NON-INTERVENTIONAL (NI) STUDY STATISTICAL ANALYSIS PLAN (SAP)

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
Statistical Analysis Plan version identifier	~~1~~2.0
Date	~~30 November 2021~~05 May 2022
EU Post Authorization Study (PAS) register number	EUPAS42869
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	Research Question: 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
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cm	centimeter
COVID-19	Coronavirus disease 2019
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HCP	health care provider
HR	hazard ratio
IPTW	inverse probability of treatment weighting
kg	kilogram
LMP	last menstrual period
m	meter
MACDP	Metropolitan Atlanta Congenital Defects Program
MI	multiple imputation
MICE	multivariate imputation by chained equations
mRNA	messenger ribonucleic acid
MSM	marginal structural model
NCHS	National Center for Health Statistics
OR	odds ratio
OTIS	Organization of Teratology Information Specialists
PASS	Post-Authorization Safety Study

Abbreviation	Definition
PCR	polymerase chain reaction
PDA	patent ductus arteriosus
PFO	patent foramen ovale
PMC	postmarketing commitment
RNA	ribonucleic acid
RR	risk ratio
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMD	standardized mean difference
SOP	standard operating procedure
Tdap	tetanus, diphtheria, and acellular pertussis

3. AMENDMENTS AND UPDATES

~~None.~~

Amendment Number	Date	SAP Section(s) Changed	Summary of Amendment(s)	Reason
1	05 May 2022	6.1 Inclusion Criteria	Removed "age 18 years or older" from the inclusion criteria	To allow for enrollment of individuals who are <18 years of age as per CBER request given vaccine authorization/approval in younger ages.
		9.1 Timing Variables	Updated the definition of trimesters to ≤13, 13.1-≤26, >26	To align with the definitions used for the study
		11 3.1 Major Congenital Malformations	Updated formula for inverse probability weighting. Updated number of bootstrap samples from 10,000 to 200	To fix an error and prevent negative values; to align with the current method of using multiple imputation
		Throughout document	Fixed minor typos and references.	To fix errors

NOTE: In this document, any text taken directly from the Non-Interventional (NI) study protocol is italicized.

4. RATIONALE AND BACKGROUND (SUMMARY)

Pfizer and BioNTech have partnered to develop a novel messenger ribonucleic acid (mRNA) vaccine (Candidate BNT162b2) against a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) for the prevention of associated coronavirus disease 2019 (COVID-19). *The* United States *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. 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 observational study described in the corresponding study protocol is being conducted 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.*

This statistical analysis plan (SAP) provides a comprehensive and detailed description of statistical approaches and techniques to analyze the data for the study.

5. RESEARCH QUESTION AND OBJECTIVE

Research Question: *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.*

6. STUDY DESIGN (SUMMARY)

This proposed study is a prospective, observational cohort study of pregnancy and infant safety outcomes in pregnant women 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*. Secondary analyses will be conducted to address the potential bias in prenatal diagnostic testing procedures to detect major congenital malformations performed prior to versus after enrollment, the separate effects of trimester of vaccine exposure for endpoints other than major congenital malformations, individual dose effects, potential bias in those who are lost to follow-up, and the effect of prior COVID-19 infection. Sensitivity analyses will be conducted to evaluate major congenital malformations identified in all pregnancies including those not ending in at least one live birth, but excluding those lost to follow-up; in pregnancies with any abnormal ultrasound findings prior to enrollment; in pregnancies restricted to those only those enrolled in the first trimester; and in an expanded comparator group including those vaccinated with the Pfizer-BioNTech COVID-19 vaccine only in the second and/or third trimester. A sensitivity analysis for the endpoint of preterm delivery will be conducted stratified by those delivering following spontaneous labor versus labor induction or delivery by cesarian section.

7. STUDY POPULATION (SUMMARY)

7.1. 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*
- ~~*Age 18 years or older*~~
- *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)*

7.2. 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)*

7.3. Follow-Up

The study entry date, i.e., the follow-up start date, for *pregnant women in the OTIS Pregnancy Registry* is the study enrollment date. *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*

8. STUDY SIZE

8.1. Sample Size

For the target sample size *of 1800 participants enrolled in the study, recruitment goals are set at 1100 participants in the Pfizer-BioNTech COVID-19 vaccine exposure cohort, and 900 participants in the comparator cohort. 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* sizes *in* each *cohort was based on several considerations for feasibility of enrollment. These included early trends in referrals of COVID-19 vaccinated pregnant women to the OTIS Pregnancy Registry, combined with 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 weeks at enrollment is expected to vary from 2 weeks to 41 weeks. Based on the gestational weeks 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 congenital malformations, 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 the first day of 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).

8.2. Power Calculations

Based on these assumptions, for the outcome of major congenital anomalies, 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, small for gestational age, and small for age postnatal growth at one year of age, *respectively, are based on previous OTIS Pregnancy Registry studies and on general population data. Table 1 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 1. 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%*

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. *Ferre 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.*

Table 1. 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]

- *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. DATA SOURCE (SUMMARY)

As part of the OTIS Pregnancy Registry protocol, data are collected using maternal interview(s) and *medical record review. To supplement the* interim and pregnancy outcome *interviews and* to *improve recall, participants are given a pregnancy exposure diary to record any additional exposures (medications, vaccinations, vitamins, etc.) or events as the pregnancy progresses.*

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.

9.1. Maternal Interviews

The maternal interviews are conducted by telephone at the intake/enrollment interview, then 1-2 interim interviews (depending on gestational age of the pregnant woman at enrollment), and lastly the pregnancy outcome interview. Data collected from each of these interviews include the following:

- *Intake/Enrollment Interview*
  - *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*
- Any COVID-19 *vaccine exposure prior to and during pregnancy*, including dates, scheduled dose, and manufacturer
- *Vaccine use from one month prior to the first day of LMP and throughout pregnancy*
- *Current medication use, both prescription and over the counter*
- *Other environmental or occupational exposures*
- *Alcohol, tobacco, caffeine and illicit drug use*
- *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*
- COVID-19 symptoms, treatments, and testing results
- Referral source

- *Interim Interviews I and II at 20-22 and 32-34 weeks' gestation (if enrolled at those times)*
  - *Update* of data since last interview, including *records of pregnancy exposures (medications, vaccinations, vitamins*, supplements, and other prescription and over-the-counter products*), results of prenatal tests, events of interest (*e.g., pregnancy complications, illnesses, *pregnancy end prior to the expected due date), and contact information*
  - COVID-19 symptoms, treatments, and testing results

- *Pregnancy Outcome Interview 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)*
  - *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*
    - COVID-19 symptoms, treatments, and testing results
    - *Additional exposures and results of prenatal tests occurring since the previous interview*

- *For women with spontaneous* or elective *abortions:*
  - *Date and type of outcome*
  - *Hospital location if applicable*
  - *Prenatal diagnosis*
  - *Pathology results if available*
  - COVID-19 symptoms, treatments, and testing results
  - *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* or elective *abortions*
  - *Sex*
  - *Delivery or birth complications including malformations*
  - *Birth size*
  - *Autopsy results if available*

9.2. Medical Records and General Pediatric Evaluation

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

Medical records from the prenatal care provider, the hospital of delivery, any specialty provider, and the pediatric care provider will be requested and abstracted for exposure, outcome and covariate/confounder data. A standard pediatric questionnaire will be completed by the physician responsible for the care of each live born infant at or near one year of age.

