COVID-19 Pregnancy Study Protocol

Mayura Shinde, DrPH, MPH,[1] Susan Andrade, ScD,[2] Jennifer G. Lyons, PhD, MPH,[1] Nicole Haug, MPH,[1] Austin Cosgrove, BA,[1] Adee Kennedy, MS, MPH,[1] Jolene Damon, MPH,[1] Patrick Dowe, MPH,[1] Jenice Ko,[1] Danijela Stojanovic, PharmD, PhD, [3] Ben Wong, PhD,[4] Leyla Sahin, MD,[5] Yueqin Zhao, PhD,[4] Darren Toh, ScD,[1] Wei Hua, MD, PhD, MHS, MS[3]

Affiliations: 1. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; 2. The Meyers Primary Care Institute, University of Massachusetts Medical School, Reliant Medical Group, and Fallon Health, Worcester, MA USA; 3. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; 4. Office of Biostatistics, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; 5. Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD

Version 1.0

May 19, 2021

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

Sentinel

COVID-19 Pregnancy Study Protocol

Table of Contents

History of Modifications

Version	Date	Modification	Author
1.0	05/19/2021	Original Version	As shown on title page

1. Introduction

Pregnant people are considered to be at high risk for developing severe illness related to respiratory infections, including COVID-19.[1] Several case series, cohort studies, and meta-analyses have been conducted describing the clinical manifestations, and maternal and perinatal outcomes in pregnancies with COVID-19.[2-3] The majority of these studies found that hospitalized pregnant patients with COVID-19 were less likely to manifest symptoms of myalgia, cough, dyspnea, and fever but more likely to be admitted to an intensive care unit and receive invasive ventilation than non-pregnant patients of reproductive age.[1-4] Preterm births were more commonly reported in pregnant patients with COVID-19 than those without COVID-19.[1] Although pregnancies affected by COVID-19 have been characterized in recent studies, little is known about the treatment management in these people and the impact of treatment used for COVID-19 on maternal and neonatal health and fetal development.

During the COVID-19 pandemic, the Sentinel System has been integral in providing enhanced data and analytic needs to support FDA's response to the pandemic. FDA has actively monitored utilization of drugs and biologics for prevention and treatment of COVID-19 and validated a diagnosis code-based algorithm for identifying COVID-19 patients using the Sentinel System.[4] Sentinel has also recently published a COVID-19 Natural History Master Protocol[5] designed to describe the course of COVID-19 disease and outcomes in certain subgroups of patients, including children, certain ethnic groups, and pregnant people.

The European Medicines Agency (EMA) has funded a project, known as CONSIGN (COVID-19 infection and medicines in pregnancy), to understand the natural history of COVID-19 disease, evaluate whether pregnant people are more likely to develop severe illness than non-pregnant people, examine the impact of COVID-19 disease in different gestational ages on pregnancy outcomes, and describe the utilization and impact of medications for COVID-19 treatment on fetal development and neonatal outcomes.[6] The CONSIGN study will be implemented in varied data sources across eight European countries.

Sentinel is capable of describing the natural history of COVID-19 disease among pregnant patients with live birth delivery in the United States. This study will implement two aims of the CONSIGN protocol: 1) compare medications used for treatment of COVID-19 and other medical conditions and 2) describe severity and clinical outcomes of COVID-19; both aims will compare pregnant patients with COVID-19 (Aims 1 and 2), pregnant patients without COVID-19 (Aim 1), and non-pregnant patients of reproductive age with COVID-19 (Aims 1 and 2). Analyses of these cohorts could address key knowledge gaps to improve the understanding of the treatment and severity of COVID-19 in pregnant patients.

2. Objectives

This protocol outlines steps for implementation of aims of the CONSIGN study including identification of cohorts for pregnant patients diagnosed with and without COVID-19 and non-pregnant patients with COVID-19 in the Sentinel System, description of treatment patterns, and assessment of the feasibility of capturing severity for COVID-19 disease and other data elements that can be collected within Sentinel.

The two main objectives of this study are:

1) To estimate the prevalence of medicines among pregnant patients with COVID-19, and compare this with pregnant patients without COVID-19, and non-pregnant patients with COVID-19.

a. To estimate the prevalence of medicines in pregnant patients with COVID-19, by age and trimester of pregnancy.

b. To compare these data with those collected for pregnant patients without COVID-19, by age and trimester of pregnancy.

c. To compare these data with those collected for non-pregnant patients of reproductive age with COVID-19, by age and time periods corresponding to trimesters in matched pregnant woman

2) To describe severity and clinical outcomes of COVID-19 disease in pregnant patients with COVID-19, and compare these data with those of non-pregnant patients of reproductive age with COVID-19.

a. To describe the severity of COVID-19 disease in pregnant patients by age, and trimester of pregnancy at diagnosis.

b. To compare these data with those of non-pregnant patients of reproductive age with COVID-19, by age and time periods corresponding to trimesters in matched pregnant woman.

The current protocol, which describes our planned Sentinel network-specific activities to study COVID-19 outcomes in pregnant people, draws upon the Sentinel Operations Center (SOC)-led COVID-19 Natural History Master Protocol[5] and the EMA CONSIGN protocol.[6] Other existing resources that will be used during study implementation include the COVID-19 Master Protocol data element list, and COVID-19 Master Protocol code lists.[5]

3. Methods

3.1. Data sources

Sentinel currently has access to a range of data sources able to support the COVID-19 analyses. To implement this study, we will identify Data Partners with the data availability and capability in conducting full study implementation. Data sources may include claims-based systems and integrated care delivery systems. Data Partners provide longitudinal data on primarily commercially insured populations, with well-established data updating and quality assurance procedures, which are used for medical product safety and effectiveness studies.[7] For COVID-19 analyses among pregnant people, data on COVID-19 laboratory results, inpatient and outpatient medication exposures, health care utilization, and other elements of clinical care will be utilized, as available.

The SOC is currently developing a rapid COVID-19 database (Rapid COVID-19 Sentinel Distributed Database) that incorporates more recently refreshed data (compared to typical Sentinel refreshed data) and COVID-19 diagnostic testing information, which will be considered as the ideal source for the study described here. If the Rapid COVID-19 Sentinel Distributed Database is utilized, distributed programs will be developed centrally, to be run at participating sites. We plan to leverage existing Sentinel tools and assess the needs for custom coding to

support analyses planned in this study.

3.2. COVID-19 case definition

COVID-19 will be defined using either COVID-19-related International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes (Table 1) *or* a positive result of an eligible COVID-19 laboratory test. Eligible laboratory tests include a reverse transcriptase polymerase chain reaction (RT-PCR) or other nucleic acid amplification test (NAAT) for SARS-CoV-2 or a SARS-CoV-2 antigen test.[8-99]

ICD-10-CM diagnosis codes

A validation study of COVID-19 code-based algorithms conducted in Sentinel among hospitalized COVID-19 cases identified after May 2020, using combinations of the International Classification of Diseases, tenth revision, Clinical Modification (ICD-10-CM codes) (U07.1, B97.29, B34.2, B97.21, or J12.81), found a positive predictive value (PPV) of 81%.[4] A positive NAAT result for SARS-CoV-2 was used as the gold standard for confirmation. The sensitivity of the algorithm in identifying positive COVID-19 cases was around 95%. The study also found U07.1 captured the majority of the COVID-19 patients identified.

