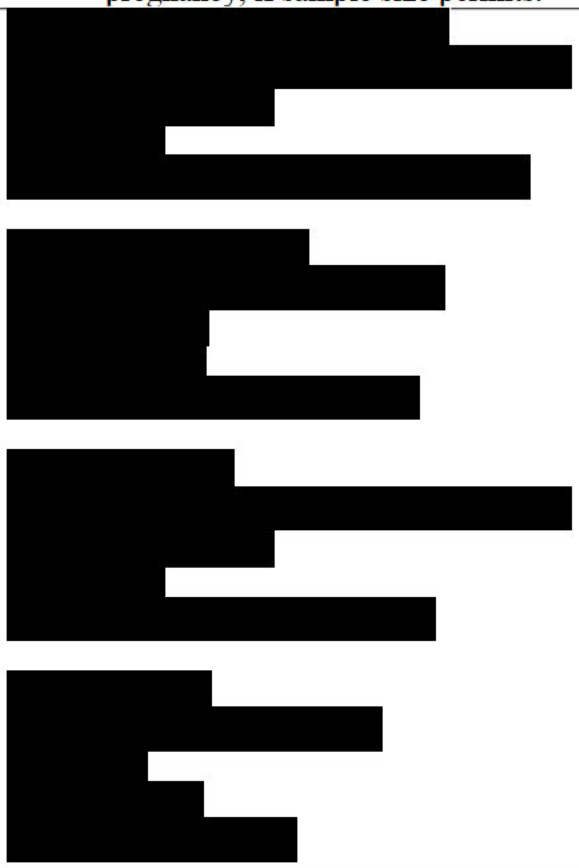
NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Post-Authorization Safety Study to Evaluate the Safety of Abrocitinib Exposure During Pregnancy in United States Healthcare Databases
Protocol number	B7451098
Protocol version identifier	1.0
Date	18 November 2022
European Union (EU) Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	Abrocitinib (PF-04965842)
Medicinal product	CIBINQO™

Research question and objectives	The study will describe and compare the adverse pregnancy and infant outcomes among women with moderate-to-severe atopic dermatitis (AD) who are exposed to abrocitinib during pregnancy and women with moderate-to-severe AD who are not exposed to abrocitinib during pregnancy.
	
	Primary objective:
	• To estimate the prevalence of adverse pregnancy and infant outcomes in women with moderate-to-severe AD who are exposed to abrocitinib during pregnancy and women with moderate-to-severe AD who are not exposed to abrocitinib during pregnancy, specifically:
	  ○ Major congenital malformations (MCMs; main outcome of interest)
	  ○ Other infant outcomes (preterm birth, small for gestational age [SGA])

	○ Pregnancy outcomes (stillbirths, spontaneous abortions) Secondary objective: • To compare the prevalence of MCMs, other infant outcomes (preterm birth, small for gestational age [SGA]), and adverse pregnancy outcomes (stillbirths, spontaneous abortions) between women with moderate-to-severe AD who are exposed to abrocitinib during pregnancy and women with moderate-to-severe AD who are not exposed to abrocitinib during pregnancy, if sample size permits.
Authors	

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Atopic Dermatitis
AE	Adverse Event
BBCIC	Biologics and Biosimilars Collective Intelligence Consortium
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CPT	Current Procedural Terminology
CSA	Clinical Study Agreement
CTS	Clinical Trial Service
DP	Data Partner
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EHR	Electronic Health Record
EU	European Union
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act
GPP	Good Pharmacoepidemiology Practice
HCPCS	Healthcare Common Procedure Coding System
HHR	Humana Healthcare Research
HPHC	Harvard Pilgrim Health Care
HPHCI	Harvard Pilgrim Health Care Institute
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IEC	Independent Ethics Committee
IL	Interleukin
IMEDS	Innovation in Medical Evidence Development and Surveillance
IRB	Institutional Review Board

JAK	Janus Kinase
LMP	Last Menstrual Period
MCM	Major Congenital Malformation
MEPREP	Medication Exposure in Pregnancy Risk Evaluation Program
NBDPS	National Birth Defects Prevention Study
NDC	National Drug Code
NIST	National Institute of Standards and Technology
OMOP	Observational Medical Outcomes Partnership
OTC	Over-the-counter
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PCORnet	Patient-Centered Clinical Research Network
PMR	Postmarketing requirement
PPV	Positive Predictive Value
QA	Quality Assurance
QC	Quality Control
QCSAP	Quality Control Statistical Analysis Plan
RR	Risk Ratio
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCDM	Sentinel Common Data Model
SGA	Small for Gestational Age
SOP	Standard Operating Procedure
US	United States
VSD	Vaccine Safety Datalink
YRR	Your Reporting Responsibility

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

4. ABSTRACT

Title: A Post-Authorization Safety Study to Evaluate the Safety of Abrocitinib Exposure During Pregnancy in United States Healthcare Databases

Version and Date of Protocol: Version 1.0, 18 November 2022

Names and Affiliations of Principal Investigators of the Protocol:
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Rationale and Background: Abrocitinib (CIBINQO™), an orally bioavailable small molecule, is a selective Janus Kinase (JAK) 1 inhibitor. Abrocitinib was approved in the United States (US) on 14 January 2022 and is indicated in the US for the treatment of adults with refractory, moderate-to-severe AD in patients whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.

The available safety data regarding abrocitinib use during pregnancy are limited. According to the US drug label, available data from pregnancies reported in clinical trials with abrocitinib are not sufficient to establish a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. However, abrocitinib exposure during pregnancy is likely to occur, so additional data are needed.

As part of the abrocitinib pharmacovigilance plan, a retrospective cohort study using secondary data will be conducted to monitor the safety of abrocitinib exposure during pregnancy in the post-approval setting. In particular, this study will describe and assess the risk of adverse pregnancy and infant outcomes in women with moderate-to-severe AD exposed to abrocitinib during pregnancy compared to women with moderate-to-severe AD who are not exposed to abrocitinib, but may be treated with other chronic systemic therapies, during pregnancy. The specific outcomes of interest will be MCMs (main outcome of interest), preterm birth, SGA, spontaneous abortions, and stillbirths.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a postmarketing requirement (PMR) to the U.S. Food and Drug Administration (FDA).

Research Question and Objectives: The objective of this study is to describe and compare the adverse pregnancy and infant outcomes among women with moderate-to-severe AD who are exposed to abrocitinib (but may be concomitantly treated with other chronic systemic therapies) during pregnancy and women with moderate-to-severe AD who are not exposed to abrocitinib (but may be treated with other chronic systemic therapies) during pregnancy.

Primary objective:

- To estimate the prevalence of adverse pregnancy and infant outcomes in women with moderate-to-severe AD who are exposed to abrocitinib during pregnancy and women

with moderate-to-severe AD who are not exposed to abrocitinib during pregnancy, specifically:

1. MCMs (main outcome of interest)
2. Other infant outcomes (preterm birth, SGA)
3. Pregnancy outcomes (stillbirths, spontaneous abortions)

Secondary objective:

- To compare the prevalence of MCMs, other infant outcomes (preterm birth, SGA), and adverse pregnancy outcomes (stillbirths, spontaneous abortions) between women with moderate-to-severe AD who are exposed to abrocitinib during pregnancy and women with moderate-to-severe AD who are not exposed to abrocitinib during pregnancy, if sample size permits.

Study Design: This US population-based, non-interventional, cohort study will evaluate the risk of adverse pregnancy and infant outcomes among women with moderate-to-severe AD who are exposed to abrocitinib during pregnancy compared to those unexposed during pregnancy. Pregnancies with start dates occurring during the period 14 January 2022 to Q4 2025, and infants born to the women, will be included. The main outcome of interest will be MCMs. Additional outcomes of interest include other adverse infant outcomes (preterm birth, SGA) and pregnancy outcomes (stillbirth, spontaneous abortion).

Population: The study population will include singleton pregnancies among women 12 to 49 years of age diagnosed with moderate-to-severe AD who are members of participating Sentinel Data Partners (DPs). Additional eligibility criteria will include at least 183 days of continuous enrollment in the medical and pharmacy claims prior to the start of pregnancy through the delivery date/pregnancy outcome, with gaps of up to 45 days in coverage being permitted.

Pregnancies for which the woman was exposed to a medication(s) that presents a known increased risk for fetal malformations or those that resulted in an infant identified with a chromosomal or genetic anomaly will be excluded. Ectopic pregnancies, molar pregnancies, or induced abortions, as well as multigestation (e.g., twin) pregnancies will also be excluded.

Variables: The exposed group will include women with moderate-to-severe AD who are exposed to abrocitinib (but may be concomitantly treated with other chronic systemic therapies) during pregnancy. Women with at least 1 day supply of abrocitinib during the pregnancy period will be classified in the exposed group. The comparator group will include women with moderate-to-severe AD who are unexposed to abrocitinib (but may be treated with other chronic systemic therapies) during pregnancy.

The outcomes of interest are MCMs (main outcome of interest), preterm birth, SGA, spontaneous abortions, and stillbirths. Endpoint adjudication will be conducted to confirm occurrences of MCMs.

Information about abrocitinib and other AD treatment exposures, demographics, maternal age, pregnancy start and trimester (estimated using claims-based algorithms), maternal comorbidities, obstetric history, lifestyle factors, healthcare utilization, pregnancy outcomes (live birth, stillbirth, spontaneous abortion) and infant/birth outcomes (MCMs, preterm birth, SGA) will be collected from the healthcare electronic databases (health plan enrollment and claims data). The claims data will be supplemented with medical records to confirm MCMs. All conditions used to define the population, exposures, comorbidities, obstetric history, lifestyle factors, and outcomes will be identified using validated algorithms, where available.

Data Sources: The study will be conducted using data provided by US DPs in the FDA's Sentinel System. The study will use curated data that are formatted to the FDA Sentinel Common Data Model (SCDM) specifications, which permits the use of publicly available Sentinel analytic tools. Health plan claims data included in the SCDM will be supplemented with medical records to confirm occurrences of MCMs.

Study Size: For the primary objective, all eligible abrocitinib-exposed pregnancies and corresponding matched unexposed pregnancies will be included. For the secondary objective, assuming a 1:3 ratio of abrocitinib-exposed to unexposed, a type 1 error of 0.05, and a target risk ratio of 2.0 for the main outcome (MCMs), 516 live birth pregnancies linked to infant records for the abrocitinib-exposed group and 1,548 live birth pregnancies from the unexposed group will achieve 80% power in the comparative analysis.

Data Analysis: First, propensity score matching (1:3 matching ratio) will occur within each DP. Within the propensity score matched population, the prevalence of the main outcome (MCMs) and additional outcomes, including other adverse infant outcomes (preterm birth, and SGA) and pregnancy outcomes (live birth, stillbirth, and spontaneous abortion), and their 95% confidence intervals (CIs) will be calculated among eligible abrocitinib-exposed and the corresponding matched unexposed pregnancies. Based on sample size estimation for the minimum number of live birth pregnancies needed to ensure 80% power for comparative analysis of the main outcome (MCMs), a comparative analysis of the risk of pregnancy and infant outcomes of abrocitinib-exposed versus unexposed pregnancies will be conducted if there are at least 516 live birth pregnancies in the abrocitinib-exposed group. The Mantel-Haenszel Chi-square test or Fisher exact test (univariate analysis), whichever appropriate, will be employed to compare the prevalence of the main outcome (MCMs) between eligible live birth pregnancies among women with moderate-to-severe AD who were exposed to abrocitinib during pregnancy and those who were not exposed to abrocitinib during pregnancy within the propensity score matched population. Multivariable conditional logistic regression will be conducted to adjust for potential residual confounding after matching if there is statistical significance in univariate analysis. Similar methods will be used for each of the secondary outcomes (i.e., preterm birth, SGA, stillbirths, and spontaneous abortions).

All analyses will be stratified by stage of pregnancy (early versus mid-to-late pregnancy).

Milestones: A final study report will be submitted to the FDA by 30 June 2028.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Final study protocol	31 December 2022
Registration in the EU PAS register	Prior to the start of data collection
Start of data collection [a]	01 March 2024
End of data collection [b]	01 December 2027
Final study report to the FDA	30 June 2028

[a] For studies with secondary data collection, the start of data collection is defined as the planned date for starting data extraction for the purposes of the primary analysis.

[b] For studies with secondary data collection, the end of data collection is defined as the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

7. RATIONALE AND BACKGROUND

Abrocitinib (CIBINQO®), an orally bioavailable small molecule, is a selective JAK1 inhibitor. The inhibition of JAK1 is thought to modulate multiple cytokines involved in the pathophysiology of AD, including interleukin (IL)-4, IL-13, IL-31, IL-22, and interferon gamma. Abrocitinib, oral film-coated tablets containing either 100 or 200 mg, was approved in the US on 14 January 2022 and is indicated in the US for the treatment of adults with refractory, moderate-to-severe AD in patients whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable (CIBINQO Prescribing Information, 2022).

AD is a common, chronic skin condition characterized by inflammation of the skin and skin barrier defects. AD lesions are characterized by erythema, itching, induration/papulation, and oozing/crusting (Hanifin & Reed, 2007; Bieber, 2012). Manifestations of AD typically appear early in life, and often precede other allergic diseases, such as asthma or allergic rhinitis. The prevalence of AD is estimated to be 15% to 30% in children, and 2% to 10% in adults (Oszukowska et al, 2015), presenting a significant burden on healthcare resources and patients' quality of life.

AD is the most frequent general skin disease that occurs during pregnancy, as it can be triggered, reactivated, and/or exacerbated by pregnancy (Vestergaard et al, 2019). New onset AD during pregnancy is estimated to be responsible for 60% to 80% of cases among women (Nasca et al, 2020). It is also estimated that 18% to 52% of women with AD will experience worsening of their symptoms during pregnancy (Kemmett & Tidman,1991; Rakita et al, 2022). Although rare, AD is directly associated with an increased risk of certain complications during pregnancy, including eczema herpeticum, staphylococcus aureas infections, premature rupture of membranes, and staphylococcal neonatal septicemia (Gurvits & Nord, 2011; Hamann et al, 2018). AD is also associated with increased maternal stress and sleep deprivation, which may also indirectly increase the risk for pregnancy complications (Vestergaard et al, 2019). There is no evidence that AD is associated with an increased risk of stillbirth, SGA, or preterm birth (Trønnes et al, 2014).