Data collected from medical records and the pediatric questionnaire include:

- Exposure to Pfizer-BioNTech COVID-19 vaccine including dose number and dates;
- Pregnancy outcome;
- Prenatal tests and results;
- Pregnancy complications;
- Mode of delivery;
- Birth weight, length and head circumference of infant;
- Apgar scores;
- Length and type of hospital stay;
- Major congenital malformations identified in the fetus or infant up through one year of age;
- Postnatal growth measures for the infant up to one year of age (measurements between 9 to 15 months of age are considered valid; if multiple measurements are available, the evaluation of weight, length and head circumference that is closest to one year of age will be used;
- COVID-19 infection, testing and treatments.

To supplement maternal report of vaccination, a copy of the COVID-19 vaccine record is also requested from participants who have been vaccinated.

10. 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 are *provided* below.

10.1. Timing Variables

- The estimated date for the first day of LMP is based on maternal report or medical record. If the first day of LMP and the menstrual cycle length are known, the first day of LMP is used to calculate the estimated date of confinement or due date. However, if a first trimester ultrasound has been performed, and the estimated due date by that ultrasound differs by seven days or more from the first day of LMP estimate, the first-trimester ultrasound-derived date will be used. If there is no first trimester ultrasound, but an ultrasound performed in the second trimester has an estimated due date that differs by14 days or more, or a third trimester ultrasound estimated due date that differs by 21 days or more from the estimate by first day of LMP, the ultrasound-derived date will be used. The earliest available ultrasound in pregnancy is used to determine if any adjustment in due date calculated by first day of LMP is necessary. When the first day of LMP and/or cycle length are unknown or when a prenatal ultrasound estimates a gestational week that is discrepant according to obstetric guidelines, the due date calculated by the earliest available ultrasound is used (ACOG, 2017).

- Weeks' gestation is defined as the number of weeks from the estimated first day of LMP which is counted as day 0 and calculated as:

  (Current date – estimated date of the first day of LMP)/7.

- The definition of trimesters is as follows:
  - First trimester: 30 days prior to the first day of LMP to ~~<~~≤13 weeks' gestation
  - Second trimester: 13.1 weeks' gestation to ~~<~~≤26 weeks' gestation
  - Third trimester: ~~>~~≥26 weeks' gestation.

- The start date for exposure ascertainment during pregnancy is defined as one month prior to the first day of LMP and calculated as the estimated date of the first day of LMP minus 30 days.

10.2. *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 manufacturer. 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.

Table 2 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*

Table 2. Variables Related to Defining the Exposure, Comparator, Outcomes, Exclusions, and Date/Time

Variable	***Role***	***Data source(s)***	***Operational definition***
Exposure to the Pfizer-BioNTech	*Exposure*	*Maternal report*	*Maternal report,* vaccine record documentation, or medical record documentation *of exposure to at least one dose of the Pfizer-BioNTech COVID-19*

Table 2. Variables Related to Defining the Exposure, Comparator, Outcomes, Exclusions, and Date/Time

Variable	***Role***	***Data source(s)***	***Operational definition***
COVID-19 vaccine		*Vaccine record (e.g., COVID-19 vaccine or yellow card)* *Medical record*	*vaccine any time from one month prior to first day of LMP to end of pregnancy*.
No COVID-19 *vaccine exposure during pregnancy*	*Comparator*	*Maternal report* *Medical record*	*Maternal report of no exposure to*, as well as no medical record documentation of, *any* COVID-19 *vaccines at any time from one month prior to first day of LMP to end of pregnancy*
Weeks' gestation	Time	Maternal report Vaccine record (e.g , COVID-19 vaccine or yellow card) Medical record	Number of weeks (rounded to the nearest 0.1 decimal) from the first day of LMP to date of interest calculated as: (Date of interest – estimated date of the first day of LMP) / 7 The date of interest is based on maternal report, vaccine record, or medical record depending on which variable the date is for and which source was used to assign a value to that variable. If the date of interest (e.g., vaccine exposure date) is in the 30 days prior to the first day of LMP, the gestational week would be between -0.1 and -4.0.
Weeks' gestation at time of receipt of the Pfizer-BioNTech COVID-19 vaccine	Timing of exposure	*Maternal report* *Vaccine record (e.g., COVID-19 vaccine or yellow card)* *Medical record*	Weeks' gestation (using calculation in row above) for date of 'Exposure to the Pfizer-BioNTech COVID-19 vaccine' based on the vaccine dose administration date from maternal report, vaccine record, or medical record
Weeks' gestation at study enrollment	Timing of study enrollment, *Confounder*	*Maternal report* *Medical record*	Weeks' gestation *at time of study enrollment, continuous and categorical (<13, 13.1-19.9, ≥20),*
Trimester of Pfizer-BioNTech COVID-19 vaccine	Timing of exposure, *Confounder*	*Maternal report* *Vaccine record (e.g., COVID-19 vaccine or yellow card)* *Medical record*	Gestational week of vaccination by trimester category: 1st trimester defined as 30 days prior to first day of LMP through 13.0 weeks' gestation 2nd trimester defined as 13.1 weeks' gestation through 26.0 weeks' gestation 3rd trimester defined as 26.1 weeks' gestation to the end of pregnancy

Table 2. Variables Related to Defining the Exposure, Comparator, Outcomes, Exclusions, and Date/Time

Variable	*Role*	*Data source(s)*	*Operational definition*
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) (Annex 2 Table A-1)*

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*
			  ○ *Those findings that are present in infants with outcomes at <36 weeks gestational 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*
			  ○ *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*
			• An OTIS investigator also conducts a blinded review of medical records and maternal report to classify of major congenital malformations
			• Both sources of data are used to come to a final classification

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Table 2. Variables Related to Defining the Exposure, Comparator, Outcomes, Exclusions, and Date/Time

