PASS information

Title:	Postmarketing commitment safety study of HZ/su to evaluate pregnancy exposures and outcomes in immunodeficient or immunosuppressed women between 18 and 49 years of age.
Protocol version identifier:	214420 (EPI-ZOSTER-039 VS US DB)
Date of last version of the protocol:	Final: 24 November 2021 Amendment 1 Final: 02 May 2022 Amendment 2 Final: 15 August 2022
EU PAS Register No:	Study not registered
Active substance:	VZV glycoprotein E (gE)
Medicinal product(s):	*Shingrix* (herpes zoster (HZ) subunit vaccine, HZ/su)
Product reference:	NA
Procedure number:	NA
Marketing Authorization Holder (MAH):	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	The study will examine the risk of selected infant and pregnancy outcomes in immunodeficient or immunosuppressed women exposed to herpes zoster subunit vaccine (HZ/su) during pregnancy. The primary outcome of interest is major congenital malformations. Secondary outcomes include infant/birth outcomes (preterm birth, small for gestational age (SGA), low birth weight (LBW), neonatal intensive care unit (NICU) admission, neonatal death), complications of pregnancy (placental abruption, preeclampsia and eclampsia), and pregnancy outcomes (livebirths, stillbirths, and spontaneous abortions).
Country of study:	United States

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MARKETING AUTHORIZATION HOLDER

MAH(s):	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
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2. LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
BBCIC	Biologics and Biosimilars Collective Intelligence Consortium
BEST	Biologics Effectiveness and Safety
CBER	Center for Biologics Evaluation and Research (Food and Drug Administration)
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPT	Current Procedural Terminology
CRF	Case Report Form
CSR	Clinical Study Report
CTS	Clinical Trial Services
DP	Data Partner
DRN	Distributed Research Network
EHR	Electronic Health Record
EMA	European Medicine Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act
GPP	Guidelines for Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline SA
HCPCS	Healthcare Common Procedure Coding System
HIV	Human Immunodeficiency Virus
HM	Hematologic Malignancies

HPHC	Harvard Pilgrim Health Care
HPHCI	Harvard Pilgrim Health Care Institute
HZ	Herpes Zoster
HZ/su	Herpes Zoster Subunit Vaccine
IBD	Inflammatory Bowel Disease
IC	Immunocompromised
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IMEDS	Innovation in Medical Evidence Development and Surveillance
IRB	Institutional Review Board
LBW	Low Birth Weight
LMP	Last Menstrual Period
MCMs	Major Congenital Malformations
MEPREP	Medication Exposure in Pregnancy Risk Evaluation Program
MS	Multiple Sclerosis
NBDPS	National Birth Defects Prevention Study
NDC	National Drug Code
NICU	Neonatal Intensive Care Unit
NIST	National Institute of Standards and Technology
OTC	Over-the-counter
PCORI	Patient-Centered Outcomes Research Institute
PCORnet	Patient-Centered Clinical Research Network

PPV	Positive Predictive Value
PsA	Psoriatic Arthritis
PsO	Psoriasis
QA	Quality Assurance
RA	Rheumatoid Arthritis
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCDM	Sentinel Common Data Model
SCT	Stem Cell Transplant
SGA	Small for Gestational Age
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedures
SOT	Solid Organ Transplant
ST	Solid Tumors
U.S.	United States
VSD	Vaccine Safety DataLink
YOA	Years of Age

3. RESPONSIBLE PARTIES

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Coordinating investigator for each country in which the study is to be performed	Not applicable
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4. ABSTRACT (AMENDED 15 AUGUST 2022)

Title	Postmarketing commitment safety study of HZ/su to evaluate pregnancy exposures and outcomes in immunodeficient or immunosuppressed women between 18 and 49 years of age.
Version and date of the protocol	Amendment 2 Final: 15 August 2022
Main author	PPD, University of Massachusetts Chan Medical School
Rationale and background	Herpes zoster (HZ) vaccine, HZ/subunit (su), a 2-dose subunit zoster vaccine was approved by the Food and Drug Administration (FDA) in October 2017 for the prevention of HZ (shingles) in adults aged 50 years and older. In July 2021, FDA approved an expanded indication to adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy. In October 2021, the Advisory Committee of Immunization Practices (ACIP) recommended HZ/su for the prevention of HZ and its complications in adults aged ≥ 19 years who are or will be immunodeficient or immunosuppressed due to disease or therapy. Safety data on the use of HZ/su in pregnant women, including pregnant women with immunocompromised (IC) conditions, are critical in assessing the safety of the vaccine in real-world settings. This safety study will use a large, distributed research network (DRN) in the United States (U.S.) to rigorously evaluate the real-world safety of HZ/su during pregnancy, focusing on the specific infant and pregnancy outcomes. The primary outcome of interest is major congenital malformations (MCMs). Participating research partners include large national insurers that currently participate in the FDA's Sentinel Surveillance System. Pregnancies among women who are diagnosed with an IC condition of systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis (PsO), psoriatic arthritis (PsA), solid organ transplant (SOT), stem cell transplant (SCT), hematologic malignancies (HM), solid tumors (ST), and human immunodeficiency virus (HIV) will be identified from the DRN.
Research question and objectives	The study aim is to evaluate the safety of HZ/su exposure during pregnancy in women with IC conditions. The primary outcome of this cohort study is MCMs among live birth

	pregnancies (as defined in Section 9.3.2.1.1). Secondary outcomes include other infant/birth outcomes (preterm birth, small for gestational age (SGA), low birth weight (LBW), neonatal intensive care unit (NICU) admission, neonatal death), complications of pregnancy (placental abruption, preeclampsia and eclampsia), and pregnancy outcomes (live birth, stillbirths, spontaneous abortions).
Study design	This will be a population-based, non-interventional, cohort study among pregnant women. The aim is to study the risk of MCMs and additional infant and pregnancy outcomes among women with IC conditions exposed to HZ/su versus those unexposed during pregnancy. Pregnancies with start dates occurring during the period July 1, 2021 to June 30, 2026, and infants born to the women, will be included. Prior to initiating a cohort study, a feasibility assessment will be conducted to identify counts of exposed live birth pregnancies during the period July 1, 2021 to June 30, 2023. If the feasibility assessment determines that it is not possible to identify an adequate number of exposed live birth pregnancies among women with IC conditions for a cohort study, a descriptive analysis will be conducted. This descriptive analysis will describe the prevalence of infant and pregnancy outcomes among exposed and unexposed pregnancies with IC conditions during the period July 1, 2021 to June 30, 2023, with no statistical comparisons performed.
Population (Amended 15 August 2022)	The study population will be pregnancies among women 18 and 49 years of age (YOA) diagnosed with an IC condition who were members of three participating Sentinel Data Partners (DP). Additional eligibility criteria will include at least ***273*** days of continuous health plan enrollment with medical and drug benefits prior to the start of pregnancy through the delivery date, 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. Multigestation (e.g., twin) pregnancies will also be excluded.
Variables	Information about HZ/su exposure, demographics ***(maternal age, race/ethnicity, U.S. region of residence),*** maternal age, pregnancy start and trimester (estimated using claims-based algorithms), maternal comorbidities, healthcare utilization, infant/birth outcomes (MCMs, preterm birth, SGA, LBW, NICU admission, neonatal death), complications of

	pregnancy (placental abruption, preeclampsia and eclampsia), and pregnancy outcomes (live births, stillbirths, spontaneous abortions) will be collected from the healthcare electronic databases (health plan enrolment and claims data), supplemented with medical records to confirm MCMs. All conditions used to define the population, exposures, comorbidities, and outcomes will be identified using validated algorithms, where available.
Data sources	This study will be conducted using data provided by U.S. Data Partners in the FDA's Sentinel System. Three Data Partners will participate in this study: CVS Health Clinical Trial Services (CTS), HealthCore, Inc., and Optum. The study will use curated data that are formatted to the FDA Sentinel Common Data Model (SCDM) specifications [Curtis, 2012; Sentinel], 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 major congenital malformations.
Study size	All pregnancies among women who meet the study inclusion/exclusion criteria will be included in this study. Assuming a 1:3 ratio of HZ/su-exposed to unexposed, a type 1 error of 0.05, and a target risk ratio of 2.0 for the primary safety outcome (MCMs), 711 live birth infants (live birth pregnancies linked to infant records) from the HZ/su-exposed group and 2133 live birth infants from the unexposed group will allow us to achieve 90% power.
Data analysis	Wherever appropriate, the Mantel-Haenszel Chi-square test or Fisher exact test (univariate analysis) will compare the prevalence of each infant/birth outcome (MCMs and secondary outcomes of interest) between eligible live birth pregnancies among women with IC conditions who were vaccinated or not vaccinated with HZ/su 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. In addition, the prevalence of each outcome and their associated 95% confidence intervals (CIs) will be calculated among women with IC conditions who were exposed to HZ/su during pregnancy versus corresponding matched women who were not exposed to HZ/su during pregnancy. All analyses will be stratified by stage of pregnancy (pre-pregnancy, first trimester, second trimester, third trimester). Similar analyses will be conducted for pregnancy complications and outcomes among all eligible pregnancies.

5. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
2	15 August 2022	Abstract (Population)	Page 12	Regulatory Feedback
2	15 August 2022	Study Population	Section 9.2.1	Regulatory Feedback
2	15 August 2022	HZ/su Exposed Group	Section 9.2.1.2	Regulatory Feedback
2	15 August 2022	Outcomes	Section 9.3.2	Regulatory Feedback
2	15 August 2022	Other Variables	Section 9.3.3	Regulatory Feedback
2	15 August 2022	Annex and Appendices	Appendix A ICD-10-CM Codes for IC Conditions	Regulatory Feedback
2	15 August 2022	Annex and Appendices	Appendix B: Validated coding algorithms for IC conditions	Regulatory Feedback
2	15 August 2022	Annex and Appendices	Appendix C: Teratogenic and Fetotoxic Medications	Regulatory Feedback
2	15 August 2022	Annex and Appendices	Appendix I: Maternal Comorbidities	Regulatory Feedback
<1>	28 April 2022	Rationale and Background Research Question and Objectives Study Design Study Population Identification of Pregnancy Episodes and Gestational Age Assumptions HZ/su Exposed Group Comparison (Unexposed) Group	Refer to:Section 7 Section 8 Section 9.1 Section 9.2.1 Section 9.2.1.1 Section 9.2.1.2 Section 9.2.1.3	Regulatory feedback

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
		Outcomes Pregnancy Outcomes Other Variables Data Sources Characterization and use of HZ/su and IC conditions during pregnancy Sensitivity Analysis Limitations of the research methods	Section 9.3.2 Section 9.3.2.2 Section 9.3.3 9.4 9.7.1 9.7.2.3 Section 9.9.1	

6. MILESTONES

Milestone	Planned date
Final protocol submission	December 15, 2021
Start of data collection[1]	Q3 2021
End of data collection[2]	Q2 2028
Study completion (CSR)	April 30, 2029
Final report submitted to the FDA's Center for Biologics Evaluation and Research (CBER)	December 31, 2029

Note: the above timelines for the cohort study are tentative and subject to change.
[1] Start of study activities
[2] Date analytic dataset with chart-confirmed cases of last health outcome available for analysis

7. RATIONALE AND BACKGROUND

HZ vaccine, HZ/su, a 2-dose subunit zoster vaccine containing recombinant glycoprotein E in combination with a novel adjuvant (AS01B), was approved by the Food and Drug Administration (FDA) in October 2017 for the prevention of HZ (shingles) in adults aged 50 years and older. The ACIP recommends HZ/su vaccination for the prevention of HZ in immunocompetent adults ≥ 50 years of age (YOA) [Dooling, 2018]. In July 2021, FDA approved an expanded indication to adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy. In October 2021, the ACIP recommended HZ/su for the prevention of HZ and its complications in adults aged ≥ 19 years who are or will be immunodeficient or immunosuppressed due to disease or therapy. Prevention of HZ through vaccination with HZ/su will help address the high unmet medical need in this population. Safety data on the use of HZ/su in pregnant women, including pregnant

women with immunocompromised (IC) conditions, are critical in assessing the safety of the vaccine in real-world settings.

