NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Rapid Surveillance and Cohort Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy in the United States
Protocol number	C3671027
Protocol version identifier	6.0
Date	05 January 2026
European Union (EU) Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	Bivalent respiratory syncytial virus (RSV) stabilized prefusion F subunit vaccine (RSVpreF), J07BX05
Medicinal product	ABRYSVO™
Research question and objectives	The study will estimate the risk of adverse pregnancy, maternal, and neonatal/infant outcomes among individuals who are exposed to ABRYSVO (RSVpreF) between 32 0/7 through 36 6/7 weeks gestation during pregnancy. The primary objective is to estimate the risk of 1) preterm birth and 2) pregnancy-associated hypertensive disorders following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised. The secondary objective is to estimate the risk of other safety outcomes of interest following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised. Specifically:

	• Pregnancy-related outcomes (stillbirth, preterm labor [without preterm delivery], premature rupture of membranes [PROM], preterm premature rupture of membranes [PPROM], placental abruption, cesarean delivery, prolonged maternal length of stay) • Maternal outcomes (thrombocytopenia, Guillain-Barré Syndrome [GBS], other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation) • Neonatal/infant outcomes (small for gestational age [SGA], large for gestational age [LGA], low birth weight) The exploratory objective is to describe the occurrence of other safety outcomes following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised. Specifically: • Admission to neonatal intensive care unit (NICU), mechanical ventilation in the neonatal period, neonatal death
Country(ies) of study	United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADEM	acute disseminated encephalomyelitis
AE	adverse event
AEM	adverse event monitoring
BEST	Biologics Effectiveness and Safety System
BmaxSPRT	binomial-based maximized sequential probability ratio test
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CPT	Current Procedural Terminology
DCT	data collection tool
EC	ethics committee
ED	emergency department
EHR	electronic health record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act
GBS	Guillain-Barré syndrome
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HCPCS	Healthcare Common Procedure Coding System
HELLP	hemolysis, elevated liver enzymes and low platelets
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMA	Heads of Medicines Agencies
HPHCI	Harvard Pilgrim Health Care Institute
HPV	human papillomavirus
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, Procedure Coding System
IIS	Immunization Information Systems
IP	inpatient
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology

Abbreviation	Definition
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITP	immune thrombocytopenia
LBW	low birth weight
LGA	large for gestational age
LMP	last menstrual period
MATISSE	MATernal Immunization Study for Safety and Efficacy
maxSPRT	maximized sequential probability ratio test
MFMU	Maternal-Fetal Medicines Unit
MMRV	measles, mumps, rubella, and varicella
NA	not applicable
NDC	National Drug Code
NICU	neonatal intensive care unit
NIS	non-interventional study
NIST	National Institute of Standards and Technology
OP	outpatient
PAPP-A	pregnancy associated plasma protein-a
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PHI	Protected Health Information
PPROM	preterm premature rupture of membranes
PPV	positive predictive value
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
PROM	premature rupture of membranes
QA	quality assurance
QC	quality control
RCA	rapid cycle analysis
RP	research partner
RSV	respiratory syncytial virus
RSVpreF	respiratory syncytial virus stabilized prefusion f subunit vaccine
RWD	real-world data
SAP	statistical analysis plan
SAS	Statistical Analysis System
SCDM	Sentinel Common Data Model
SGA	small for gestational age
Tdap	tetanus, diphtheria, and pertussis
TORCH	toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes infections
TTP	thrombotic thrombocytopenic purpura
US	United States
VSD	Vaccine Safety Datalink

Abbreviation	Definition
YRR	Your Reporting Responsibility

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

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Note: Data RP coordinating investigators have reviewed and contributed to this protocol.

4. ABSTRACT

Title: A Rapid Surveillance and Cohort Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy in the United States

Version and Date of Protocol: Version 6.0, 05 January 2026

Names and Affiliations of Principal Investigators of the Protocol:
Richard Platt, MD, MSc, Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston, MA
Sarah MacDonald, ScD, Safety Surveillance Research, Pfizer, Inc., New York, NY

Rationale and Background: ABRYSVO™ is a bivalent RSVpreF vaccine that is unadjuvanted and composed of 2 preF proteins to optimize protection against RSV A and B strains. ABRYSVO was approved in the United States (US) on 31 May 2023 for the prevention of RSV-associated lower respiratory tract disease caused in people ≥60 years of age and on 21 August 2023 for the prevention of RSV-associated lower respiratory tract illness in infants from birth up to 6 months of age by active immunization of pregnant individuals.

The available safety data regarding ABRYSVO use during pregnancy are limited to clinical trial populations. The Phase 3 clinical trial (NCT04424316), MATISSE (MATernal Immunization Study for Safety and Efficacy) evaluated the efficacy, immunogenicity, and safety of ABRYSVO when administered to pregnant women between 24 0/7 and 36 6/7 weeks gestation. In the study, the rates of adverse events (AEs), severe AEs, and life-threatening AEs among both maternal participants and infant participants (who were born to mothers who received ABRYSVO or placebo) were similar in the ABRYSVO and placebo groups.

As part of the ABRYSVO pharmacovigilance plan, the safety of ABRYSVO exposure during pregnancy in the post-approval setting will be monitored using rapid surveillance or rapid cycle analysis (RCA) to conduct near-real time monitoring of potential safety signals and a retrospective cohort study using secondary data to assess the risks of safety events. The cohort study will describe and assess the risk of preterm birth, pregnancy-associated hypertensive disorders, and other adverse pregnancy, maternal, and neonatal/infant outcomes in individuals exposed to ABRYSVO during pregnancy compared to individuals who are not exposed to ABRYSVO during pregnancy.

This non-interventional study (NIS) is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the US Food and Drug Administration (FDA) as a post-marketing requirement.

Research Question and Objectives: The overall research question is: what is the risk of preterm birth, pregnancy-associated hypertensive disorders, and other adverse pregnancy, maternal, and neonatal/infant outcomes following exposure to ABRYSVO between 32 0/7 through 36 6/7 weeks gestation during pregnancy, overall and among pregnant individuals who are immunocompromised?

1. The primary study objective is to estimate the risk of 1) preterm birth and 2) pregnancy-associated hypertensive disorders following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised.

2. The secondary study objective is to estimate the risk of the following safety outcomes of interest following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised:

    - Pregnancy-related outcomes: stillbirth, preterm labor (without preterm delivery), PROM, PPROM, placental abruption, cesarean delivery, prolonged maternal length of stay;
    - Maternal outcomes: thrombocytopenia, GBS, other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation;
    - Neonatal/infant outcomes: SGA, LGA, LBW.

3. The exploratory study objective is to describe the occurrence of the following safety outcomes of interest following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised:
    - Admission to a NICU;
    - Mechanical ventilation in the neonatal period;
    - Neonatal death.

A subset of priority outcomes (preterm birth, pregnancy-associated hypertensive disorders, stillbirth, preterm labor without preterm delivery, PROM, PPROM, SGA, LGA, LBW, and GBS) will be evaluated in the RCA.

Study Design: Electronic healthcare data in the US will be used to 1) conduct near-real time monitoring of potential safety signals (RCA), and 2) conduct a non-interventional cohort study to estimate risks for safety outcomes. Compared to the RCA, the cohort study will be conducted using a wider range of Research Partners (RPs) participating in the FDA's Sentinel System, including data sources with longer lags in data availability (eg, Medicaid). In addition, the cohort study will evaluate a wider range of secondary and exploratory outcomes. Pending sample size feasibility of each outcome, the cohort study will include comparative analyses to compare outcomes among individuals exposed to ABRYSVO during pregnancy to a comparison group of individuals unexposed to ABRYSVO during pregnancy.

Population: The source population for this study will be health plan enrollees from select data RPs that contribute data from claims and/or electronic health records (EHRs) to the FDA Sentinel System and additional health plans (eg, Medicaid) with the capability to transform the data into the Sentinel Common Data Model (SCDM).

RCA: The RCA study will include pregnancies vaccinated in the 2023-2024 season (ie, with pregnancy end dates occurring during the period from 22 September 2023 potentially up to July 2024), and, for some smaller RPs with shorter data lags, the 2024-2025 season. Additional eligibility criteria for the RCA study may include (but are not limited to): at least 90 days of continuous enrollment in the medical and pharmacy claims prior to the start of pregnancy through the delivery date, with gaps of up to 45 days in coverage permitted.

Cohort study: The cohort study will include singleton pregnancies among individuals aged 15 to 54 years with pregnancy start dates (estimated dates of last menstrual period [LMP]) occurring during the period 07 January 2023 to 30 September 2027. This period allows for the earliest included pregnancies to have reached 36 6/7 weeks prior to 22 September 2023 (date the Advisory Committee on Immunization Practices [ACIP] recommended ABRYSVO for seasonal administration to pregnant individuals between 32 0/7 to 36 6/7 weeks' gestation) and the latest included pregnancies to have the opportunity to reach 42 0/7 weeks' gestation plus 6 weeks (42 days) follow-up after the date of delivery within the data cut-off period (31 August 2028). This data cut-off period applies to the cohort studies and is calculated as the expected maximum data availability at the time of the final cohort study report; the data cut-off period for individual data RPs and collection of pregnancies for chart review may end prior to this date. Additional eligibility criteria for the cohort study will include: 1) at least 183 days of continuous enrollment in the medical and pharmacy claims prior to the start of pregnancy through the delivery date, with gaps of up to 45 days in coverage being permitted; and 2) receipt of ≥ 1 vaccine recommended for adults[a] any time prior to the date of estimated last menstrual period (LMP) (to serve as a proxy for health care/vaccine-seeking behavior).

Variables: Information about ABRYSVO exposures, outcomes (safety events), and covariates will be collected from electronic healthcare data (claims and EHRs, as available) and Immunization Information Systems (IIS) data, as available.

ABRYSVO-exposed group: The exposed group will include individuals administered ABRYSVO during 32 0/7 to 36 6/7 weeks of gestation.

Comparison groups:

RCA: The comparison groups for the RCA study will primarily include a historical vaccine-exposed group. The historical vaccine-exposed group may be defined as pregnant individuals

[a] https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

exposed to influenza or tetanus, diphtheria, and pertussis (Tdap) vaccine, or the coronavirus disease 2019 (COVID-19) bivalent booster vaccination during 32 0/7 to 36 6/7 weeks of gestation between the years 2018-2022. A concurrent ABRYSVO-unexposed group (individuals who are not administered ABRYSVO during pregnancy but have received other routine vaccinations during pregnancy) will be considered but may be impractical if pregnant individuals are often dually exposed to both ABRYSVO and other routine vaccinations.

Cohort study: The comparison group for the cohort study will include individuals who are not administered ABRYSVO during pregnancy (contemporaneous comparator).

Outcomes:

RCA: The RCA will evaluate the primary pregnancy outcomes (preterm birth and pregnancy-associated hypertensive disorders) and select priority secondary pregnancy, maternal, and neonatal/infant outcomes (stillbirth, preterm labor without preterm delivery, PROM, PPROM, SGA, LGA, LBW, and GBS).