Table 1. ICD-10-CM diagnosis codes for COVID-19

ICD-10-CM code	Description
B97.29	Other coronavirus as the cause of diseases classified elsewhere
U07.1	COVID-19, virus identified [code effective April 1, 2020]
B34.2	Coronavirus infection, unspecified site
B97.21	SARS-associated coronavirus as the cause of diseases classified elsewhere
J12.81	Pneumonia due to SARS-associated coronavirus

We will identify potential COVID-19 cases using either:

- ICD-10-CM diagnosis codes listed above in Table 1 with U07.1 code observed in outpatient or inpatient setting and other ICD-10 codes (B97.29, B34.2, B97.21, J12.81) in inpatient setting OR
- a positive result for an eligible COVID-19 laboratory test

We will also conduct a sensitivity analyses requiring any of ICD-10 codes (U07.1, B97.29, B34.2, B97.21, J12.81) identified in inpatient or outpatient setting OR a positive test results for COVID-19 to capture pregnancies that may have been identified with ICD-10 codes other than U07.1 in outpatient setting prior to approval of U07.1 in April 2020.

SARS-CoV-2 laboratory tests

Several different tests are being implemented in clinical practice to identify current SARS-CoV-2 infection. These include: 1) RT-PCR or other NAAT assays of respiratory tract specimens, 2) antigen detection assays of respiratory tract specimens.[8-9]

The laboratory test results table populated by the Data Partners will be used to identify health plan members with positive SARS-CoV-2 test results. Patients with a positive result for SARS-CoV-2 by NAAT or antigen test in any setting will meet the case definition.

3.3. Study Cohort Identification

As outlined in the CONSIGN protocol, we will identify the study population including people of reproductive age between 12 and 55 years and pregnancies among these people from January 01, 2020 to most recent data available from the data partners. In our analyses, we will identify only pregnancies resulting in live birth delivery and pregnancies resulting in other outcomes (e.g. stillbirths, spontaneous abortions, induced abortions) will not be captured.

Sentinel investigators have developed publicly-available tools to define medication exposures during pregnancy and comparatively assess pregnancy outcomes. These tools use a claims-based algorithm previously validated in the FDA-sponsored Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP).[10] The current study will use this algorithm to identify pregnancies ending in a live birth through identification of diagnosis and procedures codes documented in inpatient care setting listed in Appendix 1. Because the date of the last menstrual period (LMP) is not available in the health plan data, the algorithm calculates the length of the pregnancy episode and LMP using ICD-10-CM codes indicative of weeks of gestation, as well as ICD-10-CM codes for pre-term and post-term deliveries in the inpatient care setting (Appendix 1). For the purpose of gestational dating, the LMP is used as the start date of pregnancy.

Specifically, the algorithm first prioritizes codes specifying completed weeks gestation, then non-specific preterm delivery codes (codes that indicate preterm birth but do not indicate a specific gestational age), and lastly non-specific post-term delivery codes (codes that indicate post-term birth but do not indicate a specific gestational age) identified within 7 days of the delivery encounter. ICD-10-CM incorporates diagnosis codes for gestational age in weekly increments. We assume the approximate mid-point of the specified gestational age (e.g., assumption of 263 days [37 weeks and 4 days] for ICD-10-CM code Z3A.37 [37 completed weeks gestation]). Gestational age assumptions are listed in Appendix 1. If gestational age, preterm birth, or post-term delivery codes are not identified within 7 days of the delivery encounter, then the default assumption for gestational age for live birth deliveries is 273 days.

The pregnancy start date (i.e., LMP) is calculated by subtracting the gestational age from the date of the live birth delivery. This approach has been shown to accurately identify pregnancies and gestational length with minimal misclassification.[11,12] In CONSIGN study, the pregnancy start will be estimated by subtracting the gestational age at delivery from pregnancy end date, estimated using ultrasound test or from the woman's recall of LMP recorded in the database.[6]

Depending on the study objective evaluated we will define three primary cohorts of interest:

1. Pregnancies with COVID-19 ending in live birth delivery identified on or after January 01, 2020
2. Pregnancies without COVID-19 ending in live birth delivery identified on or after January 01, 2020
3. Non-pregnant people assigned as females identified with COVID-19 on or after January 01, 2020

We will define 3 trimesters for a given pregnancy episode based on the estimated date of LMP. The first trimester will include days 0 to 90 of gestation, the second trimester will include days 91 to 180, and the third trimester will include days 181 through the day of the hospital admission for live-birth delivery.

3.4. Medication Exposure Assessment

Medications used for treatment of COVID-19 or other medical conditions will be examined for each study objective described in Section B. Medications will be identified from outpatient pharmacy claims using National Drug Codes (NDC) and from encounter claims data using Healthcare Common Procedure Coding System (HCPCS). The date of dispensing or administration of medication will be used for medication exposure assessment.

Depending on the study objective evaluated, we will assess medication utilization either during:

- The pregnancy period (i.e., the first, second, and third trimester of pregnancy) or a pre-defined pre-pregnancy period (**Objective 1a, 2a**) OR
- A fixed time window (for e.g., 3 months) before or after COVID-19 diagnosis (**Objectives 1b, 1c, 2b**)

Drug utilization will be characterized by type, timing of medication use (trimester and time since diagnosis of COVID-19) and by COVID-19 disease severity. The following medication groups will be examined:

- Anticoagulants/platelet inhibitors
- Antivirals
- Antibacterials
- Antimycotics
- Antimycobacterials
- Immune sera and globulins
- Vaccinations
- Analgesics
- Psycholeptics
- Psychoanaleptics
- Diabetes
- Corticoisteroids
- Immunostimulants
- Immunosuppressants
- Anti-inflammatory drugs, especially non-steroidal anti-inflammatory drugs
- Nasal preparations
- Medicines for obstructive airway disease
- Cough and cold medications

Details on drug classes included in these medication groups are included in a separate appendix document and full list of NDC/HCPC codes will be extracted during the specification development. Additionally, individual drugs used for COVID-19 treatment management will also be examined.