Women with IC conditions who receive frequent medical care typically consult with their healthcare providers when considering pregnancy and receive recommended vaccines prior to pregnancy. Recent data showed that almost half (45%) of pregnancies were unintended and that there has been a decline in the rate of unintended pregnancy among females 15 to 44 YOA by 18%, from 54 per 1000 women in 2008 to 45 per 1000 women in 2011 [Finer, 2016]. While the prevalence of unintended pregnancy in women with IC conditions is unknown, women with IC conditions may also experience unintended pregnancy. In such situations, women with IC conditions could be vaccinated with HZ/su before they are aware of their pregnancy. In addition, a pregnant woman could possibly be offered the vaccine if a positive benefit risk assessment is based on the burden of an IC disease and outcome [Kroger, 2011].

It is plausible that the number of vaccine exposures during pregnancy may increase with the expansion of the HZ/su indication to adults aged 18 and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy. Although currently unquantified, the number of pregnancy exposures is expected to be very low. This is likely only in the case of an unintended pregnancy because the vaccine is not recommended in this population, as per the Advisory Committee on Immunization Practice (ACIP) guidelines [Anderson, 2022].

Epidemiological evidence suggests that the risk of HZ in pregnant women with IC conditions is comparable to and sometimes exceeds the risk seen in the general female population [Gill, 2009; Nesheim, 2018]. Evidence also points at an increased prevalence of pregnancy among women with some IC conditions [Gill, 2009; Nabhan, 2010; Nesheim, 2018]. Table 1 describes the prevalence of IC conditions in pregnant women. Note that many of the estimates provided from published studies were obtained from diagnosis data reported in the inpatient setting (e.g., delivery hospitalization data); thus, estimates for some conditions (e.g., psoriasis (PsO), inflammatory bowel disease (IBD)) may be underestimated if the woman was not experiencing complications from the condition at the time of delivery admission.

Table 1 Prevalence of IC conditions in pregnant women

IC condition	Prevalence (%) among pregnant women delivering an infant
Human immunodeficiency virus	0.03-0.13 [Ahmadzia, 2020; Arab, 2017; Nesheim, 2018]
Solid organ transplant	0.005 (liver) [Armenti, 2005][1,2] 0.0005 (lung) [Shaner, 2012][1,2]
Stem cell transplant	Not available
Systemic lupus erythematosus	0.08-0.14 [Chakravarty, 2006; Clowse, 2008[2]; Mehta, 2019[2]]
Inflammatory bowel disease	0.09-0.13 [Getahun, 2014; Nguyen, 2009]
Rheumatoid arthritis	0.04– 0.07 [Chakravarty, 2006; Kerr, 2020; Kharbanda, 2021; Kerr, 2020; Kishore, 2019]
Multiple sclerosis	0.03-0.13 [Fong, 2018; MacDonald, 2019]
Psoriasis/ Psoriatic arthritis	0.03 [Boddeda, 2018][2]
Solid tumors	Not available
Hematological malignancies	Not available

1 As voluntarily reported to registry.
2 Self-calculation

Monitoring HZ/su exposure during pregnancy and evaluating its safety in pregnant women with IC conditions is important. While the number of women of reproductive age with IC conditions is substantial, data on the subset exposed to HZ/su during pregnancy have been limited. As part of the post marketing commitment, GSK in collaboration with the Harvard Pilgrim Health Care Institute (HPHCI), propose this real-world observational post-licensure study utilizing data from a distributed research network (DRN) to monitor and to evaluate pregnancy exposures to HZ/su in women between 18 and 49 YOA who are within the proposed indication, immunodeficient or immunosuppressed due to disease or therapy. By monitoring and evaluating the real-world safety in pregnant women with IC conditions who receive HZ/su during pregnancy and in their infants, this study will generate useful information for the patients and physicians in decision-making regarding vaccination against HZ in these at-risk populations.

8. RESEARCH QUESTION AND OBJECTIVES

The study will address the question of whether there is an increased risk of MCMs and additional infant/birth and pregnancy outcomes among women between 18 and 49 years of age with IC conditions exposed to HZ/su during pregnancy.

Primary objective:

1. Evaluate the prevalence of MCMs (as defined in Section 9.3.2.1.1) among live births from women with IC conditions exposed to HZ/su compared to those not exposed to HZ/su during pregnancy.

Secondary objectives:

1. Assess the prevalence of additional infant/birth outcomes (preterm birth, small for gestational age (SGA), low birthweight (LBW), neonatal intensive care unit (NICU) admission, neonatal death) among live births in women with IC conditions exposed to HZ/su versus those not exposed to HZ/su during pregnancy.
2. Assess the prevalence of pregnancy outcomes (livebirth, stillbirth and spontaneous abortion) and pregnancy complications (placental abruption, preeclampsia and eclampsia) among livebirth and non-livebirth pregnancies in women with IC conditions exposed to HZ/su versus those not exposed to HZ/su during pregnancy.

A feasibility assessment will be conducted (see Section 9.6.1.1). If the feasibility assessment determines that it is not possible to identify an adequate number of exposed live birth pregnancies among women with IC conditions for a cohort study, a descriptive analysis will be conducted. This analysis will describe the prevalence of infant and pregnancy outcomes among exposed and unexposed pregnancies with IC conditions, with no statistical comparisons performed (see Section 9.7.3).

9. RESEARCH METHODS

9.1. Study design

A population-based, non-interventional cohort study will be performed to identify and assess birth and pregnancy outcomes from HZ/su exposed pregnancies among women ages 18-49 years with IC conditions. A comparison group of pregnancies among women with IC conditions who were not exposed to HZ/su during pregnancy will be included and will serve as a reference to account for the contribution of different IC conditions on the safety outcomes of interest. The study will be conducted using health data held by three Data Partners that participate in the FDA's Sentinel System (described in Section 9.4).

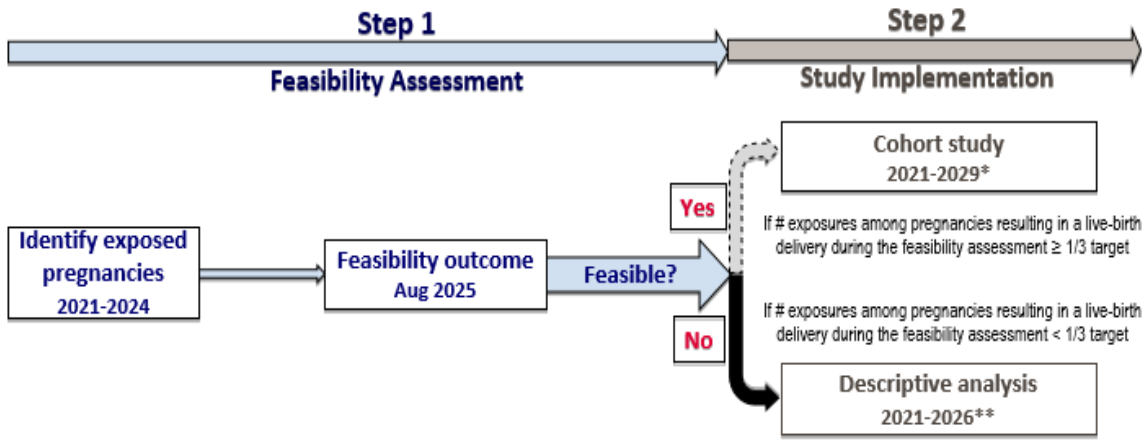
The study period for identification of exposed and unexposed pregnancies for the cohort study will be July 1, 2021 to June 30, 2026. MCMs and additional infant outcomes (preterm birth, SGA, LBW, NICU admission, neonatal death) will be assessed in pregnancies resulting in a live birth for which the mother is linked to an infant. Since infant outcomes are generally captured in the infant's health plan claims, the mother's and infant's claims will be linked (see Section 9.2.1). Infants born from these pregnancies (exposed and unexposed) will be followed for up to one year of age for assessment of MCMs, the primary outcome of interest. Pregnancy outcomes will be assessed in pregnancies resulting in a live birth, non-live birth (stillbirth, spontaneous abortion).

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. Only validated cases will be used for main descriptive or comparative analyses (see Section 9.3.2).

Prior to initiating a cohort study, a feasibility assessment will be conducted (see Section 9.6.1.1) to identify counts of exposed live birth pregnancies during the period July 1, 2021 to June 30, 2023. If the feasibility assessment determines that it is not possible to identify an adequate number of exposed live birth pregnancies (see Section 9.5) among women with IC conditions for a cohort study (i.e., ≥ 1/3 overall target), a descriptive analysis will be conducted (Section 9.7.3). The descriptive analysis will include HZ/su exposed and unexposed pregnancies (live birth and non-live birth pregnancies) among women with IC conditions identified in the feasibility assessment and their infants.

Figure 1 describes the steps and timelines for the identification of pregnancies and cohorts during the feasibility and study implementation periods.

Figure 1 Study design and study period overview



* The cohort study will identify HZ/su exposed and unexposed pregnancies for 5 years (July 1, 2021 to June 30, 2026). See Section 9.6.1 for a detailed description of the data collection period.
** The descriptive analysis will identify exposed and unexposed pregnancies for 2 years (July 1, 2021 to June 30, 2023). See Section 9.6.1 for a detailed description of the data collection period.
Note: Annual surveillance report schedule is described in Section 9.6.1.2.

9.2. Setting

The three participating Sentinel Data Partners are discussed in Section 9.4. All Data Partners have access to electronic healthcare data (including insurance claims data and/or electronic health record data) that will be used to identify the study cohorts, outcomes, and covariate information.