Cohort study: The primary outcomes of interest for the cohort study are preterm birth and pregnancy-associated hypertensive disorders. Secondary outcomes of interest include pregnancy-related outcomes (stillbirth, preterm labor (without preterm delivery), PROM, PPROM, placental abruption, cesarean delivery, and prolonged maternal length of stay); maternal outcomes (thrombocytopenia, GBS, other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation); neonatal/infant outcomes (SGA, LGA, LBW). Exploratory outcomes include admission to NICU, mechanical ventilation in neonatal period, and neonatal death.

Covariates:

RCA: Covariates used for confounding control will include maternal age at pregnancy end date (date of delivery), an indicator variable for season of vaccination (months September-January defined as in-season and all other months defined as off-season), and a composite high-risk indicator which is the union of several variables that are risk factors for preterm birth.

Cohort study: Covariates will include maternal age at pregnancy end date (date of delivery), geographic region, healthcare utilization, recorded prenatal procedures, other vaccines (before and during pregnancy), medications, estimated LMP, gestational age on the index date (date of administration of ABRYSVO or corresponding date in the comparison group), maternal comorbidities, obstetric history, lifestyle factors, and pregnancy complications during the current pregnancy.

All conditions used to define the population, exposures, comorbidities, obstetric history, lifestyle factors, and outcomes will be identified using validated algorithms, where available. Validation of the algorithms for preterm birth (primary outcome), preterm labor (without

preterm delivery), and pregnancy-associated hypertensive disorders (primary outcome) will be conducted through review of medical records for a sample of potential cases. Potential cases will be reviewed by physician adjudicators with expertise in obstetrics/gynecology.

Data Sources: The study will use data from RPs that contribute claims and/or EHR data to the Sentinel System and additional health plans (eg, Medicaid) with the capability to transform the data into the SCDM. The data sources are described in the statistical analysis plan (SAP).

Study Size:

RCA: Data on all pregnancies meeting the study eligibility criteria that received ABRYSVO within the contributing RPs will be analyzed.

Cohort study: For the primary objective, all eligible ABRYSVO-exposed pregnancies and corresponding matched unexposed pregnancies will be included. Assuming a 1:1 ratio of ABRYSVO-exposed to unexposed, a type 1 error of 0.05, and a target hazard ratio (HR) of 2.0 for the primary safety outcomes of preterm birth and pregnancy-associated hypertensive disorders, 818 and 218 pregnant individuals, respectively, from the ABRYSVO-exposed group and 818 and 218, respectively, from the unexposed group will allow the study to achieve 80% power, given the estimated background rate of preterm birth of 4.0% and pregnancy-associated hypertensive disorders of 15.0%. To detect an HR of 1.2 for the primary safety outcomes of preterm birth and pregnancy-associated hypertensive disorders, 11,848 and 3,160 pregnant individuals, respectively, are needed for both the ABRYSVO-exposed group and the unexposed group. Note that the study will not be terminated when the target sample size is reached but will continue for the specified study period.

Data Analysis: Analyses will initially be conducted separately using data from each RP. RP-specific summary-level results will be sent to the study coordinating center, which will review and aggregate results across the RPs for reporting.

RCA: Summary-level data on the counts of prespecified outcomes within strata of RP, vaccination status, demographics, and other baseline characteristics will be collected and aggregated. Counts of observed outcomes in the exposed group will be compared to expected outcomes in a referent group using a Poisson or binomial-based maximized sequential probability ratio test (maxSPRT) depending on the choice of the referent group. If the test statistic (a log likelihood ratio) exceeds a pre-specified threshold, the null hypothesis will be rejected, and a statistical signal will be declared. Such a statistical signal will be further analyzed in the cohort study (where additional propensity score analyses will be conducted) to understand if there is a true increase in risk associated with immunization.

Cohort study: Propensity score development and matching (1:1 matching ratio) will occur within each RP.

Descriptive analyses of baseline characteristics of ABRYSVO-exposed and matched unexposed pregnancies will be performed, overall and among those individuals identified with an immunocompromising condition. Risks of study outcomes (with 95% confidence intervals [CIs]) will be estimated among ABRYSVO-exposed and matched unexposed pregnancies, overall and among those individuals identified with an immunocompromising condition. Survival analysis methods (eg, Kaplan Meier curve) will also be used to describe the risk (cumulative incidence) for particular periods from administration in ABRYSVO-exposed and matched ABRYSVO-unexposed individuals.

Pending sample size feasibility for each specific outcome, comparative analyses will be conducted to compare the risks of those outcomes between the ABRYSVO-exposed and ABRYSVO-unexposed pregnancies, adjusting for potential residual confounding after propensity score matching. Cox models will be used to calculate adjusted HRs and 95% CIs for pregnancy outcomes and maternal outcomes. For neonatal/infant outcomes, conditional logistic regression will be used to estimate prevalence odds ratios and 95% CIs.

To assess the robustness of the results, sensitivity analyses will be conducted to address the potential misclassifications for outcomes, exposure, and important confounders; these will include an analysis stratified by race (Asian, Black/African American, Other, Unknown, and White) at all participating data RPs and separately at the Medicaid RP.

Milestones: The anticipated start of data collection is no later than 26 April 2024 and the end of data collection is anticipated to be no later than 31 August 2028. A final cohort study report will be submitted to FDA by 28 February 2029.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
6.0	05 January 2026	Substantial	Title Page; Abstract; Section 8 Research Question and Objectives; Section 9.3.2.2 Cohort Study Outcomes; Appendix A Algorithms for Identification of Outcomes: Cohort Study	Included placental abruption as a secondary outcome	This revision was made to address an FDA request (received 11-Dec-2025).
		Substantial	Abstract; Section 9.1 Study Design; Section 9.2 Setting; Section 9.5 Study Size	Extended the data cut-off period, widening the inclusion window of pregnancy start dates.	This revision was made to leverage as much available data as possible during the data collection period.
		Substantial	Abstract; Section 9.7.2.5 Sensitivity Analyses; Section 9.9.1 Limitations	Specified a sensitivity analysis that will stratify the primary objective by race at all RPs and separately at the Medicaid RP.	This revision was made to explore the potential for misclassification of this important confounder.
		Substantial	Section 9.3.3.2 Cohort Study Covariates	Added the following covariate: underweight.	This covariate was unintentionally missing from the protocol.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
		Substantial	Section 9.3.3.2 Cohort Study Covariates	Added the following descriptive covariates: nulliparity and number of live birth deliveries ever prior to current pregnancy.	This revision was made to capture more covariates consistently with ongoing studies by other research groups.
		Administrative	Throughout	Minor edits, updates and revisions to text	Grammatical corrections and clarifications for consistency within the protocol
		Administrative	Appendix A Algorithms for Identification of Outcomes: Cohort Study	Added a footnote at the first mention of pregnancy-associated hypertensive disorders and postpartum hypertension about the fact that none of the cited validated algorithms include O16* codes.	This revision was made to address an FDA Information Request (received 30-Jul-2025) that mentioned the potential use of O16.5 to identify postpartum hypertension.
5.0	31 March 2025	Substantial	Section 9.2.4.1 RCA Comparison (Unexposed) Groups, Table 1	Removed postpartum hypertension from the definition of hypertensive disorders of pregnancy to align with the RCA SAP. Postpartum hypertension remains in the definition of hypertensive disorders of pregnancy for the cohort study.	This revision was made to align with the RCA SAP.
			Section 9.3.1 Exposure	New codes to identify ABRYSVO were added	To reflect the availability of new codes
			Section 9.3.3.2 Cohort Study Covariates, Table 4	Additional covariates were added: Enrollment time ever prior to pregnancy, Any invasive antenatal tests performed (recorded from estimated LMP to index date), PROM birth in previous pregnancies,	These revisions were made to address FDA comments related to potential confounders/des

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				Polyhydramnios, Gestational excessive maternal weight gain, Vaginal bleeding in the second or third trimester (measured from LMP+98 days through index date), Number of pregnancies ever prior to current pregnancy.	criptive factors for PROM and PPROM.
			Section 9.3.3.2 Cohort Study Covariates, Table 4	Changed covariate Insurance Type to Research Partner type (National, Regional, Medicaid).	This revision was made to align with available data sources.
			9.7.2.4 Secondary Analysis	A secondary descriptive analysis is described to report the prevalence of ABRYSVO >7 days after the index vaccination and before 37 weeks will be reported in the ABRYSVO-exposed pregnant individuals.	This revision was made to address FDA comments related to the observation that a small proportion of the exposed group had more than one administration of ABRYSVO recorded in the data.
			Section 9.7.2.4 Secondary Analysis	Secondary descriptive analyses were added to describe the frequency of characteristics and risk factors among individuals diagnosed with PPROM and the prevalence of chorioamnionitis.	These revisions were made to better understand factors related to PPROM, a secondary outcome with an increased incidence found in the ABRYSVO-exposed in the RCA.
			Appendix A	PPROM algorithm modified to include both a	This revision was made to more accurately

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				diagnosis code and gestational age < 37 weeks.	determine preterm PROM based upon review of RCA patient profiles.
			Appendix A	List of codes to identify cesarean delivery has been updated	This revision was made to delete codes related to multigestation pregnancies (which are excluded from the study population) and add one relevant code
4.0	28 October 2024	Substantial	Section 9.2.5.2.1 Pregnancy Outcomes Section 9.3.2.2.1 Pregnancy and Neonatal/Infant Outcomes	Risk window start for pregnancy outcomes was specified as Day 1 (index date + 1).	These revisions were made to align Protocol with the RCA and Cohort Study SAPs.
			Section 9.2.5.2.3 Maternal Outcomes, Figure 3	A note was added to clarify that the risk windows vary by outcomes.	
			Section 9.3.2.2.1 Pregnancy and Neonatal/Infant Outcomes, Table 2	Definition of index date was added.	
3.0	14 June 2024	Substantial	Section 9.2.1.1.1 Inclusion Criteria	One inclusion criterion related to evidence of the specific outcome of interest between the estimated start of pregnancy until the date of vaccination was added to be consistent with the RCA	This revision was made to address FDA comment received on 14 June 2024.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				statistical analysis plan Section 4.2.1.1.1 Inclusion/exclusion criteria.	
2.0	21 May 2024	Substantial	Section 9.1 Study Design	Text was added to clarify that pregnancies and infants will be followed for 42 and 30 days, respectively at a maximum and that follow-up may be less than 42 and 30 days, respectively if censoring events occur.	This revision was made to address FDA comment #1 received on 13 May 2024.
			Section 9.2.5.2.1 Pregnancy Outcomes Section 9.2.5.2.2 Neonatal/Infant Outcomes	The wording 'up to' has been removed.	
			Section 9.2.5.2.2 Neonatal/Infant Outcomes	Missing text 'Occurrence of the event of interest' and 'earliest of the following' was added.	
			Section 9.3.2.2.2 Maternal Outcomes, Table 3	A footnote was added to Table 3.	
			Section 9.7.2.2 Cohort Study Analyses	A sentence clarifying that mean follow-up time will be summarized for pregnancies and infants was added.	
			Section 9.2.4.1 RCA Comparison (Unexposed) Groups	Clarifying text was added as follows: it is not planned to limit vaccines to 1 vaccine product in the concurrent comparator group, but rather permitting administration of any vaccine indicated in pregnancy (eg, influenza, Tdap, COVID-19 bivalent booster), that is not ABRYSVO,	This revision was made to address FDA comment #2 received on 13 May 2024.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				interchangeably in the analysis.	
			Title page and header	Protocol version identifier was updated to 2.0.	This revision was made to address FDA comment #3 received on 13 May 2024.
			Abstract (Data Analysis sub-heading) Section 9.7.2.3 Risks of Pregnancy, Maternal and Neonatal/Infant Outcomes	Change of Modelling Approach in the Analysis of Maternal Outcomes from Poisson Regression to Cox Models.	Additional change
			Section 9.1 Study Design Section 9.2.4.1 RCA Comparison (Unexposed) Groups Section 9.2.4.2 Cohort Study Comparison (Unexposed) Group	Flu Revised to Influenza.	Additional change
			Section 9.2.4.1 RCA Comparison (Unexposed) Groups)	The term ‘vaccinations’ has been revised to ‘immunizations.’	Additional change
			Section 9.7.1.1 Characterization of ABRYSVO Use Section 9.7.1.2 Sequential Statistical Analysis	Section Numbers Revised to Correct Numbering.	Additional change