Variable	*Role*	*Data source(s)*	*Operational definition*
Spontaneous abortion	*Pregnancy outcome*	*Maternal report* *Medical record*	*Non-deliberate embryonic or fetal death that occurs prior to 20 weeks' gestation* from first day of LMP (Prager et al., 2021)
Stillbirth	*Pregnancy outcome*	*Maternal report* *Medical record*	*A non-deliberate fetal death that occurs at or after 20 weeks' gestation* from first day of LMP *but prior to delivery (CDC, 2021 (b))*
Preterm delivery	*Pregnancy outcome*	*Maternal report* *Medical record*	*A spontaneous or induced delivery at <37 gestational weeks* from first day of LMP *(CDC, 2021(c))*
Small for gestational age	*Infant outcome*	*Maternal report* *Medical record*	*Birth size (weight, length, or head circumference) ≤10th 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 et al., 2017)*
Small for age postnatal growth at one year of age	*Infant outcome*	*Medical record*	*Postnatal size (weight, length or head circumference) ≤10th percentile for sex and age using NCHS pediatric growth curves and adjusted postnatal age for preterm infants*
Live birth	Outcome-specific inclusion/ exclusion	Maternal report Medical record	Singleton, twin or higher order gestation resulting in at least one live born infant

Abbreviations: *CDC, Centers for Disease Control and Prevention; LMP, last menstrual period; MACDP, Metropolitan Atlanta Congenital Defects Program; NCHS, National Center for Health Statistics; OTIS, Organization of Teratology Information Specialists; US, United States.*

10.3. Classification of Pregnancy and Infant Outcomes

The following pregnancy and infant outcome variables (refer to Table 2) are obtained by maternal report and/or medical record review (when available) as part of existing procedures for the pregnancy registry.

10.3.1. Major Congenital Malformations

- *Defined* for pregnancies ending with at least one live born infant *as a defect that has either cosmetic or functional significance to the child (e.g., a cleft lip) diagnosed during pregnancy up to 1 year of age as reported by* participants/ healthcare providers *or identified through medical record review.*
- A pregnancy with multiple births is counted as one malformed outcome if one or more of the infants/fetuses are malformed.

- *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, 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; however, these defects will be considered in a sensitivity analysis including all defects in the numerator over all pregnancies with known outcome in the denominator (excluding lost to follow-up).*
- *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.* If the major congenital malformation diagnosis is determined to be incorrect (e.g., misdiagnosed or another type of defect), the reviewer reclassifies the outcome, the change is documented in the database, and the rationale for the change is also documented. In cases where classification is not clear, consultation with the Medical Director of Metropolitan Atlanta Congenital Defects Program (MACDP) is available, as well as expert consultation from the study Scientific Advisory Board. Through this adjudication process a consensus classification is achieved.
- *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*

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1 year of age will be included if it is confirmed as a heart defect by a diagnostic procedure such as *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.*

10.3.2. Spontaneous abortion

Defined as non-deliberate embryonic/*fetal death* (miscarriage) *which occurs prior to 20 weeks'* gestation. In pregnancies involving multiples with one or more of the outcomes ending in spontaneous abortion, when there are no live births, the pregnancy is counted as one spontaneous abortion event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.

10.3.3. 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.

10.3.4. Stillbirth

Defined as non-deliberate fetal death any time in gestation at or after 20 weeks' gestation. In pregnancies involving multiples with one or more of the outcomes ending in stillbirth, when there are no live births, the pregnancy is counted as one stillbirth event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth.

10.3.5. Preterm delivery

Defined as live birth prior to 37 weeks' gestation.

10.3.6. 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 National Center for Health Statistics (NCHS) *standard pediatric growth curves for full term or preterm infants (CDC, 2000).* Prenatal growth curves specific to preterm infants will be used for premature infants (*Olsen et al., 2010).*

10.3.7. 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 NCHS pediatric growth curves (*CDC, 2000*~~(CDC, 2000),~~). *and adjusted* chronological age *for preterm infants if the postnatal measurement is obtained at less than 1 year of age* (*CDC, 2000*~~(CDC, 2000).~~) The measurements obtained closest to one year of age, and within three months prior to or after one year of age (9-15 months) are used.

10.4. 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 3 provides a description of corresponding variables to be included in this study.

Table 3. Demographic and Clinical Variables

Variable	Role	Data source(s)	Operational definition
Age	*Confounder*	*Maternal report*	*Maternal age (years) at due date, continuous and categorical (<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* Status (SES) *based on maternal and paternal occupation and education* (Categorical: high 1-2, moderate 3; low 4-5) (Hollingshead, 1975)
Geographic area of residence	*Confounder*	*Maternal report*	*Geographic area of residence (US, Canada)*
Referral source	*Confounder*	*Maternal report*	*Source options Sponsor, OTIS service, health care provider (HCP), Internet,* Referrals from other University of California Medical Centers, *Other*
Height	*Confounder*	*Maternal report*	*Maternal height in centimeters (cm)*
Pre-pregnancy body weight	*Confounder*	*Maternal report* *Medical record*	*Maternal pre-pregnancy body weight* in kilograms *(kg)*
Pre-pregnancy body mass index (BMI)	*Confounder*	*Maternal report*	Calculated as maternal pre-pregnancy body weight in kilograms (kg) divided by maternal height in meters squared (m^2). Categorized as: Underweight = <18.5 kg/m^2 Normal weight = 18.5-24.9 kg/m^2 Overweight = 25-29.9 kg/m^2 Obese = ≥30 kg/m^2
Number of prior pregnancies	*Confounder*	*Maternal report* *Medical record*	*Number of times ever pregnant* prior to current pregnancy *(1, 2-3, 4-5, ≥6)*

Table 3. Demographic and Clinical Variables

Variable	Role	Data source(s)	Operational definition
Number of previous live birth or stillbirth deliveries	*Confounder*	*Maternal report* *Medical record*	*Number of previous live birth or stillbirth deliveries*, i.e., parity defined as number of previous pregnancies ending in a live or stillbirth after 24 weeks' gestation *(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*
Type of major congenital malformation in previous pregnancies	*Confounder*	*Maternal report*	Specific *major structural or chromosomal defect* in previous pregnancies *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)*

Table 3. Demographic and Clinical Variables

Variable	Role	Data source(s)	Operational definition
Alcohol use in pregnancy	*Confounder*	*Maternal report*	Light or moderate alcohol use based on an average dose and frequency. Participants are classified in this group if they have had any amount of alcohol in pregnancy but have not exceeded ≥14 drinks per week for 4 or more weeks after conception. – Yes/No (heavy alcohol use is classified as a human teratogen which is exclusionary, thus no participants in the study would have heavy use)
Tobacco use in pregnancy	*Confounder*	*Maternal report*	Any tobacco use during pregnancy – *Yes/No*
Prenatal diagnostic tests prior to study enrollment	*Confounder*	*Maternal report* *Medical record*	≥1 diagnostic *tests performed* during pregnancy *prior to* study *enrollment (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling,* and *Amniocentesis)*
Prenatal diagnostic tests any time during pregnancy	*Confounder*	*Maternal report* *Medical record*	≥1 diagnostic *tests performed any time in pregnancy (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling,* and *Amniocentesis)*
Pregnancy complications	*Confounder or Mediator*	*Maternal report* *Medical record*	*Pregnancy induced hypertension* – Yes/No *Preeclampsia* – Yes/No *Gestational diabetes* – Yes/No Each pregnancy complication will be considered as a confounder for the endpoints of preterm delivery, small for gestational age at birth, and small for age postnatal growth at one year of age. If the complication occurs after exposure to the Pfizer-BioNTech COVID-19 vaccine in pregnancy, the complication will also be evaluated as a potential mediator of those same endpoints
Comorbid maternal medical history	*Confounder*	*Maternal report* *Medical record*	*Comorbid maternal medical history current diagnosis in pregnancy* *Chronic hypertension* – Yes/No *Asthma* – Yes/No Psychiatric disorder – Yes/No Immune disorders – Yes/No

