose) any time from one month before the first day of LMP up to and including end of pregnancy and whose pregnancy resulted in a live-born singleton	Participants who did not receive any COVID-19 vaccines any time from one month before the first day of LMP up to and including end of pregnancy and whose pregnancy resulted in a live-born singleton
Small for age postnatal growth at one year of age	Participants who received the Pfizer-BioNTech COVID-19 vaccine (1st, 2nd, 3rd, or booster dose) any time from one month before the first day of LMP up to and including end of pregnancy and whose pregnancy resulted in a live-born singleton	Participants who did not receive any COVID-19 vaccines any time from one month before the first day of LMP up to and including end of pregnancy and whose pregnancy resulted in a live-born singleton

For the endpoint of major congenital malformations, the birth prevalence among pregnancies resulting in at least one live born infant will be compared between the Pfizer-BioNTech COVID-19 vaccine exposure cohort and the comparator cohort. A point estimate of the crude (i.e. unadjusted) risk ratio (RR) of the exposed cohort versus the comparison cohort, as well as its 95% confidence interval (CI), will be computed using normal approximation method.

When the expected frequency of any of the cells of the contingency table is less than five, the CI will be obtained by an exact method using the software StatXact.

Due to the observational nature of the study, the above crude estimate of RR will be adjusted for potential confounders (Rosenbaum, 2002), provided that there are sufficient number of events. A list of potential confounders will be provided in a separate table in the SAP for each outcome prior to the final analysis, based on scientific knowledge including literature review. In addition, all of the following three criteria will be applied in accordance with the definition of confounders (Greenland et al., 1999; Xu et al., 2018): 1) by assessing each considered variable in a logistic regression model containing the exposure variable and the outcome variable to determine if inclusion of that single covariate changes the estimate of the odds ratio for exposure by 10% or more; 2) standardized mean differences greater than 0.1; 3) association with the outcome with p-value < 0.2 in the unexposed cohort. Care will be taken not to include those variables that are strongly associated with the exposure variable but only weakly associated with the outcome variable (Brookhart et al., 2006).

The confounders identified above will be used to build the propensity score for exposure (Rosenbaum, 2002). R package 'twang' or similar R package available at the time of analysis will be used for this purpose, following which standardized mean differences will be used to check the balance of the covariates between the cohorts.

The primary analysis will be performed with inverse probability of treatment weighting (IPTW) using the propensity score to estimate the causal risk ratio. In the IPTW approach, we will use stabilized weights that are further trimmed to be between 0.1 and 10 if necessary (Austin and Stuart, 2015). The bootstrap variance estimator will be used following the IPTW approach.

An additional analysis of major congenital malformations will be conducted using outcome regression, i.e., a logistic regression model will be fitted with major congenital malformation (Y) as the outcome, and exposure (A) and propensity score (L) as regressors. Outcomes regression tends to be more stable and efficient than IPTW especially given the expected rare number of events (Xu et al., 2018), and has known robust properties against model misspecification (Vansteelandt and Daniel, 2014). Standardization will be performed to obtain the estimated causal risk ratio (Hernán and Robins, 2019). The variance estimator will be obtained using bootstrap.

The analysis of spontaneous abortion and stillbirth is complicated by left truncation in the data, i.e., women enter the study at arbitrary times in gestation (Xu et al., 2012). Only those women who are enrolled prior to 20.0 weeks of gestation are eligible for the analysis of spontaneous abortion. Since they are not followed from gestational age zero, survival analysis methods will be used to handle left truncation, as well as right-censoring when a participant is lost-to-follow-up prior to 20 weeks' gestation. The Cox proportional hazards marginal structural model incorporating time-dependent vaccine exposure will be used for the causal hazard ratio (HR) of different cohorts, as well as to obtain the 95% CIs. To

account for potential confounding, propensity score methods with the IPTW approach will be applied. Stillbirth will be analyzed in a similar fashion.

The analysis of preterm delivery can also be complicated by left truncation in the data, i.e., women enter the study at arbitrary times in gestation. Only those women who are enrolled prior to 37.0 weeks of gestation are eligible for the analysis of preterm delivery. These data will be analyzed similarly to spontaneous abortion, as described above, using survival analysis methods, to handle possible left truncation and right-censoring.

The analysis of elective termination/abortion will be descriptive as the number of events is expected to be low.

