NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study informationTitle	Pregnancy and birth outcome assessment in a population-based cohort after exposure to Trumenba®
Protocol number	B1971052
Protocol version identifier	Amendment 1
Date of last version of protocol	March 20, 2017
EU Post Authorisation Study (PAS) register number	Study not registered
Active substance	Bivalent rLP2086 Trumenba
Medicinal product	Trumenba
Research question and objectives	The study will examine the risk of pregnancy outcomes and birth outcomes in women and infants, respectively, exposed to Trumenba prior to or during pregnancy. Objectives: 1. Estimate the incidence and risk ratios of pregnancy outcomes in women exposed and not exposed to Trumenba up to 28 days prior to or during pregnancy. 2. Estimate the prevalence and risk ratios of birth outcomes among infants exposed and not exposed to Trumenba vaccine in utero.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
CDC	Centers for Disease Control and Prevention
CDM	Common Data Model
CHR	Kaiser Permanente Center for Health Research
EHR	Electronic Health Record
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
EMR	Electronic Medical Record
ETL	Extract, transform, load
FDA	Food and Drug Administration
GEE	Generalized Estimating Equations
GPP	Good Pharmacoepidemiology Practices
HIV	Human Immunodeficiency Virus
HMORN	HMO Research Network
HPHCI	Harvard Pilgrim Health Care Institute
HPV	Human Papillomavirus
ICD	International Classification of Disease
IEC	Independent Ethics Committee
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine

IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LMP	Last Menstrual Period
MCV4	Meningococcal conjugate vaccine
MSOC	Mini-Sentinel Operations Center
NBDPS	National Birth Defects Prevention Study
NDC	National Drug Code
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
RR	Risk Ratio
SAB	Spontaneous abortion
SAS	Statistical Analysis Systems
SAP	Statistical Analysis Plan
Tdap	Tetanus-Diphtheria-Acellular Pertussis Vaccine
US	United States
USPI	United States Product Insert
VSD	Vaccine Safety Datalink

2. RESPONSIBLE PARTIES

This protocol was initially developed by Dr. James Stark and colleagues at Pfizer, in collaboration with Dr. Allison Naleway and colleagues at Kaiser Permanente Northwest. The protocol was revised and updated by the currently listed authorship team to reflect new data sources.

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3. ABSTRACT

Title: Pregnancy and Birth Outcome Assessment in a Population-based Cohort after Exposure to Trumenba®.

Version and Date of Protocol

Amendment 1: March 20, 2017

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Rationale and Background: Trumenba is indicated in an age group that includes women of childbearing age. There is limited safety data on Trumenba use in a real world setting among pregnant women. In order to obtain safety data regarding pregnancy exposure with Trumenba and birth outcomes, Pfizer has made a post-approval commitment to the Food and Drug Administration (FDA) to conduct an observational pregnancy study. This population-based cohort study is designed to assess pregnancy and birth outcomes following accidental or planned exposure to vaccination with Trumenba up to 28 days prior to or during pregnancy using electronic healthcare data in the United States (US).

Research Question and Objectives: The study will examine pregnancy and birth outcomes in women and infants, respectively, exposed to Trumenba up to 28 days prior to or during pregnancy. The specific objectives are: 1) to estimate the incidence and risk ratios of pregnancy outcomes, including live birth, spontaneous abortion, and stillbirth, in women exposed and not exposed to Trumenba in up to 28 days prior to or during pregnancy, and 2) to estimate the prevalence and risk ratios of birth outcomes (major congenital anomalies) among infants exposed and not exposed to Trumenba in utero.

Study Design: The study is a population-based cohort study of pregnant women exposed to at least one dose of Trumenba up to 28 days prior to or during pregnancy and infants exposed in utero and a 1:3 matched sample of Trumenba-unexposed pregnant women and infants. The study is prospectively designed, but the data will be accessed retrospectively after exposures and outcomes have occurred.

Population: Women aged ≤ 49 years at the start of pregnancy and who were continuously enrolled in their healthcare system for 292 days prior to estimated start of pregnancy until pregnancy end date will be included. Women exposed to medications that present a known increased risk to pregnancy or birth outcomes and pregnancy outcomes of gestational trophoblastic disease, ectopic pregnancy, and unknown or of uncertain outcome will be excluded.

Variables: Information about sociodemographic characteristics, health plan enrollment, prenatal care utilization, maternal comorbidities, maternal prenatal behaviors, concomitant medication use and vaccination, obstetric history, and pregnancy complications will be collected from electronic medical records, insurance claims data, and linked birth certificates.

Data Sources: Pregnancy and birth outcomes following exposure to Trumenba up to 28 days prior to or during pregnancy will be assessed using electronic healthcare data and linked birth certificates from multiple healthcare systems in the US who participate in the Sentinel System (specific partners to be determined).

Study Size: Sample size will be affected by public health recommendations made by the US Advisory Committee on Immunization Practices, from other professional advisory committees, and possibly meningococcal disease outbreaks. Based on available data from national insurers participating in the Sentinel System, the expected sample size of Trumenba-exposed pregnant women may range from 468- 936 over the 5-year study period, November 1, 2015-October 31, 2020. Estimation using an uptake pattern similar to the Meningococcal conjugate vaccine, a sample size of 468 will allow a minimal detection of increased risk ratios ranging from 1.39 to 1.78 depending on the outcome (range: 3% - 10%) with 80% power and alpha=0.05 (two-sided). A sample size of 936 will allow a minimal detection of increased risk ratios ranging from 1.27 to 1.54 depending on the outcome (range: 3% - 10%) with 80% power and alpha=0.05 (two-sided).

Data Analysis: This study will estimate the incidence of live births, spontaneous abortions, stillbirths, and prevalence of major congenital anomalies among clinically-recognized pregnant women, and will compare the occurrence of these events among Trumenba vaccine-exposed women and infants with those among women and infants not exposed to the Trumenba vaccine.

Milestones: Trumenba exposure during pregnancy and pregnancy outcomes will be evaluated annually throughout the duration of the study period. A final study report will be submitted to the FDA by October 31, 2023.

4. AMENDMENTS AND UPDATES

Number	Date	Substantial or administrative amendment	Section of Study Protocol	Amendment or Update	Reason
1	March 20, 2017	Substantive	All	Modification to data sources, sample size, matching techniques, statistical analysis, limitations	New data sources to increase base population to maximize vaccine exposures Sample size slightly increased as a result of data source changes Change to matching and statistical analysis to provide further information Clarification of limitations of proposed study design and analysis and potential need for modifications if assumptions are not met

5. MILESTONES

Milestone	Planned date
Registration to EU PAS register	31 December 2017
Start of data collection	1 March 2021
End of data collection	31 October 2022
Final study report	31 October 2023

6. RATIONALE AND BACKGROUND

On October 29, 2014, Trumenba was licensed in the United States for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in adolescents and young adults, aged 10 through 25 years. In June 2015, the Advisory Committee on Immunization Practices (ACIP) recommends vaccination for individuals aged 16 through 23 years of age and has been given a category B designation which recommends potential vaccinees to speak with their healthcare provider.

Trumenba is indicated in an age group that includes women of childbearing age. There is limited safety data on Trumenba use in a real world setting among pregnant women. In order to obtain this safety data regarding pregnancy exposure with Trumenba and birth outcomes, Pfizer has made a post-approval commitment to the FDA to conduct an observational pregnancy study. This population-based cohort study is designed to assess pregnancy and birth outcomes following accidental or planned exposure to vaccination with Trumenba up to 28 days prior to or during pregnancy using electronic healthcare data and birth certificates from multiple healthcare systems in the US who participate in the Sentinel System (specific partners to be determined). This study will provide population-based data regarding the safety of the vaccine during pregnancy, which is of public health interest. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the FDA.

Traditional post-approval pregnancy registry studies only enroll volunteers who have been exposed to a vaccine during pregnancy; this may introduce selection bias and limit the generalizability of findings. Additionally, registries often rely on self-reported vaccine exposures which may result in misclassification of exposures, and often do not capture data on pregnancy losses (especially early losses). Identifying an appropriate comparison group poses another challenge.

To overcome some of the limitations of traditional pregnancy registries, electronic health data from large care delivery systems can be used to evaluate post-licensure safety of vaccinations during pregnancy. These data systems have recently been used by the Vaccine Safety Datalink (VSD) to evaluate the safety of inactivated influenza vaccine (both seasonal and pandemic H1N1) as well as tetanus-diphtheria-acellular pertussis vaccine during pregnancy in the US.[1-5] The data systems can be used to study non-live birth pregnancy outcomes, minimize selection bias by identifying population-based cohorts, incorporate an internal comparison group, and reduce recall bias and misclassification by using vaccination data from electronic health records and linked immunization information systems (IIS). The proposed study will utilize the infrastructure and data from the Sentinel System ("Sentinel"), a large electronic health data system containing mostly administrative claims data (Section 8.2.1).

Briefly, Sentinel is an FDA-sponsored distributed database system developed to monitor the safety of licensed medical products, including vaccines. Several published protocols and reports have used Sentinel infrastructure and data to investigate medical products and birth outcomes, including influenza vaccine and spontaneous abortions.[6] Of note, Sentinel data

can be linked to medical charts, birth certificates, and immunization registries.[6,7] The current study will engage a subset of Sentinel data partners, and thus benefit from the infrastructure and collective experience of the System.

7. RESEARCH QUESTION AND OBJECTIVES

The study will examine the risk of pregnancy outcomes and birth outcomes in women and infants, respectively, exposed to Trumenba, Meningococcal Group B vaccine, up to 28 days prior to or during pregnancy. The specific objectives are:

1. *Estimate the incidence and risk ratios of pregnancy outcomes in women exposed and not exposed to Trumenba up to 28 days prior to or during pregnancy*.

   Primary endpoints include live birth, spontaneous abortion, and stillbirth.

2. *Estimate the prevalence and risk ratios of birth outcomes among infants exposed and not exposed to Trumenba vaccine in utero*.

   The primary endpoint is any major congenital anomaly.