Table 3. Demographic and Clinical Variables

Variable	Role	Data source(s)	Operational definition
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;* specific categories of medication treatments in pregnancy: Antihypertensive medications – Yes/No Asthma medications – Yes/No Psychotherapeutic medications – Yes/No Immune modulators – Yes/No
Exposure to the influenza or Tdap vaccine	*Confounder*	*Maternal report* *Medical record*	*Exposure to an influenza or Tdap vaccine any time from one month prior to first day of LMP up to and including end of pregnancy*
COVID-19 vaccine prior to pregnancy	*Confounder*	*Maternal report* *Medical record*	*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 symptoms during pregnancy	Confounder	Maternal report	Symptom inventory (Annex 2: Table A-2)
COVID-19 infection positive test during pregnancy	*Confounder*	*Maternal report* *Medical record*	*Test results* positive for COVID-19 (e.g., viral RNA/PCR) *from maternal report or medical record*
COVID-19 infection positive test prior to pregnancy	*Confounder*	*Maternal report* *Medical record*	*Test results* positive for COVID-19 (e.g., viral RNA/PCR) *from maternal report or 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;* PCR, polymerase chain reaction; RNA, ribonucleic acid.

11. 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 ~~().~~ (Chambers, et al., 2019). 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~~).~~) (van Buuren S and Groothuis-Oudshoorn K, 2011). 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~~.~~ (Pan, 2000)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~~.~~ (Little and Rubin, 2002).

12. STATISTICAL METHODS AND DATA ANALYSIS

12.1. Data Cleaning and Preparation of Datasets

The original data will be cleaned and validated by the OTIS Data Manager and exported in the form of multiple datasets to the study statisticians. A checklist will be filled out and reviewed prior to the analysis to ensure the original data have been properly validated and meet the study criteria. There will be close communications between the statisticians and the OTIS Research Manager during this process. Based on the original data, the statisticians derive variables to be used for the analyses as described in the definitions of the variables in Table 2 and Table 3.

12.2. Demographic and Baseline Characteristics

The distributions of demographic and baseline characteristics will be summarized within each exposure cohort. Continuous variables will be summarized using the following statistics: mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum. All categorical variables will be summarized using counts and percentages. Missing data or unknown responses will not be counted in the percentages.

12.3. Primary Analyses

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 cohort and the comparator cohort.*

Where feasible, comparisons will also be made using methods to control potential confounding.

The eligible populations and time periods for analyses may differ by pregnancy outcome depending on a participant's exposure status, *timing of vaccine exposure/study enrollment as it relates to the at-risk period for an outcome, in addition to type of birth (Table 4). The denominators for each exposure/comparator cohort and outcome analysis will include participants as follows:*

Table 4. 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 dose) any time from one month before the first day of LMP up*	*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, but*

Table 4. Denominators for Outcomes by Exposure/Comparator Cohort

Outcome	Pfizer-BioNTech COVID-19 Vaccine-Exposed (Exposure)	COVID-19 Vaccine-Unexposed (Comparator)
	to and including end of pregnancy, but must have follow-up at or after 20 weeks' gestation	*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*

12.3.1. Major Congenital Malformation

For the endpoint of major congenital malformations, the exposure of interest is at least one dose of the Pfizer-BioNTech COVID-19 vaccine during the first trimester. The primary comparison will be the birth prevalence of major congenital malformations between the exposed cohort and the comparator cohort among pregnancies resulting in at least one live born infant. The birth prevalence of major congenital malformations will be calculated for each cohort as the number of pregnancies ending in at least one liveborn infant with a major congenital malformation divided by the number of all pregnancies for women in the cohort ending in at least one live born infant (Table 4), multiplied by 100. *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.* The method is based on inverting an unconditional exact hypothesis test (Agresti and Min, 2001).

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 appendix to *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 (OR) for exposure by 10% or more: $|OR_2 - OR_1|/OR_1 \geq 10\%$ where OR_1 is the crude OR and OR_2 is the OR adjusting for the covariate in question;
*2) standardized mean differences (*SMD) *greater than 0.1;*
3) association with the outcome with p-value < 0.2 in the unexposed cohort (using chi-square test or two sample t-test)*. 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* (e.g, instrument-like variables) *(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 SMD *will be used to check the balance of the covariates between the cohorts.*

The primary analysis will estimate the effect of exposure on the risk for major structural defect as the causal risk ratio (Hernán and Robins, 2020) using inverse probability of treatment weighting (IPTW). The causal risk ratio is defined as $P(Y^{a=1} = 1)/\mathrm{P}(Y^{a=0} = 1)$, where $Y^{a=1}$ is the potential outcome under exposure and $Y^{a=0}$ is the potential outcome without exposure. The risks for the potential outcomes will be estimated using the inverse probability weighting:

$$\hat{P}(Y^{a=0} = 1) = n^{-1}\sum_{i=1}^{n} w_i ~~(A_i - 1)Y_i~~(1 - A_i)Y_i, \quad \hat{P}(Y^{a=1} = 1) = n^{-1}\sum_{i=1}^{n} w_i A_i Y_i,$$

*w*here Y_i and A_i denote the observed outcome ($Y_i = 1$ or 0 for presence or absence of a major congenital malformation) and exposure status ($A_i = 1$ or 0 for exposed or unexposed) among the n pregnancies, and w_i is the inverse of the probability of being in the observed exposure group estimated using the propensity score, which has been stabilized and *further trimmed to be between 0.1 and 10 if necessary (Austin and Stuart, 2015).* The causal risk ratio is then estimated by $\hat{P}(Y^{a=1} = 1)/\hat{P}(Y^{a=0} = 1)$. The 95% CIs will be obtained using the bootstrap estimated variance and asymptotic normality, with 200 bootstrap samples, i.e., resampling with replacement on the pregnant women. The propensity score will be re-computed for each bootstrap sample to account for variability in the estimation of the weights.