During pregnancy, topical treatments (including corticosteroids, calcineurin inhibitors, crisaborole, and ultraviolet therapy) tend to be the preferred therapies to treat AD, and are considered to be safe for the fetus (Vestergaard et al, 2019; Heilskov et al, 2020). Systemic therapies (such as oral corticosteroids, cyclosporin A, and azathioprine) are only recommended with specialist oversight in the event that symptoms do not respond to first-line therapy. However, the evidence for the safety of systemic therapies is considered weak (Vestergaard et al, 2019; Heilskov et al, 2020). Two other systemic therapies (methotrexate and mycophenolate mofetil) are contraindicated during pregnancy, due to strong documented associations with fetal malformations (Heilskov et al, 2020). One of the newest therapies (dupilumab) is not currently recommended during pregnancy, due to an unknown safety profile. However, several recent case studies have reported no adverse pregnancy outcomes associated with dupilumab use (Bosma et al, 2021; Lobo et al, 2021; Akhtar et al, 2022).

The available safety data regarding abrocitinib use during pregnancy are limited. In animal reproduction studies, oral administration of abrocitinib to pregnant rats and rabbits during

organogenesis at exposure 14 or 5 times the maximum recommended human dose based on AUC comparison, respectively, resulted in maternal dystocia and skeletal variations in rats and no adverse effects in rabbits. No fetal malformations were observed (CIBINQO Prescribing Information, 2022). In clinical trials, pregnant and breastfeeding women, and women planning to become pregnant or to breastfeed, were excluded. According to the US drug label, available data from pregnancies reported in clinical trials with abrocitinib are not sufficient to establish a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes (CIBINQO Prescribing Information, 2022). However, abrocitinib exposure is likely to occur given the high rates of occurrence of AD in pregnancy. Since the available data are insufficient for characterizing the associated risk in pregnant women, additional data are needed.

As part of the abrocitinib pharmacovigilance plan, a retrospective cohort study using secondary data will be conducted to monitor the safety of abrocitinib exposure during pregnancy in the post-approval setting in accordance with the FDA 2019 Guidance for Industry: Postapproval Pregnancy Safety Studies (FDA, 2019). In particular, this study will describe and assess the risk of adverse pregnancy and infant outcomes in women with moderate-to-severe AD exposed to abrocitinib during pregnancy (but may be concomitantly treated with other chronic systemic therapies) compared to women with moderate-to-severe AD who are not exposed to abrocitinib, but may be treated with other chronic systemic therapies, during pregnancy. The specific outcomes of interest will be MCMs (main outcome of interest), preterm birth, SGA, spontaneous abortions, and stillbirths.

This non-interventional study is designated as a PASS and is a PMR to the U.S. FDA.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe and compare the adverse pregnancy and infant outcomes among women with moderate-to-severe AD who are exposed to abrocitinib (but may be concomitantly treated with other chronic systemic therapies) during pregnancy and women with moderate-to-severe AD who are not exposed to abrocitinib (but may be treated with other chronic systemic therapies) during pregnancy.

Primary objective:

- To estimate the prevalence of adverse pregnancy and infant outcomes in women with moderate-to-severe AD who are exposed to abrocitinib during pregnancy and women with moderate-to-severe AD who are not exposed to abrocitinib during pregnancy, specifically:

    1. MCMs (main outcome of interest)
    2. Other infant outcomes (preterm birth, SGA)
    3. Pregnancy outcomes (stillbirths, spontaneous abortions)

Secondary objective:

- To compare the prevalence of MCMs, other infant outcomes (preterm birth, SGA), and adverse pregnancy outcomes (stillbirths, spontaneous abortions) between women with moderate-to-severe AD who are exposed to abrocitinib during pregnancy and women with moderate-to-severe AD who are not exposed to abrocitinib during pregnancy, if sample size permits.

Refer to Section 9.3.2 for definitions of these outcomes (MCMs, preterm birth, SGA, spontaneous abortions, and stillbirths).

9. RESEARCH METHODS

9.1. Study Design

A US population-based, non-interventional cohort study will be performed to identify and assess pregnancy and infant outcomes from abrocitinib-exposed pregnancies among women ages 12 to 49 years with moderate-to-severe AD. A comparison group of pregnancies among women with moderate-to-severe-AD who were not exposed to abrocitinib during pregnancy will be included as the reference group. It is possible that women in the abrocitinib-exposed and comparator groups may be treated with other chronic systemic therapies. The main outcome of interest will be MCMs. Additional outcomes of interest include other adverse infant outcomes (preterm birth, SGA) and pregnancy outcomes (stillbirth, spontaneous abortion). The study will be conducted using health data held by the DPs that participate in the FDA's Sentinel System (described in Section 9.4).

The study period for identification of exposed and unexposed pregnancies for the cohort study will be 14 January 2022 to Q4 2025. The pregnancy outcomes of interest (stillbirth, spontaneous abortion) will be evaluated among pregnancies that result in a live birth, stillbirth, or spontaneous abortion. Women will be followed from the start of pregnancy through the date of delivery/pregnancy outcome. MCMs and additional infant outcomes (preterm birth, SGA) will be assessed in the subset of pregnancies resulting in a live birth for which the mother is linked to an infant. Since infant outcomes are generally captured in the infant's health plan claims, the mothers/pregnancies will be linked to the corresponding infants (details in Section 9.2.1.1). Infants born from these pregnancies (exposed and unexposed) will be followed for up to one year of age (or until death, end of continuous health plan enrollment, or end of data collection) for assessment of MCMs, the main outcome of interest.

MCMs identified from this study will be validated by board certified teratologists. The teratologists will review the medical charts of each potential case and be blinded to treatment received during pregnancy. Additional details on the adjudication process will be available in a separate Adjudication Charter. Only validated MCM cases will be used for the descriptive or comparative analyses.

9.2. Setting

The potential participating Sentinel DPs are discussed in Section 9.4. All DPs have access to electronic healthcare data (including insurance claims data and/or electronic health record

[EHR] data) that will be used to identify the study cohorts, outcomes, and covariate information.

9.2.1. Study Population

The study population will include singleton pregnancies among women who are diagnosed with AD, with pregnancy start dates occurring during the period 14 January 2022 to Q4 2025 (see Section 9.2.1.3 for description of the algorithm for estimation of pregnancy start dates). Pregnant women with moderate-to-severe AD will be identified using secondary data from the participating Sentinel DPs.

9.2.1.1. Inclusion Criteria

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

1. Women aged 12 to 49 years old at the start of pregnancy.

2. ≥1 AD diagnosis from the 183 days prior to the start of pregnancy through the date of delivery/pregnancy outcome.

    a. AD diagnosis defined as the presence of International Classification of Diseases, 10th revision (ICD-10) diagnosis code L20.xx in an inpatient and/or outpatient setting.

3. Moderate-to-severe AD, defined as ≥1 dispensing/administration of the following treatments for AD: abrocitinib, phototherapy, dupilumab, systemic corticosteroids, or other systemic immunosuppressants (such as cyclosporine, tralokinumab, upadacitinib) in the 183 days prior to the start of pregnancy. Receipt of systemic therapies has been used in algorithms to define moderate-to-severe AD in prior claims-based studies (Eichenfield et al, 2020; Shrestha et al, 2017; Drucker et al, 2018).

4. At least 183 days of continuous enrollment in the medical and pharmacy claims prior to the start of pregnancy through the date of delivery/pregnancy outcome, with gaps of up to 45 days in coverage being permitted. The 183-day pre-pregnancy period was chosen to allow identification of moderate-to-severe AD, as well as potential confounders of interest (Section 9.3.3). In Sentinel projects, gaps of 45 days or less in health plan enrollment are typically considered administrative gaps (and not lapses in health plan coverage) and ignored.

For analyses evaluating infant outcomes, the cohort will include pregnancies resulting in live births for which the mother is linked to an infant. Each Sentinel DP will be responsible for linking mothers to infants using all available local data resources. Algorithms linking mothers to infants will vary across DPs, generally looking for equivalent health plan subscriber numbers, delivery dates and dates of birth, and shared names and addresses. Sentinel DPs are able to link approximately 74% of their infants to their mothers. Additional

details on the mother-infant linkage process in Sentinel are available elsewhere (Sentinel Initiative, 2018).

For analyses evaluating pregnancy outcomes (stillbirth and spontaneous abortion), the cohort will include pregnancies resulting in a live birth, stillbirth, or spontaneous abortion.

9.2.1.2. Exclusion Criteria

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

1. Participant was exposed to a medication(s) that presents a known increased risk for fetal malformations in the 183 days prior to, or during pregnancy (see Appendix A).

2. Participant delivered an infant identified as having a chromosomal or genetic anomaly (Appendix B).

3. Ectopic pregnancies, molar pregnancies, or induced abortions.

4. Multigestation (e.g., twin) pregnancies.

9.2.1.3. Identification of Pregnancy Episodes and Gestational Age Assumptions

Sentinel investigators have developed publicly available tools to define medication exposures during pregnancy and comparatively assess pregnancy outcomes (Sentinel, 2018). These tools use a claims-based algorithm previously validated in the FDA-sponsored Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) (Andrade et al, 2012). The current study will use this algorithm to identify pregnancies ending in live births through identification of diagnosis and procedures codes listed in Appendix C. 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 the start of the pregnancy (i.e., estimated LMP) using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) indicative of weeks of gestation, as well as ICD-10-CM codes for preterm and post-term deliveries in the inpatient care setting (Appendix D). 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 D. 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, based upon gestational lengths reported in published studies (Davidoff et al, 2006; Margulis et al, 2013). The pregnancy start date (i.e., estimated LMP) is then calculated by subtracting the gestational age from the date of the live birth delivery.

Similar to the algorithm to determine live birth pregnancy episodes, ICD-10-CM and Current Procedural Terminology (CPT) codes will be used to identify non-live birth outcomes and calculate the length of the pregnancy episode, based upon published Sentinel (Andrade et al, 2021) and Vaccine Safety DataLink (VSD) studies (Naleway et al, 2021).

9.2.1.4. Abrocitinib-Exposed Group

Among the eligible cohort of live birth pregnancies linked to an infant and among the cohort of all eligible live birth and non-live birth pregnancies, women with moderate-to-severe AD exposed to at least 1 dose of abrocitinib during pregnancy will be identified. Dispensings of abrocitinib will be identified in the pharmacy dispensing data (National Drug Codes [NDC]; Section 9.3.1) during the period 183 days prior to pregnancy and during pregnancy. The 183 days prior to pregnancy (as opposed to only during pregnancy) are evaluated so that dispensings that begin prior to pregnancy but end during pregnancy are considered when defining exposure groups. Periods of exposure to abrocitinib will be determined from the dispense date through the period encompassing the days supply of medication dispensed. Overlapping periods of exposure will be combined to create single exposure episodes. Only pregnancies for which the periods of exposure overlap (i.e., days supply overlap) with the pregnancy period will be considered as exposed to abrocitinib. Exposure will be further categorized by stage of pregnancy: early pregnancy (first trimester of pregnancy, defined as 0 to <14 weeks gestation) or mid-to-late pregnancy (second or third trimesters, defined as 14 weeks gestation through the end of the pregnancy).

9.2.1.5. Comparison (Unexposed) Group

Pregnancies among women with moderate-to-severe AD who were not exposed to abrocitinib (but may be treated with other chronic systemic therapies) during pregnancy will be selected as a comparator with a 3:1 matching ratio to the pregnancies among women who were exposed to abrocitinib.

Exposed and unexposed pregnancies will be matched according to DP, maternal age at the start of pregnancy (±5 years), start date of the pregnancy period (±90 days), and the propensity score (see Section 9.3.3 for variables to be evaluated for inclusion in the propensity score). In addition, unexposed pregnancies must have been pregnant/reached the week of gestational age of the exposed pregnancy (i.e., when exposure initially occurred) without an adverse event (AE) (i.e., spontaneous abortion or stillbirth).

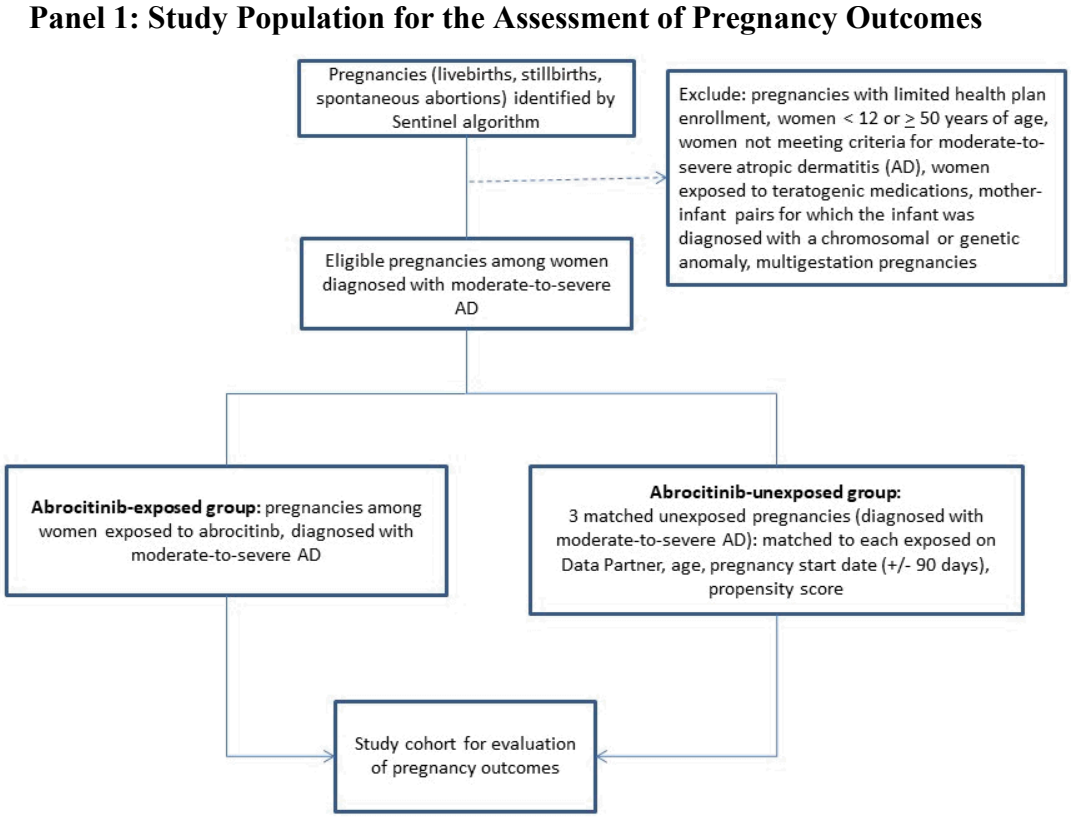
Matching with a propensity score will minimize confounding bias due to differences between the abrocitinib-exposed and comparator unexposed group. Propensity score matching is discussed below (Section 9.7.1). Matching on DP, maternal age, and the start date of the pregnancy period, will control for DP differences in abrocitinib use, age effects, and potential secular trends in abrocitinib use and obstetric outcomes.