3.5. At-risk medical conditions for developing severe COVID-19

Adults with certain underlying medical conditions are at increased risk of developing severe illness from COVID-19 disease. Both the U.S. Centers for Disease Control and Prevention (CDC) and U.K. National Health Services (NHS, July 2020) websites have provided a classification of

at-risk conditions for developing severe COVID-19 based on level of evidence.[13,14]

ICD-10-CM diagnosis codes recorded in encounter claims or NDC/HCPCS codes recorded in outpatient pharmacy or encounter claims (used as proxies for identification for at-risk medical conditions) will be identified to characterize at-risk groups for developing severe COVID-19. At-risk groups will be created for each of the at-risk medical conditions listed in Table 2 below:

Table 2. At-risk conditions for developing severe COVID-19 disease

At-risk medical conditions (diagnostic codes)	**Medicinal product proxy(ies)**
Cardiovascular incl. blood	
Cardiovascular disease/ Serious heart conditions including heart failure, coronary artery disease, cardiomyopathies	Antiarrhythmics, class I and III Cardiac stimulants excl. Cardiac glycosides Vasodilators used in cardiac diseases Other cardiac preparations Antithrombotic agents
Sickle Cell Disease	Hydroxyurea Other hematological agents
Respiratory	
Chronic lung disease including COPD, cystic fibrosis, severe asthma	Drugs for obstructive airway diseases Lung surfactants Respiratory stimulants
Endocrine	
Type 1 & 2 Diabetes	Blood glucose lowering drugs
Obesity (BMI ≥30 kg/m^2)	Peripherally acting antiobesity products Centrally acting antiobesity products
Renal	
Chronic kidney disease	Erythropoietin

At-risk medical conditions (diagnostic codes)	Medicinal product proxy(ies)
Immunological	
HIV	Protease inhibitors Combinations to treat HIV NRTI NNRTI
Immunosuppression	Immunosuppressants Corticosteroids
Cancer	
Cancer	Alkylating agents Antimetabolites Plant alkaloids and other natural products Cytotoxic antibiotics and related substances Other antineoplastic agents Hormones and related agents Hormone antagonists and related agents Immunostimulants Immunosuppressants

*At-risk conditions will be identified using diagnosis codes and medication proxy measures may not be used for defining these conditions given some of these medications could be used for multiple conditions

3.6. Severity of COVID-19

For classifying severity of COVID-19, the World Health Organization proposed 5-level severity categories will be used[6]:

- Level 1: any recorded diagnosis;
- Level 2: hospitalization for COVID-19;
- Level 3: intensive care unit (ICU) admission in those with COVID-19 related admission;
- Level 4: Acute respiratory distress requiring ventilation (ARDS) during a hospitalization for COVID-19;
- Level 5: death during a hospitalization for COVID-19 (any cause)

We will identify the highest level of COVID-19 severity observed during the specified period of evaluation (pre-pregnancy or trimester periods) in both pregnancies with COVID and non-pregnant cohort with COVID-19. Assessment of death during hospitalization for COVID-19 will

be included depending on availability of death data by Data Partners contributing in the Rapid COVID-19 database.

We further plan to describe pregnant patients with COVID-19 that received:

- Supplemental oxygen
- High-flow oxygen or non-invasive mechanical ventilation
- Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

Oxygen support including supplemental oxygen or high flow oxygen administered in inpatient setting may be under-captured in claims data sources and will be evaluated at time of analyses.

3.7. Data elements

A range of covariates have been outlined in the CONSIGN protocol for describing the maternal clinical characteristics, at-risk conditions, and obstetric complications that may influence the severity of COVID-19 and medication utilization during pregnancy. These covariates will be used for characterization and stratification/adjustment in propensity score matched analyses.

Table 3 presents the categories of variables to be collected or calculated, with caveats (particularly about availability) and comments about temporal aspects.

Table 3. Data elements

Categories	Variables	Caveats/limitations	Temporal aspects
Demographics	Age groups, ethnicity, census bureau regions	Race/ethnicity are often missing from claims data and will be reported as available from Data Partners	Most recent values prior to or on index date will be identified
Maternal baseline characteristics	Parity, reproductive history, folic acid use, smoking status, educational level, obesity, socio-economic status	Educational level, socio-economic status and parity is not available in claims data. Folic acid supplements are available over-the-counter, thus use will be under-captured; lifestyles factors including smoking and obesity may also be undercaptured in claims data and proxy measures will be used for defining smoking and obesity	Evidence of each condition during a specified pre-pregnancy period prior to pregnancy start date or during first trimester will be assessed
Maternal pre-existing or at-risk medical conditions	Cardiovascular diseases, respiratory diseases, diabetes, rheumatic diseases, cancer, mental disorders	Diagnosis codes will be used to capture history of these conditions. If these conditions cannot be well captured using diagnosis codes then drug dispensing information for these conditions will be used (Table 1)	Evidence of occurrence of conditions during a pre-pregnancy period or during pregnancy duration

Categories	Variables	Caveats/limitations	Temporal aspects
Maternal obstetric conditions	Gestational diabetes, gestational hypertension, preeclampsia, assisted reproductive technology, prior pregnancy with stillbirth, SGA, or congenital anomaly	Diagnosis or procedure code will be used for capturing occurrence or history of these conditions. Based on the enrollment information available for each woman capture of prior pregnancy outcome history may be limited	Gestational diabetes, gestational hypertension, and preeclampsia will be ascertained during the current pregnancy of interest. Prior pregnancy adverse outcomes may be assessed in woman's prior enrollment history to the day before estimated pregnancy start date (i.e., LMP) and assisted reproductive history in a pre-pregnancy prior to pregnancy start date
Vaccination status	Influenza A, pneumococcal, and pertussis vaccine	Procedure code for vaccine administration	Vaccine administration will be assessed during current pregnancy
COVID-19-related health care utilization	Supplemental oxygen, high flow oxygen or non-invasive mechanical ventilation, invasive mechanical ventilation or ECMO	Supplemental oxygen has been shown to be undercaptured in claims	Recorded in inpatient settings and assessed by trimester periods or after COVID diagnosis depending on the study objective

*Time periods for evaluation of maternal baseline characteristics, at-risk and obstetric conditions, and other health utilization will be discussed during specifications development

Code lists developed for all variables (e.g., diagnoses, medications, and procedures) are provided in Appendix 1. Medication drug classes are provided and since code lists may need to be updated over time due to the rapid evolution of coding terminologies they will be extracted at the time of specifications review.

3.8. Data Analyses

For the two study aims to be implemented from the CONSIGN protocol, we will conduct the following analyses for each study objective, as outlined in Table 4.