Provided there are sufficient number of events, i.e., at least 10 events per parameter in the regression model, an additional analysis will be conducted using outcome regression (Xu et al., 2018; Vansteelandt and Daniel, 2014). *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~~(Xu et al., 2018),~~), and has known robust properties against model misspecification (Vansteelandt and Daniel, 2014~~(Vansteelandt and Daniel, 2014).~~). In a second step, *standardization will be performed to obtain the estimated causal risk ratio* (Hernán and Robins, 2020), which has the interpretation as the marginal or population averaged risk ratio. Note that

$$P(Y^{a=1} = 1) = \sum_l P(Y = 1|A = 1, L = l)P(L = l).$$

The above can be estimated by first predicting the potential outcomes $\hat{P}(Y^{a=1} = 1|A = 1, L = l) = \hat{P}(Y = 1|A = 1, L = l)$, using the fitted outcomes regression model for the whole sample (i.e., both exposed and unexposed), assuming that their treatments are all a = 1. $\hat{P}(Y^{a=1} = 1)$ will be estimated by averaging these predicted values over the distribution of L, as in the equation above. $P(Y^{a=0} = 1)$ is estimated in a similar way. Finally, the causal risk ratio will be estimated by dividing these two estimated probabilities. The CI's are obtained by bootstrap with ~~10,000~~200 bootstrap samples, i.e. resampling with replacement of the pregnant women.

12.3.2. Spontaneous Abortion, Stillbirth, and Preterm Delivery

The analyses of spontaneous abortion, stillbirth, and preterm delivery are complicated by several factors based on the timing of study entry and the at-risk period for the outcome. The eligible populations and time periods for the analyses of each of these outcomes are as follows:

- Spontaneous abortion: *Only those women who are enrolled prior to 20.0 weeks of gestation* in both exposed and comparator cohorts, and only those women exposed to at least one dose of the Pfizer-BioNTech COVID-9 vaccine from 30 days before the first day of LMP up to 20.0 weeks' gestation.

- Stillbirth: Only those pregnancies that reach at least 20 weeks of gestation are eligible for analysis.

- 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;* pregnancies with twins or higher order multiples will be excluded.

Because *women can enter the study at arbitrary times in gestation* (i.e., *left truncation*), *participants are not followed from gestational age zero.* Those who experience the event prior to enrollment will never enter the study, leading to left truncation of the time to event. This can produce selection bias if early vaccination time causes early time to event. The event time is also right-censored whenever a subject is lost to follow-up prior to observing the outcome. In addition, vaccine exposure can occur prior to or throughout enrollment, so exposure status is time-dependent. In order to address these issues, *survival analysis methods will be used to handle possible left truncation, right-censoring, and time-dependent exposure or confounding. The Cox proportional hazards marginal structural model (MSM) incorporating time-dependent vaccine exposure* and relevant covariates *will be used to estimate the causal hazard ratio (HR) and 95% CIs* for exposure to the Pfizer-BioNTech COVID-19 vaccine (Hernán et al, 2001). For $t \geq 0$ let $a(t)$ be an indicator for exposure to the Pfizer-BioNTech COVID-19 vaccine by time t during the exposure window and let T_a denote the potential time to spontaneous abortion had a subject followed the exposure profile a. The marginal structural model is:

$$\lambda_a(t) = \lambda_0(t)\exp(\beta a(t))$$

where $\lambda_a(t)$ is the hazard of T_a at time t, λ_0 is the baseline hazard function representing the risk for a subject who never receives the vaccine, and $\exp(\beta)$ is the causal relative risk for the effect of exposure.

The method that will be used to estimate the MSM depends on whether there are time-dependent confounders that are also affected by previous exposure to the Pfizer-BioNTech COVID-19 vaccine (Hernán et al, 2001). This study considers two potential sources of time-dependent confounding: COVID-19 circulation season and COVID-19 infection in pregnancy prior to vaccination. Circulation season is an external mechanism that is not affected by a subject's previous vaccine exposure. On the other hand, infection during pregnancy is likely to be affected by previous vaccine exposure. The estimation method therefore depends on whether infection is included as a confounder.

If infection during pregnancy is not selected as a confounder, the MSM can be consistently estimated using multivariable regression. In this approach, a time-dependent proportional hazards model for the time to spontaneous abortion will be fit, with effects for the time-varying exposure as well as all selected confounders. The usual 95% Wald confidence intervals will be computed using the standard software.

If infection during pregnancy is selected as a confounder, the MSM can be consistently estimated using IPTW. To obtain the weights, a proportional hazards model is fit for the time to vaccine exposure during the exposure window, adjusting for the selected confounders (Xu et al., 2014; Yang et al., 2018~~.~~). Estimates of the conditional survival function $S(t|l)$ and density function $f(t|l)$ given the confounders l are then used to compute time-dependent propensity scores and weights. At a fixed time t, the weight for a woman with confounders $L(t)$ who is still at risk for SAB by time t is $w(t) = 1/PS(t)$, where $PS(t)$ is computed as follows:

1) For a subject who is not exposed during the window,
   $PS(t) = S(t|L(t))$ if they have not been fully vaccinated prior to the window
   $PS(t) = 1$ if they have been fully vaccinated prior to the window

2) For a subject who is exposed during the window at time D,
   $$PS(t) = \begin{cases} S(t|L(t)) & \text{if } t < D \\ f(D|L(D) & \text{if } t \geq D \end{cases}$$

When there is a strong association between confounders and exposure time, the weights can be large for some subjects, leading to a large variance in the IPTW estimator. Variability can be reduced using stabilization and trimming (Austin and Stuart, 2015). The weights will be stabilized by multiplying by $PS_0(t)$, which is computed analogous to $PS(t)$ except using the baseline quantities $S_0(t) = S(t|0)$ and $f_0(t) = f(t|0$~~).~~) (Yang et al., 2018) If necessary, the weights will be further trimmed to lie between 0.1 and 10.

The exposure time is not observed for women who never enter the study due to left truncation of the outcome. As a consequence, the exposure time may also be subject to left truncation. This is a potential source of bias in the PS estimates, and a possible limitation of the IPTW method.

The standard error $\text{se}(\hat{\beta})$ of the causal exposure effect will be estimated using the nonparametric bootstrap, and 95% CIs will be computed as $\hat{\beta} \pm 1.96\ \text{se}(\hat{\beta})$.

12.3.3. Elective Termination/Abortion

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

12.3.4. Small for Gestational Age at Birth and Small for Age Postnatal Growth at One Year of Age

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 ≤10th centile in weight, length, and head circumference. The analysis of the incidence proportion of infants with each of these outcomes will be similar to the analysis of the outcome major congenital malformations (see Section 10.3.1~~Section 10.3.1.~~ "Major Congenital Malformation) *and will be restricted to pregnancies ending in a live born singleton*; pregnancies with twins or higher

order multiples will be excluded. *For these outcomes, exposure to* any dose of *the Pfizer-BioNTech COVID-19 vaccine in any trimester will be compared to the unexposed cohort.*

12.4. Secondary Analyses

12.4.1. 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 compared to unexposed *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.