8. RESEARCH METHODS

8.1. Study design

To meet the study objectives, a population-based cohort study using US electronic healthcare data will be performed. The study and analysis is prospectively designed and the data on exposure and outcomes will be collected retrospectively. As a result, subjects will not be actively followed to assess the endpoints or other covariates. The exposed cohort will consist of women exposed to Trumenba up to 28 days prior to or during pregnancy and infants exposed to the vaccine in utero. The comparison group will be a concurrent matching cohort of women and infants not exposed to Trumenba 28 days prior to or during pregnancy or in utero. For each pregnancy that occurs in the exposed group, three pregnancies matched on maternal age, last menstrual period (LMP), data partner, and propensity score will be selected.

The incidence proportion of pregnancy outcomes (live birth, spontaneous abortion, and stillbirth) and prevalence of infant outcomes (major congenital anomalies) will be estimated in the Trumenba-exposed group and comparison group. Risk ratios with 95% confidence intervals will be calculated for spontaneous abortion, stillbirth and overall major congenital anomalies. Risk ratio estimates will be adjusted for potential confounding factors such as prenatal care utilization and behaviors, comorbid medical conditions, obstetric history, and concomitant vaccination and medication use.

8.2. Setting

8.2.1. Data Sources

This study will engage several large national and regional healthcare systems that have established electronic administrative claims databases and are current participants of the Sentinel System. Possible participants include Meyers Primary Care Institute, Group Health Research Institute, Harvard Pilgrim Health Care, Aetna, HealthCore, Inc., Blue Cross Blue Shield of Massachusetts, Optum Epidemiology, and Vanderbilt University Medical Center. Key features of all data partners include: access to large populations with well-defined demographic characteristics and enrollment periods from claims data; capture of vaccine exposure data from claims data with the option of linking to immunization registries for select states; ability to link mothers to infants through administrative and medical record data, ability to identify pregnancy outcomes and dates using validated algorithms; access to medical record data for abstraction and review; the ability to link to birth certificates for select states to obtain information on maternal confounders and gestational age; and identifiers for mother-infant linkage. Although all data partners can link their claims to medical record data, immunization registries, and birth certificates, such linkages are not automatically generated or maintained, and must be developed on a study-by-study basis (Table 1).

The Sentinel System identifies live birth pregnancies/deliveries via diagnosis and procedure codes, and then works backwards from the date of delivery to determine the estimated start of pregnancy (LMP), building in gestational age assumptions related to the time frames of prolonged gestation, post-term, preterm, and at-term.[6,8] Based upon prior VSD and Sentinel studies, the gestational age assumptions for the claims-based algorithm will assume a 70-day (10 weeks) gestational age for cases with a diagnosis or procedure code for spontaneous abortion, a 210-day (30 weeks) gestational age for cases with a diagnosis or procedure code for stillbirth, and a 273-day (39 weeks) gestational age for live birth deliveries without a diagnosis code for pre- or postterm delivery during the delivery admission/encounter date. Appendix 2 shows the gestational age assumptions for live birth deliveries with specific pre-term and post-term delivery codes. Additional details are available in Appendix 2.

Table 1. Overview of Select Data Tables in the Sentinel Common Data Model, Version 6.0

Data Table	Sample Variables	Data Source (major settings)
Enrollment	Patient identification, health plan enrollment start and stop dates, medical and drug coverage status, ability to abstract charts for patient (y/n)	Administrative data
Demographic	Patient identification, gender, study site, date of birth	Administrative data
Dispensing	Patient identification, National Drug Code (NDC) codes, dispensing date, days supply, amount dispensed	Administrative data (outpatient)

Table 1. Overview of Select Data Tables in the Sentinel Common Data Model, Version 6.0

Data Table	Sample Variables	Data Source (major settings)
Encounter	Patient identification, encounter identification, admission date, discharge date, encounter type	Administrative data (outpatient, inpatient)
Diagnosis	Patient identification, encounter identification, admission date, encounter type, diagnosis code, diagnosis code type	Administrative data (outpatient, inpatient)
Procedure	Patient identification, encounter identification, admission date, encounter type, procedure code, procedure code type	Administrative data (outpatient, inpatient)
Laboratory Result*	Patient identification, test name, test category, specimen source, LOINC code, order date, result date, result, result unit	Lab, point of care (outpatient)
State Vaccine**	Patient identification, state of IIS registry, vaccine date, vaccine code, code type, manufacturer, lot number	Immunization Information Systems (IIS)

*Data table not available at all Data Partners (DPs)
**Data table not available at all DPs. Vaccine exposures also identified via administrative data in the Procedure and Dispensing tables

8.2.2. Study Population

Women aged ≤ 49 years at the start of pregnancy and who were continuously enrolled in their healthcare system for 292 days prior to estimated start of pregnancy until pregnancy end date will be included. The 292 day period considers the 180 day period for receiving the three or two dose regimen (0, 2, 6 months or 0 and 6 months), an 84 day period (12 weeks) to account for irregular timing of vaccination schedules, and the 28 day period of exposure prior to the pregnancy. Women exposed to medications that present a known increased risk for fetal malformation (Appendix 3) will be retrospectively identified and excluded from the analysis after the data has been obtained. A woman may experience pregnancy episodes in the study period that are classified as gestational trophoblastic disease, ectopic pregnancy, induced abortions, and unknown or of uncertain outcome. These episodes will be excluded from the analysis after the data have been obtained. The unit of analysis is a pregnancy (Figure 1).

For pregnancies ending in a live birth, mothers will be linked to their infants using data available in the electronic medical record (EMR), administrative claims data, and birth certificates. Each Sentinel Data Partner will be responsible for linking mothers to infants using all available local data resources, if possible. Algorithms linking mothers to infants will vary across data partners generally looking for equivalent subscriber numbers, delivery dates

and dates of birth, and shared names and addresses. Sentinel Data Partners are able to link 80% or more of their infants to their mothers (unpublished source). Data for infants will be collected for up to six months after birth which is consistent with previous studies and allow adequate follow up time to detect major congenital anomalies.[9]

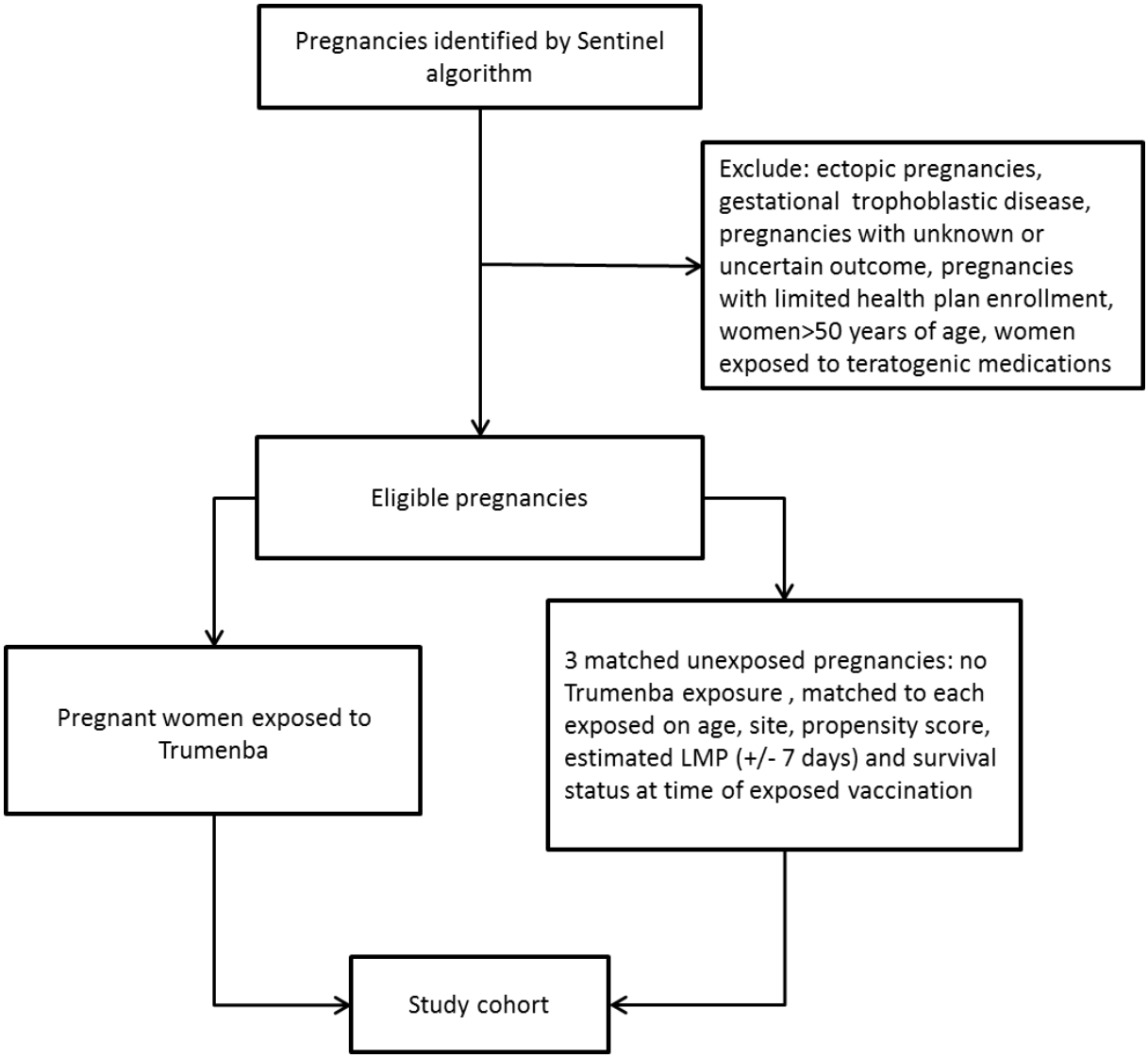

Figure 1. Study schema

8.2.2.1. Trumenba-Exposed Group

The exposure of interest in this study is receipt of at least one dose of Trumenba up to 28 days (4 weeks) prior to or during pregnancy. The risk interval, the period of time when a person is at an increased risk for an adverse event following vaccination, will be considered beginning from the time of vaccination. Subjects may receive more than one Trumenba dose in the potential exposure period (i.e., up to 28 days before pregnancy through the end of

gestation); however, the first Trumenba dose will be considered the date identifying a woman as exposed and is considered the exposure index date. In addition, a subject may receive additional doses prior to the exposure index date. For example, the exposure index date may be a woman's third dose of vaccine. If a woman receives the vaccine in the time period before the 28 days prior to pregnancy but does not receive the vaccine up to 28 days prior to or during pregnancy, she will not be considered exposed. Each dose will be recorded in the 292 day period prior to LMP, and the analysis will account for multiple doses (Section 8.7). Exposed women who meet the criteria stated above, and their linked infants, will be identified from November 1, 2015 (the first possible outcome date in the study period) through October 31, 2020 (end of the study period for identifying a pregnancy outcome). All women who meet the study criteria above will be followed for all study endpoints.