Table 4. Analyses Plan

Objective	Cohorts	Cohort identification criteria	Outcome	Stratification	Estimator
1a	Pregnant patients with COVID-19	4 cohorts for pregnancies with COVID-19 diagnosis in pre-pregnancy or trimester periods	Medication groups	Trimester of pregnancy, age groups	3-month (trimester) prevalence and 95% CI for medication utilization
1b	Matched pregnant patients with and without COVID-19	3 matched cohorts for pregnancies with and without COVID-19 examined in specific trimester of pregnancy	Medication groups	Age groups	3-month prevalence of medication use before and after *COVID-19 diagnosis date*
1c	Matched pregnant and non-pregnant patients with COVID-19	3 matched cohorts for pregnant and non-pregnant people identified by COVID diagnosis in specific trimesters	Medication groups	Age groups	3-month prevalence of medication use before and after *COVID-19 diagnosis date*
2a	Pregnant patients with COVID-19	4 cohorts for pregnancies with COVID-19 diagnosis in pre-pregnancy or trimester periods	Severity of COVID-19, clinical outcomes (as measures of severity levels 1-5 or other measures)	Trimester of pregnancy, age groups	Proportion of COVID-19 severity levels 1-5 by trimester
2b	Severe and non-severe COVID-19 within matched pregnant and non-pregnant patients	3 matched cohorts for pregnant and non-pregnant people identified by COVID diagnosis in specific trimesters	Severity of COVID-19	Age groups	Proportion of severe (severity criteria levels 2-5) and non-severe (severity level 1) patients in matched pregnant and non-pregnant patients with COVID-19

	with COVID-19	Secondary analyses: 6 Sub-cohorts of *severe* (severity criteria levels 2-5) and non-severe (severity level 1) in matched pregnant and non-pregnant patients with COVID-19.	Medication groups		3-month prevalence of medication use before and after *COVID-19 diagnosis date* in severe and non-severe sub-cohorts of matched pregnant and non-pregnant patients with COVID-19

Descriptive analyses will be conducted for study cohorts identified in each study objective characterizing the maternal baseline characteristics, pre-existing/at-risk conditions, obstetric conditions, and COVID-19 related healthcare utilization. Frequency tables including counts and proportions for these conditions will be generated.

Additionally, in study objectives 2a and 2b, assessing COVID-19 severity among pregnant patients with COVID-19, hospitalizations will be categorized based on the primary diagnosis:

- Hospitalization due to COVID-19 (no obstetric reason)
- Hospitalization with obstetric reasons and COVID-19
- Hospitalization due to obstetric reasons without COVID-19

3.8.1 Analytical approach - Study objective 1a

Study Question: To what extent do patients with COVID-19 in pregnancy use medication (overall and by type) during pregnancy?

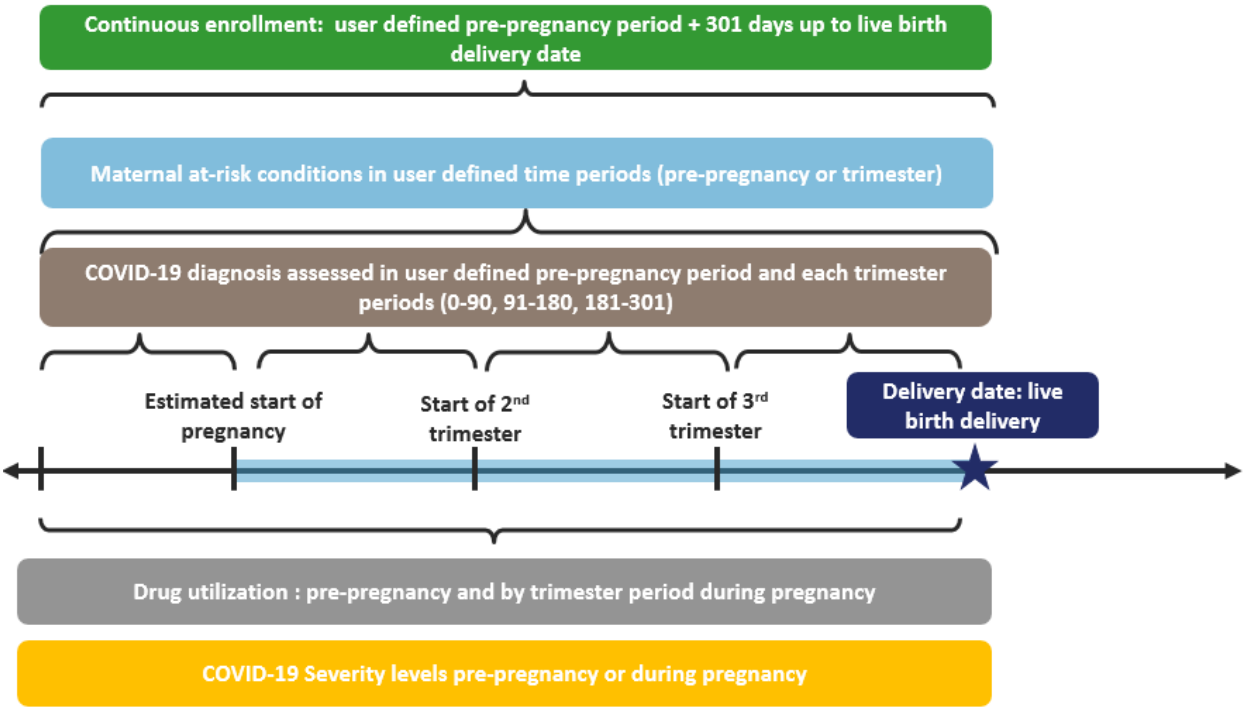
Study population will include pregnant patients with live-birth delivery on or after January 1, 2020 and had a diagnosis of COVID-19 during pregnancy. Four separate cohorts will be defined depending on COVID-19 diagnosis identified during a specified pre-pregnancy period (such as 3 or 6 months) and time periods corresponding to trimesters of pregnancy (0-90, 91-180, 181-301 days). Please refer to Figure 1 for criteria used for study population identification.

Medications will be identified using NDC or HCPCS codes and classified into groups specified in Section C.4. Medication utilization will be described for the *4 pregnancy cohorts identified with COVID-19* by presenting counts and 3-month (trimester) prevalence of medications used during pregnancy estimated as:

> number of pregnancies with COVID-19 exposed to specific medications groups in a given trimester of pregnancy/total eligible pregnancies with COVID-19 in same trimester period.

Medication utilization will be further categorized by age group and trimester of pregnancy. Prevalence of chronic at-risk conditions and trends in pregnancies diagnosed with COVID-19 by geographic region and calendar-month periods will be described.

Figure 1. Study Design for Cohort Identification in Objective 1a



3.8.2 Analytical approach - Study objective 2a

Study Question: To what extent do patients with COVID-19 in pregnancy have severe COVID-19 disease, when taking into account trimester, as well as other key factors?

Study population will include pregnant patients with COVID-19 and prevalence of COVID-19 cases meeting each severity level will be described as defined in Section C.6.

Pregnancies satisfying the highest level of COVID-19 severity will be assessed in the same trimester periods of COVID-19 diagnosis or in the trimester after the COVID-19 diagnosis. We will describe counts and proportion of COVID-19 severity by trimester in the *4 pregnant cohorts with COVID-19 diagnosis* identified in Objective 1a. (Figure 1). Stratification of COVID severity by age group will be assessed. Further stratification of COVID-19 severity by calendar month period will be considered if feasible to capture likely changes in clinical care and medication use as clinicians gained more experience treating COVID-19 patients.