12.4.2. Individual Dose Effects

We will address the potentially differential effects of the 1st, 2nd, 3rd, and booster doses of the Pfizer-BioNTech COVID-19 vaccine during the relevant pregnancy window. Each dose *will be considered a separate exposure, and a marginal structural model* (Robins et al., 2000; Hernán et al., 2001) with independent effects for the exposures *will be evaluated for each pregnancy outcome.*

Binary Outcomes: For an exposure window of interest, let A_1, A_2, A_3, and A_4 be indicators for exposure to the 1st, 2nd, 3rd, and booster doses, respectively, during the window; i.e. $A_i = 1$ if the i^{th} dose occurs during the window and $A_i = 0$ otherwise, for $i = 1, 2, 3$ and 4. The sequence (A_1, A_2, A_3, A_4) describes the pattern of exposures during the window. Let Y_{a_1,a_2,a_3,a_4} be the potential outcome that would occur if a woman was subject to the exposures $A_1 = a_1, A_2 = a_2, A_3 = a_3$ and $A_4 = a_4$, where each of a_1, a_2, a_3 and a_4 are 0 or 1. The linear logistic MSM with additive effects for each vaccine dose assumes the form

$$\text{logit}\, P\left(Y_{a_1,a_2,a_3,a_4} = 1\right) = \beta_0 + \beta_1 a_1 + \beta_2 a_2 + \beta_3 a_3 + \beta_4 a_4.$$

In this model, β_i is the log OR representing the causal effect of exposure to the i^{th} dose. The causal effects are estimated from the observed data using an IPTW estimator.

The weights for the IPTW estimator will be constructed from regression models for each of the exposure doses A_1, A_2, A_3, and A_4, adjusted for the selected confounders L. Let $\pi_1(b)$ be the probability of receiving the 1st dose during the exposure window conditional on L among subjects that received b doses prior to the exposure window. Let $\pi_2(b, a_1)$ be the probability of receiving the 2nd dose during the exposure window conditional on L among those subjects

with $A_1 = a_1$ and who received b doses prior to the start of the window. Likewise, let $\pi_3(b, a_1, a_2)$ be the probability of receiving the 3rd dose during the exposure window conditional on L among those subjects with $A_1 = a_1$ and $A_2 = a_2$ and who received b doses prior to the start of the window. Finally, let $\pi_4(b, a_1, a_2, a_3)$ be the probability of receiving the 4th dose during the exposure window conditional on L among those subjects with $A_1 = a_1$, $A_2 = a_2$ and $A_3 = a_3$ and who received b doses prior to the start of the window. The weight for a subject with exposures A_1, A_2, A_3, and A_4 and confounders L is $w = 1/PS$, where PS can be decomposed in terms of $\pi_1(b), \pi_2(b, a_1), \pi_3(b, a_1, a_2)$, and $\pi_4(b, a_1, a_2, a_3)$ as follows:

1) $A_1 = 0, A_2 = 0, A_3 = 0$, and $A_4 = 0$:
   $PS = 1 - \pi_1(0)$ if they have received no doses prior to the window
   $PS = 1 - \pi_2(1,0)$ if they have received one dose prior to the window
   $PS = 1 - \pi_3(2,0,0)$ if they have received two doses prior to the window
   $PS = 1 - \pi_4(3,0,0,0)$ if they have received three doses prior to the window
   $PS = 1$ if they have received four doses prior to the window
2) $A_1 = 1, A_2 = 0, A_3 = 0$, and $A_4 = 0$: $PS = \pi_1(0)(1 - \pi_2(0,1))$
3) $A_1 = 0, A_2 = 1, A_3 = 0$, and $A_4 = 0$: $PS = \pi_2(1,0)(1 - \pi_3(1,0,1))$
4) $A_1 = 0, A_2 = 0, A_3 = 1$, and $A_4 = 0$: $PS = \pi_3(2,0,0)(1 - \pi_4(2,0,0,1))$
5) $A_1 = 0, A_2 = 0, A_3 = 0$, and $A_4 = 1$: $PS = \pi_3(3,0,0,0)$
6) $A_1 = 1, A_2 = 1, A_3 = 0$, and $A_4 = 0$: $PS = \pi_1(0)\pi_2(0,1)(1 - \pi_3(0,1,1))$
7) $A_1 = 0, A_2 = 1, A_3 = 1$, and $A_4 = 0$: $PS = \pi_2(1,0)\pi_3(1,0,1)(1 - \pi_4(1,0,1,1))$
8) $A_1 = 0, A_2 = 1, A_3 = 0$, and $A_4 = 1$: $PS = \pi_2(1,0)(1 - \pi_3(1,0,1))\pi_4(1,0,1,0))$
9) $A_1 = 0, A_2 = 0, A_3 = 1$, and $A_4 = 1$: $PS = \pi_3(2,0,0)\pi_4(2,0,0,1)$
10) $A_1 = 1, A_2 = 1, A_3 = 1$, and $A_4 = 0$: $PS = \pi_1(0)\pi_2(0,1)\pi_3(0,1,1)(1 - \pi_4(0,1,1,1))$
11) $A_1 = 1, A_2 = 1, A_3 = 0$, and $A_4 = 1$: $PS = \pi_1(0)\pi_2(0,1)(1 - \pi_3(0,1,1))\pi_4(0,1,1,0)$
12) $A_1 = 0, A_2 = 1, A_3 = 1$, and $A_4 = 1$: $PS = \pi_2(1,0)\pi_3(1,0,1)\pi_4(1,0,1,1)$
13) $A_1 = 1, A_2 = 1, A_3 = 1$, and $A_4 = 1$: $PS = \pi_1(0)\pi_2(0,1)\pi_3(0,1,1)\ \pi_4(0,1,1,1)$

Models for the π_i terms will be estimated using the *twang* package in R as described in the primary analysis. Each model will be fit using the subset of data indicated by the arguments b, a_1, a_2 and a_3; for example, the model for $\pi_3(0,1,1)$ will be fit using the selected confounders in L as predictors among subjects who received no doses prior to the window ($b = 0$) and the 1st and 2nd dose during the window ($a_1 = 1$ and $a_2 = 1$). The weights will be stabilized and trimmed (Austin and Stuart, 2015).

Spontaneous Abortion and Preterm Delivery: For the survival outcomes, a proportional hazards marginal structural model (MSM) with time-dependent covariates will be used to estimate the causal hazard ratio for each of the exposure doses. Similar to the primary analyses, let $a_1(t)$, $a_2(t)$, $a_3(t)$, and $a_4(t)$ be indicators for exposure during the relevant exposure window to the 1st, 2nd, 3rd and booster doses of the Pfizer-BioNTech COVID-19

vaccine by time t, and let T_{a_1,a_2,a_3,a_4} denote the potential time to SAB had a subject followed the exposure functions a_1, a_2, a_3, and a_4. The marginal structural model is

$$\lambda_{a_1,a_2,a_3,a_4}(t) = \lambda_0(t)\exp(\beta_1 a_1(t) + \beta_2 a_2(t) + \beta_3 a_3(t) + \beta_4 a_4(t))$$

where $\lambda_{a_1,a_2,a_3,a_4}(t)$ is the hazard of T_{a_1,a_2,a_3,a_4} at time t, λ_0 is the baseline hazard function representing the risk for a subject who never receives either dose during the window, and $\exp(\beta_i)$ is the causal relative risks for the effect of exposure to the i^{th} dose during the window.