6. MILESTONES

Milestone	Planned date
Start of data collection[1]	26 April 2024
End of data collection[2]	31 August 2028
RCA report 1[3]	June 2024
RCA report 2	September 2024
RCA report 3	December 2024
RCA report 4	March 2025
RCA report 5	June 2025
Cohort study interim report 1[4] (extended report[5])	August 2025
Cohort study interim report 2	August 2026
Cohort study interim report 3	August 2027
Registration in the HMA-EMA Catalogue of RWD studies	Prior to the start of data collection
Cohort study final report[6]	28 February 2029

EMA = European Medicines Agency; HMA = Heads of Medicines Agencies; RWD = real-world data

1 Reflecting first extraction of the data for the first RCA report. Start of data collection date has been revised from 1 March 2024 to 26 April 2024 due to delay in final protocol endorsement by the FDA.
2 Reflecting final dataset available for analysis (including data lag time and medical chart review)
3 Quarterly RCA reports to provide a high-level summary of cumulative safety signal monitoring results. First RCA report date has been revised from March 2024 to June 2024 due to delay in final protocol endorsement by the FDA.
4 Interim reports to include the number of pregnancies exposed and unexposed, and an assessment of the accumulating data on pregnancy-related, maternal, and neonatal/infant outcomes (including preterm birth). Interim reports will not include detailed analyses. Note: Some RPs may only be able to refresh data annually; Medicaid refreshes may be less frequent and have longer data lags. All data available at the time of the interim report will be included.
5 Extended interim report to include comparative analyses. If there is insufficient sample size to conduct a comparative analysis of the primary outcomes in the overall study population at the time of the first interim report, the extended interim report will be conducted at the next subsequent interim report in which sufficient sample size is obtained.
6 Within 6 months of the end of data collection.

7. RATIONALE AND BACKGROUND

ABRYSVO is a bivalent RSVpreF vaccine that is unadjuvanted and composed of 2 preF proteins to optimize protection against RSV A and B strains. ABRYSVO was approved in the US on 31 May 2023 for the prevention of RSV-associated lower respiratory tract disease caused in people ≥60 years of age and on 21 August 2023 for the prevention of RSV-associated lower respiratory tract illness in infants from birth up to 6 months of age by active immunization of pregnant individuals. ABRYSVO is approved for administration as a single dose injection at 32 0/7 through 36 6/7 weeks' gestation. On 22 September 2023, the Advisory Committee on Immunization Practices (ACIP) recommended ABRYSVO for seasonal administration (September to January) to pregnant individuals between 32 0/7 to 36 6/7 weeks' gestation.

RSV is a major cause of severe lower respiratory disease in infants and young children. Globally, an estimated 33 million cases of RSV-associated acute lower respiratory infection occur annually among children <5 years of age, with 6.5 million cases occurring among those 0-6 months of age.[1] Further, the estimated annual incidence rate of RSV-associated hospitalizations is 5 per 1000 children <5 years of age and 20 per 1000 infants 0-6 months of age.[1] In the US, the annual incidence of RSV-associated hospitalization is an estimated 19 per 1000 among infants <1 year of age and 26 per 1000 among those 0-6 months of age, suggesting approximately 79,850 RSV-associated hospitalizations occur annually among infants <1 year of age.[2]

The available safety data regarding ABRYSVO use during pregnancy are limited. The Phase 3 clinical trial (NCT04424316), MATISSE evaluated the efficacy, immunogenicity, and safety of ABRYSVO when administered to pregnant women between 24 0/7 and 36 6/7 weeks' gestation. In the study, the rates of AEs, severe AEs, and life-threatening AEs among both maternal participants and infant participants (who were born to mothers who received ABRYSVO or placebo) were similar in the ABRYSVO and placebo groups. While there was a numerical balance in the rate of preterm birth in the full MATISSE population (vaccinated between 24 0/7 and 36 6/7 weeks), the difference was not statistically significant.

The safety profile of ABRYSVO among immunocompromised pregnant individuals, who were excluded from the Phase 3 trial (eg, individuals with autoimmune disease, human immunodeficiency virus [HIV], or treated with immunosuppressants), is unknown. Further, additional characterization of safety endpoints in a real-world population of pregnant individuals is warranted. As part of the ABRYSVO pharmacovigilance plan, this protocol describes a post-marketing safety study to evaluate the safety of ABRYSVO in the general population of pregnant individuals, including immunocompromised pregnant individuals, and their infants in a real-world setting. The safety of ABRYSVO exposure during pregnancy will be monitored using RCA to conduct near-real time monitoring of potential safety signals and a retrospective cohort study using secondary data to assess the risks of safety events. This study will describe and assess the risks of preterm birth, pregnancy-associated

hypertensive disorders, and other adverse pregnancy, maternal, and neonatal/infant outcomes in individuals exposed to ABRYSVO during pregnancy compared to individuals who are not exposed to ABRYSVO during pregnancy.

This noninterventional study is designated as a PASS and is a commitment to the US FDA as a post-marketing requirement.

8. RESEARCH QUESTION AND OBJECTIVES

The overall research question is: what is the risk of preterm birth, pregnancy-associated hypertensive disorders, and other adverse pregnancy, maternal, and neonatal/infant outcomes following exposure to ABRYSVO between 32 0/7 through 36 6/7 weeks gestation during pregnancy, overall and among pregnant individuals who are immunocompromised?

1. The primary study objective is to estimate the risk of 1) preterm birth and 2) pregnancy-associated hypertensive disorders following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised.

2. The secondary study objective is to estimate the risk of the following safety outcomes of interest following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised:

- Pregnancy-related outcomes: stillbirth, preterm labor (without preterm delivery), PROM, PPROM, placental abruption, cesarean delivery, and prolonged maternal length of stay;

- Maternal outcomes: thrombocytopenia, GBS, other immune-mediated demyelinating conditions, polyneuropathies, and atrial fibrillation;

- Neonatal/infant outcomes: SGA, LGA, and LBW.

3. The exploratory study objective is to describe the occurrence of the following safety outcomes of interest following exposure to ABRYSVO during pregnancy, overall and among pregnant individuals who are immunocompromised:

- Admission to a NICU;

- Mechanical ventilation in the neonatal period;

- Neonatal death.

Refer to Section 9.3.2 for definitions of the outcomes.

Only a subset of priority outcomes (preterm birth, pregnancy-associated hypertensive disorders, stillbirth, preterm labor without preterm delivery, PROM, PPROM, SGA, LGA, LBW, and GBS) will be evaluated in the RCA study.

9. RESEARCH METHODS

9.1. Study Design

Electronic healthcare data in the US will be used to 1) conduct near-real time monitoring of potential safety signals (RCA), and 2) conduct a non-interventional retrospective cohort study to estimate risks for safety outcomes.

RCA: RCA is a method used to conduct population-based active surveillance of vaccine-related potential AEs in near real-time using electronic healthcare data.[3] Since 2005, it has been used by the Centers for Disease Control and Prevention's (CDC's) Vaccine Safety Datalink (VSD) to monitor the safety of Tdap, measles, mumps, rubella, and varicella (MMRV), rotavirus, human papillomavirus (HPV), influenza, and coronavirus disease 2019 (COVID-19) vaccines.[4,5] With this method, hypothesized exposure-outcome associations are continuously evaluated using sequential methods as soon as newer data become available, under the null hypothesis that the vaccine does not increase the risk of the outcome. Sequential statistical analysis accounts for multiple testing of continuously accumulating data. The goal of RCA is to detect potential safety problems as soon as possible while minimizing false positive signals.

The RCA will be conducted using healthcare data held by the RPs (described in Section 9.4). The study period in the RCA will include data from 22 September 2023[b] until last available date at each RP at the time of data extraction. For some smaller RPs with shorter data refreshes, this will include data from both the 2023-2024 and 2024-2025 season; however, for other larger RPs with longer data lags, the study period may only capture the 2023-2024 season (ie, potentially up to July 2024). Given that ABRYSVO is approved as a seasonal vaccination (administered September-January), it is anticipated that the RCA will be able to primarily collect 1 season of vaccinated pregnancies through July 2024, conditional on availability of data at the time of execution of the last RCA report. For each vaccinated pregnancy included in the RCA analysis, the analysis will be designed to ensure that (1) all pregnancies have the opportunity to reach full term and (2) all study outcomes following vaccination are observable. In order to do so, the selection period will end by a date that would allow all pregnancies to have reached 42 0/7 weeks' gestation and have 6 weeks (42 days, longest fixed risk window for the outcome of GBS) of available follow-up time post-vaccination before the end of the data cut-off.

[b] Date of ACIP recommendation

Historical vaccine-exposed comparator groups will be created using data from the years 2018-2022. Pregnancy, maternal, and neonatal/infant outcomes will be identified among pregnant individuals ages 15 to 54 years exposed to ABRYSVO during 32 0/7 to 36 6/7 weeks of gestation. The comparison groups will primarily include a historical vaccine-exposed group comprised of pregnant individuals receiving influenza, Tdap, or COVID bivalent booster during 32 0/7 to 36 6/7 weeks of gestation between years 2018-2022. A concurrent ABRYSVO-unexposed group (individuals who are not administered ABRYSVO during pregnancy but administered other vaccinations) will be considered but may be impractical if pregnant individuals are often dually exposed to both ABRYSVO and other routine vaccinations.

Outcomes (pregnancy, maternal, and neonatal/infant) will be identified from the mothers' claims in all qualifying eligible pregnancies (live birth and non-live birth [eg, stillbirth]).