8.2.2.2. Unexposed Comparison Group

A matched sample of three unvaccinated women and their linked infants will be identified for each Trumenba-exposed woman to form the unexposed comparison group. All confounders used to match vaccinated and unvaccinated women will be obtained from administrative claims data. Unvaccinated women will be matched to Trumenba-vaccinated women on propensity score (Section 8.3.1), pregnancy start date or estimated LMP (+/- 7 days), maternal age at the start of pregnancy (+/- 1 year), and data partner (healthcare delivery system). Women in the Trumenba-unexposed comparison group may receive other vaccinations during pregnancy including those recommended, Inactivated Influenza Vaccine (IIV) and Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) (Appendix 4), but must not be exposed to Trumenba during the 28 days prior to pregnancy start until the pregnancy endpoint. Trumenba vaccination status between 28 days prior and 180 days prior to pregnancy start will be included as a covariate in the propensity score model (Section 8.3.1). Interactions with concomitant vaccinations will be accounted for in the analysis (Section 8.7.1). We will also match on survival status prior to the Trumenba-exposed match's time of vaccination to guarantee that at-risk time is the same for both exposed and unexposed subjects (Section 8.7.1).

Matching with a propensity score will minimize confounding bias due to differences between Trumenba-vaccinated and Trumenba-unvaccinated women. Propensity score methods are discussed below (Section 8.7.2). Matching of pregnancy start date, maternal age, and data partner will control for seasonality, age effects, and geographic differences in vaccine uptake. This is particularly important for the analysis of spontaneous abortion and stillbirth when the timing of fetal demise can impact exposure and outcome classification (Section 8.3.3.1).

8.2.2.3. Inclusion Criteria

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

1. Women aged ≤ 49 years at the start of pregnancy.

2. Women who were continuously enrolled in their healthcare system for at least 292 days prior to estimated start of pregnancy (e.g., date of last menstrual period) until pregnancy end date.

3. Eligible outcomes occurred between November 1, 2015 and October 31, 2020.

8.2.2.4. Exclusion Criteria

There are no exclusion criteria for enrollment into this prospectively-designed study. However, the data will be accessed retrospectively after exposures and outcomes have occurred. As a result, excluding subjects prior to study enrollment is not applicable. After data collection is complete and the algorithm is implemented, women exposed to medications that present a known increased risk for congenital anomalies or administered another meningococcal B vaccine (other than Trumenba) 28 days prior to LMP or during pregnancy or pregnancy episodes that are classified as gestational trophoblastic disease, ectopic pregnancy, and unknown or of uncertain outcome will be excluded from analysis.

Women who are at increased or prolonged risk of meningococcal disease (as defined by the ACIP recommendations for prevention of meningococcal disease), including women with persistent complement deficiencies and functional or anatomic asplenia (e.g., sickle cell disease), will be identified and included in a separate analysis.[10]

Exclusions will occur prior to selection of the unexposed comparison group to increase the probability of accruing three unexposed women matched to each exposed woman.

8.3. Variables

8.3.1. Propensity Score Variables

The propensity score reflects the conditional probability of a woman receiving a Trumenba vaccination given a set of covariates. Information about variables that may predict the likelihood of exposure to Trumenba vaccine prior to or during pregnancy will be collected from electronic medical records, insurance claims data, and linked birth certificates. These variables will include: age, race, ethnicity, data partner, calendar year, Trumenba vaccination status between 28 days prior and 180 days prior to LMP date, maternal comorbidities prior to LMP date (Appendix 5), number of health care encounters in 292 days preceding LMP date, and other vaccinations received 292 days prior to LMP date (Table 2). Age will serve as an exact matching variable but will also be a variable included in the propensity score model. The propensity score model will be fit separately for each data partner and matching on the propensity score will occur within data partner (Figure 2).

Table 2. Data Used for Confounders (in Propensity Score Model and Final Outcome Regression Model Fit to Matched Sample)

Variable	EMR*	Claims	Birth Certificate
Maternal demographics	X	X	
Maternal comorbidities	X	X	
Pregnancy complications	X	X	
Healthcare utilization	X	X	
Trumenba vaccination status between 28 days prior and 180 days prior to LMP	X	X	
LMP date		X	
Other vaccination during pregnancy	X	X	

*EMR data only available from integrated health care systems (to be determined)

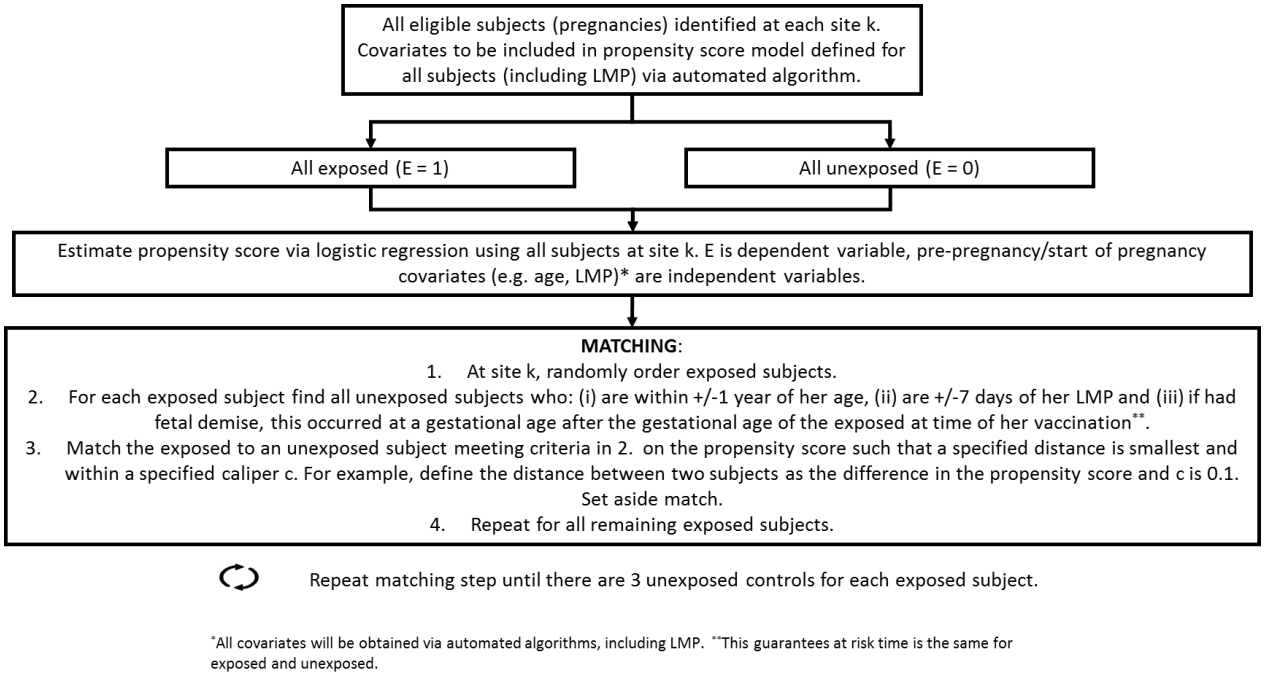

Figure 2. Matching Algorithm

8.3.2. Exposure Variables

Trumenba is administered in an ambulatory care setting as a two dose (0 or 6 months) or three dose series (0, 2, 6 months). Information on doses of Trumenba received in the 292-day period preceding the estimated pregnancy start date until the pregnancy endpoint will be collected. The 292 day period consists of three time windows: the 28 days prior to LMP, 6 months or 180 days during which the three dose series commences, and a 12 week period to account for irregular timing of vaccination. The number and timing of doses (e.g., trimester of pregnancy) will be used in the study analysis as appropriate (8.7.1). The 1st trimester of pregnancy will be defined as 0 to <14 weeks gestation, the 2nd trimester as 14 to <28 weeks, and the 3rd trimester as 28 weeks through the end of the pregnancy. A pre-pregnancy exposure period up to 28 days prior to LMP will also be summarized. Information about vaccine exposures will be collected from electronic health records or claims data (Table 3). Additional information may be obtained from linked state immunization information systems (IIS) since Trumenba may be administered outside of the participating healthcare delivery system, especially in cases of meningococcal disease outbreaks.

Table 3. Vaccine Exposure Variables

Variable	Values	Label
MENB_DOSE1	mmddyy10. or missing if not vaccinated	Date of first dose
MENB_DOSE2	mmddyy10. or missing if not vaccinated	Date of second dose
MENB_DOSE3	mmddyy10. or missing if not vaccinated	Date of third dose
MENB_SRC1	1=EMR; 2=claim; 3=IIS	Source of vaccination record
MENB_SRC2	1=EMR; 2=claim; 3=IIS	Source of vaccination record
MENB_SRC3	1=EMR; 2=claim; 3=IIS	Source of vaccination record

8.3.3. Outcome Variables

8.3.3.1. Pregnancy Outcomes

The primary pregnancy outcomes to be evaluated include live birth, spontaneous abortion, and stillbirth. A spontaneous abortion is defined as a spontaneous embryonic or fetal death that occurs prior to 20 weeks' gestation post-LMP. A stillbirth is defined as a spontaneous fetal death that occurs at or after 20 weeks' gestation but prior to delivery.

Ultrasound reports in the medical record will be reviewed to collect additional detailed information about dates of conception and fetal demise.