The following are binary endpoints: small for gestational age at birth in weight, length, and head circumference; and small for age postnatal growth at one year of age $\leq 10^{th}$ centile in weight, length, and head circumference. The analysis of the proportion of infants with each of these outcomes will be similar to the analysis of the outcome major congenital malformations and will be restricted to pregnancies ending in a live born singleton. For these outcomes, exposure to the Pfizer-BioNTech COVID-19 vaccine in any trimester will be compared to the unexposed cohort.

9.7.3. Secondary Analyses

9.7.3.1. Stratified/Subgroup Analyses

For the endpoint of major congenital malformations, the comparison will also be carried out within each of two strata, according to whether the participant had prenatal diagnostic testing, such as level 2 ultrasound, amniocentesis or chorionic villus sampling, prior to enrollment in the study or not.

In stratified analyses, the separate effects of vaccine exposure during the first, second, and third trimester of pregnancy will be studied as applicable to the following pregnancy outcomes: preterm delivery, small for gestational age, and small for age postnatal growth at one year of age.

A variable for prior COVID-19 infection will be used in the propensity score generation for the adjusted analyses, and, if numbers permit, a stratified analysis for prior COVID-19 infection will be conducted as well.

9.7.3.2. Individual Dose Effects

Secondary analyses will also address the potentially different effects of the 1^{st}, 2^{nd}, 3^{rd}, and booster doses during relevant pregnancy windows (e.g., 1^{st} trimester exposure for the outcome of major congenital anomalies, and prior to 20 weeks' gestation for the outcome of spontaneous abortion). More specifically these will be considered four separate exposures. An additive effects marginal structural model will be used for each pregnancy outcome.

9.7.3.3. Evaluation for a Pattern of Major Congenital Malformations

The following steps will be taken to evaluate any pattern of major congenital malformations:

A review of major congenital malformations will be made by category. A review of specific major congenital malformations will be conducted taking into consideration timing and biological plausibility. In addition, specific defects that are plausibly related to second or third trimester exposure will also be evaluated.

9.7.3.4. Lost to Follow-Up

Pregnancies enrolled in the cohort study for which outcome information is unobtainable within 1 year after the estimated date of delivery are considered lost to follow-up. It is possible that outcomes among pregnancies lost to-follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what impact with regard to potential biases the lost to follow-up may have on any analysis of the cohort study. Should lost to follow-up numbers be substantial, however, efforts at comparing some of the characteristics of each cohort will be made in an attempt to address this potential source of bias. However, the OTIS Research Center prior experience has been that the lost to follow-up rate is extremely low, typically 5%.

9.7.4. Sensitivity Analyses

The following sensitivity analyses will be performed for the outcome of major congenital malformations.

- A sensitivity analysis will be performed for the outcome of major congenital malformations among all pregnancies excluding those that are lost-to-follow-up. The analysis population will be those with exposure to the Pfizer-BioNTech COVID-19 vaccine at any time from one month prior to the first day of LMP to the end of the first trimester excluding those that are lost-to-follow-up. The analysis population for the comparison cohort will be all pregnancies excluding those that are lost-to-follow-up. The purpose of this analysis is to account for major congenital malformations that may occur in pregnancies that are terminated or spontaneously lost and are therefore excluded from the primary analysis of major congenital malformations among live births.

- A second sensitivity analysis will be performed for the outcome of major congenital malformations stratified on any abnormal finding (yes/no) among those with prenatal testing prior to enrollment.

- In a third sensitivity analysis, both the exposure and comparator cohorts will be restricted to women who enrolled in the study during their first trimester.

- A fourth sensitivity analysis will be conducted to expand the comparator cohort to include women who received any dose of the Pfizer-BioNTech COVID-19 vaccine only in their second or third trimester.

- Sub-analyses using graphical presentation based on gestational timing of exposure to the Pfizer-BioNTech COVID-19 vaccine will also be performed.

An additional sensitivity analysis will be performed for the outcome of preterm delivery stratified on elective cesarian section or labor induction leading to delivery prior to 37 weeks' gestation vs. delivery prior to 37 weeks' gestation following spontaneous labor.