As in the primary analyses of the survival outcomes, the MSM can be estimated by either multivariable regression or IPTW depending on whether prior infection is included as a time-dependent confounder.

The multivariable regression model will be fit as in the primary analyses except that it will include effects for the time-dependent exposures $A_1(t)$, $A_2(t)$, $A_3(t)$, and $A_4(t)$, which indicate exposure by time t to the 1st, 2nd, 3rd, and booster doses during the exposure window, respectively.

The IPTW method is based on PS models for the time to the 1st, 2nd, 3rd and booster doses. Similar to the primary analysis of the survival outcomes, proportional hazards models will be fit for the time to each of the four doses during the exposure window, adjusting for the selected confounders. The models yield estimates of the conditional survival function $S_i(t|l)$ and density function $f_i(t|l)$ given the confounders $L = l$ at time t, for each of the four doses ($i = 1, 2, 3,$ and 4). These estimates are used to compute time-dependent PS and weights. For a fixed time t, consider a woman with confounders $L(t)$ who is still at risk for the outcome by time t; let D_1, D_2, D_3, and D_4 denote the time of exposure to the 1st, 2nd, 3rd, and booster doses, respectively, if they occur during the window. For this subject, the weight at time t is $w(t) = 1/PS(t)$ where $PS(t)$ is computed as follows:

1) For a subject with $A_1 = 0$, $A_2 = 0$, $A_3 = 0$, and $A_4 = 0$,
   $PS(t) = S_1(t|L(t))$ if they have received no doses prior to the window
   $PS(t) = S_2(t|L(t))$ if they have received one dose prior to the window
   $PS(t) = S_3(t|L(t))$ if they have received two doses prior to the window
   $PS(t) = S_4(t|L(t))$ if they have received three doses prior to the window
   $PS(t) = 1$ if they have received four doses prior to the window
2) For a subject with $A_1 = 1$, $A_2 = 0$, $A_3 = 0$, and $A_4 = 0$,
$$PS(t) = \begin{cases} S_1(t|L(t)) & \text{if } t < D_1 \\ f_1(D_1|L(D_1))S_2(t|L(t)) & \text{if } t \geq D_1 \end{cases}$$
3) For a subject with $A_1 = 0$, $A_2 = 1$, $A_3 = 0$, and $A_4 = 0$,
$$PS(t) = \begin{cases} S_2(t|L(t)) & \text{if } t < D_2 \\ f_2(D_2|L(D_2))S_3(t|L(t)) & \text{if } t \geq D_2 \end{cases}$$
4) For a subject with $A_1 = 0$, $A_2 = 0$, $A_3 = 1$, and $A_4 = 0$,
$$PS(t) = \begin{cases} S_3(t|L(t)) & \text{if } t < D_3 \\ f_3(D_3|L(D_3))S_4(t|L(t)) & \text{if } t \geq D_3 \end{cases}$$

5) For a subject with $A_1 = 0$, $A_2 = 0$, $A_3 = 0$, and $A_4 = 1$,

$$PS(t) = \begin{cases} S_4(t|L(t)) & \text{if } t < D_4 \\ f_4(D_4|L(D_4)) & \text{if } t \geq D_4 \end{cases}$$

6) For a subject with $A_1 = 1$, $A_2 = 1$, $A_3 = 0$, and $A_4 = 0$,

$$PS(t) = \begin{cases} S_1(t|L(t)) & \text{if } t < D_1 \\ f_1(D_1|L(D_1))S_2(t|L(t)) & \text{if } D_1 \leq t < D_2 \\ f_1(D_1|L(D_1))f_2(D_2|L(D_2))S_3(t|L(t)) & \text{if } t \geq D_2 \end{cases}$$

7) For a subject with $A_1 = 0$, $A_2 = 1$, $A_3 = 1$, and $A_4 = 0$,

$$PS(t) = \begin{cases} S_2(t|L(t)) & \text{if } t < D_2 \\ f_2(D_2|L(D_2))S_3(t|L(t)) & \text{if } D_2 \leq t < D_3 \\ f_2(D_2|L(D_2))f_3(D_3|L(D_3))S_4(t|L(t)) & \text{if } t \geq D_3 \end{cases}$$

8) For a subject with $A_1 = 0$, $A_2 = 1$, $A_3 = 0$, and $A_4 = 1$,

$$PS(t) = \begin{cases} S_2(t|L(t)) & \text{if } t < D_2 \\ f_2(D_2|L(D_2))S_4(t|L(t)) & \text{if } D_2 \leq t < D_4 \\ f_2(D_2|L(D_2))f_4(D_4|L(D_4)) & \text{if } t \geq D_4 \end{cases}$$

9) For a subject with $A_1 = 0$, $A_2 = 0$, $A_3 = 1$, and $A_4 = 1$,

$$PS(t) = \begin{cases} S_3(t|L(t)) & \text{if } t < D_3 \\ f_3(D_3|L(D_3))S_4(t|L(t)) & \text{if } D_3 \leq t < D_4 \\ f_3(D_3|L(D_3))f_4(D_4|L(D_4)) & \text{if } t \geq D_3 \end{cases}$$

10) For a subject with $A_1 = 1$, $A_2 = 1$, $A_3 = 1$, and $A_4 = 0$,

$$PS(t) = \begin{cases} S_1(t|L(t)) & \text{if } t < D_1 \\ f_1(D_1|L(D_1))S_2(t|L(t)) & \text{if } D_1 \leq t < D_2 \\ f_1(D_1|L(D_1))f_2(D_2|L(D_2))S_3(t|L(t)) & \text{if } D_2 \leq t < D_3 \\ f_1(D_1|L(D_1))f_2(D_2|L(D_2))f_3(D_3|L(D_3))S_4(t|L(t)) & \text{if } t \geq D_3 \end{cases}$$

11) For a subject with $A_1 = 1$, $A_2 = 1$, $A_3 = 0$, and $A_4 = 1$,

$$PS(t) = \begin{cases} S_1(t|L(t)) & \text{if } t < D_1 \\ f_1(D_1|L(D_1))S_2(t|L(t)) & \text{if } D_1 \leq t < D_2 \\ f_1(D_1|L(D_1))f_2(D_2|L(D_2))S_4(t|L(t)) & \text{if } D_2 \leq t < D_4 \\ f_1(D_1|L(D_1))f_2(D_2|L(D_2))f_4(D_4|L(D_4)) & \text{if } t \geq D_4 \end{cases}$$

12) For a subject with $A_1 = 0$, $A_2 = 1$, $A_3 = 1$, and $A_4 = 1$,

$$PS(t) = \begin{cases} S_2(t|L(t)) & \text{if } t < D_2 \\ f_2(D_2|L(D_2))S_3(t|L(t)) & \text{if } D_2 \leq t < D_3 \\ f_2(D_2|L(D_2))f_3(D_3|L(D_3))S_4(t|L(t)) & \text{if } D_3 \leq t < D_4 \\ f_2(D_2|L(D_2))f_3(D_3|L(D_3))f_4(D_4|L(D_4)) & \text{if } t \geq D_4 \end{cases}$$