9.2.1. Study Population (Amended 15 August 2022)

The study population will include pregnancies among women who are diagnosed with IC conditions, with pregnancy start dates occurring during the period July 1, 2021 to June 30, 2026 (see Section 9.2.1.1 for description of the algorithm for estimation of pregnancy start dates). Singleton pregnancies among women who are diagnosed with IC conditions of systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), IBD, PsO or psoriatic arthritis (PsA), solid organ transplant (SOT), stem cell transplant (SCT), hematologic malignancies (HM), solid tumors (ST), and human immunodeficiency virus (HIV) prior to and during early pregnancy will be identified from the DRN. ***Validated algorithms in the CBER BEST assessment report [Saunders-Hastings, 2021] will be used to identify IC conditions including solid organ transplant (SOT), stem cell transplant (SCT), hematological malignancy (HM), solid tumor (ST,) human immunodeficiency virus (HIV), as these are specific to each IC condition as well as valid and consistent with the typical approaches that are used in Sentinel, as shown in Appendix B: Validated Coding Algorithms for IC conditions. ICD-10-CM Codes for IC (Appendix A) and validated coding algorithms that have high positive predictive values (PPVs), i.e. ≥75%, will be used to identify study participants who are IC.*** These IC conditions were selected because they have the highest risk of HZ, with a high prevalence in pregnant women with IC conditions (see Table 1).

For autoimmune diseases (AIDs) (systemic lupus erythematosus [SLE], multiple sclerosis [MS], rheumatoid arthritis [RA], inflammatory bowel disease [IBD], psoriasis [PsO], and psoriatic arthritis [PsA]), coding algorithms from the literature that are AID-specific (Appendix B) will be used instead of the coding algorithms in the CBER BEST assessment report [Saunders-Hastings, 2021], as the algorithms that are presented in this report are not AID-specific.

Pregnancies will be included in the study if the following inclusion criteria are met:

- Participant who is pregnant with a pregnancy start date between July 1, 2021 and June 30, 2026. Live births are to be followed for 1 year.
- Participant is a female aged 18-49 years on the pregnancy start date.
- Participant meets study definition of SLE, MS, RA, IBD, PsO/PsA, SOT, SCT, HM, ST, or HIV (see Appendix A: ICD-10-CM Codes for IC ***and Appendix B: Validated Coding Algorithms for IC conditions*****).** Codes for IC conditions will be identified in the health plan claims of the DRN during the period ***273*** days prior to the pregnancy start date through the first trimester (98 days after the pregnancy start date). 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.
- Participant has at least ***273*** days of continuous health plan enrollment with medical and drug benefits prior to the start of pregnancy through the delivery date, with gaps of up to 45 days in coverage being permitted. The ***273***-day pre-pregnancy period ***through the first trimester (a period of 98 days after the pregnancy start date)*** was chosen to allow identification of potential confounders of interest (Section 9.3.3). In Sentinel projects, gaps of 45 days or less in health plan enrolment are

typically considered administrative gaps (and not lapses in health plan coverage) and ignored.

Pregnancies will be excluded from the study if the following exclusion criterion is met:

- Participant was exposed to a medication(s) that presents a known increased risk for fetal malformations (see Appendix C: Teratogenic and Fetotoxic Medications)
- Participant delivered an infant identified as having a chromosomal or genetic anomaly (Appendix D: Diagnosis Codes for Chromosomal or Genetic Anomalies
- Ectopic pregnancies, molar pregnancies or induced abortions.
- Multigestation (e.g., twin) pregnancies.

For analyses evaluating infant outcomes (Primary Objective and Secondary Objective 1), the cohort will include pregnancies resulting in live births for which the mother is linked to an infant. Each Sentinel Data Partner will be responsible for linking mothers to infants using all available local data resources. Algorithms linking mothers to infants will vary across Data Partners, generally looking for equivalent health plan subscriber numbers, delivery dates and dates of birth, and shared names and addresses. Sentinel Data Partners are able to link approximately 74% of their infants to their mothers [Sentinel Initiative, 2018].

For analyses evaluating pregnancy outcomes (live birth, non-live births [stillbirth and spontaneous abortion]) and pregnancy complications (placental abruption, preeclampsia and eclampsia) (Secondary Objective 2), the cohort will include pregnancies resulting in a live birth and non-live birth (stillbirth), or spontaneous abortion.

For all analyses, the unit of analysis is a pregnancy episode.

9.2.1.1. 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. These tools use a claims-based algorithm previously validated in the FDA-sponsored Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP). The current study will use this algorithm to identify pregnancies ending in live births through identification of diagnosis and procedures codes listed in Appendix E: Live Birth Diagnosis and Procedure Codes. 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., LMP) using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes indicative of weeks of gestation, as well as ICD-10-CM codes for preterm and post-term deliveries in the inpatient care setting (Appendix F: Codes to Identify Preterm and Post-term Birth). 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 F: Codes to Identify Preterm and Post-term Birth. 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, 2006; Margulis, 2013]. The pregnancy start date (i.e., LMP) is then calculated by subtracting the gestational age from the date of the live birth delivery.

The LMP is widely accepted in electronic healthcare database safety studies as an estimate of the pregnancy start date and it is also in line with the European Medicines Agency (EMA) guidance. Numerous safety pregnancy studies have used LMP as an estimate of the pregnancy start date [Bateman, 2021; Hansen, 2016; Huybrechts, 2018; Kharbanda, 2021].

A published Sentinel study conducted within our Data Partners found $\geq$ 90% agreement within 7 days between the claims data and medical charts for gestational age at stillbirth and 100% agreement within 30 days. Thus, misclassification of LMP based upon our algorithm to determine gestational age and LMP is expected to be minimal [Andrade, 2021].

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, 2021] and Vaccine Safety DataLink (VSD) studies [Naleway, 2021].

9.2.1.2. HZ/su-Exposed Group (Amended 15 August 2022)

Among the eligible cohort of live birth pregnancies linked to an infant (Primary Objective and Secondary Objective 1 cohort) and among the cohort of all eligible ***live birth and non-live birth*** pregnancies (Secondary Objective 2 cohort), women with IC conditions exposed to HZ/su during pregnancy will be identified. Exposure will be further categorized by stage of pregnancy: pre-pregnancy, first trimester, second trimester, and third trimester. The first trimester of pregnancy will be defined as 0 to < 14 weeks gestation, the second trimester as 14 to < 28 weeks, and the third trimester as 28 weeks through the end of the pregnancy.

A 30-day pre-pregnancy period (prior to LMP) will be included. There is no safety signal that would indicate that there is a risk pre-pregnancy. However, published vaccine safety studies have included varying pre-pregnancy periods [Kerr, 2020, Kharbanda, 2021, Panagiotakopoulos, 2020]. More recently published studies have included no pre-pregnancy or up to a 42-day pre-pregnancy period.

9.2.1.3. Comparison (Unexposed) Group

Unexposed pregnancies among women with IC conditions who were not vaccinated with HZ/su (i.e., not receiving at least one dose of HZ/su during pregnancy) will be selected as a comparator with a 3:1 matching ratio to the pregnancies among women with IC conditions who were vaccinated with at least one dose of HZ/su (exposed pregnancies). This matching ratio of 1:3 was chosen because it is feasible, reduces bias and increases precision. Matching will be conducted separately for the eligible cohort of live birth pregnancies linked to an infant (Primary Objective and Secondary Objective 1 cohort) and among the cohort of all eligible live birth and non-live birth pregnancies (Secondary Objective 2 cohort).

We will monitor and evaluate the 1:3 matching plan during the feasibility assessment to see how the matching plan performs.

If the proposed matching plan performs poorly in practice (i.e., many unmatched HZ/su-exposed pregnancies would be excluded), we propose the following alternative matching plans:

a. Exact match strategies:
   - Exactly match on DP, combined primary IC condition categories, maternal age (± 10 years), start date of the pregnancy period (± 120 days)
   - Exactly match on DP, combined primary IC condition categories, start date of the pregnancy period (± 120 days) and put age in the propensity score

b. Propensity match strategies: Nearest neighbor matching with caliper width at 0.02, 0.03, 0.04, 0.05, 0.1 and 0.2 between propensities of the unexposed HZ/su and the HZ/su exposed

We will consider reducing the matching ratio of HZ/su-exposed to unexposed to 1:2 or 1:1 if the desired sample size cannot be achieved even with the relaxed matching plan. The corresponding sample size for 1:2 ratio will be 2436 (812 exposed and 1624 unexposed) and 2216 for 1:1 ratio (1108 exposed and 1108 unexposed) when maintaining the other assumptions (i.e., 90% power, 3% MCM prevalence, a type 1 error of 0.05 and a target risk ratio of 2.0).

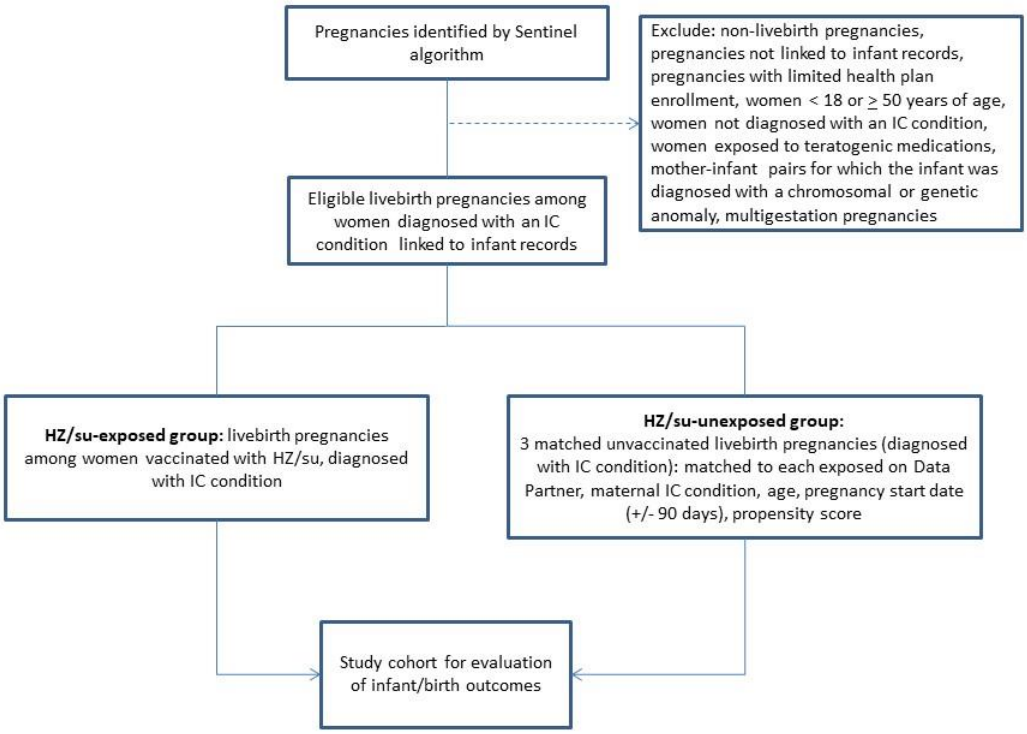
The unexposed pregnancies must be pregnant/reached the week of gestational age of the exposed pregnancy (i.e., when exposure occurred) without an adverse event (i.e., spontaneous abortion or stillbirth).