The proportion of patients with COVID-19 clinical outcomes (as measures of severity levels 1-5 or other measures) during pregnancy will be estimated as the number of pregnancies satisfying the highest COVID-19 severity level in a given trimester of pregnancy/total eligible pregnancies with COVID-19 diagnosis in same trimester period.

3.8.3 Analytical approach - Study objective 1b

Study Question: Is medication use (overall and by type) among patients with COVID-19 different compared to patients without COVID-19 in pregnancy when taking into account trimester, severity of disease, and key confounders?

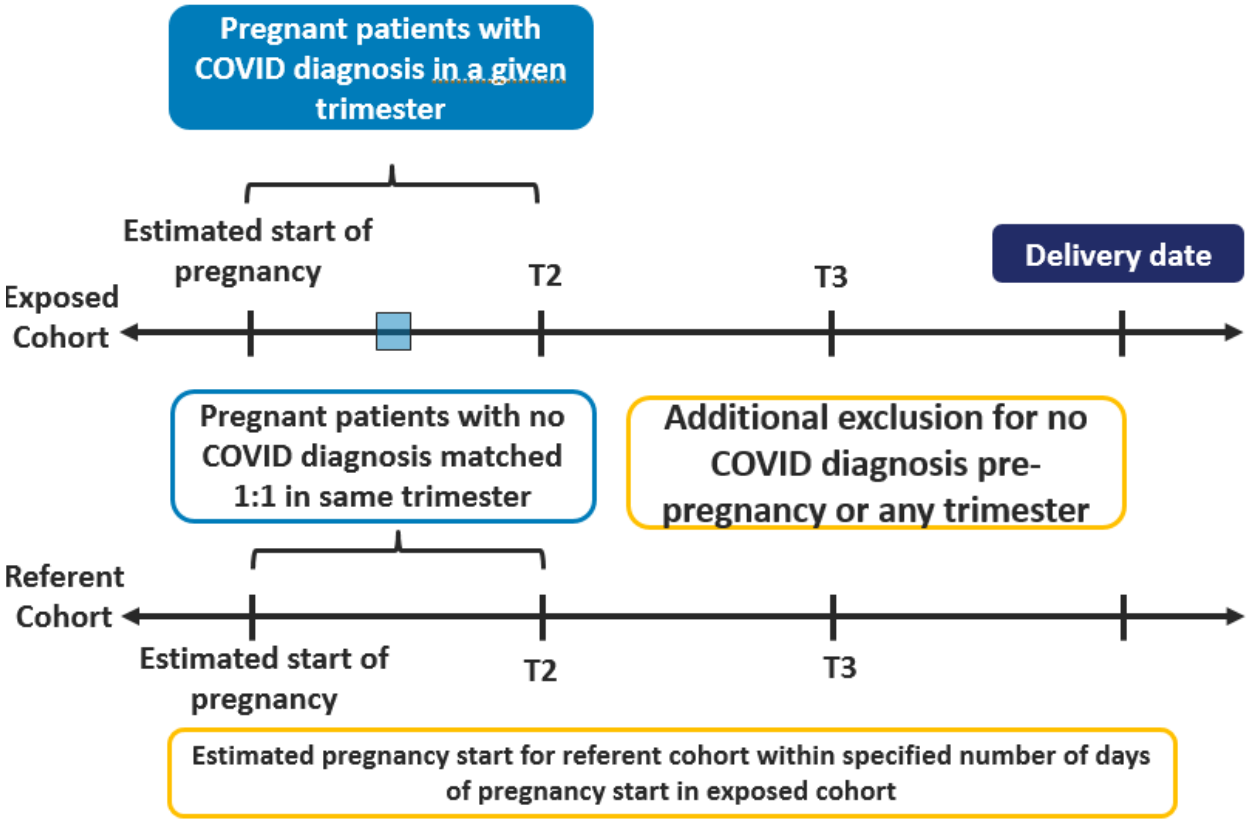
Study population: Pregnant patients with live-birth delivery on or after January 1, 2020 diagnosed with COVID-19 will be matched to pregnant patients not diagnosed with COVID-19 during pregnancy on characteristics including age group, at-risk conditions, and geographic region. Covariates to be included in the propensity score model will be discussed at the time of analysis.

Figure 2 shows the implementation of the 1:1 matching of COVID-19 exposed and unexposed pregnancies: a pregnant patient diagnosed with COVID-19 in first trimester (exposure window) will be matched to pregnant patient without COVID during the entire pregnancy period. The index date will be date of COVID-19 diagnosis. We will require that the estimated pregnancy start for the referent pregnant cohort without COVID-19 is within a specified time window (for e.g., 30 days) of the estimated pregnancy start in exposed pregnant cohort with COVID-19 to ensure we are comparing the medication use in these cohorts during the same calendar time.

For the referent pregnant cohort without COVID-19, additional exclusion criteria will be applied requiring no COVID-19 diagnosis was observed during any trimester (i.e. for the entire pregnancy period) and user specified pre-pregnancy period. For the pregnant exposed cohort with COVID-19, COVID-19 diagnosis will be examined in relevant exposure window (first, second, or third trimester).

Three matched cohorts for pregnancies with and without COVID-19 will be created with COVID-19 diagnosis assessed in different trimester periods. Depending on counts of patients with COVID-19 identified during the pre-pregnancy period, we will identify matched cohorts for pregnancies with COVID-19 during pre-pregnancy and those without COVID-19 in this objective.

Figure 2. Study Design for Cohort Identificaton in Objective 1b



Prevalence of medication use in the 3 months prior to and in the 3 months after **COVID-19 diagnosis date** will be computed for matched pregnant cohorts with and without COVID-19 depending on timing of COVID diagnosis in trimester periods. Since the referent cohort has no COVID diagnosis, we will describe the medication use in 3 months prior or after COVID-19 diagnosis date identified in the exposed pregnant cohort with COVID-19.

3.8.4 Analytical approach - Study objective 1c

Study Question: Is medication use (overall, by type) among pregnant patients with COVID-19 different compared to medication use among non-pregnant patients of reproductive age with COVID-19, when taking into account trimester, severity of disease, and key confounders?

Study population: Pregnant patients diagnosed with COVID-19 will be matched to non-pregnant patients assigned as females with COVID-19 on age group, at-risk conditions, or geographic region. *Three matched pregnant and non-pregnant cohorts* will be created with COVID-19 diagnosis assessed in different trimester periods and additional matched cohorts for pregnant and non-pregnant patients with COVID-19 during pre-pregnancy period will be considered if feasible.