8.3.3.2. Birth outcomes

Major congenital anomalies (birth defect or structural defect) are defined as a defect, which has either cosmetic or functional significance to the child (e.g., cleft lip). A detailed list of all major congenital abnormalities observed in live births compiled from the National Birth Defects Prevention Study (NBDPS) and the European Surveillance of Congenital Anomalies is provided in Appendix 7.[11, 12,] Consistent with NBDPS case definition criteria, potential cases that occur as part of a genetic syndrome or other syndrome of known etiology (e.g., trisomy 13 (ICD-9 code 758.1), trisomy 18 (ICD-9 code 758.2), or trisomy 21 (ICD-9 code 758.0)), or those that occur secondary to other major malformations (e.g., holoprosencephaly or amniotic band sequence) will be counted but they will not be included in the calculation of prevalence of major congenital anomalies. Data for infants will be collected from delivery to six months of age, or exit from the database, or death, whichever comes first. All suspected congenital anomalies will be manually reviewed to confirm the diagnosis.

Women with multiple gestations will be included in the analysis. If a live birth results in a congenital anomaly and the second birth (e.g., twin) does not, the congenital anomaly will be counted in the numerator.

8.3.4. Covariates

Information about sociodemographic characteristics, health plan enrollment, prenatal care utilization and behaviors, maternal comorbidities, concomitant medication use and vaccination, obstetric history, and pregnancy complications (until time of pregnancy endpoint) will be collected from electronic medical records, insurance claims data, and linked birth certificates. Obstetric history will include information about the number of prior pregnancies (gravidity), number of live births (parity), number of spontaneous abortions, previous pregnancies with birth defects, and history of cesarean delivery. Infants will be followed from delivery through six months of age and information will be collected about their health care utilization, vaccinations, medications, and comorbidities (Table 4). Appendix 8 Maternal and Infant Covariates lists specific variables for maternal and infant (birth – 6 months). This information will be used as appropriate and detailed in the Statistical Analysis Plan (SAP).

Table 4. Covariates and Data Sources for Mothers and Infants

Variable	EMR*	Claims	Birth Certificate
Demographics	X	X	
Comorbidities	X	X	
Health plan enrollment	X	X	
Healthcare utilization	X	X	
Vaccination	X	X	

Table 4. Covariates and Data Sources for Mothers and Infants

Variable	EMR*	Claims	Birth Certificate
Medication use	X	X	
Obstetric history	X	X	X
Pregnancy complications	X	X	
Prenatal alcohol and tobacco use	X		X

*EMR data only available from integrated health care systems (to be determined)

8.4. Data Collection Period

Data collection is anticipated to begin March 1, 2021 and end on October 31, 2022. The end of data collection reflects the time point when analytic dataset is available to perform final statistical analysis of the primary objectives.

8.4.1. Interim Assessments of Trumenba Exposure

Annual assessment of Trumenba exposure during pregnancy and in the 292 days preceding pregnancy start will be conducted to inform decision-making about sample size and possible stratified analyses. Use of Trumenba will also be assessed among pregnant women stratified by age 25 or less, and 26 through 49 years of age. Trumenba exposure by dose number and trimester of pregnancy (including the pre-pregnancy period) will be described. Pregnant women who may be at increased risk of meningococcal disease due to conditions like functional or anatomic asplenia, complement deficiencies, or Human Immunodeficiency Virus (HIV) coupled with another indication for vaccination will be identified (if possible, based upon availability of diagnosis codes in the claims data), and Trumenba exposure in these high-risk groups will be described.[10] Patterns of concomitant vaccination during the 28-day period prior to pregnancy through the end of the pregnancy period will also be described, focusing on other adolescent vaccinations including HPV, Tdap, MCV4 (meningococcal conjugate vaccine), and influenza. Sample size calculations, participation of data partners, and duration of study period will be revised and refined as more data about Trumenba exposure are available.

The prevalence of pregnancy and birth outcomes will be described based upon the claims data (unconfirmed outcomes).

8.5. Study size

Sample size will be affected by public health recommendations made by the US Advisory Committee on Immunization Practices, from other professional advisory committees, and possibly meningococcal disease outbreaks. Formal sample size calculations including estimating the minimum detectable risk to be identified are presented below.[13] The exposure

rate assumptions incorporate delivery counts from large national insurers that participate in the Sentinel System and vaccination rates in pregnancy based on the Menactra experience in the Vaccine Safety Datalink (VSD). Of note, the VSD includes data partners that also participate in the Sentinel System. An estimated range of maternal and infant outcome rates is also presented.

8.5.1. Exposure Rate Assumptions

Currently available data revealed zero Trumenba exposures among pregnant women from two potential data partners, and thus a rate of vaccine exposure during pregnancy could not be estimated in our study population. Therefore, we used an externally published rate of an alternative adolescent vaccine (Menactra) in a similar population (VSD) to estimate the rate of Trumenba exposures that will occur during pregnancy (0.9/1000) in this study.[14]

Briefly, the quadrivalent meningococcal conjugate vaccine (Menactra) was approved for use in January 2005 in the US. Initial ACIP recommendations focused on young adolescents aged 11-12 years and catch up vaccination for adolescents before entering high school (approximately 15 years of age).[15] In addition, ACIP recommended that all first-year college students living in residence halls were to be vaccinated with the conjugate vaccine. In 2007, ACIP recommended vaccination of all adolescents aged 11 through 18 years.[16] During the period from 2005 through 2009, the rate of Menactra vaccination observed in the Vaccine Safety Datalink was 0.90/1000 pregnancies.[14] Assuming the same rate of uptake during pregnancy for Trumenba and an accrual of 520,000 pregnancies over the five year study period, approximately 468 exposed pregnancies will be expected, or approximately 94 per year.

The expected number of Trumenba exposures during pregnancy (n=468) will be updated as more data become available and the final selection of Data Partners is made. The rate of Trumenba exposure during pregnancy (0.90/1000) could underestimate or overestimate the true rate of exposure during pregnancy due to differences in the underlying study populations or differences in vaccine uptake. Also, the projected number of pregnancies (520,000) was extrapolated based on 2015 data that counted pregnancies resulting in live born births from two projected data partners, assumed no increase or decrease in fertility rates across the study period, and further assumed that the net number of pregnancies gained by counting those ending in spontaneous abortion or stillbirth would be balanced by those lost due to study inclusion/exclusion criteria. To account for some of the uncertainties in our assumptions, we also provide power calculations for a sample size of 936 exposed, pregnant women (double our initial estimate of 468). These estimates will be updated and reported annually.

8.5.2. Outcome Rate Assumptions

With the exception of major congenital anomalies, the pregnancy and infant outcomes to be studied have incidence rates ranging from 5% to 10% (stillbirth and spontaneous abortion) among clinically known pregnancies. The prevalence of major congenital anomalies (overall) is approximately 3%.[9]

8.5.3. Power Calculations

The power calculations below present the minimum detectable risk ratios for events ranging from 30 per 1,000 to 100 per 1,000. Assuming a sample size of 468 exposed women, 3 matched unexposed per exposed woman, 80% power, and a two-sided test with Type 1 error rate alpha=0.05, the minimal detectable risk ratio ranges from 1.39 to 1. Increasing the sample size to 936 exposed women (with all other parameters the same) the minimal detectable risk ratio ranges from 1.27 to 1.54 (Figure 3). These power calculations are estimates based on the exposure and outcome rate projections described in 8.5.1 and 8.5.2. The correlation coefficient for the outcomes between matched exposed and unexposed women is assumed to be 0.2.[13]

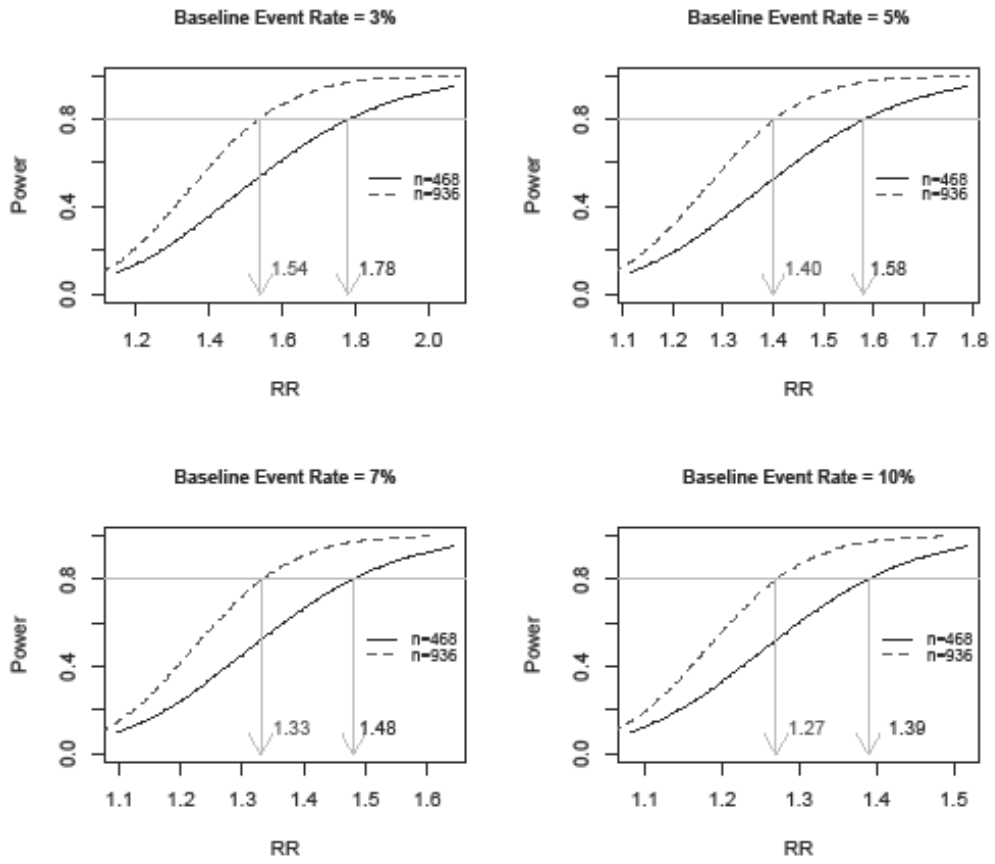

Figure 3. Minimal Detectable Risk Ratios and Power for Sample Sizes of 468 and 936 Trumenba-exposed Pregnancies with Baseline Event Rates Ranging from 30 per 1,000 to 100 per 1,000 and alpha=0.05.