Matching with a propensity score will minimize confounding bias due to differences between the HZ/su-exposed and comparator unexposed group. Propensity score matching is discussed below (Sections 9.3.3 and 9.7). Matching on DP, maternal age, and the start date of the pregnancy period, will control for DP differences in HZ/su use, age effects, and potential secular trends in HZ/su use and obstetric outcomes.

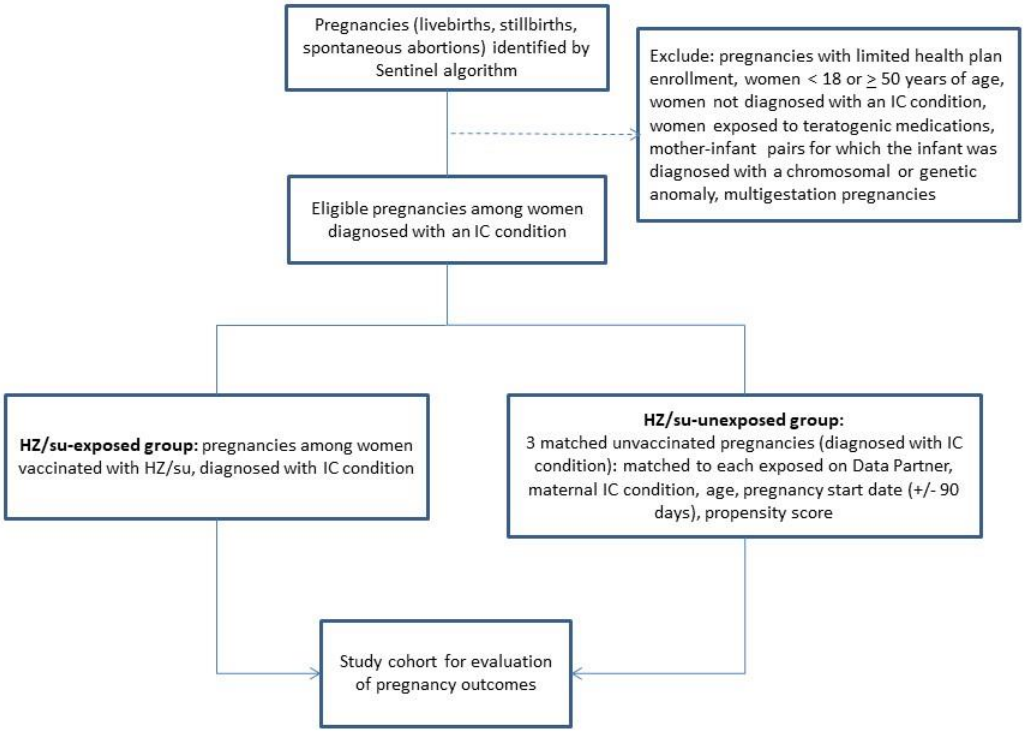
For each of these study samples, the unit of analysis is a pregnancy episode (Figure 2).

Figure 2 Study schema on study populations for the assessment of infant outcomes and pregnancy outcomes

Panel 1: Study Population for the Assessment of Infant Outcomes



Panel 2: Study Population for the Assessment of Pregnancy Outcomes



9.3. Variables

9.3.1. Exposure

Among the eligible cohort of live birth pregnancies linked to an infant (Primary Objective and Secondary Objective 1 cohort) and among the cohort of all eligible live birth and non-live birth pregnancies (Secondary Objective 2 cohort), HZ/su exposure will be defined as receipt of at least one dose of HZ/su during pregnancy. HZ/su vaccination will be identified by means of CPT code 90750 and National Drug Code (NDC) codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11. We may include additional codes for identification of HZ/su exposure if relevant codes become available in the future. Pregnancies among women receiving at least one dose of HZ/su during pregnancy will be considered exposed. If a woman receives the vaccine before the start of pregnancy but does not receive the vaccine during the 30-day pre-pregnancy period or during pregnancy, she will not be considered exposed and would be considered for the comparator unexposed group. As described in Section 9.2.1.2, exposure will be further categorized by stages of pregnancy: pre-pregnancy, first trimester, second trimester, third trimester.

9.3.2. Outcomes (Amended 15 August 2022)

Outcomes to be evaluated include MCMs and additional infant/birth outcomes (preterm birth, SGA, LBW, NICU admission and neonatal death), complications of pregnancy (placental abruption, preeclampsia and eclampsia) and pregnancy outcomes (live birth, non-live birth [stillbirth and spontaneous abortion]). The primary outcome of this cohort study is MCMs of the infants.

As indicated in Section 9.2.1., the IC diagnoses of pregnant women and pregnancy outcomes will be identified from the health plan claims of the DRN containing ICD-10-CM Codes for IC conditions ***and validated coding algorithms for IC conditions*** during the period ***273***days prior to the pregnancy start date through the first trimester (98 days after the pregnancy start date).

MCMs will be confirmed through chart review. Other outcomes will not be confirmed through chart review. Many of these ICD-10-CM algorithms for the secondary outcomes have not yet been validated. We will conduct a literature search prior to final analysis to determine potential validated algorithms for these secondary outcomes. Recent published studies provide evidence of the validity of ICD-10-based algorithms to identify adverse pregnancy outcomes. An international study reported moderate to high PPVs for ICD-10 codes for select secondary outcomes proposed in this study: 76.4% for LBW; 70.4% for SGA; 81.2% for preeclampsia [Watson, 2021].

Another recently published study in a US population reported higher PPVs for ICD-10-CM codes for preeclampsia and eclampsia (ranging from 89-100%) [Labgold, 2021]. In addition, an ongoing Sentinel COVID-19 pregnancy study, used ICD-10-CM codes to identify adverse pregnancy outcomes including preeclampsia/eclampsia, SGA and LBW. These algorithms were approved by the FDA team in the Hua 2021 study. Pregnancy episodes ending in a non-live birth pregnancy outcome will be identified using validated algorithms developed through Sentinel and non-Sentinel (e.g., VSD) projects [Andrade, 2021; Naleway, 2021].

9.3.2.1. Infant/Birth Outcomes (Primary Objective and Secondary Objective 1)

Infant/birth outcomes to be evaluated include MCMs, preterm birth, SGA, LBW, NICU admission, and neonatal death. These outcomes will be identified in claims data through diagnosis codes among live births for which the mother and infant are linked (Section 9.2.1). Codes for placental abruption, preeclampsia, and eclampsia will be identified in the mothers' claims. For selected outcomes (MCMs, SGA, LBW, NICU), 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 $\leq$ 30 days after birth) especially when there is a delay in the enrolment of the infant in the health plan.

9.3.2.1.1. Major Congenital Malformations

An 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 major congenital malformations observed in live births compiled from the National Birth Defects Prevention Study (NBDPS) and the European Surveillance of Congenital Anomalies is provided in Appendix G Major Congenital Anomalies [Boyd, 2011; CDC, 2020; Rasmussen, 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 D: Diagnosis Codes for Chromosomal or Genetic Anomalies), 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 major congenital malformations. Data for infants 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 (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 ICD-9-CM code for SGA, the positive predictive value (PPV) and specificity were high [Phiri, 2015]. Although the sensitivity of the SGA code was low, this study also showed that if misclassification is non-differential with respect to exposure, the relative risk estimates will be nearly unbiased for evaluations of factors associated with SGA.

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. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes for preterm delivery and for gestational age < 37 weeks (Appendix F). Codes to Identify Preterm and Post-term Birth) are incorporated in the algorithm to determine pregnancy periods.

9.3.2.1.4. Low Birth Weight

LBW is a birth weight of < 2,500 grams. LBW (ICD-10-CM P05.0X, P07.0X, P07.1X) 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.

9.3.2.1.5. NICU Admissions

NICU admissions (CPT codes 99468, 99469) 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. A prior study reported a high PPV for NICU codes recorded in the mother's and infant's claims data (PPV=92%) [Andrade, 2012].

9.3.2.1.6. Neonatal Deaths

Potential infant deaths during the 28 days after birth will be identified in hospital discharge disposition data included in the health plan claims files.

9.3.2.1.7. Placental Abruption

Placental abruption (ICD-10-CM O45.X) will be identified by searching the mother's claims from 20 weeks gestation through the date of delivery.

9.3.2.2. Pregnancy Complications and Outcomes (Secondary Objective 2)

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. Placental abruption (ICD-10-CM O45.X) will be identified by searching the mother's claims from 20 weeks gestation through the date of delivery. Preeclampsia and eclampsia (ICD-10-CM O11.X, O14.X, O15.X) will be identified by searching the mother's claims from 20 weeks gestation through the date of delivery. A prior study conducted at one U.S. hospital found that the sensitivity of preeclampsia and eclampsia inpatient codes are generally low, however the PPV and specificity were high [Labgold, 2021].

Pregnancy outcomes will be identified in claims data through diagnosis and procedure codes (Appendix E. Live Birth Diagnosis and Procedure Codes and Appendix H. Spontaneous Abortion and Stillbirth Codes). Pregnancy episodes resulting in a live birth will be identified using validated algorithms (see Section 9.2.1.1) that have been used in Sentinel and non-Sentinel projects [Andrade, 2012; Andrade, 2016; Johnson, 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, 2021; Naleway, 2021].

9.3.3. Other Variables (Amended 15 August 2022)

The propensity score reflects the conditional probability of a woman being exposed to HZ/su during pregnancy given baseline potential confounders. Potential confounders to be used in the estimation of the propensity score will be identified in the ***273*** 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. Separate propensity score models will be fit for the cohorts of eligible live birth pregnancies and cohorts of all eligible pregnancies. Information about variables that may predict the likelihood of exposure will be collected from health plan claims data. These variables will include maternal age, calendar year, maternal comorbidities (Appendix I:. Maternal Comorbidities), tobacco use, alcohol use, drug dependence, maternal obesity, and maternal race/ethnicity, and U.S. region of residence (Midwest, West, South, Northeast). In addition, the number of healthcare encounters (outpatient, emergency department, inpatient) in the ***273*** days preceding the pregnancy start date will be identified.

The propensity score model will be fit separately for each DP and matching on the propensity score will occur within DP. The propensity score will be calculated by each DP using logistic regression. The main reason to use DP-specific propensity score is to protect sensitive individual and institutional information. It is also desirable to generate and match propensity scores within DP and match within DP because DP can be representative of background variables at the DP level (e.g., insurance coverage), which will not be available at individual level. The large number of enrollees of each DP is additional assurance that the best control will be within DP. Further description of the analytical steps of the data is provided in the SAP.