Confounding will be handled by using historical background incidence rates stratified by select covariates (described in Section 9.7.2).

Cohort Study: The cohort study will also be conducted using healthcare data held by the RPs (described in Section 9.4). The study period for identification of both exposed and unexposed pregnancies (based upon pregnancy start dates) will be 07 January 2023 to 30 September 2027. This period allows for the earliest included pregnancies to have reached 36 6/7 weeks prior to 22 September 2023 (date ACIP recommended ABRYSVO for seasonal administration to pregnant individuals between 32 0/7 to 36 6/7 weeks' gestation) and the latest included pregnancies to have the opportunity to reach 42 0/7 weeks' gestation plus 6 weeks (42 days) follow-up after the date of delivery within the data cut-off period (31 August 2028). This data cut-off is the expected maximum data availability at the time of the final cohort study report; the data cut-off period for individual data RPs and collection of pregnancies for chart review may end prior to this date. Pregnancy, maternal, and neonatal/infant outcomes will be identified among pregnant individuals ages 15 to 54 years exposed to ABRYSVO during 32 0/7 to 36 6/7 weeks of gestation. The comparison group will include individuals who are not administered ABRYSVO during pregnancy (contemporaneous comparator); individuals included in the comparison group could have received another vaccine (eg, Tdap, influenza) during pregnancy.

Pregnancies that result in a live birth or non-live birth will be identified and individuals will be followed from the index date (date of administration of ABRYSVO or corresponding date in the comparison group) through 6 weeks (42 days) after delivery, an occurrence of the outcome of interest, receipt of ABRYSVO after 36 6/7 weeks gestation, the latest gestational age at which an outcome can occur (applies to preterm birth, preterm labor, and PPROM outcomes), end of continuous health plan enrollment, or death, whichever occurs first, (see Table 2 and Table 3) for the assessment of each of the pregnancy and maternal outcomes. The 42-day follow-up period after delivery allows capture of outcomes with a 42-day risk window (see Section 9.3.2.2) after ABRYSVO exposure for individuals exposed on their

delivery date. For the analyses evaluating neonatal/infant outcomes, the study population will be restricted to pregnancies resulting in live births for which the mother is linked to an infant. For each neonatal/infant outcome, infants born from these pregnancies (exposed and unexposed) will be followed for 30 days from birth, an occurrence of neonatal or infant outcome, end of health plan enrollment, or death, whichever occurs first, (see Table 2) for assessment of outcomes. The 30-day follow-up period allows capture of infant outcomes recorded at follow-up ambulatory visits and inpatient visits that may not be recorded in the delivery admission. Start and end dates for follow-up of individual pregnancy, maternal, and neonatal/infant outcomes are described in Section 9.3.2.2. Confounding will be handled by propensity score matching and further covariate adjustment will be conducted for potential residual confounding after matching.

9.2. Setting

The source population will be health plan enrollees from data RPs that contribute data from claims and EHRs to the FDA Sentinel System (Section 9.4). Potential additional data sources outside of the FDA Sentinel system may include Medicaid and regional health plan data sources; these data sources are expected to include similar electronic healthcare data. The data sources are described in the SAP. Compared to the RCA, the cohort study is expected to be conducted using a wider range of RPs, including data sources with longer lags in data availability (eg, Medicaid).

RCA: The study period for identification of exposed pregnancies and contemporary comparator groups (based upon pregnancy end dates) for the RCA study will be from 22 September 2023[c] until last available date at each RP at the time of data extraction. For some smaller RPs with shorter data refreshes, this will include data from both the 2023-2024 and 2024-2025 seasons. However, for other larger RPs with longer data lags, the study period may only capture the 2023-2024 season (ie, potentially up to July 2024). Historical vaccine-exposed comparator groups will be created using data from the years 2018-2022.

Cohort study: The study population for the cohort study will include individuals with pregnancy start dates occurring during the period 07 January 2023 to 30 September 2027 (see Section 9.2.2 for a description of the algorithm for estimation of pregnancy start and end dates).

Additional eligibility criteria are listed in the below sections.

[c] Date of ACIP recommendation

9.2.1. Inclusion/Exclusion Criteria

9.2.1.1. RCA Study

The ideal comparison group in the RCA study is a contemporary group of individuals who receive any vaccine other than ABRYSVO during their pregnancy. However, if concurrent vaccinated comparison groups are deemed impractical based on preliminary descriptive analyses (see Section 9.2.4.1), the RCA study will implement a historical vaccinated comparator group to restrict the analysis to individuals who are otherwise vaccine-seeking.

The RCA cohort will include all qualifying eligible pregnancies (live birth and non-live births) for analyses evaluating each outcome (select pregnancy, maternal, and neonatal/infant outcomes) in mothers' claims data to include as large a sample as possible for detection of safety signals.

9.2.1.1.1. Inclusion Criteria

Inclusion criteria for the RCA study may include but are not limited to:

1. Individuals aged 15 to 54 years old[d] at pregnancy end date (delivery date) recorded with female sex in the demographic file of the SCDM.

2. At least 90 days of continuous enrollment in the medical and pharmacy claims prior to the start of pregnancy through the delivery date, with gaps of up to 45 days in coverage permitted. In Sentinel projects, gaps of 45 days or less in health plan enrollment are typically considered administrative gaps (and not lapses in health plan coverage) and are ignored.

3. No evidence of specific outcome of interest between estimated start of pregnancy until the date of vaccination. For example, when evaluating hypertensive disorders of pregnancy as an outcome, a Tdap exposed pregnancy at 32 weeks of gestation with evidence of hypertensive disorders of pregnancy at 28 weeks will be excluded for having evidence of the outcome prior to the exposure.

9.2.1.1.2. Exclusion Criteria

There are no exclusion criteria for the RCA.

[d] Age window represents the widest age window deemed operationally feasible

9.2.1.2. Cohort Study

9.2.1.2.1. Inclusion Criteria

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

1. Individuals aged 15 to 54 years old[d] at pregnancy end date (delivery date) recorded with a female sex in the demographic file of the SCDM.

2. Receipt of ≥1 vaccine recommended for adults[e] any time prior to the date of estimated LMP, using all available history in the claims and/or EHR data. This criterion will serve as a proxy for health care (vaccine)-seeking behavior.

3. At least 183 days of continuous enrollment in the medical and pharmacy claims prior to the start of pregnancy through the date of delivery/pregnancy outcome, with gaps of up to 45 days in coverage being permitted. A longer period of continuous enrollment is required in the cohort study, as compared to the RCA, to allow identification of immunocompromised conditions, as well as other potential confounders of interest (Section 9.3.3).

9.2.1.2.2. Exclusion Criteria

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

1. Multigestation (eg, twin or higher order) pregnancies.

2. Receipt of AREXVY (RSV vaccine, adjuvanted) or other non-Pfizer RSV vaccine during the pregnancy period (estimated LMP to date of delivery).

3. Receipt of ABRYSVO before 32 0/7 weeks gestation.

4. Pregnancies ending before 32 0/7 weeks gestation.

In the cohort study, the study population for evaluation of pregnancy and maternal outcomes will include all eligible live birth and non-live birth pregnancies. For the analyses evaluating neonatal/infant outcomes, the study population will be restricted to pregnancies resulting in live births for which the mother is linked to an infant (see Section 9.2.2) for more complete identification of outcomes in the first 30 days of life.

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

[e] https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

9.2.2. Identification of Pregnancy Episodes and Linkage of Pregnancies to Infant Data

An algorithm developed by the Sentinel Operations Center will be used to identify pregnancies and the length of the pregnancy episode.

The algorithm is based on published Sentinel and non-Sentinel studies that have developed and validated algorithms to identify live birth and non-live birth pregnancy episodes.[6-11] This algorithm uses electronic healthcare data to determine end-of-pregnancy events (spontaneous abortion, stillbirth, elective abortion, live birth) and to assign estimated pregnancy start and end dates. The algorithm first identifies end-of-pregnancy events using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis, International Classification of Diseases, 10th Revision, Procedure Coding System (ICD-10-PCS), Current Procedural Terminology, 4th Edition (CPT-4), and Healthcare Common Procedure Coding System (HCPCS) codes to identify pregnancy episodes, with subsequent prioritization and cleaning steps to remove implausible events (eg, a live birth occurring at 10 weeks gestation). The start of pregnancy (estimated date of LMP) is then estimated indirectly using a hierarchy of pregnancy markers, including ICD-10-CM diagnosis codes indicative of weeks of gestation (ie, Z3A codes), prenatal screening tests, pre- and post-term codes around the end-of-pregnancy event, and codes indicating trimester of pregnancy or prenatal care visits. If no codes are observed around the pregnancy outcome, then the user defines the default pregnancy duration for each pregnancy outcome (eg, based on the median gestational age noted for each pregnancy outcome in published algorithm studies).

Pregnancy episodes are classified into trimester periods with first trimester including 0 to 97 days of gestation, the second trimester including days 98 to 195, and the third trimester from days 196 through the pregnancy outcome date. Further, live-birth pregnancies are classified into preterm, early term, full term, late term, and post-term based on pregnancy duration.

Details on pregnancy algorithm can be found at:
(https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse/files/file150-type04-pregepi.md).

Each RP will be responsible for linking mothers to infants (for neonatal/infant outcomes analyses in the cohort study) using all available local data resources. Algorithms linking mothers to infants will vary across RPs, generally looking for equivalent health plan subscriber numbers, delivery dates and dates of birth, and shared names and addresses. Sentinel RPs link approximately 73% of infants to their mothers,[12] ranging from 70-80% in Commercial insurers with access to protected health information (PHI) on individuals. Additional details on the mother-infant linkage process in Sentinel are available elsewhere.[13] The percentage of mothers linked to infants in Medicaid data is 60%.[14]

9.2.3. ABRYSVO-Exposed Group

The ABRYSVO-exposed group in the RCA and cohort analyses will include individuals who were administered ABRYSVO during 32 0/7 through 36 6/7 weeks of gestation meeting eligibility criteria. Receipt of the vaccine will be identified in claims and/or EHR data through pharmacy dispensing and procedure codes. The index date (to define the date of cohort entry and covariate assessment) will be the date of receipt of ABRYSVO.

The period of exposure ascertainment (32 0/7 through 36 6/7 weeks' gestation) for the main analyses in the RCA and main cohort analysis is limited to the indicated window approved by the FDA.

9.2.4. Comparison (Unexposed) Group

9.2.4.1. RCA Comparison (Unexposed) Groups

The RCA analysis will be limited to the outcomes listed in Table 1. These outcomes will be evaluated as dichotomous endpoints occurring at the end of the pregnancy, with the exception of GBS which will be evaluated within a fixed risk window of 42 days beginning the day after the vaccination. For rare outcomes (eg, GBS) that have <6 expected events in the exposed group during the surveillance period, a historical comparator group will be used. The threshold of 6 outcomes relates to the ability of a 1:1 matched binomial probability model to find a solution using the maximum sequential probability ratio test (maxSPRT) methods. Historical comparators are routinely used when evaluating rare outcomes because the expected outcome rates in the comparator can be generated using multiple years of prior data, thereby reducing the time to declare a statistical signal and/or reach a stopping boundary.