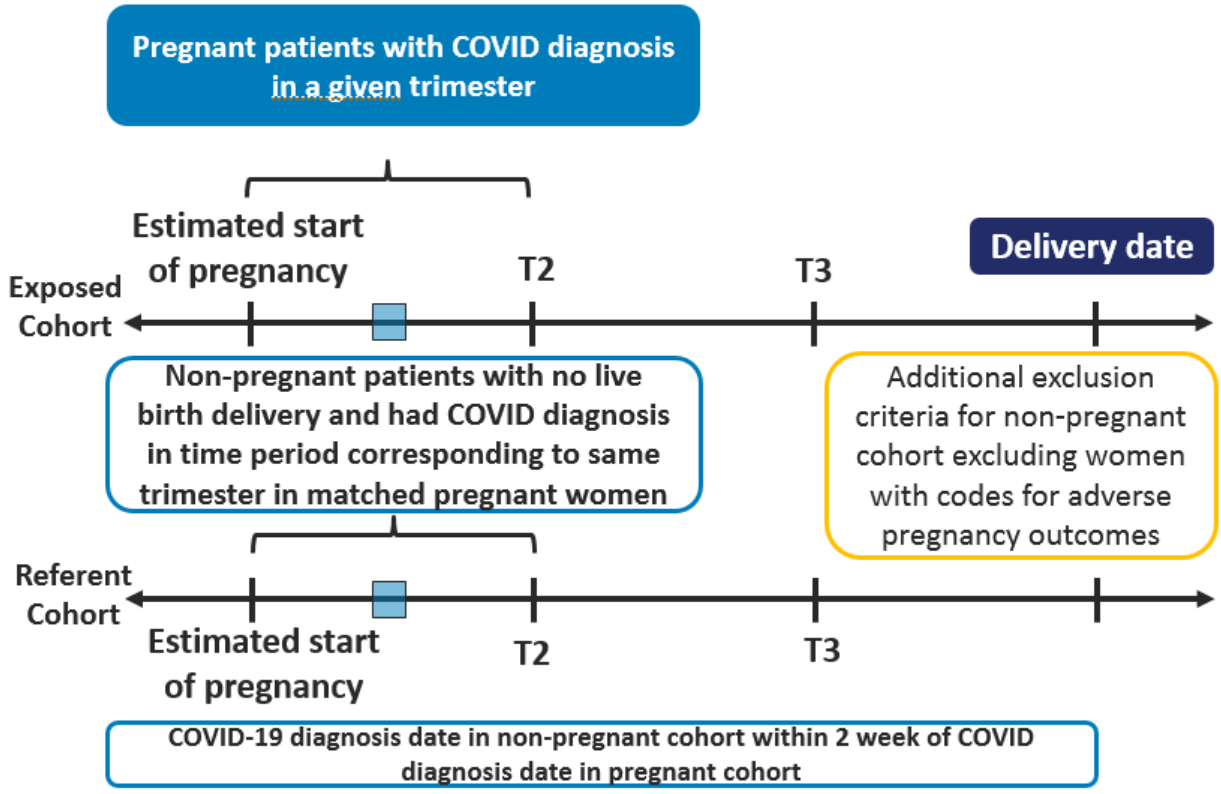
The non-pregnant cohort will include patients assigned as females without live-birth delivery diagnosed with COVID-19 identified during the same time period as the corresponding matched pregnant patient, were the same age (in years), and had first continuous enrollment period that

overlapped the pregnancy period of the matched pregnant patient. Further, pregnancies resulting in other pregnancy outcomes such as stillbirth, spontaneous abortions may inadvertently be included in the referent non-pregnant cohort hence additional exclusion will be specified to exclude pregnancies resulting in other pregnancy outcomes from the non-pregnant cohort.

The prevalence of medication use will be described in the 3 months prior to and in the 3 months after COVID-19 diagnosis date for the matched pregnant and non-pregnant cohorts with COVID-19. In order to ensure that medication use before and after COVID-19 diagnosis is assessed during the same time in pregnant and non-pregnant cohort with COVID-19, we will require that COVID-19 diagnosis date in non-pregnant cohort is observed within 2 weeks of COVID-19 diagnosis date in the pregnant cohort.

We will also estimate the 3 monthly prevalence of medications used for treatment of COVID-19 depending on the utilization observed for these medications before and after COVID-19 diagnosis dates in matched pregnant and non-pregnant patients with COVID-19. Figure 3 shows the implementation of the 1:1 matching of the COVID-19 pregnant and non-pregnant cohorts.

Figure 3. Study Design for Cohort Identification in Objective 1c



3.8.5 Analytical approach - Study objective 2b

Study Question: Do patients with COVID-19 in pregnancy have increased risk of severe COVID-19 compared to non-pregnant patients of reproductive age with COVID-19?

Study population: Similar to objective 1c we will identify pregnant patients diagnosed with COVID-19 matched to non-pregnant patients assigned as females with COVID-19 on age group, and at-risk conditions, or geographic region. *Three matched pregnant and non-pregnant cohorts* will be created with COVID-19 diagnosis assessed in different trimester periods and we will require the COVID-19 diagnosis date in non-pregnant cohort is observed within 2 weeks of COVID-19 diagnosis in the matched pregnant cohort with COVID-19.

For comparing COVID-19 severity in pregnant and non-pregnant patients with COVID-19, we will estimate proportion of patients with severe (severity criteria levels 2-5) and non-severe (severity level 1) patients assessed in the same trimester periods of COVID-19 diagnosis. Further, we will estimate proportion of severe and non-severe patients in pregnant and non-pregnant patients with COVID-19 stratified by age.

As a secondary analyses, we aim to describe medication use before and after COVID-19 diagnosis in 6 sub-cohorts of *severe* and non-severe patients withCOVID-19 in matched pregnant and non-pregnant population. We will describe the prevalence of medication use in the 3 months prior to and in the 3 months after **COVID-19 diagnosis date** estimated in the matched severe and non-severe pregnant and non-pregnant cohorts with COVID-19. This will help understand whether medication use varies by pregnancy status in patients with severe and non-severe COVID-19.