At least 15 FDA sponsored Sentinel safety studies were displayed when searching the keyword “propensity score” in the referenced web address using a similar propensity score matching approach with multiple DPs. Two examples are provided here:

1. Sixteen DPs participated in an analysis assessing the risk of cutaneous small-vessel vasculitis associated with the use of direct oral anticoagulant and warfarin among patients with atrial fibrillation aged 21 to 99 years. The final report is provided on the Sentinel web site.
2. Four DPs participated in a study estimating the risk of intentional self-harm and hospitalized depression comparing brand name sertraline to its authorized generic using. Four reports are provided on the Sentinel web site.

Because nearest neighbor matching tends to result in less biased estimates compared with the other matching algorithms [Austin, 2014], Sentinel developed SAS macros to facilitate such a matching algorithm. The general framework of using distributed network to conduct propensity score matching and distributed regression analysis has been developed by Sentinel [Toh, 2020] and used extensively for Federal or Patient-Centered Outcomes Research Institute (PCORI) sponsored comparative effectiveness and safetystudies [Toh, 2020].

9.4. Data sources

This study will be conducted using health plan data held by three DPs (CVS Health CTS, HealthCore, and Optum) that are national insurers 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 pregnancy exposures studies and other HZ/su studies. In addition, all have experience in 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 United States, established under the Sentinel Initiative [Bateman, 2021; Platt, 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 DPs are provided below:

- **CVS Health** 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 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.
- **Optum (UnitedHealth).** Initially founded as Epidemiology Research Institute, and later acquired in 1999 by Ingenix (renamed to Optum), Optum Epidemiology has a nearly 40-year history in regulatory drug safety research. Optum Epidemiology scientists leverage their extensive applied experience with real world data sources to inform the design and implementation of clinical and pharmacoepidemiology

research; safety profile and effectiveness evaluations; and risk assessment. Optum's rich data assets include the Optum Research Database comprised of administrative claims data from health plans of a large U.S. national health insurer, with data beginning in 1993. For 2017, data are available for approximately 14.6 million commercially insured individuals with medical and pharmacy coverage. Additional Optum data assets include Electronic Health Records.

The DPs use the Sentinel Common Data Model (SCDM) for standardization of demographic and clinical data elements [Curtis, 2012; Sentinel]. 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 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, 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 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 HCPCS levels II and III codes. ICD-10-CM Procedure Coding System and CPT 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 electronic health record (EHR) is accessible), and how far back records are requested. We expect chart reviews to be conducted for approximately 5% of pregnancies based on validation studies [Andrade, 2013; Cheetham, 2020; Cooper, 2008; Hansen, 2016; He, 2020]. 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 will be included in this study.

As the IC conditions included are heterogeneous and the number of MCMs for the primary outcome is likely small, the prevalence of each MCMs among each IC condition under study is not available. For sample size calculation for the cohort study, we employed the prevalence of overall MCMs (3%) in the general population [Holmes, 1976; Leppig, 1987; Marden, 1964; Van Regemorter, 1984] which might have a lower prevalence than among women with IC conditions. Therefore, the sample size calculated is relatively conservative. Assuming a 1:3 ratio of HZ/su-exposed to unexposed, a type 1 error of 0.05, and a target risk ratio of 2.0 for the primary safety outcome of MCMs, 711 live birth infants (live birth pregnancies linked to infant records) from the HZ/su-exposed group and 2133 live birth infants from the unexposed group will allow us to achieve 90% power.

The Power Analysis and Sample Size software (NCCS Statistical Software) was used in the sample size calculation.

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, 2021] and Joint Task Force Transformation Initiative 2017).

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 Innovation in Medical Evidence Development and Surveillance (IMEDS) program, the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) and Patient-Centered Clinical Research Network (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 and budgets, 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. Data Collection Period

Data collection (start of study period) is anticipated to begin July 1, 2021. As the number of pregnant women with IC conditions who receive HZ/su during pregnancy is expected to be small, two steps are proposed for this study. A feasibility assessment (Section 9.6.1.1) will be conducted first to determine whether sufficient numbers of live births from vaccinated pregnant women with IC conditions could be identified, followed by either a cohort study or descriptive analysis depending on the outcome of the feasibility assessment (see Figure 1).

The feasibility assessment will identify live birth deliveries from vaccinated and unvaccinated pregnant women with IC conditions for two years (July 1, 2021, to June 30, 2023). When the feasibility assessment is completed, the total number of eligible (HZ/su-exposed with live birth) pregnancies will be calculated. If target numbers are reached a full-scale cohort study will be conducted. If target numbers are not reached in the feasibility assessment period, a descriptive analysis will be conducted (see Section 9.7.3).

The cohort study will identify HZ/su exposed and unexposed pregnancies for 5 years (July 1, 2021 to June 30, 2026), including 2 years rolled from the feasibility assessment and 3 additional years. The last pregnant woman will be enrolled on June 30, 2026; but, since the expected pregnancy period will be approximately 9 months, follow-up of pregnant women will continue until March 30, 2027. Infants will be followed for up to one year after birth, with data collection ending Q1 2028. Data tables will be completed in Q3 2028. The clinical study report will be completed on April 30, 2029 and submission of the clinical study report to FDA will be completed on December 30, 2029.

The descriptive analysis will include HZ/su exposed and unexposed pregnancies (live birth and non-live birth pregnancies) among women with IC conditions identified in the feasibility assessment and their infants (July 1, 2021 to Jun 30, 2023). Infants will be followed up for up to one year after birth, with data collection ending in Q1 2025. The clinical study report will be completed in Q3 2026 and submission of the clinical study report to FDA will be completed in Q4 December 2026.

9.6.1.1. Feasibility Assessment

During the feasibility period, annual assessments will be conducted to summarize the counts of HZ/su-exposed and unexposed live birth pregnancies among women with IC conditions (18-49 YOA). The counts of exposure to at least one dose of HZ/su will be stratified by calendar year of delivery, maternal age at pregnancy start date (5-year age groups), and IC condition.

Counts of women of childbearing age (18-49 YOA) with IC conditions who are HZ/su-exposed and unexposed will similarly be determined.

If the number of HZ/su-exposed pregnancies (live birth pregnancies linked to an infant) identified during the feasibility assessment is equal to or above 1/3 of the number of HZ/su-exposed pregnancies needed for the cohort study (n = 711 for cohort study and n = 237 for feasibility assessment, respectively), the feasibility assessment outcome will be categorized as 'Yes'. This indicates the target number of exposed pregnancies linked with live births could probably be identified during the five-year cohort study identification period, although it is not guaranteed.

If the number of HZ/su pregnancies identified during the feasibility assessment is less than one third of the target number of exposed pregnancies needed for the cohort study (i.e., n >237), the feasibility assessment outcome will be categorized as 'No'. Should this be the case, the descriptive analysis, rather than the cohort study, will be conducted.

9.6.1.2. Annual surveillance reports

Annual surveillance reports will be developed during the period when live-birth pregnancies are identified in the feasibility assessment (2021-2024; including pregnancies identified during the period July 1, 2021- June 30, 2023). Annual surveillance reports will continue to be developed as data accrue during the period of the cohort study (2025-2028; including pregnancies identified during the period July 1, 2021- June 30, 2026) or during period of the descriptive analysis (2025; including only pregnancies identified during the period July 1, 2021- June 30, 2023), as relevant.

9.7. Data analysis

Whenever possible, publicly available Sentinel analytic tools will be used for the distributed analyses; these are the same tools used by FDA for similar analyses. 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. Characterization of Use of HZ/su and IC Conditions During Pregnancy

Annual descriptive analyses to estimate the counts of HZ/su exposed pregnancies among women with IC conditions will be performed. Data from the first two years will be used to determine the feasibility of a full-scale cohort study (see Section 9.6.1.1). Analyses will be performed in the cohort of pregnant women aged 18 to 49 years diagnosed with IC conditions meeting health plan enrollment (medical and pharmacy benefits) inclusion criteria. The analysis will be conducted for pregnancies resulting in live births. The counts of pregnancies exposed to HZ/su overall and in each trimester (including a 30-day pre-pregnancy period) will be estimated. Counts of pregnancies unexposed to HZ/su will be tabulated by maternal age, calendar year of pregnancy outcome, and IC condition. Similarly, counts of women of childbearing age (18 to 49 years) exposed to HZ/su with IC conditions will be estimated.

9.7.2. Cohort Study

If the feasibility assessment (Section 9.6.1.1) identifies that the number of HZ/su-exposed pregnancies is equal to or above the target number of exposed pregnancies, a subsequent cohort study will be conducted.

Infant/birth outcomes and pregnancy complications will be assessed among eligible live birth pregnancies linked to infant records. Pregnancy outcomes will be assessed in the population of all pregnant women meeting eligibility criteria.

Propensity scores and matching will occur within each Data Partner. Potential confounders are described in Section 9.3.3. The methodology will be described in detail in the Statistical Analysis Plan (SAP).

9.7.2.1. Primary Objective and Secondary Objective 1

The Mantel-Haenszel Chi-square test or Fisher exact test (univariate analysis), wherever appropriate, will be employed to compare the prevalence of the primary outcome (MCMs) between eligible live birth pregnancies among women with IC conditions who were vaccinated with HZ/su during pregnancy and those who were not vaccinated with HZ/su 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. In addition, the prevalence of MCMs and their associated 95% CIs will be calculated among women with IC conditions who were exposed to HZ/su during pregnancy versus the corresponding matched women who were not exposed to HZ/su during pregnancy. All analyses will be stratified by stage of pregnancy (pre-pregnancy, first trimester, second trimester, third trimester).

Similar methods will be used for each of the secondary infant/birth outcomes (e.g., preterm birth, SGA, LBW, NICU admission, neonatal death).

9.7.2.2. Secondary Objective 2

Pregnancy outcomes will be compared between eligible pregnancies among women with IC conditions who were vaccinated with HZ/su during pregnancy and those who were not vaccinated with HZ/su during pregnancy. Univariate and multivariable statistical analyses will be performed as stated in the primary objective and secondary objective 1 (Section 9.7.2.1) for all outcomes. The prevalence of the pregnancy outcomes (live birth, stillbirth, and spontaneous abortion) and pregnancy complications (placental abruption, preeclampsia and eclampsia) and their 95% CIs will be calculated between the two groups of women. All analyses will be stratified by stage of pregnancy (pre-pregnancy, first trimester, second trimester, third trimester).

9.7.2.3. Sensitivity analyses

To ensure the robustness of the results, we will conduct sensitivity analyses to address the potential misclassification of the outcomes, potential unobserved confounders, and potential selection bias. When conducting the propensity score matching, we will use the nearest neighborhood matching with caliper width equal to 0.01 of the propensity score as the primary choice [Austin, 2010]. Other choices of caliper (i.e., 0.02 to 0.051) will also be compared to strike a desirable balance between the sample size and balances of baseline characteristics. Detailed sensitivity analyses and assessment of potential biases are documented in the SAP.