13) For a subject with $A_1 = 1$, $A_2 = 1$, $A_3 = 1$, and $A_4 = 1$,

$$PS(t) = \begin{cases} S_1\left(t|L(t)\right) & \text{if } t < D_1 \\ f_1\left(D_1|L(D_1)\right)S_2(t|L(t)) & \text{if } D_1 \le t < D_2 \\ f_1\left(D_1|L(D_1)\right)f_2\left(D_2|L(D_2)\right)S_3(t|L(t)) & \text{if } D_2 \le t < D_3 \\ f_1\left(D_1|L(D_1)\right)f_2\left(D_2|L(D_2)\right)f_3\left(D_3|L(D_3)\right)S_4(t|L(t)) & \text{if } D_3 \le t < D_4 \\ f_1\left(D_1|L(D_1)\right)f_2\left(D_2|L(D_2)\right)f_3\left(D_3|L(D_3)\right)f_4\left(D_4|L(D_4)\right) & \text{if } t \ge D_4 \end{cases}$$

The PS model for the 1st dose will be fit using data from subjects who did not receive any doses prior to the exposure window. For the 2nd dose, the model will be fit using data from subjects who received at one dose prior to or during the window. Similarly, for the 3rd and booster doses, the models will be fit using data from subjects who received all previous doses prior to or during the window. Weight stabilization and trimming will be administered as in the primary analyses.

Confidence intervals for either the multiple regression or IPTW method will be computed as in the primary analyses.

12.4.3. Evaluation for a Pattern of Major Congenital Malformations

As most known human teratogens are associated with specific clusters of major congenital malformations rather than an overall increase in the risk of all specific major congenital malformations, a qualitative review will be conducted (Alwan and Chambers, 2015). 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, including multiple malformation syndromes, categories of major congenital malformations, such as cardiac malformations, limb reduction anomalies, etc. *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.*

12.4.4. 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 rates exceed 10%, *in an attempt to address this potential source of bias,* baseline demographic *characteristics* including maternal age, socioeconomic status, race and ethnicity will be compared between those lost-to-follow-up in *each cohort* vs. those who are retained.

However, the OTIS Research Center prior experience has been that the lost to follow-up rate is extremely low, typically 5%.

12.5. 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.*

- *Analysis 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.

12.6. Interim Analyses

Descriptive analyses will *be presented in annual interim reports, 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. Each report will be a composite of the cumulative data to date and will supersede any previous reports. 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.*

12.7. Analysis Software

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

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14. LIST OF TABLES

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Table A-1. List of known human teratogens

Exposure	Notes
Angiotensin-converting enzyme inhibitors/ Angiotensin II receptor blockers	Exposure in the 2nd or 3rd trimester
Acitretin	Any exposure within 2 years of LMP.
Alcohol Use, Heavy	Must average 14 or more standard drinks over four or more weeks post-conception
Aminopterin	Exposure occurring on or after LMP
Antiseizure / Anticonvulsant Medications	Exposure occurring on or after LMP
Antineoplastics, Other	Exposure occurring on or after LMP
Cocaine	Exposure occurring on or after LMP
Cytomegalovirus (CMV)	Primary infection occurring on or after LMP
Type I and Type II Diabetes	Any diagnosis
Etretinate	Any exposure within 10 years of LMP.
Fever, High	102 degrees or higher for 24 hours or longer on or after LMP
Fluconazole, Systemic	≥7 days total (consecutive or non-consecutive) on or after LMP

Table A-1. List of known human teratogens

Exposure	Notes
Isotretinoin	Exposure occurring on or after LMP
Lenalidomide	Exposure occurring on or after LMP
Lithium	Exposure occurring on or after LMP
Methimazole	Exposure occurring on or after LMP
Methotrexate	Exposure occurring on or after LMP
Propylthiouracil (PTU)	Exposure occurring on or after LMP
Radiation, High Dose	≥ 5 rads to the uterus on or after LMP
Rubella	Exposure occurring on or after LMP
Thalidomide	Exposure occurring on or after LMP
Toxoplasmosis	Primary infection occurring on or after LMP
Varicella	Primary infection occurring on or after LMP
Vitamin A, High Dose	>50,000 IU per day on or after LMP
Warfarin (Coumadin, Jantoven) derivatives	Exposure occurring on or after LMP
Zika, Confirmed	Positive test result

Table A-2. COVID-19 Symptom Checklist Used in Maternal Interviews

1. **Did you experience any of the following symptoms?** *(Not related to pregnancy or any chronic condition)*	**Symptom Present?**		
Fever >100.4° F (38° C)	☐ Yes, Date: / / to / /	☐No	☐Unk
Subjective fever (felt feverish)	☐ Yes, Date: / / to / /	☐No	☐Unk
Chills	☐ Yes, Date: / / to / /	☐No	☐Unk
Rigors (Repeated shaking w/ chills, feeling of being cold w/ shivers)	☐ Yes, Date: / / to / /	☐No	☐Unk
Body aches (muscle aches/myalgia)	☐ Yes, Date: / / to / /	☐No	☐Unk
Headache	☐ Yes, Date: / / to / /	☐No	☐Unk
Runny nose	☐ Yes, Date: / / to / /	☐No	☐Unk
Sore throat	☐ Yes, Date: / / to / /	☐No	☐Unk
Cough (new onset or worsening of chronic cough)	☐ Yes, Date: / / to / /	☐No	☐Unk
Wheezing	☐ Yes, Date: / / to / /	☐No	☐Unk
Shortness of breath	☐ Yes, Date: / / to / /	☐No	☐Unk
Chest pain	☐ Yes, Date: / / to / /	☐No	☐Unk
Nausea or vomiting	☐ Yes, Date: / / to / /	☐No	☐Unk
Abdominal pain	☐ Yes, Date: / / to / /	☐No	☐Unk
Diarrhea (≥ 3 loose/looser than normal stools/24 hr period)	☐ Yes, Date: / / to / /	☐No	☐Unk
Loss of smell	☐ Yes, Date: / / to / /	☐No	☐Unk
Loss of taste	☐ Yes, Date: / / to / /	☐No	☐Unk
Loss of appetite	☐ Yes, Date: / / to / /	☐No	☐Unk
Dermatology symptom, specify:	☐ Yes, Date: / / to / /	☐No	☐Unk
Other, specify:	☐ Yes, Date: / / to / /	☐No	☐Unk
Other, specify:	☐ Yes, Date: / / to / /	☐No	☐Unk
Other, specify:	☐ Yes, Date: / / to / /	☐No	☐Unk
Asymptomatic (no symptoms)	☐Yes ☐No		