This matching ratio of 1:3 was chosen because it increases precision of analysis (compared to a matching ratio of 1:1). Matching will be conducted separately for the eligible cohort of live birth pregnancies linked to an infant and among the cohort of all eligible pregnancies (live births, stillbirths, and spontaneous abortions).

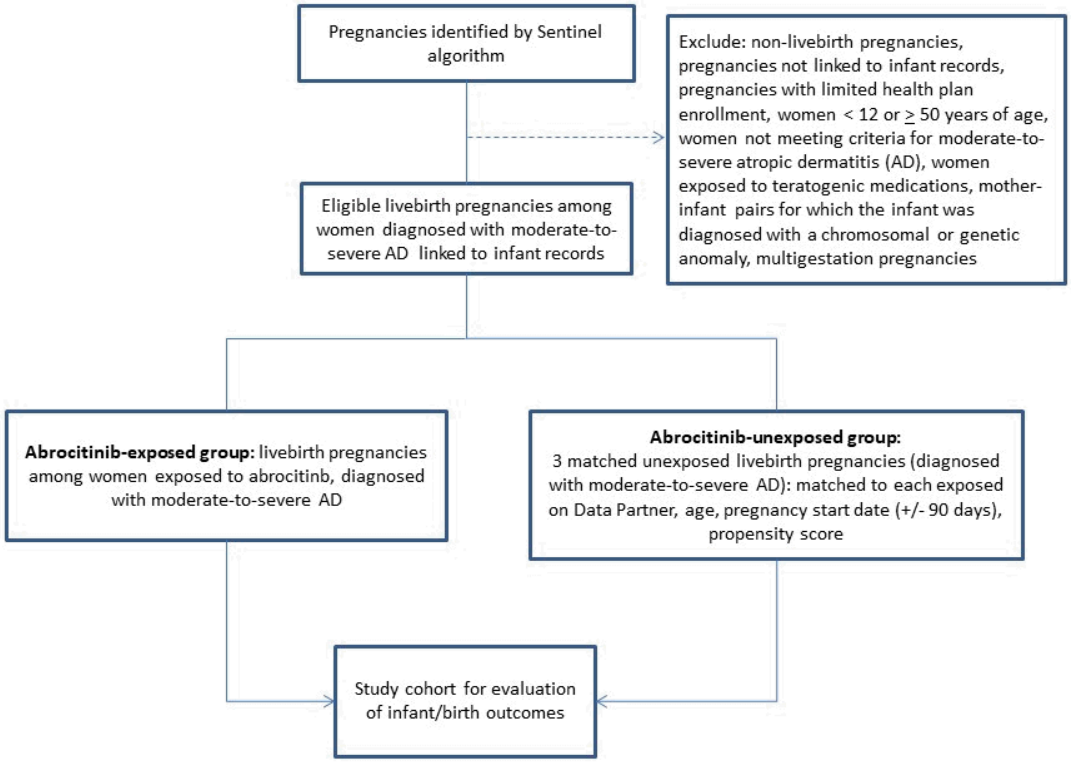
The Statistical Analysis Plan (SAP) will describe an alternative matching plan (e.g., matching factors) should the proposed matching plan perform poorly in practice (i.e., many unmatched abrocitinib-exposed pregnancies would be excluded). Alternative methods (e.g., inverse probability of treatment weights) will also be considered.

For each of these study samples, the unit of analysis is a pregnancy episode (Figure 1).

Figure 1. Study schema on study populations for the assessment of pregnancy and infant outcomes



Panel 2: Study Population for the Assessment of Infant Outcomes



9.3. Variables

9.3.1. Exposure

Exposure to abrocitinib will be identified using the outpatient pharmacy dispensing file by means of NDC codes 00069-0235-30, 0069-0335-30, and 0069-0435-30. We may include additional codes for identification of abrocitinib exposure if relevant codes become available in the future. As described in Section 9.2.1.4, exposed time will be determined using the dispense dates and days supply information recorded in the dispensing file and further categorized by stage of pregnancy (early pregnancy stage [first trimester of pregnancy, defined as 0 to <14 weeks gestation] and mid-to-late pregnancy stage [second or third trimesters, defined as 14 weeks gestation through the end of the pregnancy]).

9.3.2. Outcomes

Outcomes to be evaluated include MCMs and adverse infant outcomes (preterm birth, SGA), and pregnancy outcomes (live birth, stillbirth and spontaneous abortion). The main outcome of this cohort study is MCMs of the infants.

MCMs will be confirmed through chart review. Other outcomes will not be confirmed through chart review.

9.3.2.1. Infant Outcomes

Infant outcomes to be evaluated include MCMs, preterm birth, and SGA. These outcomes will be identified in claims data through diagnosis codes among live births for which the mother and infant are linked. Both the infants' and mothers' claims will be searched to ensure more complete capture of infants' diagnoses. The infant's diagnoses may be captured in the mother's health plan claims data shortly after birth (generally ≤30 days after birth), especially when there is a delay in the enrollment of the infant in the health plan.

9.3.2.1.1. Major Congenital Malformations

A MCM (birth defect or structural defect) is defined as a defect, which has either cosmetic or functional significance to the child (e.g., cleft lip). A detailed list of all MCMs observed in live births compiled from the National Birth Defects Prevention Study (NBDPS) and the European Surveillance of Congenital Anomalies is provided in Appendix E (Boyd et al, 2011; CDC, 2020; Rasmussen et al, 2003). Consistent with the NBDPS case definition criteria, potential cases that occur as part of a genetic syndrome or other syndrome of known etiology (Appendix B), or those that occur secondary to other major malformations (e.g., holoprosencephaly or amniotic band sequence) will not be included in the calculation of prevalence of MCMs. Data for infants (≥1 diagnosis code in the inpatient or outpatient setting) will be collected from delivery to 1 year of age, health plan disenrollment, death, or end of dataset (whichever comes first). Relevant codes will also be identified in the mothers' claims data for the first 30 days after the infant's date of birth.

MCMs identified from this study will be reviewed by board certified teratologists to confirm the diagnosis. The teratologists will review the medical charts of each potential case and be blinded to treatment. Only validated cases will be used in the main analyses.

9.3.2.1.2. Small for Gestational Age

SGA (presence of any inpatient or outpatient code for ICD-10-CM P05.0X, P05.1X) infants will be identified by searching both the infant's and mother's claims for the first 30 days after the infant's date of birth. While a prior study has reported a low sensitivity for the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for SGA, the positive predictive value (PPV) and specificity were high (Phiri et al, 2015). Although the sensitivity of the SGA code was low, this study also showed that the specificity of SGA was high, so the relative risk estimates will be nearly unbiased for evaluations of factors associated with SGA. Another international study reported a PPV of 70.4% for ICD-10 codes used to identify SGA (Watson et al, 2021).

9.3.2.1.3. Preterm Birth

A preterm birth occurs if the gestational age at birth is <37 completed weeks. Pregnancy periods of <37 weeks duration will be identified. ICD-10-CM codes for preterm delivery and

for gestational age <37 weeks (Appendix D) are incorporated in the algorithm to determine pregnancy periods. A published Sentinel study conducted within our DPs found high agreement between the ICD-10-CM codes for gestational age recorded in claims data compared to gestational age at delivery recorded in the medical chart (≥90% agreement within 7 days) (Andrade et al, 2021).

9.3.2.2. Pregnancy Outcomes

The pregnancy outcomes to be evaluated include live birth, non-live birth (stillbirth), and spontaneous abortion. A stillbirth is defined as a spontaneous (non-deliberate) fetal death that occurs at or after 20 weeks' gestation but prior to delivery. A spontaneous abortion is defined as a spontaneous (non-deliberate) embryonic or fetal death that occurs prior to 20 weeks' gestation. Pregnancy outcomes will be identified in claims data through diagnosis and procedure codes (Appendix C and Appendix F). Pregnancy episodes resulting in a live birth will be identified using validated algorithms (see Section 9.2.1.3) that have been used in Sentinel and non-Sentinel projects (Andrade et al, 2012; Andrade et al, 2016; Johnson et al, 2013; Sentinel Initiative, 2018). Pregnancy episodes ending in a non-live birth pregnancy outcome will be identified using algorithms developed through Sentinel and non-Sentinel (e.g., VSD) projects (Andrade et al, 2021; Naleway et al, 2021). The stillbirth algorithm criteria includes the presence of a diagnosis code indicating gestational age ≥20 weeks and occurrence of either >1 stillbirth-related code or no other pregnancy outcome code (i.e., livebirth, spontaneous abortion, induced abortion) in the inpatient or outpatient setting (PPV=82.5%; Andrade et al, 2021). The spontaneous abortion algorithm identifies spontaneous abortions based upon ≥1 spontaneous abortion diagnosis or procedure code in the inpatient or outpatient setting with no occurrence of a livebirth diagnosis code (PPV=95%; Naleway et al, 2021).

9.3.3. Other Variables

Information about variables that may predict the likelihood of exposure and/or outcome will be collected from health plan claims data. These variables (i.e., potential confounders) will include maternal age at pregnancy start, calendar year, healthcare utilization, maternal race/ethnicity, concomitant medications including non-abrocitinib AD treatment, AD treatment history, maternal comorbidities, obstetric history, and lifestyle factors (details in Appendix G). Comorbidities, obstetric history, and lifestyle factors will be identified in the 183 days prior to the pregnancy start date through the first trimester (period 98 days after the pregnancy start date). This baseline period was selected to provide an adequate covariate evaluation window to capture diagnoses/encounters for most chronic conditions in the health plan claims. Diagnoses recorded through the first trimester will be included to account for women who may not have frequent visits prior to pregnancy and may have a more complete assessment of medical conditions during the first prenatal care visit. In addition, the number of healthcare encounters (outpatient, emergency department, inpatient) in the 183 days preceding the pregnancy start date will be identified.

Information on exposure to other AD treatments in the pre-pregnancy period (phototherapy, dupilumab, systemic corticosteroids, or systemic immunosuppressants [such as cyclosporine,

tralokinumab, upadacitinib]) will be determined to identify and describe the eligible /population.

9.4. Data Sources

This study will be conducted using health plan data held by DPs participating in the FDA's Sentinel System. In addition to providing claims data, the DPs will provide scientific input and feedback to support this study. All participating DPs have experience in previous studies evaluating medication safety during pregnancy. In addition, all have experience linking pregnant women with their infants within the database.

The Sentinel System is an active surveillance system that uses routine querying and analytical tools to evaluate electronic healthcare data from a distributed data network for monitoring the safety of regulated medical products in the US, established under the Sentinel Initiative (Behrman et al, 2011; Platt et al, 2018). The average enrollment length for patients across data sources in Sentinel is similar to other claims databases of members with medical and pharmacy coverage. About 25% of patients have over three years of enrollment, and patients with chronic conditions such as diabetes and older members typically have longer than average enrollment periods within these databases.

Brief descriptions of the potential participating DPs are provided below:

- **CVS Health Clinical Trial Services (CTS)**, an affiliate of Aetna, uses Aetna health insurance administrative, medical and drug claims and laboratory results data for safety surveillance, collaborative research activities, and distributed research networks including the FDA Sentinel, the Patient-Centered Clinical Research Network (PCORnet), NIH Collaboratory, Observational Medical Outcomes Partnership (OMOP), and the Innovation in Medical Evidence Development and Surveillance (IMEDS) program. Aetna, a CVS Health company, is one of the nation's leading healthcare benefits companies, serving 38 million people with information and resources to help them make better-informed decisions about their healthcare. CVS Health CTS (Aetna) became an FDA Sentinel DP in 2010 and continues to be one of the largest contributors of data for public health purposes.
- **HealthCore, Inc.**, a wholly owned subsidiary of Anthem, Inc., uses real-world data to conduct outcomes, health economics, pharmacoepidemiologic, and late phase research. The HealthCore Integrated Research Database is a proprietary, fully integrated, longitudinal claims database that combines medical, pharmacy, and laboratory information drawn from 72.5 million unique individuals with medical coverage and more than 51 million individuals with medical and pharmacy claims information since 2006. In addition, The HealthCore Integrated Research Environment has the ability to link claims data in the HealthCore Integrated Research Database to complementary data sources, including inpatient and outpatient medical records, national vital statistics records, cancer and vaccine registries (state-by-state), disease and device registries, member and provider surveys, and point of care clinical data. Using these resources, HealthCore conducts a range of real-world research designed to meet client needs, including retrospective database studies, medical record review studies, cross-sectional

and longitudinal patient and provider surveys, and prospective site-based studies, including pragmatic clinical trials.

- **Harvard Pilgrim Health Care (HPHC**) is one of the country's premier health plans. It is a large non-profit health plan with diverse enrollees across New England. Approximately 3.7 million researchable lives are available for study by Harvard Pilgrim Health Care Institute (HPHCI), a research and academic partnership between Harvard Medical School and HPHC.