8.6. Data management

The Harvard Pilgrim Health Care Institute (HPHCI) in Boston, Massachusetts will serve as the data coordination center ("Coordinating Center") for the proposed study. Coordinating Center staff or contractors will be responsible for writing and distributing Statistical Analysis Systems (SAS) programs that can be used to collect data from Electronic Health Record (EHR) and administrative databases at participating Data Partners. The distributed data network will allow Data Partners to maintain physical and operational control of their data while allowing use of the data to meet the study needs. The Coordinating Center will create and implement a secure distributed querying web-based portal to enable secure distribution of analytic queries, data transfer and document storage. The system will meet all required State and Federal security guidelines for health data (e.g., FISMA, HIPAA), specifically FISMA compliant for FISMA Moderate Risk security controls as specified in the National Institute of Standards and Technology (NIST) Special Publication 800-53.

Since distributed data networks require use of a common data model that allows data standardization across network partners, the Sentinel Common Data Model (CDM) will be used because each of the Data Partners has experience using this data model as active participants in the Sentinel Initiative (Table 1). Given the study needs, the CDM may need to be expanded to account for details such as inclusion of birth certificate data. We will design and support the necessary data model updates to meet the study needs. This also will require detailed data quality checking to ensure that the data extracted for this study is consistent, meets minimum requirements, and any anomalies are identified and remediated. Participating Data Partners will be responsible for constructing standardized datasets using the distributed analytic code provided by the Coordinating Center, and their own processes for linking eligible participants identified in the administrative claims data to their EHRs, medical records, birth certificates, or state immunization registries.

8.7. Data analysis

The incidence of live births, spontaneous abortions, and stillbirths and the prevalence of major congenital anomalies among clinically-recognized pregnant women, in the Trumenba-exposed and unexposed cohorts will be estimated. The comparison will contrast the occurrence of events in the Trumenba-exposed cohort to the unexposed cohort to determine if there is an elevated risk associated with exposure to Trumenba. The period of time when a woman can be at risk for an event varies by endpoint and is detailed below. The extent and timing of exposure can vary by number of doses received and the trimester when the exposure occurred, respectively. Stratified analyses will be performed by number of doses received and by trimester and a dose by trimester interaction if sample size is adequate. Interaction with a concomitant vaccination is possible given that both influenza and Tdap are recommended during pregnancy. To account for a concomitant vaccination interaction, an interaction term will be included in the model. If sample size allows a stratified analysis by concomitant vaccine will occur. Additionally, women who are at greater risk of meningococcal disease, including women with persistent complement deficiencies and functional or anatomic asplenia (e.g., sickle cell disease) will be included in a separate analysis. Specific analytic details will be noted in the SAP. Finally, a temporal scan will be

conducted to identify any clusters of increased risk of spontaneous abortion and stillbirth following vaccination (Section 8.7.6).

8.7.1. Statistical Analysis

Before any analyses are carried out, the data will be examined for quality and completeness. Variable distributions will be examined for outliers, and will be assessed to ensure that they meet the assumptions of the planned analysis. The baseline characteristics will be presented as means and standard deviations for continuous variables and as percentages for categorical variables. Nominal variables will be dummy coded for inclusion as predictors in multivariable analyses. All inferential tests will be carried out at a two-tailed alpha level of 0.05.

The outcome variables will be assumed to follow the binomial distribution, and log binomial regression model will be used to examine the association between vaccine exposure and the risk of experiencing each of the outcomes. The log binomial regression model enables the direct estimation of relative risk. The primary covariate of interest is the vaccine exposure variable which will be dummy coded with the unexposed women as the reference group. The relative risk comparing exposed to unexposed women can be estimated by exponentiating the coefficient estimate associated with the vaccine exposure variable. Confounders included in the propensity score model to account for random remaining imbalances will also be included in the log binomial regression model. The confounders to be included in the model include sociodemographic characteristics, health plan enrollment, prenatal care utilization and behaviors, maternal comorbidities, obstetric history, past use of Trumenba (between 28 days prior to and 180 days prior to pregnancy), and medication and concomitant vaccination use. In the log binomial regression model we will additionally include pregnancy-related variables (pregnancy complications, health encounters) up until the time of exposure of the exposed subject for both exposed and unexposed subjects in a given matched stratum to try to adjust for additional confounding by such pregnancy characteristics. The reason these pregnancy related characteristics are included in the log binomial regression but not in the Propensity Score model (which only includes measurements up to LMP date for unexposed and exposed subjects) is that the propensity score model is fit before matching occurs and therefore timing of exposure in the exposed subject is not yet defined for unexposed subjects.

Matching the exposed to the unexposed will introduce correlation into the data as the matched sets are more similar to each other than they would be if pregnancies are randomly sampled. If this correlation is not taken into account, the standard errors of the relative risk estimates will not be valid. The generalized estimating equations (GEE) method will be applied to the log-binomial regression analysis to account for the correlation due to matching. The parameter estimates from GEE are consistent even when the covariance structure is mis-specified.

8.7.2. Propensity score modeling and matching

Due to the nature of an observational study, the exposed and unexposed women may not be directly comparable because they may systematically differ at baseline. Propensity score matching has been widely used to draw causal inference from observational studies. The

propensity score is defined as the conditional probability of receiving Trumenba vaccination given a set of covariates. Instead of attempting to create a match based on each of the covariates, one can match the exposed to the unexposed based on the propensity score alone. This method enables matching not only at the mean level of the covariates, but also balances the distribution of observed characteristics across the two groups to make them comparable. This helps to eliminate confounding and contribute to overall bias reduction. Compared to matching directly on the covariates, propensity score matching also has the advantage of reducing the difficulty of matching on many high-dimensional covariates, which greatly facilitates the matching process. One caveat is that propensity score matching cannot control for unobservable/unmeasurable differences, propensity score matching essentially only helps to control for the measurable differences between the exposed and unexposed.

To establish the concurrent comparison group, the propensity for receiving Trumenba will be modeled using logistic regression, and propensity scores will be used to match 3 unexposed women to each exposed woman. The outcome variable in the logistic regression model will be vaccination, which is a binary variable indicating whether a study subject has been vaccinated (or not vaccinated). The model is fit using all eligible pregnancies identified by the Sentinel algorithm. All covariates, including LMP date, will be defined for all eligible pregnancies via claims data prior to fitting the model.

The predictor variables in the model will include all covariates listed under Section 8.3.1. No selection criteria will be applied to these predictor variables, i.e., all these predictors will enter the logistic model regardless of their statistical significance. The logistic model is fit to all eligible pregnancies. The propensity score for every eligible pregnancy (regardless of vaccination status) is the predicted probability of a subject being vaccinated given this set of observed predictors, and will take values between 0 and 1.

We do not expect missing data. In the case that we do encounter missing data in covariates; we will use multiple imputation to impute missing values. Additional details are given in the SAP.

Figure 2 is a flowchart summarizing the algorithm under which 3 matched controls will be selected for each exposed subject.

To form matched pairs of vaccinated and unvaccinated subjects, we will use matching without replacement, i.e., each unvaccinated subject can only be selected to match a given vaccinated subject once, and once matched, will not be allowed as a potential match for other vaccinated subjects. In terms of matching method, we will apply the nearest neighbor matching method with a pre-specified caliper distance of 0.1 where the distance measure will be the propensity score distance defined as the absolute difference in estimated propensity scores between two subjects.[17]

After selecting the matched cohorts, we will perform balance diagnostics to compare the distribution of baseline covariates between the vaccinated and the unvaccinated to evaluate performance of the propensity score matching. To assess the balance between the matched cohorts, we will compare means and prevalence of baseline covariates, variance of

continuous variables, and means of interactions of two covariates. We will also employ graphical methods such as quantile-quantile plots and non-parametric density plots to compare the distribution of the baseline characteristics between the exposed and unexposed groups.

8.7.3. Spontaneous abortion

Incidence proportions will be calculated to estimate the risk of spontaneous abortion. The study population will include pregnant women at-risk for having a spontaneous abortion. The at-risk period for an exposed woman varies depending on the timing of the vaccination relative to the timing of LMP. If vaccination occurred in the 28 days prior to LMP, then the period in which a subject is at-risk for a spontaneous abortion begins at the start of the pregnancy (LMP) until 20 weeks of gestation. If vaccination occurs after the start of the pregnancy but before 20 weeks gestation, the at-risk period begins once the vaccination occurred. By the fact that we will match on survival status at the time of the exposed subject's vaccination time, the at-risk period for the unexposed matches will begin at the same time as the matched exposed woman allowing for a concurrent follow-up period. For example, if a woman is vaccinated at week 8 of gestation, the follow-up period for both the exposed and three matched unexposed women will begin at week 8. Observing concurrent follow-up for the exposed and unexposed groups allows for a direct comparison of risk associated with Trumenba. An alternative follow-up period for the unexposed group is at the start of pregnancy. Following on the previous example, an unexposed woman could have a spontaneous abortion in week 6, prior to the matched exposed woman's vaccination. Accrual of these events could provide an overestimate of the incidence in the unexposed group and could result in an underestimate of the true relative risk of spontaneous abortion associated with Trumenba.

Women with vaccine exposures within 4 weeks of pregnancy start date will be included to ensure that vaccine exposures occurring during pregnancy are not missed because of imprecision in the estimated pregnancy start date and epidemiologic interest of a possible association. Only medical record confirmed cases will be included in the analysis. Vaccination dates will also be confirmed as part of the medical record review. Risk ratios and 95% confidence intervals will be calculated using log-binomial regression. The log binomial regression will be restricted to those matched strata where the exposed subject's exposure is prior to 20 weeks gestation as the outcome spontaneous abortion cannot occur after 20 weeks. Additional analyses that specifically match based on an early definition of "exposed" (rather than "any exposure during pregnancy") will also be considered and described in the SAP.