9.7.3. Descriptive Analysis

If the feasibility assessment (Section 9.6.1.1) identifies that the number of HZ/su-exposed live birth pregnancies identified during the feasibility assessment is less than one third of the number of HZ/su-exposed live birth pregnancies needed for the cohort study, a descriptive analysis will be conducted among all HZ/su-exposed pregnancies and their matched comparators. Prevalence and 95% CIs of MCMs and additional infant/birth, complications of pregnancy, and pregnancy outcomes will be estimated in the matched HZ/su-exposed and unexposed cohorts. Additional analyses will not be conducted.

9.7.4. Statistical Analysis Plan

Detailed methodology for summary and statistical analyses of data collected in this study including sensitivity analyses and assessment of potential biases 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 above, 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 quality assurance procedures as the Sentinel

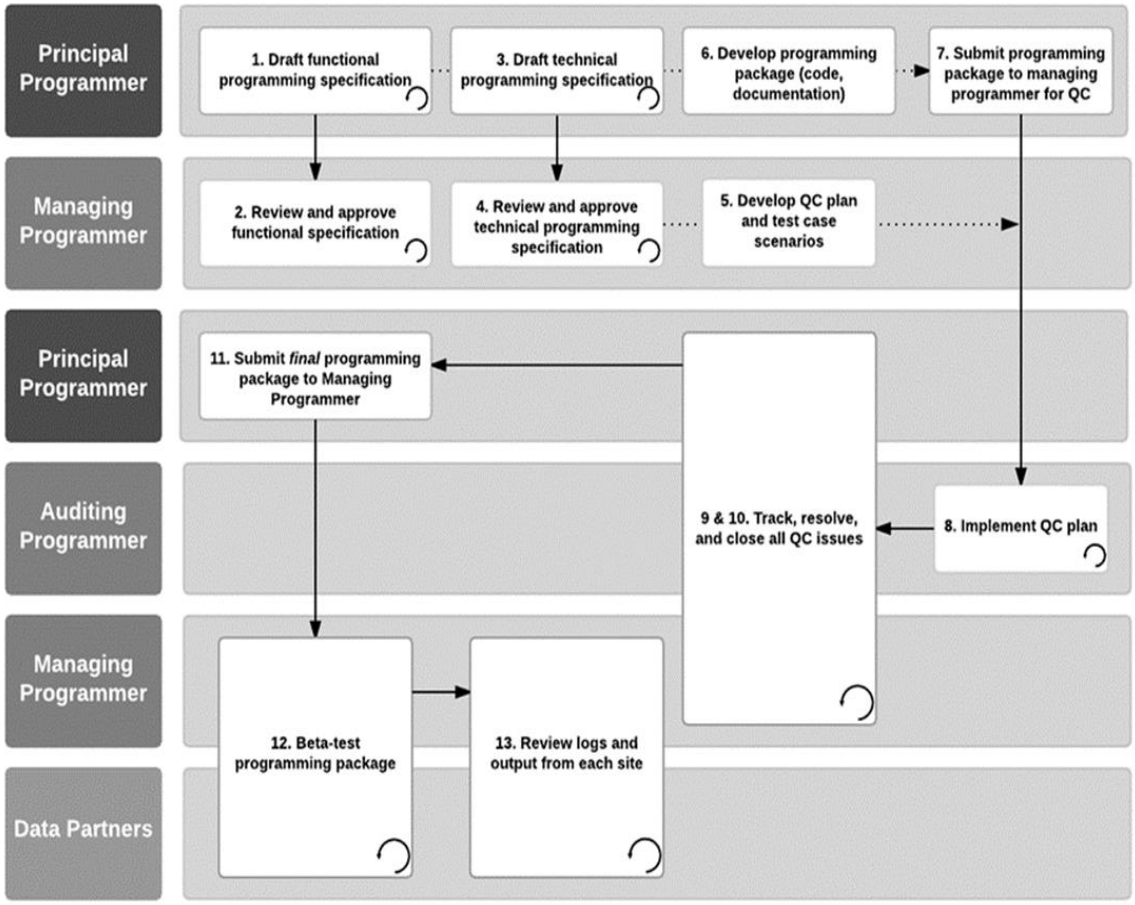
System and the same curated datasets used by FDA to conduct Sentinel analyses. The quality assurance approach assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across DPs. Full quality assurance processes and details on the Sentinel data curation approach are documented on the Sentinel website [Sentinel Initiative, 2021]. The data curation approach is consistent with guidance set forth by the FDA in its current recommendations for data quality assurance, specifically, "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (Guidance), section IV.E "Best Practices – Data Sources: QA and Quality Control", published in May 2013 [FDA, 2013].

The Quality Assurance 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.

In addition to quality assurance of data elements, HPHCI adopts standard SAS programming quality assurance and quality control processes used by the Sentinel System to check SAS programs and deliverables. Figure 3 illustrates the SOPs for SAS programming quality assurance and quality control 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 3 Standard Operating Procedure for SAS Programming Quality Assurance and Quality Control in the Sentinel System



9.9. Limitations of the research methods

9.9.1. Limitations of the research methods

Several limitations are inherent in the conduct of studies of vaccine 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, and potential confounders can occur. In addition, only medically attended events are recorded in the healthcare database, 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, 2018], which would likely not be related to vaccine exposures. In addition, some secondary outcomes of interest will be rare and may be difficult to assess within the study period (e.g., neonatal death). Neonatal deaths will only be captured in hospital discharge data which may lead to under ascertainment of this outcome.

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. Some potential covariates are incompletely captured in the health plan data, e.g., over-the-counter (OTC) folate intake, alcohol use, and tobacco use. This limitation relates to the constraint about claims databases. Some confounders (e.g., alcohol use) will not be completely captured although we do not expect the capture will differ by the exposure. We will conduct a sensitivity analysis to exclude such variables and treat them as unmeasured confounders. A detailed description of the bounding factor is provided in the SAP Section 8.7.1 to estimate the magnitude of effect of an unobserved confounder needed to change the statistical inference. We will also compare the results with and without such covariates.

The linkage of the infants to their mothers has been found to be approximately 70-80% and infants without linkage to their mothers will not be included in current study. Another potential for selection bias exists given that we will evaluate the risk of MCMs (primary 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 cohort study. Thus, a feasibility assessment will be conducted to determine whether it is practical to conduct the cohort study. If an inadequate number of exposed live births are identified in the feasibility assessment, a descriptive analysis 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 U.S., and may only represent the commercially insured patient population in the U.S.

9.9.2. Strengths of research methods

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 (i.e., bias introduced when competing events are examined separately).

Using electronic healthcare data to assess the risk of birth and pregnancy outcomes after exposure to HZ/su overcomes many challenges associated with conducting a traditional pregnancy registry. The electronic healthcare data approach differs from a traditional pregnancy registry that passively collects information on women exposed to the product in a prospective format. The traditional pregnancy registry may fail to provide clinically meaningful information because of selection bias due to the limited number of pregnant women voluntarily enrolled in the registry, difficulty in recruiting an appropriate comparison group, and loss to follow-up. Using electronic healthcare data with a well-defined population can overcome some limitations of the 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 primary 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 and consent

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

The study will be conducted with a waiver of informed consent. This study will involve numerous individuals from multiple health plans and delivery systems. Thus, it could not be practically conducted without a waiver of informed consent. The proposed study has minimal risk; potential breaches of privacy and confidentiality are the primary study risks These risks will be minimized by ensuring that rigorous security procedures are applied to data collection, management, and transfer. Some of these procedures include using a study identification number in place of direct patient identifiers; transferring data using secure, encrypted websites; and ensuring that appropriate data transfer agreements are in place between institutions prior to data sharing. Additionally, only trained and authorized study staff will be allowed to access study data Secure data storage methods, such as password-protected electronic files and locked paper files, will be used by all participating DPs and the data Coordinating Center at HPHCI.

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

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.

10.3. Ethical conduct of the study

The study will be conducted in accordance with all legal and regulatory requirements. Additionally, we will adhere to commonly accepted research practices, including those described in the following guidance documents: European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [EMA, 2018], Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology [ISPE, 2015], FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [FDA, 2005] and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets [FDA, 2013].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The current non-interventional safety study will be based on secondary use of data previously captured from consumers or healthcare professionals for other purposes. Data to be used in this study will include medical chart reviews (including follow-up on data with healthcare professionals) and electronic healthcare records. Therefore, the submission of individual cases of adverse events/adverse reactions is not required.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Posting of information on publicly available registers and publication policy

Study information from this protocol will be posted on the publicly available GSK register following finalization of the protocol and prior to start of data collection.

GSK also aims to publish the results of these studies in the searchable, peer-reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis. At the time of publication, this protocol will be fully disclosed. Any publications will follow guidelines, including those for authorship (e.g., guidelines established by the International Committee of Medical Journal Editors 2018) and for reporting of observational studies in epidemiology (e.g., Strengthening the Reporting of Observational Studies in Epidemiology 2007) [Von Elm, 2007].

Posting of study protocols and results will be done according to the following:

Observational studies evaluating a product:

- The key design elements of this protocol and results summaries will be posted on the GSK Clinical Study register and Clinicaltrials.gov register in compliance with the applicable regulations/GSK policy according to the timelines described below. Key

design elements of this protocol will also be posted on The European Union electronic "Register of Post-Authorisation Studies" (EU PAS Register) in compliance with the applicable regulation. Redacted version of the full protocol will be published on the EU PAS register prior to start of data collection.

- Protocol summaries will be registered prior to start of data collection.
- Results summaries along with protocol and SAP will be posted within 12 months of analysis completion date.
- Where required by regulation, summaries will also be posted on applicable national or regional registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK Biologicals will also provide the investigator with the full summary of the study results.

Post-authorization safety study:

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports.

12.2. Provision of study reports to regulatory authorities

The final study report will provide an overview of the study background, objectives, methods, and findings and will be submitted to regulatory agencies by the vaccine manufacturer. Final study results, as well as the main methodological components developed as part of this study, will be disseminated as oral or poster presentations at scientific meetings and as peer-reviewed publications.

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14. ANNEXES AND APPENDICES

Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	214420	15 August 2022	List of stand-alone documents
2	214420	15 August 2022	Glossary of terms
3	214420	15 August 2022	List of principal and coordinating investigators
4	214420	15 August 2022	Sponsor Information
5	214420	15 August 2022	Additional Information
6	214420	15 August 2022	Protocol Investigator Agreement
7	214420	15 August 2022	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Adverse event (AE):	Any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Adverse Event of Special interest (AESI):	An AESI is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.
Database:	A database is a set of pre-existing tables and views containing data. The term "pre-existing" implies that the analysis will be done on retrospective data and the term "views" implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc.).
Database study:	A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-) encoding via CRF/electronic CRF and retesting of human biological samples.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
eTrack:	GSK's tracking tool for clinical/ epidemiological trials.