If the estimated rate of accrual of an outcome suggests ≥ 6 events in the exposed group during the surveillance period (~2 years), a concurrent comparator will be considered. The planned concurrent comparator is pregnant individuals vaccinated with seasonal influenza, COVID, or Tdap vaccines, but remain unexposed to ABRYSVO during 32 0/7 through 36 6/7 weeks of gestation and it will be finalized based on immunization patterns during the same gestational age range proposed for ABRYSVO vaccination. Since ABRYSVO-exposed vaccinees are likely to be exposed to other vaccines that overlap the risk window following ABRYSVO administration, it may be challenging in the RCA to exactly "match" the profile of ABRYSVO-exposed vaccinees to comparator-exposed vaccinees, ie, matching an ABRYSVO+influenza vaccinee to an influenza only vaccinee. Such an approach may more precisely isolate the potential effects of ABRYSVO but may also cause losses in sample size if matches cannot be made within the data that are incrementally arriving. Thus, it is planned to treat any vaccine indicated in pregnancy (eg, influenza, Tdap, COVID-19 bivalent booster) that is not ABRYSVO interchangeably. Additionally, if many pregnant individuals are dually exposed to both ABRYSVO and other routine immunizations, a sufficiently sized concurrent

comparator group may not be available to continue the analysis and a historical comparator group will be used for all outcomes.

The historical unexposed group will consist of pregnant individuals meeting the age and pre-pregnancy enrollment inclusion criteria who receive either the influenza, COVID, or Tdap vaccines between 32 0/7 to 36 6/7 weeks of gestation during the years 2018-2022.

Table 1. Priority outcomes evaluated in RCA

Type of Outcome	Outcome
Pregnancy	Preterm birth
Pregnancy	Hypertensive disorders of pregnancy (composite of gestational hypertension, preeclampsia, eclampsia, Hemolysis, Elevated Liver Enzymes and Low Platelets (HELLP) syndrome, chronic hypertension superimposed with preeclampsia/eclampsia)
Pregnancy	Stillbirth
Pregnancy	Preterm labor without delivery
Pregnancy	PROM
Pregnancy	PPROM
Infant	SGA
Infant	LGA
Infant	LBW
Maternal	GBS

9.2.4.2. Cohort Study Comparison (Unexposed) Group

Pregnancies among individuals not administered ABRYSVO will be selected as a comparator with a 1:1 matching ratio to the pregnancies among individuals who were exposed to ABRYSVO. For the unexposed pregnancies, the individual must be pregnant/reached the week of gestational age of the exposed pregnancy (ie, index date) when ABRYSVO was administered (without a non-live birth event [eg, induced abortion, or stillbirth] occurring beforehand). The index date for the ABRYSVO-unexposed group will be the equivalent of the gestational age at vaccination administration (in days) in the exposed match. For example, if an exposed individual was vaccinated at 32 weeks and 3 days of gestation, the index date for unexposed matches would be set to 32 weeks and 3 days after their estimated LMP. See Section 9.7.2.1 for a description of the proposed matching plan. Separate unexposed groups will be selected for the analysis of pregnancy and maternal outcomes (all eligible pregnancies) and the analysis of neonatal/infant outcomes (subset of live birth pregnancies linked to an infant).

The use of a contemporaneous comparator in the proposed cohort study, rather than a historical comparator, has the following strengths: (1) it avoids bias due to temporal changes in the risks or coding for outcomes; (2) it allows for comparable assessment of potential confounders (through matching and propensity score estimation), accounting for the gestational age at administration of the vaccine; and (3) it allows for evaluation of safety events for which the risks may vary over time or during the course of pregnancy/perinatal period. To avoid the concern from the RCA study that there might be a small number of individuals who both, receive another vaccine (eg, seasonal influenza, COVID, Tdap) and do not receive ABRYSVO, individuals will not be required to receive another vaccine during pregnancy. However, per the inclusion criteria, all individuals will be required to receive a vaccine in the pre-pregnancy period, to ensure similarity in terms of healthcare/vaccine-seeking behavior.

Other approaches to a comparator population have also been considered. For example, use of a concurrent vaccine-specific comparator (eg, individuals receiving Tdap but not ABRYSVO) may be problematic if the timing of administration of ABRYSVO is more likely to occur later in the pregnancy period compared to the vaccinated comparator (eg, at 36 vs 27 weeks' gestation), or if insufficient counts of the comparator vaccine-only pregnant individuals (not also exposed to ABRYSVO) are available for evaluation. Additionally, "self-matching" using a self-controlled study design such as self-controlled risk interval analysis, would be problematic given that risk intervals during late pregnancy (given the approved gestational age for ABRYSVO during 32 0/7 through 36 6/7 weeks' gestation) would be compared to risk intervals in the postpartum period.

9.2.5. Follow-up

9.2.5.1. Follow-up: RCA study

With the exception of GBS, all outcomes will be evaluated as dichotomous endpoints occurring at the end of the pregnancy. GBS will be evaluated within a fixed risk window of 42 days starting from the day after the vaccination.

9.2.5.2. Follow-up: Cohort Study

9.2.5.2.1. Pregnancy Outcomes

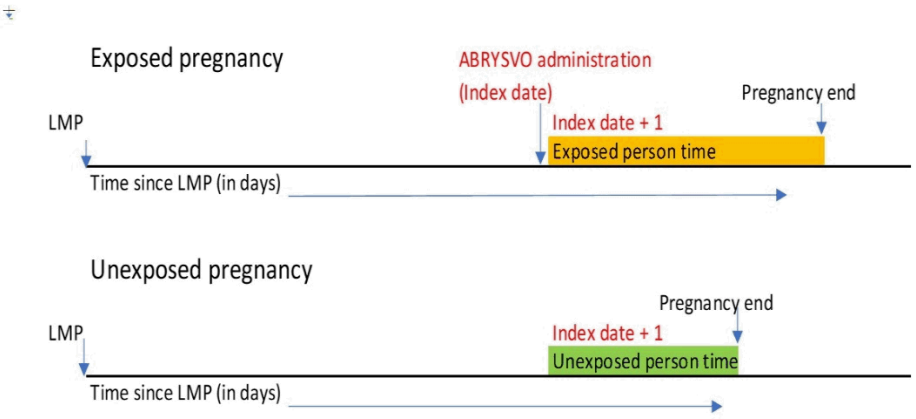
For analysis of pregnancy outcomes (Section 9.3.2), pregnant individuals will be followed from 1 day after the index date or the date of delivery, as relevant, until the earliest of the following (Figure 1):

- Occurrence of the event of interest;
- The latest gestational age at which an outcome can occur (applies to preterm birth, preterm labor, and PPROM outcomes);

- Receipt of ABRYSVO after 36 6/7 weeks gestation; or
- 6 weeks (42 days) after the end of pregnancy (applies to pregnancy-associated hypertensive disorders) or the end of pregnancy/delivery admission discharge date (applies to all other outcomes).

See Table 2 for a description of the follow up periods for specific outcomes.

Figure 1. Cohort design to assess pregnancy outcomes



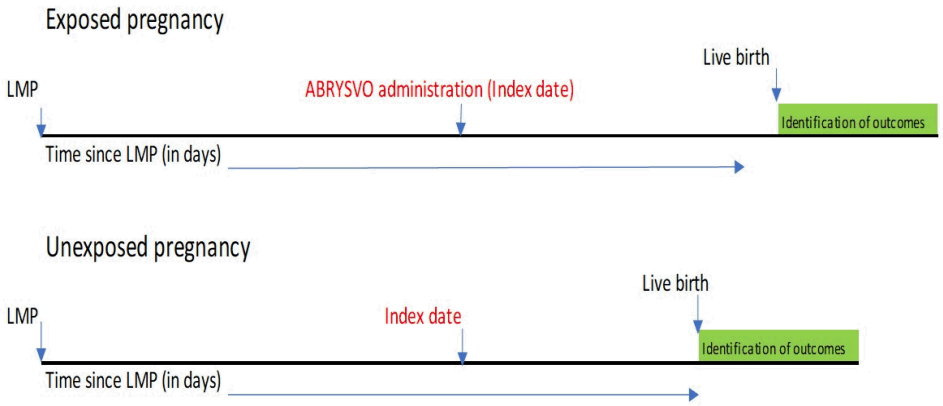
Abbreviations: LMP = last menstrual period

9.2.5.2.2. Neonatal/infant Outcomes

For the analysis of neonatal/infant outcomes (Section 9.3.2) infants will be followed for events from birth until the earliest of the following (Figure 2):

- Occurrence of the event of interest,
- 28 days after birth (for NICU admission, mechanical ventilation in the neonatal period, neonatal deaths) or 30 days after birth (for other neonatal/infant outcomes);
- End of health plan enrollment; or
- Death.

Figure 2. Cohort design to assess neonatal/infant outcomes



Abbreviations: LMP = last menstrual period

9.2.5.2.3. Maternal Outcomes

For the analysis of maternal outcomes, individuals will be followed from the start of the risk window (the index date or up to 5 days after the index date, depending on the outcome) until (Figure 3):

- The end of the risk window, as defined in Section 9.3.2;
- End of health plan enrollment;
- Receipt of ABRYSVO after 36 6/7 weeks gestation; or
- Death

See Table 3 for a description of risk windows for specific outcomes.

Figure 3. Cohort design to assess maternal outcomes

Abbreviations: LMP = last menstrual period

Note that the risk windows vary by outcome (see Table 3)

9.3. Variables

9.3.1. Exposure

Exposure to ABRYSVO during 32 0/7 to 36 6/7 weeks of gestation will be identified in claims and/or EHR data. Receipt of ABRYSVO will be identified using CPT code 90678, CVX code 305, and National Drug Code (NDC) codes 00069-0207-01, 00069-0344-01, 00069-0344-05, 00069-0344-10, 00069-2465-01, 00069-2465-10, and 00069-2465-19. Additional codes for identification of ABRYSVO exposure may be included, if relevant codes become available in the future.

9.3.2. Outcomes

9.3.2.1. RCA Outcomes

The subset of priority outcomes to be evaluated in RCA include: preterm birth, pregnancy-associated hypertensive disorders, stillbirth, preterm labor without preterm delivery, PROM, PPROM, SGA, LGA, LBW, and GBS.

All safety events of interest will be identified in claims and EHRs (where available) using diagnosis codes, with procedure, revenue, and/or pharmacy dispensing codes as appropriate. Neonatal/infant outcomes will be identified in mothers' or infants' claims and/or EHR data through diagnosis codes among all eligible pregnancies, to include as large a sample as possible for detection of safety signals.

Definitions of pregnancy and neonatal/infant outcomes are provided in Table 2.

The 42-day risk window after vaccine administration for GBS (Table 3) is based upon published VSD and Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program studies and the Biologics Effectiveness and Safety System (BEST) Initiative.[15-17] In addition, if cases of GBS are identified in the RCA, the RCA report will note whether or not the cases occurred in the 1-21 day window (in addition to the 1-42 day window).