- **Humana Healthcare Research (HHR)** is a subsidiary of Humana Inc., which is headquartered in Louisville, KY, is a leading health plan and well-being company focused on making it easy for people to achieve their best health with clinical excellence through coordinated care. The research team conducts health economics and outcomes research focused on treatment effectiveness, drug & patient safety, patient centered research, adherence, medical and pharmacy benefit design, disease management programs, and other healthcare services. The research team also helps conduct internal research for the company. Team expertise includes areas of distributed research networks, multisite research, adherence, clinical outcomes, overall health costs, pragmatic trials Medicare benefit designs & coverage gaps, Medication Therapy Management services, survey data linking to claims, impact of clinical programs and prescription formulary design. The team is/has been a core part of several distributed research networks including the FDA Sentinel, the Patient-Centered Clinical Research Network (PCORnet), NIH Collaboratory, Observational Medical Outcomes Partnership (OMOP), and the Innovation in Medical Evidence Development and Surveillance (IMEDS) program. This involves experience in creating systems that have used a variety of common data models (Sentinel, OMOP, and PCORnet) and utilizing external facing DataMarts such as PopMedNet to allow for query receipt, review and execution. These databases represent geographic coverage for the entire US population and represent over 27 million lives.

- **HealthPartners Institute** (the Institute) is a 501c(3) nonprofit organization dedicated to conducting high-quality, public-domain health research, often in collaboration with other academic and research organizations throughout the world. HealthPartners Institute employs 33 career research investigators and more than 400 clinician researchers and encompasses vast and varied areas of research including neurosciences, critical care, dental and oral health, maternal and child health, chronic disease, cancer, clinical research, health economics, mental health, Struthers Parkinson's Center, and Park Nicollet International Diabetes Center. In addition to participation in the Innovation in Medical Evidence Development and Surveillance (IMEDS) network, the Institute also participates in several national research networks including the Health Care Systems Research Network, the Vaccine Safety Datalink, the Sentinel Initiative, the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC), and the Mental Health Research Network (MHRN). The Institute is linked to an integrated health care system that provides health insurance for more than 1 million members and health care for more than 1.2 million patients.

The DPs use the SCDM for standardization of demographic and clinical data elements (Curtis et al, 2012; Sentinel Initiative, 2018). Publicly available routine analytical tools include reusable, modular Statistical Analysis System (SAS) programs. These analytical tools are designed to be executed against the SCDM to permit rapid queries, including descriptive analyses and complex methodologies (e.g., comparative analyses), across DPs. Specific information in the SCDM includes, but is not limited to, the following types of data:

- **Enrollment data**: One record per covered individual per unique enrollment span is included in the SCDM. Individuals are assigned a unique identifier by their insurer, which is linkable to all other data in the SCDM. Due to changes in employment status, individuals may be enrolled multiple times with the same insurer, and the length of each given enrollment "span" may vary substantially. Each record in the enrollment file indicates the patient identifier, enrollment start and end dates, and whether the patient was enrolled in medical coverage, pharmacy coverage, or both during that range. Likewise, a final field indicates whether the DP can request medical charts for a given patient during a given enrollment span.

- **Demographic data**, including birth date, sex, race/ethnicity, and ZIP code of their most recently recorded primary residence.
- **Pharmacy dispensing data**, including the date and NDC identifier for each dispensed prescription, the nominal days' supply, and the number of individual units (pills, tables, vials, etc.) dispensed. Products purchased over-the-counter (OTC) or at some cash-only retail locations selling prescription drug products (e.g., through the Walmart Prescription Program) are not captured.
- **Medical encounter data**, including the healthcare provider most responsible for the encounter as well as the facility in which the encounter occurred and its ZIP code. Admission and discharge dates (if applicable) are also included, as is the encounter type (either an ambulatory visit, an emergency department visit, an inpatient hospital stay, a non-acute inpatient stay, or an otherwise unspecified ambulatory visit). Discharge disposition (alive, expired, or unknown) as well as discharge status (to where a patient was discharged) are also included for inpatient hospital stays and non-acute inpatient stays. Finally, laboratory data are available for some, but not all, of the DPs; and the level of completeness for laboratory information for those DPs with such data varies (Raebel et al, 2014).
- **Diagnosis data**, including the date of diagnosis, its associated encounter identifier, admission date, provider identifier, and encounter type. Diagnoses are recorded with ICD-9-CM and ICD-10-CM codes. For inpatient hospital and non-acute inpatient stay encounters, the SCDM includes both principal and non-principal discharge diagnosis data. Outcomes and covariates will be identified using ICD-10-CM codes.
- **Procedure data**, including the procedure date, its associated encounter identifier, admission date, provider identifier, and encounter type. Procedures are coded as ICD-9-CM and ICD-10-CM Procedure Coding System procedure codes, CPT categories II, III,

or IV codes, revenue codes, as well as Healthcare Common Procedure Coding System (HCPCS) levels II and III codes. ICD-10-CM Procedure Coding System, CPT, and HCPCS codes will be used for the analysis.

In addition to access to health plan claims data, all DPs have experience in medical chart retrieval procedures. The expected timeline for chart retrieval is generally between 3 to 6 months, depending on the facility/provider's willingness to participate. Many factors affect retrieval, including the number of facilities/providers to which outreach must be conducted, the type of chart (inpatient vs. ambulatory and whether an EHR is accessible), and how far back records are requested. It is anticipated that approximately 70-85% of requested charts will be returned with enough information (i.e., complete chart) to determine the presence or absence of MCM. Typically, the completeness of medical chart retrieval depends on the type of chart, the facility/provider, how many charts requested, and the type of information.

9.5. Study Size

All pregnancies among women who meet the study inclusion/exclusion criteria from 14 January 2022 to Q4 2025 will be eligible for this study. A descriptive analysis will be conducted for the primary objective (prevalence of MCMs, other adverse infant outcomes, and pregnancy outcomes). Table 1 shows the scenarios of precision achieved with different abrocitinib-exposed sample sizes for the prevalence estimates for the main outcome (MCMs). For example, 145 abrocitinib-exposed live birth pregnancies are needed to estimate the prevalence of MCM with ±3% precision. These estimates assume a prevalence of overall MCMs (3%) based upon estimates in the general population (Holmes, 1976; Leppig et al, 1987; Marden et al, 1964; CDC, 2008)

Table 1. Sample Size Calculations for the Main Outcome (MCMs)

Outcome	Reference Prevalence	Sample Size Needed in Abrocitinib-Exposed Group to Estimate Prevalence with Specified Precision								
		1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%
MCM	3.0%	1,143	521	303	201	145	111	89	73	61

MCM = major congenital malformation
Sample size calculations were performed in the PASS software; precision is calculated as the half-width of the two-sided 95% CI using the Wilson (score) method for binomial proportions.

Further, a comparative analysis will be conducted to address the secondary objective, contingent on sufficient sample size. To determine the feasibility of a comparative cohort study, we assumed a prevalence of overall MCMs (3%) based upon estimates in the general population (Holmes, 1976; Leppig et al, 1987; Marden et al, 1964; CDC, 2008). Table 2 presents the minimum number of live birth pregnancies in the mother-infant linked subset needed to ensure 80% power to detect a risk ratio (RR) of 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 for MCMs, assuming a two-sided test, a type 1 error rate of 0.05, and a 1:3 ratio of abrocitinib-exposed to unexposed pregnancies.

Table 2. Sample Size Estimation for the Minimum Number of Live Birth Pregnancies Needed to Ensure 80% Power for Comparative Analysis of the Main Outcome (MCMs)

Treatment Group	Minimal Sample Size Needed							
	RR=1.5	RR=2.0	RR=2.5	RR=3.0	RR=3.5	RR=4.0	RR=4.5	RR=5.0
Exposed	1,751	516	264	168	120	93	75	62
Unexposed	5,253	1,548	792	504	360	279	225	186

The Power Analysis and Sample Size software 2020 was used in the sample size calculation. Type 1 error rate (two-sided) is assumed at 0.05.

Assuming a 1:3 ratio of abrocitinib-exposed to unexposed, a type 1 error of 0.05, and a target RR of 2.0 for the primary safety outcome of MCMs, 516 live birth pregnancies linked to infant records from the abrocitinib-exposed group and 1548 live birth pregnancies from the unexposed group will allow us to achieve 80% power. This target RR was chosen given that associations with a RR of >2.0 are unlikely to be explained by confounding alone and this cutoff for the magnitude of effect increases the quality of evidence from an observational study (Guyatt et al, 2011). Therefore, a comparative analysis will be conducted if there are at least 516 live birth pregnancies in the abrocitinib-exposed group.

9.6. Data Management

HPHCI, located in Boston, Massachusetts, will serve as the Coordinating Center for the proposed study. HPHCI staff or contractors will be responsible for writing and distributing SAS programs that can be used to evaluate data from the administrative claims databases at participating DPs. The distributed network will allow DPs to maintain physical and operational control of their data while allowing use of the data to meet the study needs. HPHCI 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, 2021).

HPHCI brings expertise in conducting multi-site evaluations using disparate electronic healthcare data systems, including extensive work with the Health Care Systems Research Network, the VSD, FDA Sentinel, the National Institutes of Health, Health Care Systems Research Collaboratory, the IMEDS program, the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) and PCORnet. HPHCI will oversee all project activities, including scientific leadership, management of the partnership, coordination of activities with the DPs and other participants, oversight of the project plan, establishment of secure infrastructure used for collaboration, and training related to use of the SCDM and associated querying tools. The DPs will establish and maintain the administrative, hardware, and software capabilities and capacity to respond to data requests in a timely manner. They will also provide data science support with epidemiologic review.

9.6.1. Chart Abstraction Forms

As used in this protocol, the term chart abstraction form should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

For patients that are selected for chart review of MCMs, a chart abstraction form is required and should be completed for each included patient. The completed original chart abstraction form are the sole property of Harvard Pilgrim Health Care, Inc. and should not be made available in any form to third parties, except for authorized representatives of of DPs and their chart abstraction vendors, Pfizer or appropriate regulatory authorities, without written permission from Harvard Pilgrim Health Care, Inc. The investigator shall ensure that the chart abstraction form are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the chart abstraction form and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The chart abstraction form must be signed by the investigator or by an authorized staff member to attest that the data contained on the chart abstraction form are true. Any corrections to entries made in the chart abstraction form or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the chart abstraction form must match those charts.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all health plan members (sufficient information to link records, e.g., chart abstraction forms and hospital records), copies of all chart abstraction forms, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless HPHCI, the DPs, and Pfizer have expressly agreed to a different period of

retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

Whenever possible, publicly available Sentinel analytic tools will be used for the analyses; these are the same tools used by FDA for similar analyses of distributed databases. Modifications to the tools may be needed to meet study objectives, in which case the SAS programming data quality assurance (QA) Standard Operating Procedures (SOP) will be followed (see Section 9.8). All statistical calculations will be done in SAS 9.2 or higher.

9.7.1. Propensity Score Development and Matching

First, propensity scores and matching (1:3 matching ratio) will occur within each DP. The propensity score reflects the conditional probability of a woman being exposed to abrocitinib during pregnancy given baseline potential confounders. Potential confounders are described in Section 9.3.3. Separate propensity score models will be fit for the cohorts of eligible live birth pregnancies and cohorts of all eligible pregnancies. The propensity score model will be fit separately for each DP and matching will occur within DP. The methodology will be described in the SAP. In addition, the SAP will describe alternative matching plans and methods, should the proposed matching plan perform poorly in practice (i.e., many unmatched abrocitinib-exposed pregnancies would be excluded). All analyses will be conducted within the propensity score matched population.

9.7.2. Characterization of Use of Abrocitinib During Pregnancy

Descriptive analyses will be performed in the propensity score matched cohort of pregnant women age 12 to 49 years with moderate-to-severe AD (AD diagnosis with pre-pregnancy exposure to systemic AD treatments or phototherapy) meeting inclusion/exclusion criteria. Frequencies of the abrocitinib-exposed and matched unexposed pregnancies among women with moderate-to-severe AD will be tabulated by maternal age, calendar year of live birth delivery, and other maternal characteristics.

9.7.3. Prevalence of Pregnancy and Infant Outcomes

Pregnancy outcomes will be assessed in the propensity score matched population of pregnant women (pregnancies ending in live birth, stillbirth, or spontaneous abortion) meeting the eligibility criteria. Infant outcomes will be assessed among the subset of eligible live birth pregnancies linked to infant records.

The prevalence (%) of the main outcome (MCMs) and additional outcomes, including other adverse infant outcomes (preterm birth, and SGA) and pregnancy outcomes (live birth, stillbirth, and spontaneous abortion), and their 95% CIs will be calculated among eligible abrocitinib-exposed pregnancies and the corresponding matched unexposed pregnancies. For the main outcome, only MCM cases confirmed within the medical records will be included in

the numerator of prevalence estimates. All analyses will be stratified by stage of pregnancy (early versus mid-to-late pregnancy). Exposure in early pregnancy (first trimester; period of organogenesis) will be the primary period for evaluation, given that exposures after this period would not be causally related to MCMs (the main outcome) and we expect a lower frequency of exposure to systemic AD therapies in later pregnancy (once the pregnancy is recognized by the patient and health care provider).

9.7.4. Comparative Analysis

Based on sample size estimation for the minimum number of live birth pregnancies needed to ensure 80% power for comparative analysis of the main outcome (MCMs; see Section 9.5), a comparative analysis of the risk of infant and pregnancy outcomes of abrocitinib-exposed versus unexposed pregnancies will be conducted if there are at least 516 live birth pregnancies in the abrocitinib-exposed group.

The Mantel-Haenszel Chi-square test or Fisher exact test (univariate analysis), whichever appropriate, will be employed to compare the prevalence of the main outcome (MCMs) between eligible live birth pregnancies among women with moderate-to-severe AD who were exposed to abrocitinib during pregnancy and those who were not exposed to abrocitinib during pregnancy. Multivariable conditional logistic regression will be conducted to adjust for potential residual confounding after matching if there is statistical significance in univariate analysis. All analyses will be stratified by stage of pregnancy (early versus mid-to-late pregnancy). Similar methods will be used for each of the secondary outcomes (i.e., preterm birth, SGA, stillbirths, and spontaneous abortions), if applicable.