8.7.4. Stillbirth

Incidence proportions will be calculated to estimate the risk of stillbirth. The study population will include pregnant women at risk for having a stillbirth from ≥ 20 week of gestation until the end of gestation. Thus, women with events occurring prior to the 20th week of gestation will not be included in the at-risk population. Similar to the spontaneous abortion endpoint, the at-risk period for an exposed woman varies depending on the timing of the vaccination relative to the timing of LMP. If vaccination occurred in the 28 days prior to

LMP, then the period in which a subject is at-risk for a stillbirth begins at the start of the twentieth week of gestation. If vaccination occurs on or after the twentieth week of gestation, the at-risk period begins once the vaccination has occurred. Similar to the spontaneous abortion endpoint, the at-risk period for the unexposed matches will begin at the same time as the matched exposed woman allowing for a concurrent follow-up period because of the nature of our matching procedure.

Women with vaccine exposures within 4 weeks of pregnancy start date will be included to ensure that vaccine exposures occurring during pregnancy are not missed because of imprecision in the estimated pregnancy start date and because of epidemiologic interest of a possible association. Only medical record confirmed cases will be included in the analysis. Vaccination dates will also be confirmed as part of the medical record review. Risk ratios and 95% confidence intervals will be calculated using log-binomial regression.

8.7.5. Live birth

The incidence of live births will be calculated for both the Trumenba-exposed cohort and unexposed cohort. For the Trumenba-exposed cohort, the study population will consist of all clinically recognized known pregnancies exposed to Trumenba up to 28 days prior to or at any time during pregnancy. The comparison group will consist of a matched sample of all clinically recognized known pregnancies not exposed to Trumenba up to 28 days prior to or during pregnancy. Live births occurring among the clinically recognized pregnancies will be the numerator.

8.7.6. Temporal scan methods

In vaccine safety studies, precise estimation of the risk interval, the period of time when a person is at an increased risk for an adverse event following vaccination is critical; risk can be underestimated in the interval that includes days in which there is no true increased risk, and using too short of an interval can limit statistical power.[18] Risk interval choice should be informed by biologic plausibility; however, for the outcomes described in this study, the underlying pathophysiology is largely unknown and therefore it is difficult to pre-specify appropriate risk intervals. To address this limitation temporal scan methods can be used to identify potential risk periods of interest in relation to vaccine exposures. The temporal scan statistic will be used to detect and evaluate temporal clusters of vaccination among women with the outcomes of interest.[18, 19] This is an exploratory analysis designed to be hypothesis generating. Information generated about potential non-uniform risk intervals will be used appropriately and detailed in the statistical analysis plan.

The temporal scan statistic was developed to test whether a disease is randomly distributed over time, or whether there exists a statistically significant clustering of cases over a certain time window. It compares the number of observed and expected observations inside a scanning window to outside the window. This is repeated as the scanning window moves across time. It uses multiple window sizes, and the one with the largest excess of observed cases is least likely due to chance, and hence most likely a cluster. When used prospectively, it can be an effective tool for disease surveillance to detect any outbreak.

In this study, to identify any clustering of endpoints such as spontaneous abortion or stillbirth, the temporal scan statistic will be applied to the data collected from the vaccinated women. The null hypothesis is that the adverse event is uniformly distributed with respect to time. The alternative hypothesis is that there is an elevated risk of the adverse event within a scanning window compared to outside the window. Binominal distribution will be assumed for the outcome variable, and the likelihood ratio (LR) test will be carried out for inference. P-value for the LR test statistic will be obtained using Monte Carlo simulations by comparing the rank of the maximum likelihood from the real data to the maximum likelihood from the random replica generated under the null. A p-value of 0.05 or less will be deemed statistical significant.

Vaccine exposures in the four weeks preceding the pregnancy start date through the end of the time period associated with each outcome will be considered.

8.7.7. Major Congenital Anomalies

The overall risk of major congenital anomalies will be calculated. For both the exposed and unexposed groups, the numerator will consist of medical record confirmed anomalies. The number of live births in each of the exposed and unexposed groups will compose the respective denominator. To be considered exposed, a pregnant women will have received at least one Trumenba vaccination up to 28 days prior to or at any time during pregnancy. The comparison group will not have been exposed to Trumenba up to 28 days prior to or during pregnancy.

Infants with anomalies due to maternal infection (e.g., congenital rubella syndrome) will be excluded (Table 5). Infants born to diabetic mothers and mothers with malignant neoplasms in the six months preceding pregnancy start will also be excluded. Potential cases that occur as part of a genetic syndrome or other syndrome of known etiology (e.g., trisomy 13 (ICD-9 code 758.1), trisomy 18 (ICD-9 code 758.2), or trisomy 21 (ICD-9 code 758.0)), or those that occur secondary to other major malformations (e.g., holoprosencephaly or amniotic band sequence) will be counted but they will not be included in the calculation of prevalence of major congenital anomalies. An overall risk estimate will be calculated using log-binomial regression restricted to those matched strata where exposure in the exposed subject occurs at or prior to 14 weeks. This restriction will be necessary as it is biologically implausible that exposures occurring after 14 weeks gestation (period of organogenesis) would be causally related to congenital anomalies. Stratified analysis looking at vaccine exposures from 28 days to 0 weeks gestation (pre-pregnancy) and vaccine exposures from 4-10 weeks gestation (period where developing fetus is most susceptible to teratogenic exposures) will also be calculated if the sample size is adequate. As in the case of spontaneous abortion, additional analyses that more specifically match on an early definition of "exposed" (rather than "any exposure during pregnancy") will also be considered and described in the SAP.

Table 5. Exclusion Criteria for Congenital Anomalies Analysis

Condition	Maternal Code	Infant Code
Autosomal deletion syndromes		758.31, 758.32, 758.33
Turner Syndrome		758.6
Klinefelter Syndrome		758.7
Infectious		
Rubella	056.x, 647.5x, 655.3	056.x, 771.0
Cytomegalovirus (CMV)	078.5x. 647.6x	078.5x, 771.1
Varicella	052.x, 647.6x	052.x
Syphilis	091.x-097.x, 647.0x	090.x-097.x
Toxoplasmosis	130.x, 647.8x	130.x, 771.2

8.7.8. Statistical Analysis Plan

Detailed methodology for summary and statistical analyses of data collected in this study including sensitivity analyses for pre-pregnancy exposure period, risk windows, and other potential comparison groups will be documented in a Statistical Analysis Plan (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 primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality control

The data assurance and characterization approach used by the Sentinel Initiative will be emulated. This data quality assurance approach involves distribution of a distributed program that is executed locally by the participating data partners, with aggregate output tables returned to the Coordinating Center for review. The quality assurance approach assesses consistency with the CDM, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across Partners. The quality assurance process for data elements is shown in Figure 4.

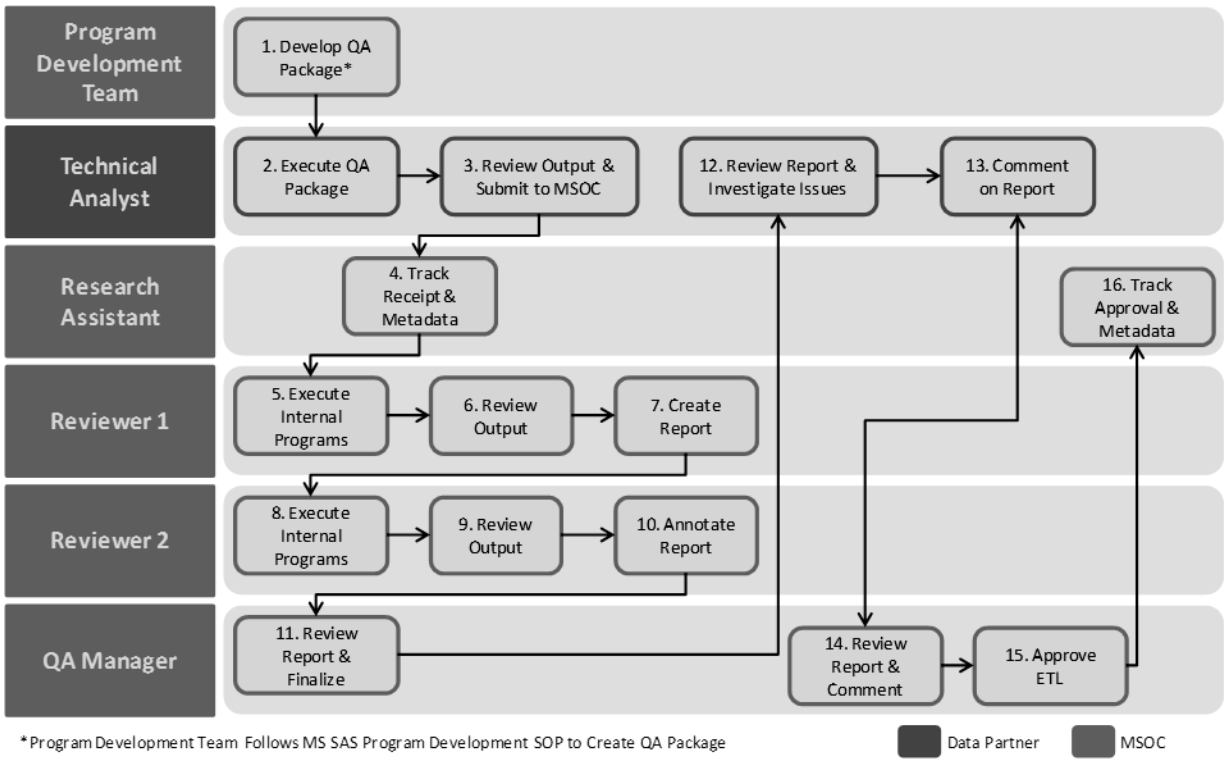

Figure 4. Quality assurance process for data elements included in the Sentinel Common Data Model (SCDM) [Abbreviations: MSOC: Mini-Sentinel Operations Center; ETL: extract, transform, load]

In addition to quality assurance of data elements, the Coordinating Center will also use standard SAS programming quality assurance and quality control processes to check SAS programs and deliverables. Figure 5 illustrates the Sentinel Initiative SAS data programming Standard Operating Procedure that will form the basis of programming quality checks.