9.3.2.2. Cohort Study Outcomes

Outcomes to be evaluated in the cohort study include preterm birth (primary outcome) and pregnancy-associated hypertensive disorders (primary outcome); other adverse pregnancy outcomes (stillbirth, preterm labor without delivery, PROM, PPROM, placental abruption, cesarean delivery, prolonged maternal length of stay); maternal outcomes (thrombocytopenia, GBS, other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation); and neonatal/infant outcomes (SGA, LGA, LBW, admission to NICU (exploratory outcome), mechanical ventilation in neonatal period (exploratory outcome), neonatal death (exploratory outcome). The latter outcomes are considered exploratory given the expected low capture/outcome misclassification using claims data. Note that NICU duration, a potential outcome of interest described in the study synopsis, will not be evaluated in the present study given the inability to identify this outcome using claims data.

All safety events of interest will be identified in claims and EHRs (where available) using diagnosis codes, with procedure, revenue, and/or pharmacy dispensing codes as appropriate. Algorithms for identification of outcomes are shown in Appendix A.

To the greatest extent possible, validated algorithms will be used for the study, if available, and risk window definitions were selected to align with studies from the FDA's Sentinel, BEST Initiative, and CDC's VSD.[5,15,18]

Validation of the algorithms for preterm birth (primary outcome), preterm labor (without preterm delivery), and pregnancy-associated hypertensive disorders (primary outcome) will be conducted through review of medical records for a sample of potential cases from select RPs. Potential cases will be reviewed by physician adjudicators with expertise in obstetrics/gynecology (eg, board certified in Obstetrics and Gynecology, Maternal Fetal Medicine, or Family Medicine) to confirm the diagnosis. The adjudicators will review the medical charts of each potential case sampled and be blinded to treatment. A Chart Review Plan and chart abstraction/adjudication forms will be developed in consultation with the physician adjudicators and RPs. If the algorithms demonstrate adequate performance characteristics (using predefined criteria, eg, a minimum positive predictive value (PPV), to be defined in the SAP), then all algorithm-identified cases will be included in the final analysis without additional analysis to adjust for outcome misclassification. If the algorithms

do not demonstrate adequate performance, then the validation results will be used to inform or adjust risk ratios in sensitivity analyses. Medical record validation of other study outcomes will not be conducted.

Additional details about medical record validation will be provided in a separate validation plan document.

9.3.2.2.1. Pregnancy and Neonatal/Infant Outcomes

Pregnancy outcomes will be identified in the mothers' claims and/or EHR data through diagnosis or procedure codes for all eligible pregnancies.

For the cohort study, neonatal/infant outcomes will be identified in claims and/or EHR data through diagnosis, procedure, inpatient disposition, and/or revenue codes among live births for which the mother and infant are linked. Both infants' and mothers' claims will be searched in the cohort study to ensure more complete capture of infants' diagnoses in the first 30 days of life. The infant's diagnoses may be captured in the mother's health plan claims data shortly after birth (generally ≤30 days after birth), especially when there is a delay in the enrollment of the infant in the health plan.

Pregnancy and neonatal/infant outcomes, including clinical definitions, method for identification in the data sources, and the follow up period are provided in Table 2. To the greatest extent possible, clinical definitions were selected to align with the American College of Obstetricians and Gynecologists (https://www.acog.org/clinical) and Brighton Collaboration (https://brightoncollaboration.us/category/pubs-tools/case-definitions/) definitions.

Table 2. RCA and Cohort Study: Pregnancy and neonatal/infant outcomes

Outcome	Clinical definition and method for identification in the data sources	Risk window start (days following index date[a] [Day 0])	Risk window end
Pregnancy Outcomes			
Preterm birth (primary outcome of interest)[b]	Live birth before 37 0/7 weeks (<259 days) of gestation; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of preterm birth (ie, live birth before 37 0/7 weeks of gestation) • 36 6/7 weeks of gestation (latest gestational age at which a preterm birth can occur) • Other event marking the end of pregnancy (eg, pregnancy termination)
Pregnancy-associated	See definitions for specific conditions below (gestational	1	Earliest of the following:

Table 2. RCA and Cohort Study: Pregnancy and neonatal/infant outcomes

Outcome	Clinical definition and method for identification in the data sources	Risk window start (days following index date[a] [Day 0])	Risk window end
hypertensive disorders (primary outcome)[b]	hypertension, preeclampsia, eclampsia, HELLP syndrome, chronic hypertension superimposed with preeclampsia/eclampsia, postpartum hypertension)		• Occurrence of gestational hypertension, preeclampsia/eclampsia, HELLP syndrome, postpartum hypertension • 42 days after index date • Receipt of ABRYSVO after 36 6/7 weeks gestation
Gestational hypertension	New-onset hypertension on or after 20 0/7 weeks' gestation; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of gestational hypertension • Live birth or stillbirth delivery admission • 42 days after index date • Other event marking the end of pregnancy (pregnancy termination) • Receipt of ABRYSVO after 36 6/7 weeks gestation
Preeclampsia/ eclampsia	Preeclampsia: New-onset hypertension on or after 20 0/7 weeks' gestation and proteinuria or maternal organ dysfunction (renal insufficiency, impaired liver function, pulmonary edema, cerebral or visual disturbances, thrombocytopenia). Eclampsia: New-onset seizures (with preeclampsia) in the absence of other causative conditions; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of preeclampsia/eclampsia • Live birth or stillbirth delivery admission discharge date • 42 days after index date • Other event marking the end of pregnancy (pregnancy termination) • Receipt of ABRYSVO after 36 6/7 weeks gestation
HELLP syndrome	Variant of preeclampsia with hemolysis, elevated liver enzymes, and low platelet count; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of HELLP syndrome • Live birth or stillbirth delivery admission discharge date • 42 days after index date • Other event marking the end of pregnancy (pregnancy termination)

Table 2. RCA and Cohort Study: Pregnancy and neonatal/infant outcomes

Outcome	Clinical definition and method for identification in the data sources	Risk window start (days following index date[a] [Day 0])	Risk window end
			• Receipt of ABRYSVO after 36 6/7 weeks gestation
Chronic hypertension superimposed with preeclampsia/ eclampsia	Development of preeclampsia or eclampsia among those with pre-existing hypertension; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of chronic hypertension superimposed with preeclampsia/eclampsia • Live birth or stillbirth delivery admission discharge date • 42 days after index date • Other event marking the end of pregnancy (pregnancy termination) • Receipt of ABRYSVO after 36 6/7 weeks gestation
Postpartum hypertension	Pregnancy-associated hypertension occurring after delivery; to be identified via diagnosis codes	Delivery date	Earliest of the following: • Occurrences of postpartum hypertension • End of the study period • End of health plan enrollment • Death • 42 days after index date • Receipt of ABRYSVO after 36 6/7 weeks gestation
Stillbirth[b]	Spontaneous pregnancy loss on or after 20 0/7 weeks of gestation; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of stillbirth • Live birth delivery admission • Other event marking the end of pregnancy (pregnancy termination) • Receipt of ABRYSVO after 36 6/7 weeks gestation
Preterm labor without delivery[b]	Presence of regular uterine contractions that occur without a live birth/stillbirth delivery before 37 0/7 weeks of gestation; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of preterm labor without delivery • 36 6/7 weeks gestation (latest gestational age at which a preterm labor can occur) • Live birth or stillbirth delivery admission • Other event marking the end of pregnancy (pregnancy termination)
PROM [b]	Rupture of membranes prior to the onset of labor; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of PROM

Table 2. RCA and Cohort Study: Pregnancy and neonatal/infant outcomes

Outcome	Clinical definition and method for identification in the data sources	Risk window start (days following index date[a] [Day 0])	Risk window end
			• Live birth or stillbirth delivery admission • Other event marking the end of pregnancy (pregnancy termination) • Receipt of ABRYSVO after 36 6/7 weeks gestation
PPROM [b]	Rupture of members prior to the onset of labor that occurs before 37 0/7 weeks' gestation; to be identified via diagnosis codes	1	Earliest of the following: • Occurrence of PPROM • Occurrence of preterm birth (ie, live birth or stillbirth before 37 weeks of gestation) • 36 6/7 weeks of gestation (latest gestational age at which PPROM can occur) • Other event marking the end of pregnancy (pregnancy termination)
Placental abruption	Placental detachment from the inner wall of the uterus on or after 20 0/7 weeks of gestation and before delivery; to be identified via diagnosis codes	1	Earliest of the following • Occurrence of placental abruption • Live birth or stillbirth delivery admission • Other event marking the end of pregnancy (pregnancy termination) • Receipt of ABRYSVO after 36 6/7 weeks gestation
Prolonged maternal length of stay	Days of stay for delivery hospital admission (descriptive) categorized by 1) vaginal delivery ≤2 days vs >2 days or 2) cesarean delivery ≤4 days vs >4 days; to be identified using inpatient admission and discharge dates	Delivery admission date	Discharge date of the delivery hospitalization
Cesarean section	Surgical delivery of an infant through incision in the mother's abdomen and uterus; to be identified via procedure codes	Delivery date	Discharge date of the delivery hospitalization
Neonatal/Infant Outcomes			
SGA[b]	Less than 10th percentile of birth weight for gestational age; to be identified via diagnosis codes	Birth	Earliest of the following (in the infant): • Diagnosis of small size for gestational age

Table 2. RCA and Cohort Study: Pregnancy and neonatal/infant outcomes

Outcome	Clinical definition and method for identification in the data sources	Risk window start (days following index date[a] [Day 0])	Risk window end
			• End of the study period • End of health plan enrollment • Death • 30 days after birth[c]
LGA[b]	Birthweight more than 90th percentile for gestational age; to be identified via diagnosis codes	Birth	Earliest of the following (in the infant): • Diagnosis of large size for gestational age • End of the study period • End of health plan enrollment • Death • 30 days after birth[c]
LBW[b]	Birth weight less than 2500 grams; to be identified via diagnosis codes	Birth	Earliest of the following (in the infant): • Diagnosis of LBW • End of the study period • End of health plan enrollment • Death • 30 days after birth[c]
NICU admission (exploratory outcome)	Admission to a neonatal intensive (critical) care unit; to be identified via inpatient procedure and revenue codes	Birth	Earliest of the following (in the infant): • Record of NICU admission • End of the study period • End of health plan enrollment • Death • 28 days after birth
Mechanical ventilation in the neonatal period (exploratory outcome)	Use of an external device to assist/control breathing; to be identified using procedure codes	Birth	Earliest of the following (in the infant): • Record of mechanical ventilation • End of the study period • End of health plan enrollment • Death • 28 days after birth
Neonatal death (exploratory outcome)	Infant death during the 28 days after birth; to be identified using hospital discharge disposition data	Birth	Earliest of the following (in the infant): • Record of neonatal death • End of the study period • End of health plan enrollment • 28 days after birth

a The index date is defined as the date of administration of ABRYSVO or the corresponding date in the comparison group.
b Outcome to be evaluated using RCA; follow up period may be modified for RCA

Table 2. RCA and Cohort Study: Pregnancy and neonatal/infant outcomes

Outcome	Clinical definition and method for identification in the data sources	Risk window start (days following index date[a] [Day 0])	Risk window end

c The 30-day window is being used to ensure complete ascertainment if outcome is not documented at birth (eg, if it is later documented during an outpatient visit or hospital transfer). The 30-day window will not be used in RCA.