9.7.5. Sensitivity Analyses

To ensure the robustness of the results, we will conduct sensitivity analyses to address the potential misclassifications for outcomes, exposure and important confounders using the diagnosis codes, procedure codes and/or other coding system in healthcare insurance database. Detailed sensitivity analyses and assessment of potential biases will be documented in a SAP.

9.7.6. Statistical Analysis Plan

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a 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.

9.8. Quality Control

As described in Section 9.4, the distributed network utilizes a common data model that enables data standardization across DPs. Furthermore, each of the participating DPs has experience with this data model given its role as an active participant in the Sentinel System. This study will use the same data QA procedures as the Sentinel System and the same curated datasets used by FDA to conduct Sentinel analyses. The QA approach assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions,

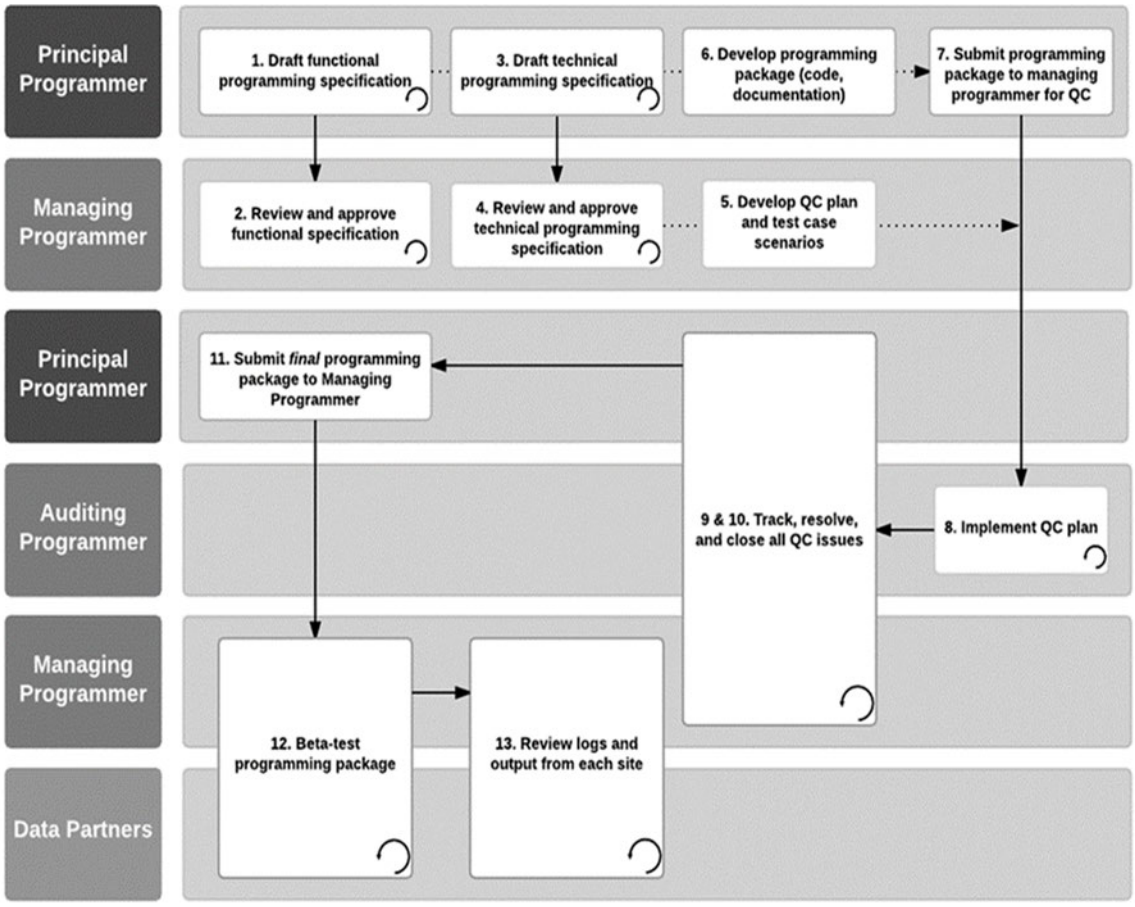
evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across DPs. Full QA processes and details on the Sentinel data curation approach are documented on the Sentinel website (Sentinel, 2021). The data curation approach is consistent with guidance set forth by the FDA in its current recommendations for data QA, 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 (QC)", published in May 2013 (FDA, 2013).

The QA procedures used in this study are the same as used for the FDA Sentinel Initiative. Further details about these procedures can be found on the Sentinel Initiative website: https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model/sentinel-data-quality-assurance-practices.

In addition to QA of data elements, HPHCI adopts standard SAS programming QA and QC processes used by the Sentinel System to check SAS programs and deliverables. Figure 2 illustrates the SOPs for SAS programming QA and QCSAP in the Sentinel System.

By signing onto this protocol, the investigators agree to be responsible for implementing and maintaining a quality management system with written development procedures and functional area SOPs to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

Figure 2. Standard Operating Procedure for SAS Programming QA and QC in the Sentinel System



9.9. Strengths and Limitations of the Research Methods

9.9.1. Limitations

Several limitations are inherent in the conduct of studies of medication exposures during pregnancy with healthcare databases. The algorithms used to define data study variables may be imperfect and these rely on the accuracy and precision of coding for these items. As a result, misclassification of exposures, outcomes, potential confounders, and the study's eligibility criteria can occur. Notably, due to the difficulty in identifying moderate-to-severe AD using claims data, we defined our study population based upon an algorithm that includes criterion requiring evidence of systemic AD treatments, medications which may also be used in the treatment of other chronic conditions (e.g., asthma). Thus, our population, in particular the unexposed comparison cohort, may include patients with mild AD. In addition, only medically attended events are recorded in the healthcare databases, thereby missing events without medical attendance such as early spontaneous abortions. Early fetal losses are often not captured in claims databases (or other data sources), but are generally reported to be mainly associated with chromosomal abnormalities (Zhang et al, 2018). Data on infant deaths (a censoring variable) may also be incomplete due to limitations of health plan claims data;

however, we do not expect the capture will differ by the exposure. To minimize the potential for outcome misclassification, highly specific outcome definitions from validated claims-based algorithms will be used when possible.

Although appropriate methodologies (e.g., propensity score matching) will be applied to statistically adjust for differences between exposed pregnancies versus unexposed pregnancies in this study, it is possible that residual confounding may be present. In addition, depending on the number of events observed, we may be limited in the ability to include additional covariate information in regression models (i.e., multivariable adjustment for potential residual imbalances after propensity score matching may not be possible if only a few events are observed). Some potential covariates are incompletely captured in the health plan data, such as alcohol use and tobacco use. This limitation relates to the constraint about claims databases and we do not expect the capture will differ by the exposure. We will conduct a sensitivity analyses (described in the SAP) to estimate the magnitude of effect of unmeasured confounding needed to change the statistical inference and we will also compare the results with and without such covariates likely to be incompletely captured in the data.

The linkage of the infants to their mothers has been found to be approximately 70-80% (Sentinel, 2018) and infants without linkage to their mothers will not be included in current study to evaluate the main outcome of interest (MCMs). Linkage rates are lower for pregnancies among women <20 (linkage rate: 45%) and ≥45 years of age (linkage rate: 26%). Another potential for selection bias exists given that we will evaluate the risk of MCMs (main outcome of interest) and other infant outcomes among only live births. Specifically, a bias may result if the exposure is associated with pregnancy loss (competing events). Sensitivity analyses and assessment of potential biases are planned and will be detailed in the SAP.

An important potential limitation of the study is that an adequate sample size might be difficult to achieve for a comparative cohort study. If an inadequate number of exposed live births are identified, only descriptive analyses of the prevalence of infant and pregnancy outcomes will be conducted.

Lastly, the results of this study may not be generalizable to patients who receive care in very different health systems in the US, and may only represent the commercially insured patient population in the US.

9.9.2. Strengths

To mitigate the effect of these limitations the study will use well-recognized algorithms and methods for identification of pregnancies, pregnancy outcomes, and potential confounders of interest, with preference for using the same methods as those used within the FDA Sentinel System. We will also conduct sensitivity analyses and methods to assess and/or control for potential selection bias (e.g., bias introduced when competing events are examined separately).

Using electronic healthcare data to assess the risk of pregnancy and infant outcomes after exposure to abrocitinib overcomes many challenges associated with conducting a traditional

pregnancy registry. Biases may be reduced as most exposures during pregnancy would be captured in the database and exposed and unexposed groups have been identified from the same source population. In addition, ascertainment of important study outcomes like spontaneous abortion and stillbirth may be improved. Medical record review of MCMs further improves ascertainment of valid data for the main outcome of interest. Collectively, this study design improves validity and interpretability of the study results. This method is more efficient, complete and objective in data collection than self-reporting; therefore, it may lead to less information bias with higher data quality.

9.10. Other Aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site (i.e., DPs) in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

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

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

As the Coordinating Center for the current study, HPHCI has the responsibility to obtain approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from an IRB/IEC. Participating DPs can either cede IRB review to HPHCI or seek approval from their local IRB. All correspondence with the IRB/IEC will be retained in the study files by HPHCI.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in:

- FDA Draft Guidance for Industry: Postapproval Pregnancy Safety Studies (FDA, 2019)
- European Medicines Agency (EMA) Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (EMA, 2019)
- Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) (ISPE, 2016)
- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making (Berger et al, 2017)
- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) (CIOMS, 2009)
- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (EMA, 2021)
- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (FDA, 2005)
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data (FDA, 2013)

- International Ethical Guidelines for Health-related Research Involving Humans issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (CIOMS, 2016)

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis

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

11.2. Human Review of Unstructured Data

This study 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 AEs with explicit attribution to any Pfizer drug that appear 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, including exposure during pregnancy, 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 exposure during pregnancy in studies of pregnant women, data on the exposure to abrocitinib during pregnancy, are not reportable unless associated with serious or non-serious AEs.

- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors*".

These trainings must be completed by research staff members prior to the start of data collection. 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.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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.

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. Additionally, this study will be disclosed and registered in the EU PAS Register.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable

APPENDIX A. TERATOGENIC AND FETOTOXIC MEDICATIONS

Women exposed to any of following potentially teratogenic or fetotoxic medications in the 183 days prior to and during pregnancy will be excluded from the study population. Exposures will be identified from NDC or HCPCS codes in the health plan claims data (outpatient pharmacy dispensing and encounter files).

Drug Class	Drug Name
Vitamin A Analog	Isotretinoin
Vitamin A Analog	Bexarotene
Vitamin A Analog	Acitretin
Prostaglandin Analog	Misoprostol
Antineoplastic	Methotrexate
Immunosuppressant	Mycophenolate Mofetil
Immunologic	Azathioprine
Immunologic	Thalidomide
Anticoagulant	Warfarin
Mood Stabilizer	Lithium
Antiarrhythmic	Amiodarone
Antiarrhythmic	Dronedarone
Anticonvulsant	Carbamazepine
Anticonvulsant	Fosphenytoin
Anticonvulsant	Mephobarbital
Anticonvulsant	Phenobarbital
Anticonvulsant	Phenytoin (phenytoin sodium)
Anticonvulsant	Primidone
Anticonvulsant	Topiramate
Anticonvulsant	Valproic Acid and derivatives (valproate sodium, divalproex)
Antirheumatic	Leflunomide
ACE-I	Benazepril
ACE-I	Captopril
ACE-I	Enalapril
ACE-I	Fosinopril
ACE-I	Lisinopril
ACE-I	Moexipril
ACE-I	Perindopril
ACE-I	Quinapril
ACE-I	Ramipril
ACE-I	Trandolapril
ARB	Candesartan
ARB	Eprosartan
ARB	Irbesartan
ARB	Losartan
ARB	Olmesartan
ARB	Telmisartan
ARB	Valsartan
Misc Antihypertensive	Aliskiren
SSRI	Paroxetine
Antiinfectives	Trimethoprim

Drug Class	Drug Name
Antiinfectives	Trimetrexate

ACE-I = Angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blockers; SSRI = selective serotonin reuptake inhibitor

APPENDIX B. DIAGNOSIS CODES FOR CHROMOSOMAL OR GENETIC ANOMALIES

Live birth pregnancies among women who deliver an infant with any of following diagnoses for chromosomal or genetic anomalies will be excluded from the study population. Diagnoses will be identified in the one-year period after birth.

ICD-10-CM Diagnosis	Description
Q90.x	Down syndrome
Q91.x	Trisomy 18 and Trisomy 13
Q92.xx	Other trisomies and partial trisomies of the autosomes, not elsewhere classified
Q93.xx	Monosomies and deletions from the autosomes, not elsewhere classified
Q95.x	Balanced rearrangements and structural markers, not elsewhere classified
Q96.x	Turner's syndrome
Q97.x	Other sex chromosome abnormalities, female phenotype, not elsewhere classified
Q98.x	Other sex chromosome abnormalities, male phenotype, not elsewhere classified
Q99.x	Other chromosome abnormalities, not elsewhere classified
Q87.4xx	Marfan's syndrome
D82.1	Di George's syndrome

APPENDIX C. LIVE BIRTH DIAGNOSIS AND PROCEDURE CODES

Live birth pregnancies will be identified with the following diagnosis and procedure codes as described in Section 9.2.1.3.