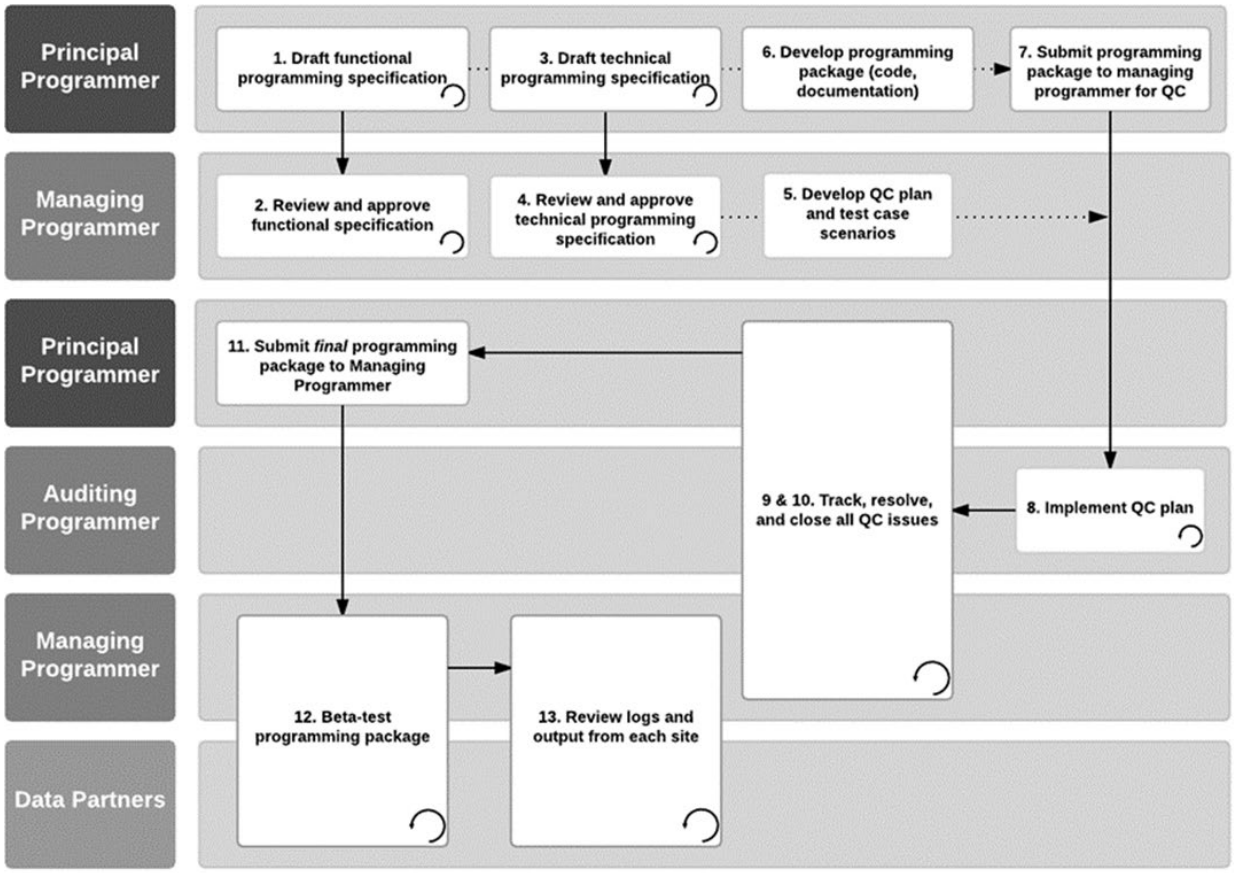
3.9. Data management and quality control

The SOC will be responsible for writing and distributing SAS programs that can be used to evaluate data from participating Data Partners. The distributed 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 SOC will maintain 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., Federal Information Security Management Act [FISMA], Health Insurance Portability and Accountability Act of 1996), specifically FISMA compliant for FISMA security controls as specified in the National Institute of Standards and Technology (NIST) Special Publication 800-53 (NIST and Joint Task Force Transformation Initiative 2017).

Sentinel's standard data quality assurance (QA) procedures will not be usable for all data elements and data sources since those QA procedures are conducted on data formatted in the Sentinel Common Data Model (SCDM). Thus, ad hoc QA procedures will be developed for specific studies requiring the use of such data elements or data sources. The standard Sentinel quality assurance approach, which may be usable for other study questions, assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions, examines logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across Data Partners. Data curation will be consistent with guidance set forth by the FDA in its current recommendations for data quality assurance, specifically, "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (Guidance), section IV.E "Best Practices – Data Sources: QA and Quality Control," published in May 2013 (FDA 2013).

In addition to quality assurance of data elements, the SOC adopts standard SAS programming quality assurance and quality control processes to check SAS programs and deliverables. Figure 4 illustrates the Standard Operating Procedures for SAS programming quality assurance and quality control within the Sentinel System.

Figure 4. Standard Operating Procedures for SAS Programming Quality Assurance and Quality Control in the Sentinel System



(Circular arrow in some boxes indicates iterative process, incorporating feedback.)

3.10. Limitations to consider and methods to address

3.10.1. Misclassification

Misclassification of COVID-19 status is possible. Cases of COVID-19 identified in the member populations at the Data Partners may be missed because: 1) people with asymptomatic, very mild, or mild COVID-19 may not seek medical attention or testing; 2) COVID-19 patients may be unable to access SARS-CoV-2 testing or unwilling to undergo SARS-CoV-2 testing; or 3) false-negative SARS-CoV-2 assays may occur due to improper sampling procedures or test insensitivity. Conversely, non-COVID-19 cases may be misclassified as COVID-19 due to false-positive test results or ICD-10-CM COVID-19 diagnoses reflecting "rule out" diagnoses rather than true cases of COVID-19. We will examine pregnancies diagnosed with COVID-19 by calendar month and across geographic regions to address misclassification of COVID-19 cases that may have occurred due to accessibility to COVID-19 testing and surge in COVID-19 across different regions over time.

Validation of ICD-10-CM-based diagnostic coding algorithms estimated a PPV of 81%, based on a positive NAAT result for SARS-CoV-2 as the gold standard for confirmation. The sensitivity of the algorithm in identifying positive COVID-19 cases was around 95% for confirmed diagnoses.[4] However, the algorithm was validated in hospitalized COVID-19 and may not have similar sensitivity or specificity for COVID-19 patients diagnosed in outpatient setting.

There is also potential for misclassification regarding estimation of pregnancy start given that gestational age or preterm diagnosis codes will be used for determining pregnancy start. This will be especially important to consider when evaluating precise timing of medication use and diagnoses, such as COVID-19. The validated algorithm proposed to be used in our analyses has shown sensitivity of 98% and PPV of 91% in identifying term live birth deliveries and estimated gestational age was within 14 days for 77% of delvieries compared to gold standard gestational age obtained from the infants birth certificate files.[10] Pregnancy episodes that do not end in a live birth (e.g., stillbirth, termination, etc.) cannot be captured with the existing Sentinel live-birth pregnancy tool; however, we will exclude these pregnancy outcomes when identifying the non-pregnant cohort.

3.10.2. Issues in ascertaining medications used for COVID-19 during pregnancy:

Little is known about the treatment management of COVID-19 during pregnancy. Ascertainment of exposure to medications of interest by trimester will depend on the setting in which the medication is administered (e.g., hospital, ambulatory) and the type of drug. Outpatient dispensing data and encounter claims data will be used for determining the timing of treatment initiation based on dispensing dates and encounter dates. Inpatient treatments may not be captured in claims-based systems, and when they are captured, treatment timing may not be available. Integrated care delivery systems may include data from both settings. Further, there is potential time trend in clinical care and medication use during pregnancy as clinicians gained more experience treating COVID patients.

3.10.3. Issues with healthcare utilization variables:

During the COVID-19 pandemic, healthcare utilization variables, such as ambulatory encounters, emergency department visits, hospital admission, ICU admission, duration of ICU stay, and mechanical ventilation, might not appropriately classify patients' true disease severity. Health care utilization may be affected by state and local "stay at home" orders and local health care resource demand and supply and may vary by time, region, and even hospital in the same region. Surges in COVID-19 cases and shifting of the epidemic center as the pandemic continues will add more complexity to determining how the impact of the uncertainty of these variables can be adequately addressed in sensitivity analyses.