Immunocompromised condition	Participants that are immunocompromised are those who are at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy.
Key coded information:	Refers to encoded or otherwise pseudo-anonymized PII from which direct identifiers have been removed and replace by a unique identifier or random code. Key coded PII shall not be considered anonymized information.
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Participant:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database. Synonym: subject
Post-Authorization Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorization and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorization' means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).
Primary completion date:	Primary completion date is defined as the date of final collection of data for all primary outcomes/endpoints.
Prospective study:	A study in which the participants/cases are identified and then followed forward in time in order to address one or more study objectives. A prospective study usually involves primary data collection.

Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. Note: Any change that falls under the definition of a protocol amendment (e.g., a change that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Protocol amendment:	The International Council on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Retrospective study:	A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Study population:	Sample of population of interest.
Surveillance	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

Annex 3 List of principal and coordinating investigators

The list of investigators and their contact details are available upon request.

Annex 4 Sponsor Information

1. Sponsor:

GlaxoSmithKline Biologicals (GSK)
Rue de l'Institut, 89
1330 Rixensart, Belgium

2. Sponsor medical expert for the study: Agnes Mwakingwe-Omari

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

4. Study contact for reporting of a Serious Adverse Event (SAE):

GSK central back-up study contact for reporting SAEs: refer to protocol Section 11 Management and reporting of adverse events/adverse reactions.

Study contact for reporting SAEs: refer to the local study contact information document.

Annex 5 Amendments to the protocol

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	15 August 2022
Amendment 1	02 May 2022
Protocol	24 November 2021

Detailed description of the current Protocol amendment

a. List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Abstract (Study Population) Page 12	Additional eligibility criteria will include at least ~~183~~ ***273*** days of continuous health plan enrollment	Define minimum requirement for days of health plan enrollment.
9.2.1 Study Population Page 21	…. ***Validated algorithms in the CBER BEST assessment report [Saunders-Hastings, 2021] will be used to identify IC conditions including solid organ transplant (SOT), stem cell transplant (SCT), hematological malignancy (HM), solid tumor (ST,) and human immunodeficiency virus (HIV), as these are specific to each IC condition as well as valid and consistent with the typical approaches that are used in Sentinel, as shown in Appendix B: Validated Coding Algorithms for IC conditions. ICD-10-CM Codes for IC (Appendix A) and validated coding algorithms that have high positive predictive values (PPVs), i.e. >75%, will be used to identify study participants who are IC.*** These IC conditions were selected because they have the highest risk of HZ, with a high prevalence in pregnant women with IC conditions (see Table 1). ***For autoimmune diseases (AIDs) (systemic lupus erythematosus [SLE], multiple sclerosis [MS], rheumatoid arthritis [RA], inflammatory bowel disease [IBD], psoriasis [PsO], and psoriatic arthritis [PsA]), other coding algorithms from the literature that are AID-specific (Appendix B) will be used instead of the coding algorithms in the CBER BEST***	Addition of reference to validated coding algorithms for identification of singleton pregnancies. Added days of minimum health plan enrollment and explanation for that choice.

Section # and Name	Description of Change	Brief Rationale
	assessment report [Saunders-Hastings, 2021], as the algorithms that are presented in this report are not AID-specific. The ~~183~~ ***273***-day pre-pregnancy period ***through the first trimester (a period of 98 days after the pregnancy start date)*** was chosen to allow identification of potential confounders of interest	
9.2.1.2 HZ/su Exposed Group Page 24	among the cohort of all eligible ***live birth and non-live birth pregnancies*** (Secondary Objective 2 cohort)	Addition to cohort for evaluation of Secondary Objective 2
9.3.2 Outcomes Page 27	IC diagnoses of pregnant women and pregnancy outcomes will be identified from the health plan claims of the DRN containing ICD-10-CM Codes for IC conditions ***and validated coding algorithms for IC conditions*** during the period ~~183~~ ***273*** days prior to the pregnancy start date through the first trimester (98 days after the pregnancy start date).	Addition of reference to Section 9.2.1 in Outcomes
9.3.3 Other Variables Page 31	Potential confounders to be used in the estimation of the propensity score will be identified in the ~~183~~ ***273*** days prior to the pregnancy start date through the first trimester the number of healthcare encounters (outpatient, emergency department, inpatient) in the ~~183~~ ***273*** days preceding the pregnancy start date will be identified.	Update time for estimation of propensity score and recording of healthcare encounters.
Appendix A Page 66	Individuals with ICD-10-CM codes for SLE, MS, RA, IBD, PsO or PsA, SOT, SCT, HM and ST, and HIV during the period 183 273 days prior to pregnancy through the first trimester will be identified from the data network.	Define minimum requirement for days of health plan enrollment
Appendix B Page 65	***Validated coding algorithms for IC conditions*** ***Algorithms for the IC conditions are described below:*** ***1) HIV/AIDS: ≥2 claims for ANY HIV/AIDS diagnostic or procedural codes. a. This category is viewed as immunocompromised regardless of treatment status (treatment [RX]-independent)*** ***b. EXCLUDE cases where the most recent claim is MORE THAN 6 months prior to the index date.*** ***2) Hematologic Malignancy and Related Conditions: ≥2 claims for ANY relevant diagnostic codes. a. This category is viewed***	Details of coding algorithms for IC conditions

Section # and Name	Description of Change	Brief Rationale
	as immunocompromised regardless of treatment status (RX-independent). ***b. EXCLUDE cases where the most recent claim is MORE THAN 6 months prior to the index date.*** ***3) Solid Malignancy: ≥2 claims for ANY solid malignancy diagnostic codes AND one of: a. ≥2 claims for ANY codes for chemotherapy or radiation*** ***b. ≥2 claims for ANY codes for immune-modulating or immunosuppressant therapy*** ***c. EXCLUDE cases where the most recent claim is MORE THAN 6 months prior to the index date.*** ***NOTE: Codes for brachytherapy may also be considered by users seeking to apply a more inclusive definition of radiation therapy. It is recommended that this category be ignored in regular applications of the algorithm, but it may be of value to those with a specific interest in brachytherapy.*** ***4) Transplant and Related Conditions: ≥1 claims for ANY transplant or related condition diagnostic codes AND one of: a. ≥2 claims for ANY codes for chemotherapy or radiation*** ***b. ≥2 claims for ANY codes for immune-modulating or immunosuppressant therapy*** ***c. EXCLUDE cases where the most recent claim is MORE THAN 6 months prior to the index date.*** ***NOTE: Codes for brachytherapy may also be considered by users seeking to apply a more inclusive definition of radiation therapy. It is recommended that this category be ignored in regular applications of the algorithm, but it may be of value to those with a specific interest in brachytherapy.*** ***For autoimmune diseases (AIDs) (systemic lupus erythematosus [SLE], multiple sclerosis [MS], rheumatoid arthritis [RA], inflammatory bowel disease [IBD], psoriasis [PsO], and psoriatric arthritis [PsA]), we prefer to use other coding algorithms from the literature that are AID-specific instead of the coding algorithms in the CBER Biologics Effectiveness and Safety (BEST) Initiative report [Saunders-Hastings, 2021], as the algorithms that are presented in this report are not AID-specific. We will use algorithms that are valid and consistent with the typical***	

Section # and Name	Description of Change	Brief Rationale
	approaches that are used in Sentinel as described below. ***SLE*** ***>1 rheumatologist diagnosis code for SLE (ICD-10 M32.1, M32.8, M32.9) in the 365-day baseline period prior to the index date.*** – ***The above algorithm has demonstrated a PPV of 95% and sensitivity of 83% [Hanly, 2014].*** ***MS*** ***≥3 of any combination of inpatient diagnoses (any position) of MS (ICD-10 G35), ambulatory visit (AV) diagnoses of MS, emergency department (ED) diagnoses of MS, and MS-specific disease-modifying therapy fills/infusions during the 365-day baseline period. At least one of these must be an inpatient, AV, or ED diagnosis of MS.*** – ***This algorithm has demonstrated a PPV of 95-97% and sensitivity of 85-93% [Culpepper, 2019].*** ***RA*** ***≥1 inpatient claim with a diagnosis code for RA (ICD-10 M05, M06) OR ≥2 physician outpatient claims with RA diagnosis during an office visit and/or emergency visit that are at least 30 days apart in the 365-day baseline period prior to the index date*** – ***The above algorithm has no demonstrated PPV but has been used extensively in the literature [MacLean, 2000].*** ***IBD*** ***≥1 inpatient claim with a diagnosis code for IBD (ICD-10 K50, K51) OR ≥2 physician outpatient claims with IBD diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date [Weng, 2007]*** – ***The above algorithm has no demonstrated PPV but has been used extensively in the literature [Weng, 2007].*** ***PsO*** ***≥1 dermatologist diagnosis code for PsO (ICD-10 L40) in the 365-day baseline period prior to the index date.*** – ***The above algorithm has demonstrated a PPV of 90% and sensitivity of 88%***	

Section # and Name	Description of Change	Brief Rationale
	[Asgari, 2013]. This algorithm assumes PsO without PsA. ***PsA*** ***≥2 rheumatologist diagnosis code for PsA (ICD-10 L40.5) in the 365-day baseline period prior to the index date.*** – ***The above algorithm has demonstrated a PPV of 81% and sensitivity of 77% [Asgari, 2013]. This algorithm assumes PsA without PsO.***	
Appendix C **Page 69**	Women exposed to any of following potentially teratogenic or fetotoxic medications in the ~~183~~ ***273*** days prior to and during pregnancy will be excluded from the study population.	Define time frame for exclusion following exposure to teratogenic or fetotoxic medication during pregnancy..
Appendix I **Page 87**	Maternal comorbidities will be identified in the ~~183~~ ***273*** days prior to the pregnancy start date through the first trimester	Time frame for identification of maternal comorbidities.

Annex 6 Additional Information

Appendix A. ICD-10-CM Codes for IC Conditions (Amended 15 August 2022)

Individuals with ICD-10-CM codes for SLE, MS, RA, IBD, PsO or PsA, SOT, SCT, HM and ST, and HIV during the period ***273*** days prior to pregnancy through the first trimester will be identified from the data network. The ICD-10-CM codes for IC conditions are presented below.