Code	Code Category	Description
0W8NXZZ	ICD-10-PCS	Division of Female Perineum, External Approach
10900ZC	ICD-10-PCS	Drainage of Amniotic Fluid, Therapeutic from Products of Conception, Open Approach
10903ZC	ICD-10-PCS	Drainage of Amniotic Fluid, Therapeutic from Products of Conception, Percutaneous Approach
10904ZC	ICD-10-PCS	Drainage of Amniotic Fluid, Therapeutic from Products of Conception, Percutaneous Endoscopic Approach
10907ZC	ICD-10-PCS	Drainage of Amniotic Fluid, Therapeutic from Products of Conception, Via Natural or Artificial Opening
10908ZC	ICD-10-PCS	Drainage of Amniotic Fluid, Therapeutic from Products of Conception, Via Natural or Artificial Opening Endoscopic
10D00Z0	ICD-10-PCS	Extraction of Products of Conception, Classical, Open Approach
10D00Z1	ICD-10-PCS	Extraction of Products of Conception, Low Cervical, Open Approach
10D00Z2	ICD-10-PCS	Extraction of Products of Conception, Extraperitoneal, Open Approach
10D07Z3	ICD-10-PCS	Extraction of Products of Conception, Low Forceps, Via Natural or Artificial Opening
10D07Z4	ICD-10-PCS	Extraction of Products of Conception, Mid Forceps, Via Natural or Artificial Opening
10D07Z5	ICD-10-PCS	Extraction of Products of Conception, High Forceps, Via Natural or Artificial Opening
10D07Z6	ICD-10-PCS	Extraction of Products of Conception, Vacuum, Via Natural or Artificial Opening
10D07Z7	ICD-10-PCS	Extraction of Products of Conception, Internal Version, Via Natural or Artificial Opening
10D07Z8	ICD-10-PCS	Extraction of Products of Conception, Other, Via Natural or Artificial Opening
10E0XZZ	ICD-10-PCS	Delivery of Products of Conception, External Approach
10S07ZZ	ICD-10-PCS	Reposition Products of Conception, Via Natural or Artificial Opening
O1002	ICD-10-CM	Pre-existing essential hypertension complicating childbirth
O1012	ICD-10-CM	Pre-existing hypertensive heart disease complicating childbirth
O1022	ICD-10-CM	Pre-existing hypertensive chronic kidney disease complicating childbirth
O1032	ICD-10-CM	Pre-existing hypertensive heart and chronic kidney disease complicating childbirth
O1042	ICD-10-CM	Pre-existing secondary hypertension complicating childbirth
O1092	ICD-10-CM	Unspecified pre-existing hypertension complicating childbirth
O114	ICD-10-CM	Pre-existing hypertension with pre-eclampsia, complicating childbirth
O1204	ICD-10-CM	Gestational edema, complicating childbirth
O1214	ICD-10-CM	Gestational proteinuria, complicating childbirth
O1224	ICD-10-CM	Gestational edema with proteinuria, complicating childbirth
O134	ICD-10-CM	Gestational [pregnancy-induced] hypertension without significant proteinuria, complicating childbirth
O1404	ICD-10-CM	Mild to moderate pre-eclampsia, complicating childbirth
O1414	ICD-10-CM	Severe pre-eclampsia complicating childbirth

Code	Code Category	Description
O1424	ICD-10-CM	HELLP syndrome, complicating childbirth
O1494	ICD-10-CM	Unspecified pre-eclampsia, complicating childbirth
O164	ICD-10-CM	Unspecified maternal hypertension, complicating childbirth
O2402	ICD-10-CM	Pre-existing type 1 diabetes mellitus, in childbirth
O2412	ICD-10-CM	Pre-existing type 2 diabetes mellitus, in childbirth
O2432	ICD-10-CM	Unspecified pre-existing diabetes mellitus in childbirth
O24420	ICD-10-CM	Gestational diabetes mellitus in childbirth, diet controlled
O24424	ICD-10-CM	Gestational diabetes mellitus in childbirth, insulin controlled
O24425	ICD-10-CM	Gestational diabetes mellitus in childbirth, controlled by oral hypoglycemic drugs
O24429	ICD-10-CM	Gestational diabetes mellitus in childbirth, unspecified control
O2482	ICD-10-CM	Other pre-existing diabetes mellitus in childbirth
O2492	ICD-10-CM	Unspecified diabetes mellitus in childbirth
O252	ICD-10-CM	Malnutrition in childbirth
O2662	ICD-10-CM	Liver and biliary tract disorders in childbirth
O2672	ICD-10-CM	Subluxation of symphysis (pubis) in childbirth
O6012X0	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, not applicable or unspecified
O6012X1	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 1
O6012X2	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 2
O6012X3	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 3
O6012X4	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 4
O6012X5	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, fetus 5
O6012X9	ICD-10-CM	Preterm labor second trimester with preterm delivery second trimester, other fetus
O6013X0	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, not applicable or unspecified
O6013X1	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 1
O6013X2	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 2
O6013X3	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 3
O6013X4	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 4
O6013X5	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, fetus 5
O6013X9	ICD-10-CM	Preterm labor second trimester with preterm delivery third trimester, other fetus
O6014X0	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, not applicable or unspecified
O6014X1	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 1

Code	Code Category	Description
O6014X2	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 2
O6014X3	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 3
O6014X4	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 4
O6014X5	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, fetus 5
O6014X9	ICD-10-CM	Preterm labor third trimester with preterm delivery third trimester, other fetus
O6022X0	ICD-10-CM	Term delivery with preterm labor, second trimester, not applicable or unspecified
O6022X1	ICD-10-CM	Term delivery with preterm labor, second trimester, fetus 1
O6022X2	ICD-10-CM	Term delivery with preterm labor, second trimester, fetus 2
O6022X3	ICD-10-CM	Term delivery with preterm labor, second trimester, fetus 3
O6022X4	ICD-10-CM	Term delivery with preterm labor, second trimester, fetus 4
O6022X5	ICD-10-CM	Term delivery with preterm labor, second trimester, fetus 5
O6022X9	ICD-10-CM	Term delivery with preterm labor, second trimester, other fetus
O6023X0	ICD-10-CM	Term delivery with preterm labor, third trimester, not applicable or unspecified
O6023X1	ICD-10-CM	Term delivery with preterm labor, third trimester, fetus 1
O6023X2	ICD-10-CM	Term delivery with preterm labor, third trimester, fetus 2
O6023X3	ICD-10-CM	Term delivery with preterm labor, third trimester, fetus 3
O6023X4	ICD-10-CM	Term delivery with preterm labor, third trimester, fetus 4
O6023X5	ICD-10-CM	Term delivery with preterm labor, third trimester, fetus 5
O6023X9	ICD-10-CM	Term delivery with preterm labor, third trimester, other fetus
O632	ICD-10-CM	Delayed delivery of second twin, triplet, etc.
O670	ICD-10-CM	Intrapartum hemorrhage with coagulation defect
O678	ICD-10-CM	Other intrapartum hemorrhage
O679	ICD-10-CM	Intrapartum hemorrhage, unspecified
O68	ICD-10-CM	Labor and delivery complicated by abnormality of fetal acid-base balance
O690XX0	ICD-10-CM	Labor and delivery complicated by prolapse of cord, not applicable or unspecified
O690XX1	ICD-10-CM	Labor and delivery complicated by prolapse of cord, fetus 1
O690XX2	ICD-10-CM	Labor and delivery complicated by prolapse of cord, fetus 2
O690XX3	ICD-10-CM	Labor and delivery complicated by prolapse of cord, fetus 3
O690XX4	ICD-10-CM	Labor and delivery complicated by prolapse of cord, fetus 4
O690XX5	ICD-10-CM	Labor and delivery complicated by prolapse of cord, fetus 5
O690XX9	ICD-10-CM	Labor and delivery complicated by prolapse of cord, other fetus
O691XX0	ICD-10-CM	Labor and delivery complicated by cord around neck, with compression, not applicable or unspecified
O691XX1	ICD-10-CM	Labor and delivery complicated by cord around neck, with compression, fetus 1
O691XX2	ICD-10-CM	Labor and delivery complicated by cord around neck, with compression, fetus 2
O691XX3	ICD-10-CM	Labor and delivery complicated by cord around neck, with compression, fetus 3

Code	Code Category	Description
O691XX4	ICD-10-CM	Labor and delivery complicated by cord around neck, with compression, fetus 4
O691XX5	ICD-10-CM	Labor and delivery complicated by cord around neck, with compression, fetus 5
O691XX9	ICD-10-CM	Labor and delivery complicated by cord around neck, with compression, other fetus
O692XX0	ICD-10-CM	Labor and delivery complicated by other cord entanglement, with compression, not applicable or unspecified
O692XX1	ICD-10-CM	Labor and delivery complicated by other cord entanglement, with compression, fetus 1
O692XX2	ICD-10-CM	Labor and delivery complicated by other cord entanglement, with compression, fetus 2
O692XX3	ICD-10-CM	Labor and delivery complicated by other cord entanglement, with compression, fetus 3
O692XX4	ICD-10-CM	Labor and delivery complicated by other cord entanglement, with compression, fetus 4
O692XX5	ICD-10-CM	Labor and delivery complicated by other cord entanglement, with compression, fetus 5
O692XX9	ICD-10-CM	Labor and delivery complicated by other cord entanglement, with compression, other fetus
O693XX0	ICD-10-CM	Labor and delivery complicated by short cord, not applicable or unspecified
O693XX1	ICD-10-CM	Labor and delivery complicated by short cord, fetus 1
O693XX2	ICD-10-CM	Labor and delivery complicated by short cord, fetus 2
O693XX3	ICD-10-CM	Labor and delivery complicated by short cord, fetus 3
O693XX4	ICD-10-CM	Labor and delivery complicated by short cord, fetus 4
O693XX5	ICD-10-CM	Labor and delivery complicated by short cord, fetus 5
O693XX9	ICD-10-CM	Labor and delivery complicated by short cord, other fetus
O694XX0	ICD-10-CM	Labor and delivery complicated by vasa previa, not applicable or unspecified
O694XX1	ICD-10-CM	Labor and delivery complicated by vasa previa, fetus 1
O694XX2	ICD-10-CM	Labor and delivery complicated by vasa previa, fetus 2
O694XX3	ICD-10-CM	Labor and delivery complicated by vasa previa, fetus 3
O694XX4	ICD-10-CM	Labor and delivery complicated by vasa previa, fetus 4
O694XX5	ICD-10-CM	Labor and delivery complicated by vasa previa, fetus 5
O694XX9	ICD-10-CM	Labor and delivery complicated by vasa previa, other fetus
O695XX0	ICD-10-CM	Labor and delivery complicated by vascular lesion of cord, not applicable or unspecified
O695XX1	ICD-10-CM	Labor and delivery complicated by vascular lesion of cord, fetus 1
O695XX2	ICD-10-CM	Labor and delivery complicated by vascular lesion of cord, fetus 2
O695XX3	ICD-10-CM	Labor and delivery complicated by vascular lesion of cord, fetus 3
O695XX4	ICD-10-CM	Labor and delivery complicated by vascular lesion of cord, fetus 4
O695XX5	ICD-10-CM	Labor and delivery complicated by vascular lesion of cord, fetus 5
O695XX9	ICD-10-CM	Labor and delivery complicated by vascular lesion of cord, other fetus
O6981X0	ICD-10-CM	Labor and delivery complicated by cord around neck, without compression, not applicable or unspecified
O6981X1	ICD-10-CM	Labor and delivery complicated by cord around neck, without compression, fetus 1

Code	Code Category	Description
O6981X2	ICD-10-CM	Labor and delivery complicated by cord around neck, without compression, fetus 2
O6981X3	ICD-10-CM	Labor and delivery complicated by cord around neck, without compression, fetus 3
O6981X4	ICD-10-CM	Labor and delivery complicated by cord around neck, without compression, fetus 4
O6981X5	ICD-10-CM	Labor and delivery complicated by cord around neck, without compression, fetus 5
O6981X9	ICD-10-CM	Labor and delivery complicated by cord around neck, without compression, other fetus
O6982X0	ICD-10-CM	Labor and delivery complicated by other cord entanglement, without compression, not applicable or unspecified
O6982X1	ICD-10-CM	Labor and delivery complicated by other cord entanglement, without compression, fetus 1
O6982X2	ICD-10-CM	Labor and delivery complicated by other cord entanglement, without compression, fetus 2
O6982X3	ICD-10-CM	Labor and delivery complicated by other cord entanglement, without compression, fetus 3
O6982X4	ICD-10-CM	Labor and delivery complicated by other cord entanglement, without compression, fetus 4
O6982X5	ICD-10-CM	Labor and delivery complicated by other cord entanglement, without compression, fetus 5
O6982X9	ICD-10-CM	Labor and delivery complicated by other cord entanglement, without compression, other fetus
O6989X0	ICD-10-CM	Labor and delivery complicated by other cord complications, not applicable or unspecified
O6989X1	ICD-10-CM	Labor and delivery complicated by other cord complications, fetus 1
O6989X2	ICD-10-CM	Labor and delivery complicated by other cord complications, fetus 2
O6989X3	ICD-10-CM	Labor and delivery complicated by other cord complications, fetus 3
O6989X4	ICD-10-CM	Labor and delivery complicated by other cord complications, fetus 4
O6989X5	ICD-10-CM	Labor and delivery complicated by other cord complications, fetus 5
O6989X9	ICD-10-CM	Labor and delivery complicated by other cord complications, other fetus
O699XX0	ICD-10-CM	Labor and delivery complicated by cord complication, unspecified, not applicable or unspecified
O699XX1	ICD-10-CM	Labor and delivery complicated by cord complication, unspecified, fetus 1
O699XX2	ICD-10-CM	Labor and delivery complicated by cord complication, unspecified, fetus 2
O699XX3	ICD-10-CM	Labor and delivery complicated by cord complication, unspecified, fetus 3
O699XX4	ICD-10-CM	Labor and delivery complicated by cord complication, unspecified, fetus 4
O699XX5	ICD-10-CM	Labor and delivery complicated by cord complication, unspecified, fetus 5
O699XX9	ICD-10-CM	Labor and delivery complicated by cord complication, unspecified, other fetus
O700	ICD-10-CM	First degree perineal laceration during delivery
O701	ICD-10-CM	Second degree perineal laceration during delivery
O7020	ICD-10-CM	Third degree perineal laceration during delivery, unspecified