For all live birth pregnancies linked to an infant, the Maternal-Fetal Medicines Unit (MFMU) Neonatal Morbidity Index[19] will also be estimated to report prematurity-associated morbidity in an exploratory analysis, characterizing by the most severe category met (death, major morbidity, minor morbidity).

9.3.2.2.2. Maternal Outcomes

Maternal outcomes are listed along with their risk windows in Table 3. Outcomes will be identified in the mothers' claims data through diagnosis codes among all eligible pregnancies. Specified outcome-specific risk windows reflect a period of potentially increased risk following vaccination.

The risk windows for thrombocytopenia are based upon the published literature and the BEST Initiative.[15,20] The 42-day risk window after vaccine administration for GBS, other immune-mediated demyelinating conditions, and polyneuropathies are based upon published VSD and Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program studies and the BEST Initiative.[15-17] The exception is acute disseminated encephalomyelitis (ADEM), with a risk window of 5-28 days following administration, based on prior literature and Brighton Collaboration recommendations.[21,22]

Events recorded outside these intervals will not be counted.

Table 3. Cohort Study: Maternal outcomes

Outcome	Clinical conditions encompassed within outcome category[b]	Risk window start (days following index date [Day 0])	Risk window end (days following index date)[c]
Thrombocytopenia	Immune thrombocytopenia (ITP)	1	42
	Thromboembolic events associated with thrombocytopenia	1	28
	Thrombotic thrombocytopenic purpura (TTP)	1	28
GBS[a]	Guillain-Barré syndrome	1	42
Other immune-mediated demyelinating conditions	Acute disseminated encephalitis and encephalomyelitis	5	28
	Acute transverse myelitis in demyelinating disease of central nervous system	1	42
	Optic neuritis	1	42
	Neuromyelitis optica	1	42
	Other acute demyelinating diseases	1	42
Acute polyneuropathies excluding GBS	Inflammatory polyneuropathy, serum neuropathy, other inflammatory polyneuropathies, chronic inflammatory demyelinating polyneuritis, multifocal motor neuropathy, other inflammatory polyneuropathies, drug-induced polyneuropathy, other polyneuropathies	1	42
Atrial fibrillation	Atrial fibrillation, paroxysmal, persistent, or chronic	0	42

a Outcome to be evaluated using RCA. A 21-day risk window will also be evaluated in a secondary analysis for the cohort study.

b Identified via diagnosis codes

c Follow-up will end at the earliest of the occurrence of the maternal outcome of interest; end of the risk window; end of health plan enrollment; receipt of ABRYSVO after 36 6/7 weeks gestation; or death (see Section 9.2.5.2.3)

9.3.3. Other Variables

9.3.3.1. RCA Covariates

Covariates used for confounding control include maternal age at pregnancy end date (date of delivery), an indicator variable for season of vaccination (months September-January defined as in-season and all other months defined as off-season), and a composite high-risk indicator which is the union of several variables that are risk factors for pre-term birth. The composite high-risk factor (to be described in the SAP) includes evidence of any of the following conditions: prior preterm birth or prior preterm labor; preterm labor during the current pregnancy; tobacco or smoking cessation medications; multiple gestation; pre-existing hypertension, gestational hypertension, eclampsia, preeclampsia, or use of anti-hypertensive medications; substance abuse, alcohol use, or drug dependency; recent prior live birth delivery; assisted reproduction; evidence of short cervix (lower part of uterus) or cervix shortening; placenta previa; gestational diabetes, diabetes, or use of diabetic medications; infections including COVID-19, urinary tract infections, sexually transmitted infections, or certain vaginal infections (including bacterial vaginosis or trichomoniasis); magnesium sulfate injection; encounter for high-risk pregnancy.

9.3.3.2. Cohort Study Covariates

Table 4 presents variables that will be used for descriptive analysis, matching, and propensity score estimation(s) in analysis of pregnancy and neonatal/infant outcomes. These variables will include maternal age at pregnancy end date, geographic region, healthcare utilization, recorded prenatal procedures, other vaccines (before and during pregnancy), medications, estimated LMP, gestational age on the index date, maternal comorbidities, obstetric history, lifestyle factors, and pregnancy complications during the current pregnancy. These variables will be identified using claims or EHR structured data (where available), and IIS data (where available). Presence of codes within the specified windows in Table 4 will be used to identify the covariates (ie, the conditions are not required to be newly diagnosed). Additional covariates may be considered based upon the most recent evidence at the time of the analysis. Detailed definitions and algorithms will be included in the SAP.

Table 4. Cohort Study: Covariates used for descriptive analysis, matching or propensity score estimation

Variable	Descriptive	Matching	Propensity scores
Maternal age (as of pregnancy end date; 5-year age groups, combining 45-54 year age groups)	X		X
Geographic region (based on the most recent information at the time of data refresh)	X		X
Race/ethnicity	X		

Table 4. Cohort Study: Covariates used for descriptive analysis, matching or propensity score estimation

Variable	Descriptive	Matching	Propensity scores
Immunocompromising conditions (recorded in the 12 months before or on the index date); composite variable • Including immunodeficiencies, immunosuppressant medication use, HIV and other immunosuppressing conditions, and receipt of organ or bone marrow transplants	X	X	
Hypertensive disorders (including pre-existing hypertension recorded in the 12 months before the index date and pregnancy-associated hypertension from estimated LMP to index date [excluding the index date]); composite variable	X	X	
Estimated pregnancy start date (LMP)	X	X	
Gestational age on the index date [a]	X		
Comorbidities (recorded in the 12 months before or on the index date); separate variables for the following conditions: • Chronic anemia • Antiphospholipid syndrome • Diabetes (type 1 and type 2) • Cardiovascular disease • Cerebrovascular diseases • Chronic respiratory disease, excluding asthma • Asthma • Chronic kidney disease • Chronic liver disease • Cancer • Epilepsy • Infections • Connective tissue disorders • Thyroid disorders • Mood disorders • Nutritional deficiencies • Obesity (capture anticipated to be incomplete in the data sources) • Excessive stress • Systemic lupus erythematosus • Underweight	X		X[b]
Other vaccines recommended for routine use (recorded in 12 months before or on the index date); separate variables for the following vaccines: • COVID-19 • Influenza • Tdap • Other	X		X
Enrollment time ever prior to pregnancy	X		

Table 4. Cohort Study: Covariates used for descriptive analysis, matching or propensity score estimation

Variable	Descriptive	Matching	Propensity scores
Research Partner type (National, Regional, Medicaid) (in 12 months before or on the index date)	X		
Healthcare utilization recorded in the 6 months prior to pregnancy	X		X
Prenatal tests and procedures performed (recorded from estimated LMP to index date); categories for number of unique tests/procedures performed (0, 1-2, >2) • Nuchal translucency ultrasound • Assay of estriol • Inhibin A • PAPP-A serum • Free beta-human chorionic gonadotropin • Alpha-fetoprotein • Fetal anatomic exam • Second or third trimester ultrasound • Glucose screening • Administration of Rho(D) immune globulin • Fetal fibronectin • Sex hormone-binding protein	X		X
Any invasive antenatal tests performed (recorded from estimated LMP to index date)	X		X
Lifestyle factors (recorded in the 12 months before or on the index date); separate variables for the following conditions: • Alcohol use • Smoking • Substance use and dependence (capture anticipated to be incomplete)	X		X
Reproductive history (recorded using diagnosis codes specific to reproductive history in the 12 months before or on the index date); separate variables for the following: • Poor reproductive or obstetric history • Recurrent pregnancy loss (capture anticipated to be incomplete) Reproductive history (in all data available before the index date; if feasible in the data sources): • Preterm birth in previous pregnancies (capture anticipated to be incomplete) • PROM birth in previous pregnancies (capture anticipated to be incomplete) • Uterine and cervical factors (leiomyoma, dilation and curettage, cold knife conization, electrosurgical excision, procedural abortion)	X		X

Table 4. Cohort Study: Covariates used for descriptive analysis, matching or propensity score estimation

Variable	Descriptive	Matching	Propensity scores
Pregnancy complications and factors during the current pregnancy (recorded from the estimated LMP to the index date [including the index date]); separate variables for the following factors: • Early bleeding in pregnancy • Gestational diabetes • Assisted reproduction • Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH) infections • Polyhydramnios • Gestational excessive maternal weight gain Additional pregnancy factors during the current pregnancy • Short interpregnancy interval (< 6 months from prior pregnancy end date) • Shortened cervix documented after 22 weeks gestation • Vaginal bleeding in the second or third trimester (measured from LMP+98 days through index date)	X		X
Number of pregnancies ever prior to current pregnancy	X		
Number of live birth deliveries ever prior to current pregnancy	X		
Nulliparity	X		
Teratogenic medications (recorded from 183 days before pregnancy start until the index date [including the index date])	X		X
Preterm labor (without delivery) during the current pregnancy (recorded from the estimated LMP to before the index date [excluding the index date])	X		
Mode/method of delivery	X		
Infant characteristics • Gestational age at birth • Sex • Race/ethnicity	X		

a For the cohort study, gestational age will be accounted for by selecting the index date for the ABRYSVO-unexposed group to be the equivalent of the gestational age at vaccination administration (in days) in the exposed match.
b Systemic lupus erythematosus is a condition included within the immunocompromising conditions composite variable (matching variable) and thus will not be included as a separate propensity score variable.

9.4. Data Sources

The study will use data from data RPs that contribute claims and/or EHRs to the Sentinel System and additional health plans (eg, Medicaid) with the capability to transform the data into the SCDM. In addition to providing electronic healthcare data, the RPs will provide scientific input and feedback to support this study.

The participation of RPs will be confirmed before finalizing the SAP. Inclusion of data sources for specific analyses will be based on the following:

- Ability to identify pregnant individuals and link them to their infants
- Anticipated number of pregnant individuals receiving ABRYSVO
- Lag in claims and/or structured EHR data

The FDA Sentinel System is an active surveillance system that uses routine querying and analytical tools to evaluate electronic healthcare data from a distributed data network for monitoring the safety of regulated medical products in the US, established under the Sentinel Initiative.[23,24] Sentinel data RPs typically update their curated Sentinel database on a routine (tri-annual or annual) basis. If possible, this study will leverage more frequent data updates to the Sentinel System. This study will focus on the research-eligible populations from each of the RPs participating in the study and will use the most recent data available within each participating partner's Sentinel Distributed Database at the time of analysis.