ICD-10	IC Condition	Description
M32.*	SLE	Systemic lupus erythematosus
L93.*		Lupus erythematosus
G35.*	MS	Multiple sclerosis
M05.*	RA	Rheumatoid arthritis with rheumatoid factor
M06.*		Other rheumatoid arthritis
K50.*	IBD	Crohn's disease
K51.*		Ulcerative colitis
L40.*	PsO/PsA	Psoriasis
I25.75-I25.76*	SOT	Solid organ transplant – complications, aftercare, status
I25.811		
I25.812		
T86.1-T86.4*		
T86.81*		
Z48.21-Z48.288		
Z94.0-Z94.4		
Z94.83		
T86.0*	SCT	Stem cell transplant – complication, aftercare, status
T86.5		
Z48.290		
Z94.81		
Z94.84		
C81-C96.*	HM	Malignant neoplasm of lymphoid, hematopoietic and related tissue
D45		
C00- C80.*	ST	Solid malignant neoplasm
C97		
D03.*		
O9A.1*		
O98.7*	HIV	Human immunodeficiency virus disease complicating pregnancy
B20		Human immunodeficiency virus

SLE: Systemic Lupus Erythematosus, MS: Multiple Sclerosis, RA: Rheumatoid Arthritis, IBD: Inflammatory Bowel Disease, PsO: Psoriasis, PsA: Psoriatic Arthritis, SOT: Solid Organ Transplant, SCT: Stem Cell Transplant, HM: Hematologic Malignancies, ST: Solid Tumors, HIV: Human Immunodeficiency Virus.

Appendix B. *Validated coding algorithms for IC conditions (Amended 15 August 2022)*

We will use the validated algorithms in the CBER Biologics Effectiveness and Safety (BEST) Initiative report [Saunders-Hastings, 2021] to identify IC conditions (solid organ transplant [SOT], stem cell transplant [SCT], hematological malignancy [HM], solid tumor [ST], human immunodeficiency virus [HIV]), as these are specific to each IC condition as well as valid and consistent with the typical approaches that are used in Sentinel. Algorithms for the IC conditions are described below:

1) HIV/AIDS: ≥2 claims for ANY HIV/AIDS diagnostic or procedural codes. a. This category is viewed as immunocompromised regardless of treatment status (treatment [RX]-independent)

b. EXCLUDE cases where the most recent claim is MORE THAN 6 months prior to the index date.

2) Hematologic Malignancy and Related Conditions: ≥2 claims for ANY relevant diagnostic codes. a. This category is viewed as immunocompromised regardless of treatment status (RX-independent).

b. EXCLUDE cases where the most recent claim is MORE THAN 6 months prior to the index date.

3) Solid Malignancy: ≥2 claims for ANY solid malignancy diagnostic codes AND one of: a. ≥2 claims for ANY codes for chemotherapy or radiation

b. ≥2 claims for ANY codes for immune-modulating or immunosuppressant therapy

c. EXCLUDE cases where the most recent claim is MORE THAN 6 months prior to the index date.

NOTE: Codes for brachytherapy may also be considered by users seeking to apply a more inclusive definition of radiation therapy. It is recommended that this category be ignored in regular applications of the algorithm, but it may be of value to those with a specific interest in brachytherapy.

4) Transplant and Related Conditions: ≥1 claims for ANY transplant or related condition diagnostic codes AND one of: a. ≥2 claims for ANY codes for chemotherapy or radiation

b. ≥2 claims for ANY codes for immune-modulating or immunosuppressant therapy

c. EXCLUDE cases where the most recent claim is MORE THAN 6 months prior to the index date.

NOTE: Codes for brachytherapy may also be considered by users seeking to apply a more inclusive definition of radiation therapy. It is recommended that this category be ignored in regular applications of the algorithm, but it may be of value to those with a specific interest in brachytherapy.

For autoimmune diseases (AIDs) (systemic lupus erythematosus [SLE], multiple sclerosis [MS], rheumatoid arthritis [RA], inflammatory bowel disease [IBD], psoriasis [PsO], and psoriatic arthritis [PsA]), we prefer to use other coding algorithms from the literature that are AID-specific instead of the coding algorithms in the CBER Biologics Effectiveness and Safety (BEST) Initiative assessment report [Saunders-Hastings, 2021], as the algorithms that are presented in this report are not AID-specific. We will use algorithms that are valid and consistent with the typical approaches that are used in Sentinel as described below.

SLE

≥1 rheumatologist diagnosis code for SLE (ICD-10 M32.1, M32.8, M32.9) in the 365-day baseline period prior to the index date.

- ***The above algorithm has demonstrated a PPV of 95% and sensitivity of 83% [Hanly, 2014].***

MS

≥3 of any combination of inpatient diagnoses (any position) of MS (ICD-10 G35), ambulatory visit (AV) diagnoses of MS, emergency department (ED) diagnoses of MS, and MS-specific disease-modifying therapy fills/infusions during the 365-day baseline period. At least one of these must be an inpatient, AV, or ED diagnosis of MS.

- ***This algorithm has demonstrated a PPV of 95-97% and sensitivity of 85-93% [Culpepper, 2019].***

RA

≥1 inpatient claim with a diagnosis code for RA (ICD-10 M05, M06) OR ≥2 physician outpatient claims with RA diagnosis during an office visit and/or emergency visit that are at least 30 days apart in the 365-day baseline period prior to the index date

- ***The above algorithm has no demonstrated PPV but has been used extensively in the literature [MacLean, 2000].***

IBD

≥1 inpatient claim with a diagnosis code for IBD (ICD-10 K50, K51) OR ≥2 physician outpatient claims with IBD diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date [Weng, 2007]

- ***The above algorithm has no demonstrated PPV but has been used extensively in the literature [Weng, 2007].***

PsO

≥1 dermatologist diagnosis code for PsO (ICD-10 L40) in the 365-day baseline period prior to the index date.

- ***The above algorithm has demonstrated a PPV of 90% and sensitivity of 88% [Asgari, 2013]. This algorithm assumes PsO without PsA.***

PsA

≥2 rheumatologist diagnosis code for PsA (ICD-10 L40.5) in the 365-day baseline period prior to the index date.

- ***The above algorithm has demonstrated a PPV of 81% and sensitivity of 77% [Asgari, 2013]. This algorithm assumes PsA without PsO.***

Appendix C. Teratogenic and Fetotoxic Medications (Amended 15 August 2022)

Women exposed to any of following potentially teratogenic or fetotoxic medications in the ***273*** 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
Antiinfectives	Trimetrexate

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

Appendix D. 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 E. Live Birth Diagnosis and Procedure Codes

Live birth pregnancies will be identified with the following diagnosis and procedure codes as described in Section 9.2.1.1.

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

Code	Code Category	Description
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
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

Code	Code Category	Description
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
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

Code	Code Category	Description
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
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

Code	Code Category	Description
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
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

Code	Code Category	Description
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
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

Code	Code Category	Description
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
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

Code	Code Category	Description
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
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

Code	Code Category	Description
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

Code	Code Category	Description
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
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 F. 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 9.2.1.1.

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 G. 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
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 H. 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, 2021; Naleway, 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
O03.83	ICD-10-CM	Metabolic disorder following complete or unspecified spontaneous abortion	Spontaneous abortion

Code	Code Category	Description	Pregnancy Outcome
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
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

Code	Code Category	Description	Pregnancy Outcome
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 I. Maternal Comorbidities (Amended 15 August 2022)

Maternal comorbidities will be identified in the ***273*** 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
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
Respiratory disease	J41-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
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

Annex 7 Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	214420 (EPI-ZOSTER-039 VS US DB)
Date of protocol amendment	Amendment 2 Final: 15 August 2022
Title	Postmarketing commitment safety study of HZ/su to evaluate pregnancy exposures and outcomes in immunodeficient or immunosuppressed women between 18 and 49 years of age.
Sponsor signatory	Agnes Mwakingwe-Omari Clinical Epidemiology Program Lead, GlaxoSmithKline Biologicals
Signature	_____
Date	_____

Annex 8 Protocol Amendment 2 Pharmacovigilance Signatory Approval

eTrack study number and Abbreviated Title	214420 (EPI-ZOSTER-039 VS US DB)
Date of protocol amendment	Amendment 2 Final: 15 August 2022
Title	Postmarketing commitment safety study of HZ/su to evaluate pregnancy exposures and outcomes in immunodeficient or immunosuppressed women between 18 and 49 years of age.
QPPV signatory	PPD PPD Clinical Safety and Pharmacovigilance, GSK
Signature	_____
Date	_____

Note: In order to comply with the pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) must be involved in the review, content approval and sign off (in addition to sponsor signatory) of Post-Authorization Safety studies (PASS) protocols (GVP Module 1). This also applies to Targeted Safety Study (TSS) protocols.

Annex 9 Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, ENCePP guide for methodological standards in pharmacoepidemiology, the International Society of Pharmacoepidemiology guidelines for good pharmacoepidemiology practices, and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions and to implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	214420 (EPI-ZOSTER-039 VS US DB)
Date of protocol amendment	Amendment 2 Final: 15 August 2022
Title	Postmarketing commitment safety study of HZ/su to evaluate pregnancy exposures and outcomes in immunodeficient or immunosuppressed women between 18 and 49 years of age.
Investigator name	PPD , Harvard Medical School & Harvard Pilgrim Health Care Institute
Signature	_____
Date	_____

Annex 10 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	4, 7, 8, 9
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7, 8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	8, 9.1,
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	4, 9.5, 9.7
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1, 9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	9.2
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.1, 9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2, 9.3.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1, 9.2

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorized according to time windows?	☒	☐	☐	9.2.1, 9.7.2.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1, 9.2, 9.7.2

Comments:

Chart validation of HZ/su exposure will not be conducted. Regarding the potential problem of HZ/su codes appearing that do not represent true instances of vaccination, it seems unlikely in this claims-based system. Affirmative coding for vaccination in the Sentinel system has been found to be accurate. For the cohort analyses, all participants will have both medical and drug coverage, thus their HZ/su vaccinations, even if occurring in a pharmacy setting, will be captured.

Dose-specific analyses will not be conducted.

No detailed consideration of the pharmacokinetics and pharmacodynamics of HZ/su appears in the protocol.

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1, 9.7.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1, 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1, 9.9

Comments:

Sensitivity analyses will be detailed in the SAP.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Any planned subgroup analyses will be detailed in the SAP.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3, 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1, 9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2, 9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3, 9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.3.3, 9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2

Comments:

Sensitivity analyses will be detailed in the SAP.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

11.3. There is not a system in place for independent review of the study result. However, study deliverables including data tables and summaries of results (study reports) will be reviewed by all stakeholders including the HPHCI, the participating Data Partners, and GSK staff. Additionally, the study will be submitted to the FDA its review and approval.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	9.9
12.1.2 Information bias?	☐	☒	☐	9.9
12.1.3 Residual/unmeasured confounding?	☐	☒	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5, 9.6.1

Comments:

12.1. The protocol does not explicitly discuss the magnitude or direction of bias from selection bias, information bias, or residual confounding, but the design was chosen to mitigate bias, and the multiple analyses (including secondary and sensitivity) will provide evidence for or against the existence of bias in the primary analyses (to be detailed in the SAP).

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6, 10.1, 10.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☒	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Note: The Sponsor confirms his/her agreement with the completed ENCePP checklist by signing the Protocol Sponsor Signatory Approval page.

Signature Page for 214420 TMF-14907123 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 19-Aug-2022 14:17:50 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 20-Aug-2022 22:53:59 GMT+0000

Signature Page for TMF-14907123 v1.0