9.7.5. Missing Data

Multiple imputation (MI) will be conducted to handle the missing data. Missing values typically occur in less than 5% of the cases for any single covariate based on prior experience. They are assumed to be missing at random. When there are missing values in any of the selected confounders, multiple imputation (MI) will be conducted, using the R package MICE (multivariate imputation by chained equations). Demographic information, pregnancy history, information about current pregnancy, and concurrent diseases will be used as possible 'predictors' in MICE. The generalized R^2 will be used as a measure of correlations between each 'target' (i.e., the variable to be imputed) and a predictor. If the value of R (i.e., square root of R^2) is over 0.1, the variable will be retained as a predictor. Predictors with strong collinearity might be excluded (for example, one of race and ethnicity, and one of gravidity and parity). Although each outcome within each cohort comparison has its unique set of participants, MI is conducted for missing data using the entire dataset, i.e., on all cohorts combined.

For the outcome of spontaneous abortion, for some cases the exact date of the event might be unknown, and instead a window for possible spontaneous abortion time is available. This is known as interval censored data, and can also be handled using MI. An exact spontaneous abortion time will be imputed by sampling uniformly from the corresponding time window.

The number of above imputations will be 10, i.e., 10 datasets with imputed data will be created. Each imputed data set gives a point estimate of the regression coefficients as well as its standard deviation, which will be combined across the 10 datasets to obtain the final estimate of the causal RR/HR and their 95% CI's. Further details will be provided in the SAP.

9.7.6. Analysis Software

All summaries and statistical analyses will be performed using the current version of open-source statistical programming language R and StatXact.

9.8. Quality Control

Data used in this study are secondary use of data collected as part of the existing OTIS Pregnancy Registry protocol, which includes established quality control practices. Interview

and examination data will be recorded on hard copies of forms, and medical records and medical record abstraction forms will be electronic or hard copies of forms. These records and forms will be retained at the Research Center. Data from these forms will be extracted and entered into a customized database located at the Research Center. The data will be extracted and entered by trained study personnel with extensive experience with this type of information. Entries will be periodically reviewed for logical errors, and a random subset of intake and outcome forms will be double-checked for data entry accuracy. The method and duration of storage of data is addressed in the informed consent, that each participant will agree to in order to receive medical record information. All records are maintained for a minimum of 15 years following study completion.

Access to the database will be controlled by password. Hard copies of participant files and signed consent forms will be kept in a locked cabinet under the supervision of the study investigators.

The data will be entered by trained study personnel with extensive experience with this type of information. Data will be collected and entered into the database according to the SOPs for data collection and data entry established for this study.

The data manager will calculate monthly error rates for each data entry staff person and for the study overall and will recommend and initiate training/retraining where quality standards are not being met. The study manager will oversee this process and verify that training standards are achieved.

For the study endpoint of major congenital malformations, verification of the outcome identified, and classification is performed on a monthly basis is provided by blinded review by co-investigator, Kenneth Lyons Jones, MD.

9.9. Limitations of the Research Methods

This study will use data from the well-established OTIS Pregnancy Registry which collects detailed data on prenatal/birth exposures (including timing of exposures during pregnancy) and outcomes. The primary limitation of this cohort study utilizing volunteer participants is potential selection bias in that women who agree to enroll in the study may represent particularly high- or low-risk pregnancies (Johnson et al., 2001). For example, women who receive the vaccine and have a history of spontaneous abortion (high baseline risk) may be more likely to preferentially enroll than women who did not receive the vaccine and who did not have a history of prior spontaneous abortion because of concerns about their pregnancy. In addition, the study results will be strictly generalizable to women fitting the profile of the sample of women who enroll. The use of inverse probability weighting to account for differences between the exposure and comparator cohorts will address these concerns to some extent. The data analysis stratifying on use of prenatal testing and on gestational timing of enrollment will also help control for confounding introduced by potential selection bias.

Another limitation of the study design relates to the evaluation of the incidence of spontaneous abortion. Incidence rates of early spontaneous abortion, i.e., at 7-9 weeks post-

LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. Therefore, spontaneous abortion will be defined as late first-trimester and early second-trimester pregnancy loss. Analysis of spontaneous abortion will be restricted to those who enroll prior to 20 weeks' gestation. In addition, if a high proportion of women enroll later in pregnancy, other survival biases may be introduced. A sensitivity analysis by gestational age at enrollment will be performed in order to address these questions. Analyses will be stratified by gestational age at enrollment to help address the potential selection bias.