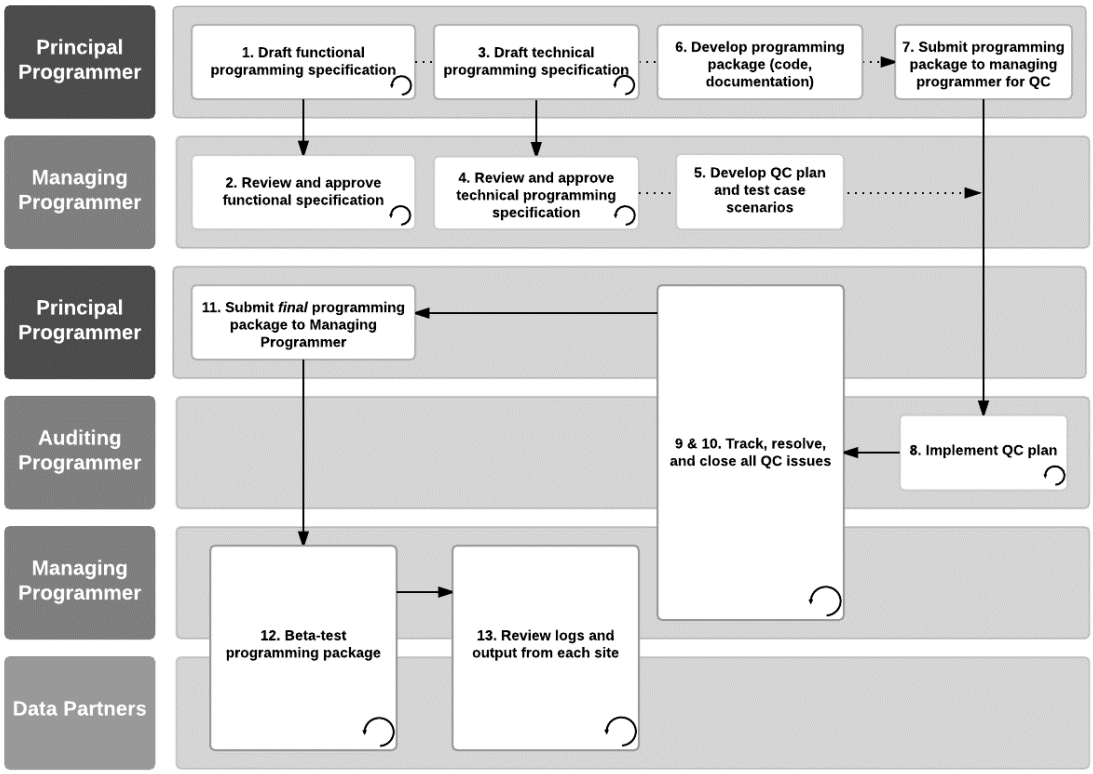

Figure 5. SAS Programming SOP from Sentinel

8.9. Limitations of the research methods

8.9.1. Limitations

Several limitations exist in the conduct of pregnancy studies with electronic healthcare databases. First, though data files are standardized on an annual basis, the algorithm is dependent on local coding practices and the availability of data including linkage to birth certificates. Women may receive vaccination outside of the healthcare delivery system; thus, vaccine exposures could be misclassified and potentially reducing the observed counts of women and infants exposed to Trumenba. Gestational age data are not always available in the EMR or claims data, or may be imprecise estimates. For example, an inaccurate gestational age at or around 20 weeks could misclassify the outcome as a stillbirth instead of spontaneous abortion. In addition, inaccurate gestational age estimation may lead to exposure misclassification. Incomplete and/or inaccurate diagnoses and behaviors documented in electronic healthcare data could result in misclassification of outcomes and covariates. These potential limitations will be lessened by confirming outcomes through manual review of medical records, and by incorporating data when available from state immunization registries and birth certificates.

Women who seek medical care from the system may not be representative of the entire US population. Geographic heterogeneity in vaccine coverage may exist and thus generalizability may be limited.

Although propensity score matching will be used to minimize differences between the Trumenba-exposed women and unexposed women, there may still be residual confounding between the groups that could bias the risk estimates.

This study will identify clinically-recognized pregnancies. Pregnancies resulting in fetal loss prior to clinical recognition and the associated causes cannot be assessed. Evidence suggests up to 22% of pregnancies end before clinical detection.[20] As a result, absolute estimates or risk for spontaneous abortion will be underestimated for both the Trumenba exposed and comparison groups; however, the extent of the differential underestimation cannot be determined. For example, if Trumenba presents an increased risk for spontaneous abortion in the first 2 menstrual cycles (e.g., ~ 8 weeks gestation) and these fetal losses are not clinically recognized, then this study will not be able to assess this association.

8.9.2. Strengths

Using electronic health care data to assess the risk of pregnancy-associated birth outcomes after exposure to Trumenba overcomes many challenges associated with conducting a traditional pregnancy registry. The electronic health care data approach differs from a traditional pregnancy registry that passively collects information on women exposed to the product in a prospective format. As a result, the traditional pregnancy registry may fail to provide clinically meaningful information because of selection bias due to the limited number of pregnant women voluntarily enrolled in the registry, difficulty in recruiting an appropriate comparison group, and loss to follow-up. Using electronic healthcare data with a well-defined population can overcome some of the limitations of the traditional pregnancy registry. Selection bias can be reduced as most exposures during pregnancy would be captured in the database and Trumenba-exposed and Trumenba-unexposed comparison groups have been identified from the same source population. In addition, ascertainment of important study outcomes like spontaneous abortion and stillbirth will be improved. Medical record review of outcomes further improves ascertainment of valid data. Collectively, this study design improves validity and interpretability of the study results.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The medical record review will be conducted with a waiver of informed consent. This study will involve a large number of women from multiple health plans and delivery systems so it could not be practicably conducted without a waiver of informed consent. Each data partner will request waiver. The proposed study has minimal risk; potential breaches of privacy and confidentiality are the primary study risks and these risks will be minimized by ensuring that

rigorous security procedures will be applied to data collection, management, and transfer. Some of these procedures include using a study identification number in place of direct patient identifiers, transferring data using secure, encrypted websites, and ensuring that appropriate data transfer agreements are in place between institutions prior to data sharing. Additionally, only trained study staff will be allowed to access study data, and secure storage methods, such as password protected electronic files and locked paper files, will be used by all participating data partners and the data coordinating center.

9.2. Patient withdrawal

Not applicable.

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

It is the responsibility of the principal investigator from the HPHCI to have prospective approval of the study protocol, protocol amendments, informed consents, and other relevant documents, if applicable, from the IRB/IEC. The study protocol and data collection forms will be reviewed by the HPHCI IRB/IEC. Participating data partners can either cede IRB review to the HPHCI IRB/IEC or seek approval from their local IRB. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. 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 Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, and European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual.

In addition, this protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appears in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug

administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

- Scenarios involving drug exposure, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For those safety events with an explicit attribution to or associated with use of, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

COMMUNICATION OF ISSUES

Interim looks and the final study report will be submitted to the FDA. Final study results will be disseminated at scientific conferences and a manuscript of the study will be submitted to a peer reviewed journal for publication. Interim looks may also be presented at scientific conferences. The study will be registered with the European Union (EU) Post-Authorization Study register prior December 31, 2017.

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 investigator 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.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

12. REFERENCES

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Appendix 1. LIST OF STAND ALONE DOCUMENTS

None.

Appendix 2. ESTIMATION OF LMP

1. Pregnancy outcomes other than live births

Pregnancy Outcome	Gestational age	
	Weeks	*Days*
Stillborn	30	210
Spontaneous abortion	10	70
Induced abortion	8	56
Ectopic pregnancy	8	56
Trophoblastic disease	10	70

Diagnosis codes and procedures codes in the inpatient, ambulatory, and emergency department setting will be used to identify these pregnancy outcomes

2. Livebirths

   a. Diagnosis and procedure codes will be identified in both the inpatient and emergency department setting.

   b. Gestational age assumptions based upon the presence/absence of codes for preterm and postterm birth:

ICD-9-CM codes for preterm and postterm birth and completed weeks of gestation, and their use in the gestational age algorithm*

ICD-9-CM code	**Definition**	**Gestational age**	
		Weeks	**Days**
Preterm Birth Codes			
765.21	Less than 24 completed weeks of gestation	24	168
765.22	24 completed weeks of gestation		
765.23	25-26 completed weeks of gestation	26	182
765.24	27-28 completed weeks of gestation	28	196
765.00-765.09	Extreme immaturity		
765.25	29-30 completed weeks of gestation	30	210
765.26	31-32 completed weeks of gestation	32	224
765.27	33-34 completed weeks of gestation	34	238
765.28	35-36 completed weeks of gestation	36	252
765.10-765.19	Other preterm infants	35	245
765.20	Preterm with unspecified weeks of gestation		
644.21	Onset of delivery before 37 completed weeks of gestation		

Post-term Birth Codes			
645.1x	Post-term pregnancy, delivered, with or without mention of antepartum condition (over 40 weeks to 42 completed weeks gestation)	41	287
766.21	Post-term infant (gestation period over 40 weeks to 42 completed weeks)	41	287
645.2x	Prolonged pregnancy, delivered (pregnancy which has advanced beyond 42 completed weeks gestation)	42	294
766.22	Prolonged gestation of infant (gestation period over 42 completed weeks)	42	294
* ICD-9-CM codes will be mapped to ICD-10-CM codes. If there are no preterm codes or postterm codes listed above during the mother's hospital admission: start date of pregnancy is the admit date of the delivery hospital admission minus 273 days.			