Code	Code Category	Description
O7021	ICD-10-CM	Third degree perineal laceration during delivery, IIIa
O7022	ICD-10-CM	Third degree perineal laceration during delivery, IIIb
O7023	ICD-10-CM	Third degree perineal laceration during delivery, IIIc
O703	ICD-10-CM	Fourth degree perineal laceration during delivery
O704	ICD-10-CM	Anal sphincter tear complicating delivery, not associated with third degree laceration
O709	ICD-10-CM	Perineal laceration during delivery, unspecified
O740	ICD-10-CM	Aspiration pneumonitis due to anesthesia during labor and delivery
O741	ICD-10-CM	Other pulmonary complications of anesthesia during labor and delivery
O742	ICD-10-CM	Cardiac complications of anesthesia during labor and delivery
O743	ICD-10-CM	Central nervous system complications of anesthesia during labor and delivery
O744	ICD-10-CM	Toxic reaction to local anesthesia during labor and delivery
O745	ICD-10-CM	Spinal and epidural anesthesia-induced headache during labor and delivery
O746	ICD-10-CM	Other complications of spinal and epidural anesthesia during labor and delivery
O747	ICD-10-CM	Failed or difficult intubation for anesthesia during labor and delivery
O748	ICD-10-CM	Other complications of anesthesia during labor and delivery
O749	ICD-10-CM	Complication of anesthesia during labor and delivery, unspecified
O750	ICD-10-CM	Maternal distress during labor and delivery
O751	ICD-10-CM	Shock during or following labor and delivery
O755	ICD-10-CM	Delayed delivery after artificial rupture of membranes
O7581	ICD-10-CM	Maternal exhaustion complicating labor and delivery
O7582	ICD-10-CM	Onset (spontaneous) of labor after 37 completed weeks of gestation but before 39 completed weeks gestation, with delivery by (planned) cesarean section
O7589	ICD-10-CM	Other specified complications of labor and delivery
O759	ICD-10-CM	Complication of labor and delivery, unspecified
O76	ICD-10-CM	Abnormality in fetal heart rate and rhythm complicating labor and delivery
O770	ICD-10-CM	Labor and delivery complicated by meconium in amniotic fluid
O778	ICD-10-CM	Labor and delivery complicated by other evidence of fetal stress
O779	ICD-10-CM	Labor and delivery complicated by fetal stress, unspecified
O80	ICD-10-CM	Encounter for full-term uncomplicated delivery
O82	ICD-10-CM	Encounter for cesarean delivery without indication
O8802	ICD-10-CM	Air embolism in childbirth
O8812	ICD-10-CM	Amniotic fluid embolism in childbirth
O8822	ICD-10-CM	Thromboembolism in childbirth
O8832	ICD-10-CM	Pyemic and septic embolism in childbirth
O8882	ICD-10-CM	Other embolism in childbirth
O9802	ICD-10-CM	Tuberculosis complicating childbirth
O9812	ICD-10-CM	Syphilis complicating childbirth
O9822	ICD-10-CM	Gonorrhea complicating childbirth
O9832	ICD-10-CM	Other infections with a predominantly sexual mode of transmission complicating childbirth
O9842	ICD-10-CM	Viral hepatitis complicating childbirth
O9852	ICD-10-CM	Other viral diseases complicating childbirth

Code	Code Category	Description
O9862	ICD-10-CM	Protozoal diseases complicating childbirth
O9872	ICD-10-CM	Human immunodeficiency virus [HIV] disease complicating childbirth
O9882	ICD-10-CM	Other maternal infectious and parasitic diseases complicating childbirth
O9892	ICD-10-CM	Unspecified maternal infectious and parasitic disease complicating childbirth
O9902	ICD-10-CM	Anemia complicating childbirth
O9912	ICD-10-CM	Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating childbirth
O99214	ICD-10-CM	Obesity complicating childbirth
O99284	ICD-10-CM	Endocrine, nutritional and metabolic diseases complicating childbirth
O99314	ICD-10-CM	Alcohol use complicating childbirth
O99324	ICD-10-CM	Drug use complicating childbirth
O99334	ICD-10-CM	Smoking (tobacco) complicating childbirth
O99344	ICD-10-CM	Other mental disorders complicating childbirth
O99354	ICD-10-CM	Diseases of the nervous system complicating childbirth
O9942	ICD-10-CM	Diseases of the circulatory system complicating childbirth
O9952	ICD-10-CM	Diseases of the respiratory system complicating childbirth
O9962	ICD-10-CM	Diseases of the digestive system complicating childbirth
O9972	ICD-10-CM	Diseases of the skin and subcutaneous tissue complicating childbirth
O99814	ICD-10-CM	Abnormal glucose complicating childbirth
O99824	ICD-10-CM	Streptococcus B carrier state complicating childbirth
O99834	ICD-10-CM	Other infection carrier state complicating childbirth
O99844	ICD-10-CM	Bariatric surgery status complicating childbirth
O9A12	ICD-10-CM	Malignant neoplasm complicating childbirth
O9A22	ICD-10-CM	Injury, poisoning and certain other consequences of external causes complicating childbirth
O9A32	ICD-10-CM	Physical abuse complicating childbirth
O9A42	ICD-10-CM	Sexual abuse complicating childbirth
O9A52	ICD-10-CM	Psychological abuse complicating childbirth
P030	ICD-10-CM	Newborn affected by breech delivery and extraction
P032	ICD-10-CM	Newborn affected by forceps delivery
P033	ICD-10-CM	Newborn affected by delivery by vacuum extractor [ventouse]
P034	ICD-10-CM	Newborn affected by Cesarean delivery
P035	ICD-10-CM	Newborn affected by precipitate delivery
P0700	ICD-10-CM	Extremely low birth weight newborn, unspecified weight
P0701	ICD-10-CM	Extremely low birth weight newborn, less than 500 grams
P0702	ICD-10-CM	Extremely low birth weight newborn, 500-749 grams
P0703	ICD-10-CM	Extremely low birth weight newborn, 750-999 grams
P0710	ICD-10-CM	Other low birth weight newborn, unspecified weight
P0714	ICD-10-CM	Other low birth weight newborn, 1000-1249 grams
P0715	ICD-10-CM	Other low birth weight newborn, 1250-1499 grams
P0716	ICD-10-CM	Other low birth weight newborn, 1500-1749 grams
P0717	ICD-10-CM	Other low birth weight newborn, 1750-1999 grams
P0718	ICD-10-CM	Other low birth weight newborn, 2000-2499 grams
P0720	ICD-10-CM	Extreme immaturity of newborn, unspecified weeks of gestation
P0721	ICD-10-CM	Extreme immaturity of newborn, gestational age less than 23 completed weeks
P0722	ICD-10-CM	Extreme immaturity of newborn, gestational age 23 completed weeks

Code	Code Category	Description
P0723	ICD-10-CM	Extreme immaturity of newborn, gestational age 24 completed weeks
P0724	ICD-10-CM	Extreme immaturity of newborn, gestational age 25 completed weeks
P0725	ICD-10-CM	Extreme immaturity of newborn, gestational age 26 completed weeks
P0726	ICD-10-CM	Extreme immaturity of newborn, gestational age 27 completed weeks
P0730	ICD-10-CM	Preterm newborn, unspecified weeks of gestation
P0731	ICD-10-CM	Preterm newborn, gestational age 28 completed weeks
P0732	ICD-10-CM	Preterm newborn, gestational age 29 completed weeks
P0733	ICD-10-CM	Preterm newborn, gestational age 30 completed weeks
P0734	ICD-10-CM	Preterm newborn, gestational age 31 completed weeks
P0735	ICD-10-CM	Preterm newborn, gestational age 32 completed weeks
P0736	ICD-10-CM	Preterm newborn, gestational age 33 completed weeks
P0737	ICD-10-CM	Preterm newborn, gestational age 34 completed weeks
P0738	ICD-10-CM	Preterm newborn, gestational age 35 completed weeks
P0739	ICD-10-CM	Preterm newborn, gestational age 36 completed weeks
P0821	ICD-10-CM	Post-term newborn
P0822	ICD-10-CM	Prolonged gestation of newborn
Z370	ICD-10-CM	Single live birth
Z372	ICD-10-CM	Twins, both liveborn
Z373	ICD-10-CM	Twins, one liveborn and one stillborn
Z3750	ICD-10-CM	Multiple births, unspecified, all liveborn
Z3751	ICD-10-CM	Triplets, all liveborn
Z3752	ICD-10-CM	Quadruplets, all liveborn
Z3753	ICD-10-CM	Quintuplets, all liveborn
Z3754	ICD-10-CM	Sextuplets, all liveborn
Z3759	ICD-10-CM	Other multiple births, all liveborn
Z3760	ICD-10-CM	Multiple births, unspecified, some liveborn
Z3761	ICD-10-CM	Triplets, some liveborn
Z3762	ICD-10-CM	Quadruplets, some liveborn
Z3763	ICD-10-CM	Quintuplets, some liveborn
Z3764	ICD-10-CM	Sextuplets, some liveborn
Z3769	ICD-10-CM	Other multiple births, some liveborn
Z379	ICD-10-CM	Outcome of delivery, unspecified
Z3800	ICD-10-CM	Single liveborn infant, delivered vaginally
Z3801	ICD-10-CM	Single liveborn infant, delivered by cesarean
Z381	ICD-10-CM	Single liveborn infant, born outside hospital
Z382	ICD-10-CM	Single liveborn infant, unspecified as to place of birth
Z3830	ICD-10-CM	Twin liveborn infant, delivered vaginally
Z3831	ICD-10-CM	Twin liveborn infant, delivered by cesarean
Z384	ICD-10-CM	Twin liveborn infant, born outside hospital
Z385	ICD-10-CM	Twin liveborn infant, unspecified as to place of birth
Z3861	ICD-10-CM	Triplet liveborn infant, delivered vaginally
Z3862	ICD-10-CM	Triplet liveborn infant, delivered by cesarean
Z3863	ICD-10-CM	Quadruplet liveborn infant, delivered vaginally
Z3864	ICD-10-CM	Quadruplet liveborn infant, delivered by cesarean
Z3865	ICD-10-CM	Quintuplet liveborn infant, delivered vaginally
Z3866	ICD-10-CM	Quintuplet liveborn infant, delivered by cesarean
Z3868	ICD-10-CM	Other multiple liveborn infant, delivered vaginally
Z3869	ICD-10-CM	Other multiple liveborn infant, delivered by cesarean

Code	Code Category	Description
Z387	ICD-10-CM	Other multiple liveborn infant, born outside hospital
Z388	ICD-10-CM	Other multiple liveborn infant, unspecified as to place of birth
59400	CPT-4	Routine obstetric care including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care
59409	CPT-4	Vaginal delivery only (with or without episiotomy and/or forceps);
59410	CPT-4	Vaginal delivery only (with or without episiotomy and/or forceps); including postpartum care
59510	CPT-4	Routine obstetric care including antepartum care, cesarean delivery, and postpartum care
59514	CPT-4	Cesarean delivery only;
59515	CPT-4	Cesarean delivery only; including postpartum care
59610	CPT-4	Routine obstetric care including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care, after previous cesarean delivery
59612	CPT-4	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy and/or forceps);
59614	CPT-4	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy and/or forceps); including postpartum care
59618	CPT-4	Routine obstetric care including antepartum care, cesarean delivery, and postpartum care, following attempted vaginal delivery after previous cesarean delivery
59620	CPT-4	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery;
59622	CPT-4	Cesarean delivery only, following attempted vaginal delivery after previous cesarean delivery; including postpartum care

APPENDIX D. CODES TO IDENTIFY PRETERM AND POST-TERM BIRTH

The estimated duration of pregnancy will be identified with the following diagnosis codes as described in Section 9.2.1.3.

ICD-10-CM Code	Description	Estimated Duration of Pregnancy
P0739	Preterm newborn, gestational age 36 completed weeks	256
Z3A36	36 weeks gestation of pregnancy	256
P0738	Preterm newborn, gestational age 35 completed weeks	249
Z3A35	35 weeks gestation of pregnancy	249
P0737	Preterm newborn, gestational age 34 completed weeks	242
Z3A34	34 weeks gestation of pregnancy	242
P0736	Preterm newborn, gestational age 33 completed weeks	235
Z3A33	33 weeks gestation of pregnancy	235
P0735	Preterm newborn, gestational age 32 completed weeks	228
Z3A32	32 weeks gestation of pregnancy	228
P0734	Preterm newborn, gestational age 31 completed weeks	221
Z3A31	31 weeks gestation of pregnancy	221
P0733	Preterm newborn, gestational age 30 completed weeks	214
Z3A30	30 weeks gestation of pregnancy	214
P0732	Preterm newborn, gestational age 29 completed weeks	207
Z3A29	29 weeks gestation of pregnancy	207
P0731	Preterm newborn, gestational age 28 completed weeks	200
Z3A28	28 weeks gestation of pregnancy	200
P0726	Extreme immaturity of newborn, gestational age 27 completed weeks	193
Z3A27	27 weeks gestation of pregnancy	193
P0725	Extreme immaturity of newborn, gestational age 26 completed weeks	186
Z3A26	26 weeks gestation of pregnancy	186

APPENDIX E. MAJOR CONGENITAL ANOMALIES

Data for infants will be collected from date of birth to 1 year of age, health plan disenrollment, death, or end of dataset whichever comes first. Relevant codes will also be identified in the mothers' claims data for the first 30 days after the infant's date of birth. Code list may be modified based upon future studies to validate algorithms using ICD-10-CM codes.