As early prenatal testing is so prevalent in the US and Canada, it may be difficult to achieve adequate numbers of participants if all pregnancies with prenatal testing prior to enrollment are excluded from the analysis. Therefore, the study will include pregnant women enrolled prior to outcome but after a prenatal test has been performed as long as the test does not indicate the presence of a major congenital malformation. The FDA guidance document (FDA Postapproval Pregnancy Safety Studies Draft Guidance for Industry, 2019) acknowledges that such an approach may be necessary to accrue adequate numbers. However, this practice could potentially bias the results by lowering the overall estimate of the birth prevalence of major congenital malformations (Honein et al., 1999).

The calculation of frequency of major congenital malformations excludes fetal losses (spontaneous abortions, elective terminations/abortions, or fetal deaths) for which no major congenital malformations have been detected as they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or pregnancies with major congenital malformations. The study attempts to obtain information on major congenital malformations detected at the time of the outcome. However, the malformation status of the aborted fetus may not be known. For this reason, the primary comparison for the endpoint of the study will be conducted among pregnancies ending in at least one live birth; a separate sensitivity analysis of the endpoint will be conducted including all pregnancies with known outcome.

It is expected that exposure to the Pfizer-BioNTech COVID-19 vaccine will occur in unintended pregnancies as more than half of all pregnancies in the US are unintended (Henshaw, 1998). Therefore, the possibility of confounding by age, race, and other demographic variables will be considered. For example, the rate of unintended pregnancies is higher among low-income women/families than among the other socioeconomic cohorts. It is possible that demographic variables will be associated with vaccination as well (MMWR, 2021). As such, in reviewing annual reports, if clear differences in demographic factors (i.e., age, race/ethnicity, socioeconomic status, education) are noted, enhancement of recruitment efforts to increase diversity will be taken into consideration.

Although all possible efforts will be made to retain participants in the registry or follow up with their healthcare providers, some participants will be lost during follow up. It could be possible that participants lost during follow up and with missing data on outcomes may be different compared to those with complete follow up data. In previous OTIS studies, lost-to-follow-up rates have been low, typically <5% (Chambers et al., 2016). However, the characteristics of women lost to follow up will be compared to those who are retained in order to understand the direction and magnitude of the bias due to loss to follow up.

The study design has relative strengths with respect to the control of a large number of potential confounders. Information will be collected repeatedly throughout pregnancy on a variety of factors which may be related to exposure and to pregnancy outcome, and the use of a vaccine comparison cohort can aid in addressing confounding. Misclassification bias due to poor recall is thought to be reduced in prospective study designs such as this, as each participant is interviewed at several predetermined intervals during pregnancy. Another strength of the study design is the anticipated minimal lost-to-follow-up rate. Based on previous experience of the investigators in the OTIS Pregnancy Studies and other similar studies, and the frequent participant contact, lost-to-follow-up is expected to be less than 5%, and therefore not expected to pose a threat to the validity of study results.

Finally, the sample size that is projected to be achievable for this study has limitations in statistical power for the outcome of major congenital malformations. The investigators and the Scientific Advisory Board's expert review and comment on the data and the inclusion of evaluation of a pattern of major anomalies are strengths.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information. If automated/algorithmic methods, such as natural language processing, will be used to convert unstructured data to structured data during the implementation of the protocol, no patient personal data will be accessed.

10.2. Participant Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

This protocol and informed consent documents are approved by the Institutional Review Board (IRB) at the University of California, San Diego. The chairperson or the recording secretary of the IRB sign a form indicating approval. Notification of the Board's approval of the study is provided to the Sponsor prior to initiation of the study.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practice (ISPE, 2016), in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2013) and HIPAA (Health Insurance Portability and Accountability Act) (National Institutes of Health, 2002; Andrews et al., 1996).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In this structured pregnancy database, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the study endpoints will be prepared by the OTIS Research Center and provided to the Pfizer team. Pfizer will communicate the results to FDA and other regulatory authorities as appropriate. Conference abstracts and manuscripts based on specific endpoints of interest may be developed for publication purposes and will be reviewed by Pfizer for comment. The final report will be disclosed on the EU PAS Register.

In addition, the OTIS Research Center will develop annual interim reports and any additional *ad hoc* reports with the advice of the VAMPSS Scientific Advisory Board members. Each report will be a composite of the cumulative data to date and will supersede any previous reports. Descriptive analyses may be presented, but no formal interim statistical analysis is planned. The rationale for this is that given sample size limitations, an interim analysis will likely be statistically underpowered to provide informative results. However, at each interim Scientific Advisory Board review, consideration will be given to any findings that might indicate that a formal interim analysis should be performed. The final analysis will be conducted when the cohort study has been completed.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable

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