Appendix 3. TERATOGENIC MEDICATIONS

Drug Class	Drug Name	Comments	Plan	Risk window for exclusion or adjustment
Vitamin A Analog	Isotretinoin		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Vitamin A Analog	Bexarotene		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Vitamin A analog	Acitretin		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Prostaglandin Analog	Misoprostol	Including Misoprostol/ Diclofenac Combination	Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Antineoplastic	Methotrexate		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Immuosuppressant	Mycophenolate Mofetil		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Immunologic	Azathioprine		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Immunologic	Thalidomide		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Anticoagulant	Warfarin		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Mood Stabilizer	Lithium		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Antiarrhythmic	Amiodarone		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Antiarrhythmic	Dronedarone		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Anticonvulsant	Carbamazepine		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Anticonvulsant	Fosphenytoin		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Anticonvulsant	Mephobarbital		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Anticonvulsant	Phenobarbital		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy

Anticonvulsant	Phenytoin (phenytoin sodium)		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Anticonvulsant	Primidone		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Anticonvulsant	Topiramate		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Anticonvulsant	Valproic Acid and derivatives (valproate sodium, divalproex)		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
Antirheumatic	Lefluonamide		Exclude using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Benzepril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Captopril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Enalapril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Fosinopril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Lisinopril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Moexipril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Perindopril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Quinapril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Ramipril	Including ACE-I Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ACE-I	Trandolapril	Including ACE-I	Adjust for in	6 months prior to

		Combination Antihypertensives	analyses using GPI or NDC code	LMP through end of pregnancy
ARB	Candesartan	Including ARB Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ARB	Eprosartan	Including ARB Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ARB	Irbesartan	Including ARB Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ARB	Losartan	Including ARB Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ARB	Olmesartan	Including ARB Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ARB	Telmisartin	Including ARB Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
ARB	Valsartan	Including ARB Combination Antihypertensives	Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
Misc Antihypertensive	Aliskiren		Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
SSRI	Paroxetine		Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
Antiinfectives	Trimethoprim		Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy
Antiinfectives	Trimetrexate		Adjust for in analyses using GPI or NDC code	6 months prior to LMP through end of pregnancy

Appendix 4. VACCINATION RECOMMENDATIONS DURING PREGNANCY

Vaccine	May 2012 ACIP recommendations [B]	FDA Pregnancy Category [C]
Influenza, inactivated	Recommended	B (Fluarix, FluLaval, Agriflu); C (Fluzone, Fluvirin, Afluria)
Tetanus–diphtheria (Td)	Should be considered if otherwise indicated	C
Hepatitis B	Recommended in some circumstances	C
Meningococcal, polysaccharide (MPSV4)	May be used if otherwise indicated	C
Rabies	May be used if otherwise indicated	C
Measles, mumps, rubella (MMR)	Contraindicated	C
Varicella	Contraindicated	C
Influenza, live attenuated (LAIV)	Contraindicated	C
Zoster	Contraindicated	C
BCG	Contraindicated	C
Tetanus–diphtheria–pertussis (Tdap)	Recommended	B (Boostrix); C (Adacel)
Human papillomavirus (HPV)	Not recommended	B
Hepatitis A	May be used if benefit outweighs risk	C
Pneumococcal (PCV13, PPSV23)	Inadequate data for specific recommendation	C
Typhoid (parenteral and oral)	Inadequate data for specific recommendation	C
Meningococcal, conjugate (MCV)	Inadequate data for specific recommendation	B (Menveo); C (Menactra)
Polio (IPV)	May be used as needed	C
Yellow fever	May be used if benefit outweighs risk	C
Japanese encephalitis	Inadequate data for specific recommendation	B
Anthrax	Low risk of exposure—not recommended; high risk of exposure—may be used	D
Vaccinia (smallpox)	Pre-exposure—contraindicated; postexposure—recommended	D

[b] CDC. Guidelines for vaccinating pregnant women, from the recommendations of the ACIP, December 2012 version

[c] As summarized in the December 2012 version of ACIP Guidelines. The FDA pregnancy categories include the following: Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the 1st trimester of pregnancy (and there is no evidence of risk in later trimesters); Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women; Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Appendix 5. MATERNAL COMORBIDITIES

Condition	Code*
Diabetes	250.xx
Malignant neoplasms	140-208
Congenital cardiovascular disorder	648.5x
Heart disease	093, 112.81, 130.3, 391, 393.x-398.x, 410.xx-429.xx, 648.5, 648.6x, 745.xx,746.xx, 747.1x-747.4x, 759.82
Pre-existing hypertension	401.x-405.x
Hypertensive disorders of pregnancy	642
Renal disease in pregnancy	646.2
Gestational diabetes	648.8x, 648.0x
Glucose tolerance test	82950, 82951
Insulin	V58.67
Obesity	278.xx
Obesity Pregnancy	649.1x- 649.2x
BMI	V85.xx
Other exposures: asbestos, lead	V15.84,V15.85,V15.86
Supervision of pregnancy	V22.x, V23.x
Hemorrhage in early pregnancy	640.xx
Bleeding in pregnancy	641.xx, 649.5x
Excessive vomiting during pregnancy	643.xx
Infectious and parasitic diseases complicating pregnancy	647.xx
Thyroid dysfunction during pregnancy	648.1x
Congenital cardiovascular disorders complicating pregnancy	648.5x
Epilepsy complicating pregnancy	649.4x
Anemia (excluding iron deficiency) and hypercoagulability	281.xx-289.xx
Chronic liver disease and cirrhosis	571.xx
Heart disease (Includes congenital defects and Marfan's)	093, 112.81, 130.3, 391,
393.x-398.x, 410.xx-429.xxx, 648.5, 648.6x, 745.xx,746.xx, 747.1x-747.4x, 759.82	ICD9
Immunodeficiency and organ transplant	279.xx, V42.x
Lung disease	011.xx, 135, 491.xx-511.xx, 12.0, 512.8, 513.x-517.x, 518.0, 518.1, 518.3, 518.4, 518.6, 518.8x, 714.81
Nutritional deficiencies	260.x-269.x
Renal disease	274.1x, 580.xx-591.xx, 593.71-593.73, 593.9, 753.1x, 753.3
Neurologic	340, 341.xx, 348.xx, 438.xx, 345.xx
Rheumatologic disease	446.xx, 710.x, 714.0-714.4, 714.8, 714.89, 714.9

Appendix 6. COMPLICATIONS OF PREGNANCY

Condition	Code*
Hemorrhage in early pregnancy	640.x
Bleeding in pregnancy	641.x, 649.5x
Hypertension complicating pregnancy	642.x
Excessive vomiting during pregnancy	643.x
Renal disease during pregnancy	646.2x
Infectious and parasitic diseases complicating pregnancy	647.x
Diabetes during pregnancy	648.0x, 648.8x
Thyroid dysfunction during pregnancy	648.1x
Drug dependence during pregnancy	648.3x
Congenital cardiovascular disorders complicating pregnancy	648.5x
Maternal smoking	649.0x
Maternal obesity	649.1x, 278.0x
Epilepsy complicating pregnancy	649.4x

Appendix 7. CONGENITAL ANOMALIES

Central Nervous System	Code*
Anencephaly, Craniorachischisis	740.0, 740.1
Encephalocele, Cranial Meningocele, Encephalomyelocele	742.0
Spina bifida	741.0, 741.9
Holoprosencephaly	742.2
Hydrocephalus (with or without Dandy-Walker or other structural lesion)	742.3
Microcephalus	742.1
Neural Tube defects: Anencephaly, Craniorachischisis, Encephalocele, Cranial Meningocele, Encephalomyelocele, Spina bifida	740.0, 740.1, 742.0, 741.0, 741.9
Eye	
Anophthalmia, Microphthalmia	743.00, 743.10-743.12
Cataracts and Other Lens Defects	743.30-743.36
Glaucoma and Anterior Segment Defects without Aniridia	743.2x
Ear	
Anotia, Microtia	744.01, 744.23
Heart	
Anomalous Pulmonary Venous Return	747.41, 747.42
Atrioventricular septal defects (AV canal)	745.60, 745.61, 745.69
Conotruncal Heart Defects	745.0, 745.10, 745.11, 745.2, 747.11, 747.3
Ebstein Malformation	746.2
Laterality Defects – heterotaxy	759.3
Obstructive heart defects (includes hypoplastic left heart)	746.00, 746.02, 746.1, 746.3, 746.7, 747.10, 747.11, 747.22
Septal heart defects	745.4, 745.8, 745.9
Single Ventricle	745.3
Severe congenital heart disease: single ventricle, tricuspid atresia, Ebstein's anomaly, hypoplastic left heart, hypoplastic right heart, common arterial truncus, transposition of great vessels, atriventricular septal defects, tetralogy of fallot, pulmonary valve atresia, aortic valve atresia/stenosis, coarctation of aorta, total anomalous pulmonary venous return	745.00, 745.10, 745.2-745.3, 745.6, 746.00, 746.1-746.3, 746.7, 747.1, 747.41
Orofacial/Respiratory	
Choanal Atresia	748.x
Cleft Lip +/- Palate	
Cleft Palate 749.0, 749.00-749.04	749.1, 749.10-749.14, 749.2, 749.20-749.25
Gastrointestinal	
Biliary Atresia	751.61
Esophageal Atresia +/- TE Fistula	750.3
Intestinal Atresia/Stenosis	751.1, 751.2
Pyloric Stenosis	750.5
Genitourinary/Renal	
Exstrophy, Bladder	753.5
Exstrophy, Cloacal	751.5
Hypospadias- 2nd or 3rd degree	752.61
Renal Agenesis/Hypoplasia	753.0x
Renal dysplasia	753.16
Congenital hydronephrosis	753.20
Posterior urethral valve and/or prune belly	753.60, 756.72

Musculoskeletal	
Abdominal wall defects: Gastroschisis, Omphalocele	756.79
Diaphragmatic Hernia	756.6
Limb deficiencies: Limb Deficiency, Intercalary, Limb Deficiency, Longitudinal, Limb Deficiency, Transverse, Limb Deficiency, NEC	755.2-755.9
Amniotic Bands	762.8
Sacral Agenesis	756.13
Craniosynostosis	756.0

Appendix 8. MATERNAL AND INFANT COVARIATES

Maternal Covariate	Infant Covariate (birth – 6 months)
Age at pregnancy start	Gender
Age at pregnancy end	Number of health care visits
Race	Number of well child visits
Ethnicity	Vaccinations (date, type)
Data partner	Diagnoses (diagnosis code, type)
Health plan enrollment dates	Medication (generic name, date prescribed, date filled, dosage, days supply)
Number of prenatal care visits	
Smoking during pregnancy	
Alcohol use during pregnancy	
Prenatal vitamin use	
Gravidity	
Parity	
Number of previous spontaneous abortions	
Number of previous pregnancies with congenital anomalies	
Previous Cesarean delivery	
Comorbidities (from Appendix 5)	
Vaccinations (date, type)	
Medication (generic name, date prescribed, date filled, dosage, days supply)	