Major congenital anomalies		ICD-10 Code(s)
Central nervous system	Anencephaly	Q00.0
	Craniorachischisis	Q00.1
	Iniencephaly	Q00.2
	Encephalocele (including encephalomyelocele and cranial meningocele)	Q01.0-Q01.2, Q01.8, Q01.9
	Spina bifida	Q05.0-Q05.9, Q07.01, Q07.03
	Holoprosencephaly	Q04.2
	Hydrocephalus (with or without dandy-walker or other structural lesion)	Q03.0, Q03.1, Q03.8, Q03.9
	Microcephalus	Q02
Eye	Anophthalmia, microphthalmia	Q11.0, Q11.1, Q11.2
	Cataracts and other lens defects	Q12.x
	Glaucoma and anterior segment defects without aniridia	Q13.0, Q13.1, Q13.2, Q13.4, Q13.8x, Q13.9, Q15.0
Ear	Anotia, microtia	Q16.0, Q17.2
Heart	Anomalous pulmonary venous return	Q26.2, Q26.3, Q26.4
	Atrioventricular septal defects (av canal)	Q21.2
	Conotruncal heart defects	Q20.0, Q20.1, Q20.3, Q21.3, Q25.21, Q25.5, Q25.79
	Ebstein malformation	Q22.5
	Laterality defects – heterotaxy	Q89.3
	Obstructive heart defects (includes hypoplastic left heart)	Q22.0, Q22.1, Q22.3, Q22.4, Q22.9, Q23.0, Q23.4, Q25.1, Q25.2x, Q25.3, Q25.4
	Septal heart defects	Q21.0, Q21.1, Q21.8, Q21.9
	Single ventricle	Q20.4
	Severe congenital heart disease: single ventricle, tricuspid atresia, ebstein's anomaly, hypoplastic left heart, hypoplastic right heart, common arterial truncus, transposition of great vessels, atrioventricular septal defects, tetralogy of fallot, pulmonary valve atresia, aortic valve atresia/stenosis, coarctation of aorta, total anomalous pulmonary venous return	Q20.0, Q20.3, Q20.4, Q20.5, Q21.2, Q21.3, Q22.0, Q22.1, Q22.3, Q22.4, Q22.5, Q22.6, Q22.8, Q22.9, Q23.0, Q23.4, Q25.1, Q25.21
Orofacial/Respiratory system	Choanal atresia	Q30.0

Major congenital anomalies		ICD-10 Code(s)
Cleft Lip +/- Palate	Cleft palate	Q35, Q35.1, Q35.3, Q 35.5, Q35.59, Q35.9
	Cleft Lip	Q36, Q36.0, Q36.1, Q36.9, Q36.90, Q36.99
	Cleft palate with cleft lip	Q37, Q37.0, Q37.1, Q37.2, Q37.3, Q37.4, Q37.5, Q37.8, Q37.9, Q37.99
Gastrointestinal	Biliary Atresia	Q44.2, Q44.3
	Esophageal atresia +/- tracheoesophageal fistula	Q39.0, Q39.1, Q39.3, Q39.4
	Intestinal atresia/stenosis	Q41.x, Q42.x
	Pyloric stenosis	Q40.0

Major congenital anomalies		ICD-10 Code(s)
Genitourinary/Renal system	Exstrophy, bladder	Q64.1x
	Exstrophy, cloacal	Q64.1x
	Hypospadias- second or third degree	Q54.0–Q54.4, Q54.8, Q54.9
	Renal agenesis/hypoplasia	Q60.x
	Renal dysplasia	Q61.4
	Congenital hydronephrosis	Q62.0
	Posterior urethral valve and/or prune belly	Q64.2, Q79.4
Musculoskeletal system	Abdominal wall defects: gastroschisis, omphalocele	Q79.2, Q79.3
	Diaphragmatic hernia	Q79.0, Q79.1
	Reduction defects of upper limb	Q71.0–Q71.6x, Q71.8x, Q71.9x
	Reduction defects of lower limb	Q72.0–Q72.9x
	Reduction defects of unspecified limb	Q73.0, Q73.1, Q73.8
	Amniotic bands	P02.8, Q79.8
	Sacral Agenesis	Q76.49
	Craniosynostosis	Q75.0

APPENDIX F. SPONTANEOUS ABORTION AND STILLBIRTH DIAGNOSIS AND PROCEDURE CODES

Pregnancies ending in a spontaneous abortion or stillbirth will be identified with the following diagnosis and procedure codes using previously published algorithms (Andrade et al, 2021; Naleway et al, 2021).

Code	Code Category	Description	Pregnancy Outcome
O02.1	ICD-10-CM	Missed abortion	Spontaneous abortion
O03.0	ICD-10-CM	Genital tract and pelvic infection following incomplete spontaneous abortion	Spontaneous abortion
O03.1	ICD-10-CM	Delayed or excessive hemorrhage following incomplete spontaneous abortion	Spontaneous abortion
O03.2	ICD-10-CM	Embolism following incomplete spontaneous abortion	Spontaneous abortion
O03.30	ICD-10-CM	Unspecified complication following incomplete spontaneous abortion	Spontaneous abortion
O03.31	ICD-10-CM	Shock following incomplete spontaneous abortion	Spontaneous abortion
O03.32	ICD-10-CM	Renal failure following incomplete spontaneous abortion	Spontaneous abortion
O03.33	ICD-10-CM	Metabolic disorder following incomplete spontaneous abortion	Spontaneous abortion
O03.34	ICD-10-CM	Damage to pelvic organs following incomplete spontaneous abortion	Spontaneous abortion
O03.35	ICD-10-CM	Other venous complications following incomplete spontaneous abortion	Spontaneous abortion
O03.36	ICD-10-CM	Cardiac arrest following incomplete spontaneous abortion	Spontaneous abortion
O03.37	ICD-10-CM	Sepsis following incomplete spontaneous abortion	Spontaneous abortion
O03.38	ICD-10-CM	Urinary tract infection following incomplete spontaneous abortion	Spontaneous abortion
O03.39	ICD-10-CM	Incomplete spontaneous abortion with other complications	Spontaneous abortion
O03.4	ICD-10-CM	Incomplete spontaneous abortion without complication	Spontaneous abortion
O03.5	ICD-10-CM	Genital tract and pelvic infection following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.6	ICD-10-CM	Delayed or excessive hemorrhage following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.7	ICD-10-CM	Embolism following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.80	ICD-10-CM	Unspecified complication following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.81	ICD-10-CM	Shock following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.82	ICD-10-CM	Renal failure following complete or unspecified spontaneous abortion	Spontaneous abortion

Code	Code Category	Description	Pregnancy Outcome
O03.83	ICD-10-CM	Metabolic disorder following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.84	ICD-10-CM	Damage to pelvic organs following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.85	ICD-10-CM	Other venous complications following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.86	ICD-10-CM	Cardiac arrest following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.87	ICD-10-CM	Sepsis following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.88	ICD-10-CM	Urinary tract infection following complete or unspecified spontaneous abortion	Spontaneous abortion
O03.89	ICD-10-CM	Complete or unspecified spontaneous abortion with other complications	Spontaneous abortion
O03.9	ICD-10-CM	Complete or unspecified spontaneous abortion without complication	Spontaneous abortion
01965	CPT-4	Anesthesia for incomplete or missed abortion procedures	Spontaneous abortion
59812	CPT-4	Treatment of incomplete abortion, any trimester, completed surgically	Spontaneous abortion
59820	CPT-4	Treatment of incomplete abortion completed surgically, first trimester	Spontaneous abortion
59821	CPT-4	Treatment of incomplete abortion completed surgically, second trimester	Spontaneous abortion
O31.0	ICD-10-CM	Papyraceous fetus	Stillbirth
O31.00	ICD-10-CM	Papyraceous fetus, unspecified trimester	Stillbirth
O31.00X0	ICD-10-CM	Papyraceous fetus, unspecified trimester, not applicable or unspecified	Stillbirth
O31.00X1	ICD-10-CM	Papyraceous fetus, unspecified trimester, fetus 1	Stillbirth
O31.00X2	ICD-10-CM	Papyraceous fetus, unspecified trimester, fetus 2	Stillbirth
O31.00X3	ICD-10-CM	Papyraceous fetus, unspecified trimester, fetus 3	Stillbirth
O31.00X4	ICD-10-CM	Papyraceous fetus, unspecified trimester, fetus 4	Stillbirth
O31.00X5	ICD-10-CM	Papyraceous fetus, unspecified trimester, fetus 5	Stillbirth
O31.00X9	ICD-10-CM	Papyraceous fetus, unspecified trimester, other fetus	Stillbirth
O31.01	ICD-10-CM	Papyraceous fetus, first trimester	Stillbirth
O31.02	ICD-10-CM	Papyraceous fetus, second trimester	Stillbirth
O31.02X0	ICD-10-CM	Papyraceous fetus, second trimester, not applicable or unspecified	Stillbirth
O31.02X1	ICD-10-CM	Papyraceous fetus, second trimester, fetus 1	Stillbirth
O31.02X2	ICD-10-CM	Papyraceous fetus, second trimester, fetus 2	Stillbirth
O31.02X3	ICD-10-CM	Papyraceous fetus, second trimester, fetus 3	Stillbirth
O31.02X4	ICD-10-CM	Papyraceous fetus, second trimester, fetus 4	Stillbirth
O31.02X5	ICD-10-CM	Papyraceous fetus, second trimester, fetus 5	Stillbirth
O31.02X9	ICD-10-CM	Papyraceous fetus, second trimester, other fetus	Stillbirth

Code	Code Category	Description	Pregnancy Outcome
O31.03	ICD-10-CM	Papyraceous fetus, third trimester	Stillbirth
O31.03X0	ICD-10-CM	Papyraceous fetus, third trimester, not applicable or unspecified	Stillbirth
O31.03X1	ICD-10-CM	Papyraceous fetus, third trimester, fetus 1	Stillbirth
O31.03X2	ICD-10-CM	Papyraceous fetus, third trimester, fetus 2	Stillbirth
O31.03X3	ICD-10-CM	Papyraceous fetus, third trimester, fetus 3	Stillbirth
O31.03X4	ICD-10-CM	Papyraceous fetus, third trimester, fetus 4	Stillbirth
O31.03X5	ICD-10-CM	Papyraceous fetus, third trimester, fetus 5	Stillbirth
O31.03X9	ICD-10-CM	Papyraceous fetus, third trimester, other fetus	Stillbirth
O36.4	ICD-10-CM	Maternal care for intrauterine death	Stillbirth
O36.4XX0	ICD-10-CM	Maternal care for intrauterine death, not applicable or unspecified	Stillbirth
O36.4XX1	ICD-10-CM	Maternal care for intrauterine death, fetus 1	Stillbirth
O36.4XX2	ICD-10-CM	Maternal care for intrauterine death, fetus 2	Stillbirth
O36.4XX3	ICD-10-CM	Maternal care for intrauterine death, fetus 3	Stillbirth
O36.4XX4	ICD-10-CM	Maternal care for intrauterine death, fetus 4	Stillbirth
O36.4XX5	ICD-10-CM	Maternal care for intrauterine death, fetus 5	Stillbirth
O36.4XX9	ICD-10-CM	Maternal care for intrauterine death, other fetus	Stillbirth
P95	ICD-10-CM	Stillbirth	Stillbirth
Z37.1	ICD-10-CM	Single stillbirth	Stillbirth
Z37.3	ICD-10-CM	Twins, one liveborn and one stillborn	Stillbirth
Z37.4	ICD-10-CM	Twins, both stillborn	Stillbirth
Z37.6	ICD-10-CM	Other multiple births, some liveborn	Stillbirth
Z37.60	ICD-10-CM	Multiple births, unspecified, some liveborn	Stillbirth
Z37.61	ICD-10-CM	Triplets, some liveborn	Stillbirth
Z37.62	ICD-10-CM	Quadruplets, some liveborn	Stillbirth
Z37.63	ICD-10-CM	Quintuplets, some liveborn	Stillbirth
Z37.64	ICD-10-CM	Sextuplets, some liveborn	Stillbirth
Z37.69	ICD-10-CM	Other multiple births, some liveborn	Stillbirth
Z37.7	ICD-10-CM	Other multiple births, all stillborn	Stillbirth

APPENDIX G. MATERNAL COMORBIDITIES, OBSTETRIC HISTORY, AND LIFESTYLE FACTORS

Maternal comorbidities, obstetric history, and lifestyle factors will be identified in the 183 days prior to the pregnancy start date through the first trimester (period 98 days after the pregnancy start date). Code list may be modified based upon future studies to validate algorithms using ICD-10-CM codes.

Condition	Code
Diabetes (pre-existing)	E08-E13.x, O24.0-O24.33, O024.8x
Heart disease	I01.x, I02.0, I05-I09.x, I11.x, I13.x, I20-I51.x
Pre-existing hypertension	I10-I16.x, O10.x, O11.x
Cerebrovascular disease	G45.x, G46.x, I60-I69.x
Malignant neoplasms	C00-C96.x
Thyroid disease	E00-E07.x
Epilepsy	G40.x
Anemia (excluding iron deficiency)	D51-D64.x
Chronic liver disease and cirrhosis	K72.1-K74.6x
Coagulopathy	D65-D68.x, D69.1, D69.3-D69.6
Immunodeficiency and organ transplant	D80-D89.x, Z94.x
Asthma	J45.xx
Other respiratory disease	J41-J44.xx, J46-J94.x, J96.1-J96.x, J98.09-J98.4
Nutritional deficiencies	E40-E64.x
Renal disease	N00-N19.x, O12.11, O12.21, O26.831
Neurologic	G36-G37.x, G39.x, G40.x, I69.x
Depression	F31.3-F31.5, F32.x, F33.x, F34.1
Allergic rhinitis	J30.1-J30.9
Autoimmune disorders (alopecia areata, celiac disease, Crohn's disease, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis, psoriasis, polyarteritis nodosa and allied conditions, systemic lupus erythematosus and diffuse disease of connective tissue)	L63.xx, K90.0, K50.xx, K51.xx, M45.x, M08.1, M05-M06.xx, M08.0xx, M08.2x-M08.48x, L40.xx, M30.x, M32-M35.xx
Skin infections (e.g., chickenpox, eczema herpeticum, impetigo, molluscum dermatitis)	B01.x, B00.0, L01.xx, B08.1

Condition	Code
Obesity/BMI > 30	E66.01, E66.09, E66.1, E66.2, E66.8, E66.9, Z68.30-Z68.45, O99.210-O99.211
Other exposures: Lead, asbestos	Z77.011, Z77.090
Infectious and parasitic diseases complicating pregnancy	O98.011, O98.111, O98.211, O98.311, O98.411, O98.511, O98.611, O98.711, O98.811, O98.911
Drug dependence	F11-F16.x, F18-F19.x, O99.32x, Z71.51
Alcohol use	O99.31x, F10.x, Z71.41
Tobacco use	O99.330-O99.335, F17.2-F17.299, T65.2x, Z71.6, Z72.0
Recurrent pregnancy loss	N96
Female infertility	N97.X
Complications associated with artificial fertilization	N98.X
Poor reproductive or obstetric history	O09.2X

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