3.10.4. Generalizability

COVID-19 pregnancies identified in the proposed study may not be fully representative of the US population given we are planning to use data from a subset of Data Partners in the Sentinel Distributed Database providing COVID laboratory results information. For example, in commercial insurance data sources, publicly insured people may be underrepresented, and uninsured people are not represented. Further, we are identifying pregnancies resulting in live birth delivery and pregnancies having other pregnancy outcomes will not be captured.

4. Human subjects considerations

This Sentinel project is a public health surveillance activity conducted under the authority of the Food and Drug Administration and, accordingly, is not subject to Institutional Review Board oversight.[15, 16, 17]

5. References

1. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. Published online September 1, 2020:m3320. doi:10.1136/bmj.m3320

2. Ellington S. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–June 7, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69. doi:10.15585/mmwr.mm6925a1

3. Yin M-Z, Zhang L, Deng G-T, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection During Pregnancy In China: A Retrospective Cohort Study. *medRxiv*. Published online April 11, 2020:2020.04.07.20053744. doi:10.1101/2020.04.07.20053744

4. Validation of Hospitalized COVID-19 Detected from Claims-Based Algorithms. Sentinel Initiative. Published June 1, 2020. Accessed February 26, 2021. https://www.sentinelinitiative.org/methods-data-tools/methods/validation-hospitalized-covid-19-detected-claims-based-algorithms

5. Master Protocol Development: COVID-19 Natural History. Sentinel Initiative. Published June 4, 2020. Accessed February 16, 2021. https://www.sentinelinitiative.org/methods-data-tools/methods/master-protocol-development-covid-19-natural-history

6. CONSIGN study: COVID-19 infection and medicines in pregnancy- a multinational registry based study. European Network of Centres for Pharmacoepidemiology & Pharmacovigilance. Accessed February 16, 2021. http://www.encepp.eu/encepp/viewResource.htm?id=39439

7. Platt R, Brown JS, Robb M, et al. The FDA Sentinel Initiative - An Evolving National Resource. *N Engl J Med*. 2018;379(22):2091-2093. doi:10.1056/NEJMp1809643

8. Cheng MP, Papenburg J, Desjardins M, et al. Diagnostic Testing for Severe Acute Respiratory Syndrome–Related Coronavirus-2. *Ann Intern Med*. Published online April 13, 2020. doi:10.7326/M20-1301

9. Center for Disease Control and Prevention. ICD-10-CM Coding and Reporting Guidelines. April 1, 2020 through September 30, 2020. Accessed February 16, 2021. https://www.cdc.gov/nchs/data/icd/COVID-19-guidelines-final.pdf?fbclid=IwAR06h6zP8KkehNzjEqlpGvACzMBhP26Khp9WG1JqbfLUQpYOt_LCqwGVHxU

10. Li Q, Andrade SE, Cooper WO, et al. Validation of an algorithm to estimate gestational age in electronic health plan databases. *Pharmacoepidemiol Drug Saf*. 2013;22(5):524-532. doi:10.1002/pds.3407

11. Andrade SE, Toh S, Houstoun M, et al. Surveillance of Medication Use During Pregnancy in the Mini-Sentinel Program. *Matern Child Health J*. 2016;20(4):895-903. doi:10.1007/s10995-015-1878-8

12. Raebel MA, Ellis JL, Andrade SE. Evaluation of gestational age and admission date assumptions used to determine prenatal drug exposure from administrative data. *Pharmacoepidemiology and Drug Safety*. 2005;14(12):829-836. doi:10.1002/pds.1100

13. CDC. COVID-19. People with certain medical conditions. Centers for Disease Control and Prevention. Published February 11, 2020. Accessed February 22, 2021. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

14. Who's at higher risk from coronavirus (COVID-19). nhs.uk. Published June 2, 2020. Accessed February 22, 2021. https://www.nhs.uk/conditions/coronavirus-covid-19/people-at-higher-risk/whos-at-higher-risk-from-coronavirus/

15. Basic HHS Policy for Protection of Human Research Subjects, 45 CFR §46.102(l)(2). Accessed March 3, 2021. https://www.ecfr.gov/

16. Federal Policy for the Protection of Human Subjects, 82 Federal Register 7149, 7172, 7175-76. Published January 19, 2017. Accessed March 4, 2021. https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects

17. Rosati K, Jorgensen N, Soliz M, Evans BJ. Sentinel Initiative Principles and Policies: HIPAA and Common Rule Compliance in the Sentinel Initiative. Feb. 1, 2018. Available at: https://www.sentinelinitiative.org/sites/default/files/communications/publications-presentations/HIPAA-Common-Rule-Compliance-in-Sentinel-Initiative.pdf.

6. Appendix

Appendix 1: ICD-10-CM Algorithm for Gestational Age

The ICD-10 algorithm for gestational age incorporates codes for (1) gestational age in weekly increments from gestational week 20 through gestational week 42 or greater (codes Z3A20-Z3A49, referred to as the "Z codes"), (2) preterm delivery (other than the Z codes), and (3) postterm delivery (other than the Z codes). We identified ICD-10 codes for preterm delivery and postterm delivery by implementing forward-backward mapping of ICD-9-CM codes included in the initial version of the pregnancy tool. Of note, there are no codes equivalent to the Z codes in the ICD-9-CM coding scheme.

Priorities:

If multiple codes for specific weeks of gestation (Z codes), preterm delivery, and/or postterm delivery are available, the ICD-10 algorithm for gestational age prioritizes the following codes:

(1) **Codes that specify weeks of gestation, including all Z codes ranging from 20 weeks through >=42 weeks of gestation in one-week increments, and codes that indicate preterm delivery with weeks of gestation specified in one-week increments (other than Z codes)**. If multiple codes are observed, codes indicating longer gestational age are prioritized over those indicating shorter gestational age. We assume the approximate mid-point of the specified gestational age [e.g., 263 days (37 weeks and 4 days) for 37 weeks gestation].

(2) **Codes that indicate preterm delivery without specifying weeks of gestation.** If multiple codes are observed, codes with more specificity (e.g., preterm delivery, 2nd trimester of pregnancy or 'extreme immaturity') are prioritized over those with less specificity (e.g., preterm newborn, unspecified weeks of gestation). Further, codes indicating longer gestational age are prioritized over those indicating shorter gestational age.

(3) **Codes that indicate postterm delivery without specifying weeks of gestation.** If multiple codes are observed, codes indicating longer gestational age are prioritized over those indicating shorter gestational age.

If no codes for preterm or postterm delivery are observed, then the default assumption for gestational age is 273 days. However, this assumption is user specified and can be modified.

Gestational age and preterm/postterm codes used for estimation of pregnancy duration are provided in a separate appendix document.