All data RPs that participate in Sentinel capture longitudinal medical care information on outpatient medication dispensings, vaccine administrations, and inpatient and outpatient diagnoses and procedures. Each Sentinel data RP can request access to full-text medical records for outcome validation for a subset of participants in the Sentinel Distributed Database. Data RPs use the SCDM for standardization of demographic and clinical data elements.[13,25] Publicly available routine analytical tools include reusable, modular Statistical Analysis System (SAS [SAS Institute Inc.; Cary, North Carolina]) programs. These analytical tools are designed to be executed against the SCDM to permit rapid queries, including descriptive analyses and complex methodologies (eg, comparative analyses), across data RPs. Specific information in the SCDM includes, but is not limited to, the following types of data:

- **Enrollment data**: 1 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 RP 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 (eg, 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 RPs; and the level of completeness for laboratory information for those RPs with such data varies.[26]

- **Diagnosis data**, including the date of diagnosis, its associated encounter identifier, admission date, provider identifier, and encounter type. Diagnoses are recorded with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes. For inpatient hospital and non-acute inpatient stay encounters, the SCDM includes both principal and non-principal discharge diagnosis data. Outcomes and covariates will be identified using ICD-10-CM codes.

- **Procedure data**, including the procedure date, its associated encounter identifier, admission date, provider identifier, and encounter type. Procedures are coded as ICD-9-CM and ICD-10-CM Procedure Coding System procedure codes, CPT categories II, III, or IV codes, revenue codes, as well as Healthcare Common Procedure Coding System (HCPCS) levels II and III codes. ICD-10-CM Procedure Coding System, CPT, and HCPCS codes will be used for the analysis.

9.5. Study Size

RCA: Data on all pregnancies meeting the study eligibility criteria that received ABRYSVO within the contributing RPs will be analyzed.

Cohort Study: All pregnancies among individuals who meet the study inclusion/exclusion criteria with pregnancy start dates between 07 January 2023 and 30 September 2027 will be eligible for this study. Table 5 presents sample sizes needed for the ABRYSVO-exposed to

detect a range of HRs for a comparative analysis of the primary outcomes, assuming a 2-sided test, a type 1 error rate of 0.05, a 1:1 ratio of ABRYSVO-exposed to unexposed pregnancies, power of 0.8, and an estimated background rate of preterm birth of 4.0% and pregnancy-associated hypertensive disorders of 15.0%. These background rate estimates are based upon historical data among pregnant persons administered routine vaccinations (influenza, COVID-19, or Tdap) in our RCA study population during the period 2018-2022.

Table 5. Cohort Study: Sample size calculations for comparative analyses assuming a 1:1 propensity score matching

Outcome	Reference Event Rate	Sample Size Needed in ABRYSVO-Exposed Group to Detect HRs					
		1.1	1.2	1.5	2	2.5	3
Preterm birth	4.0% [a]	43,485	11,848	2,393	818	468	325
Pregnancy-associated hypertensive disorders	15.0%[a]	11,596	3,160	639	218	125	87
Rare outcome	1%	173,937	47,391	9,571	3,269	1,871	1,300
Very rare outcome	0.1%	1,739,364	473,909	95,704	32,687	18,709	12,997
Extremely rare outcome	0.01%	17,393,640	4,739,090	957,035	326,868	187,089	129,970

The Power Analysis and Sample Size software 2020 was used in the sample size calculation. Type 1 error rate (2-sided) is assumed at 0.05.
a. Background rate estimates are based upon historical data among pregnant persons administered routine vaccinations (influenza, COVID-19, Tdap) in our RCA study population during the period 2018-2022.

Assuming a 1:1 ratio of ABRYSVO-exposed to unexposed, a type 1 error of 0.05, and a target HR of 2.0 for the primary safety outcomes of preterm birth and pregnancy-associated hypertensive disorders, 818 and 218 pregnant individuals, respectively, from the ABRYSVO-exposed group and 818 and 218 respectively from the unexposed group will allow us to achieve 80% power. For more rare outcomes with event rates ranging from 1% (eg, PPROM)[27] to 0.01% (eg, atrial fibrillation),[28] a sample size of 3,269 to 326,868 is needed for both the ABRYSVO-exposed group and the unexposed group. This target HR was chosen given that associations with a HR of >2.0 are unlikely to be explained by confounding alone and this cut-off for the magnitude of effect increases the quality of evidence from an observational study.[29] To detect an HR of 1.2 for the primary safety outcomes of preterm birth and pregnancy-associated hypertensive disorders, 11,848 and 3,160 pregnant individuals, respectively, are needed for both the ABRYSVO-exposed group and the unexposed group. Note that the study will not be terminated if the target sample size is reached but will continue for the specified study period.

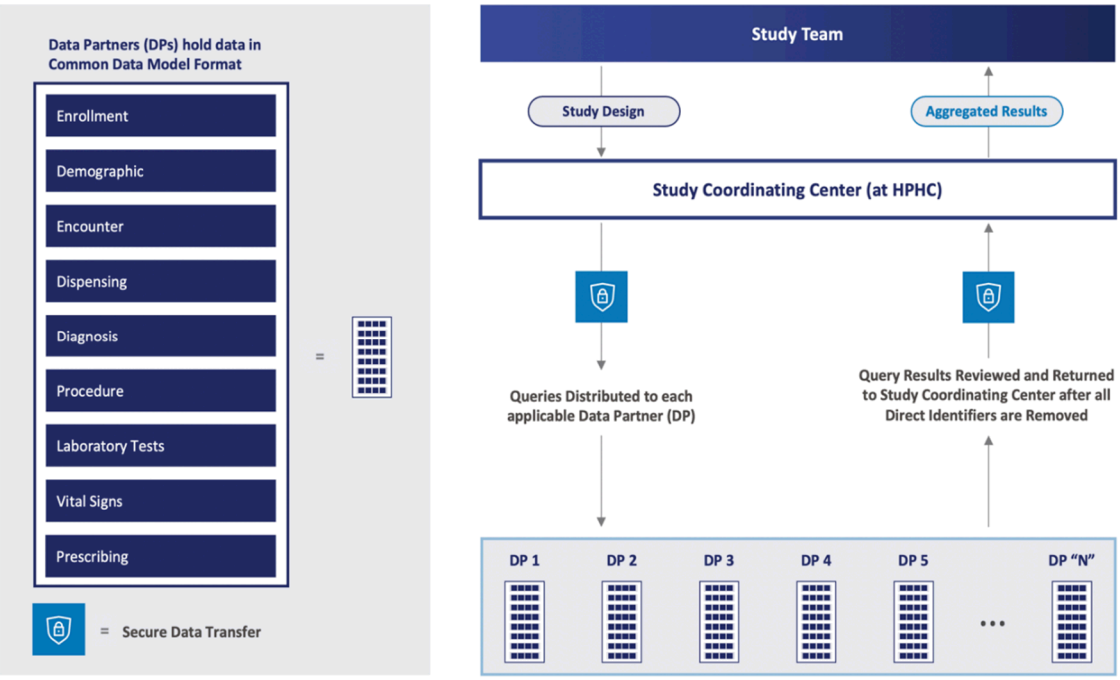
9.6. Data Management

Harvard Pilgrim Health Care Institute (HPHCI), located in Boston, Massachusetts, will serve as the coordinating center for the study. HPHCI staff or contractors will be responsible for writing and distributing SAS programs that can be used to evaluate the data included in databases at participating data RPs. The distributed network will allow data RPs 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 (eg, 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.[30]

The RPs will establish and maintain the administrative, hardware, and software capabilities and capacity to respond to data requests in a timely manner. RPs will also provide data science support with epidemiologic review.

The general analytic workflow is depicted in Figure 4. First, the study coordinating center (at HPHCI) will submit a computer program designed to meet the needs of the study to each participating data RP via a secure portal. Next, the participating RPs will receive and run the computer program behind their firewalls, using data formatted to the SCDM. Then, the RPs will review the aggregate analysis results and return them to the study coordinating center through a secure portal. Next, the study coordinating center will review and aggregate the results across the RPs. As a final step, the aggregated results will then be transferred to the study team, including extended researchers and the study sponsor.

Figure 4. General analytic workflow



9.6.1. Data Collection Tools

As the analyses will be based on secondary data, the only data collection tool (DCT) that may be applicable will be data abstraction forms that will be developed for the purpose of validation of select outcomes. Details of how data will be handled during validation will be described in a validation plan that would be developed prior to implementing validation in the data sources.

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study. RPs should approve any data collection method; if the suggested DCT is not approved by the RP regulatory team, the RP will use their own approved DCT. DCTs will not include person-identifiable information such as name, address, phone number, social security number, medical record number, or provider name.

A DCT is required and should be completed for each individual included in the chart validation activities. For some RPs, the completed original DCT are the sole property of Pfizer, while for others, remains confidential to the individual RP. The DCT should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer, or RP, when applicable. For some RPs, no individual data will be shared with HPHCI or Pfizer, only aggregate results will be shared. HPHCI and the RPs shall ensure that the DCTs are securely

stored at the study sites in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

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

The source documents are the hospital or the physician's chart. In these cases, data collected on the DCTs must match those charts. For some RPs, no source documents such as hospital or the physician's chart will be shared with Pfizer, HPHCI or other RPs.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, HPHCI as the coordinating center, or RPs who are retaining their own study records, agree to keep all study-related records, including the identity of all participating patients (sufficient information to link records, eg, DCTs and hospital records), copies of all DCTs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by HPHCI, or the RP, according to local regulations or as specified in the research agreement with Pfizer, whichever is longer. HPHCI, or the RP, must ensure that the records continue to be stored securely for so long as they are retained.

If HPHCI, or the RPs who are retaining their own study records, becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer. For RPs that will be retaining study records, no records will be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless HPHCI, the RPs, and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

HPHCI and/or the RPs (who are retaining their own study records) must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

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

When appropriate, publicly available Sentinel analytic tools will be used for the analyses; these are the same tools used by FDA for similar analyses of distributed databases. Modifications to the tools may be needed to meet study objectives, in which case the SAS programming data quality assurance (QA) Standard Operating Procedures will be followed (see Section 9.8). All statistical calculations will be performed using SAS 9.4 or higher.

Analyses will initially be conducted separately using data from each RP. RP-specific aggregated results will be sent to the study coordinating center, which will combine aggregated results across the RPs for reporting. The study coordinating center will follow each RP's policy with respect to masking low cell counts. Pooled analysis of effect estimates from all RPs will be conducted using privacy-preserving summary-level data sets (eg, risk set–level data sets) or another appropriate method.

9.7.1. RCA Study

9.7.1.1. Characterization of ABRYSVO Use

In the RCA study, descriptive analysis of baseline characteristics of ABRYSVO-exposed pregnancies will be performed. Counts of pre-specified outcomes of interest will be reported.

9.7.1.2. Sequential Statistical Analysis

For outcomes utilizing a historical comparator, ABRYSVO-exposed outcomes will be compared against expected outcome counts based on the total pregnancies contributed in the ABRYSVO-exposed group and historical referent rates of outcome occurrence. Background incidence estimates of outcomes will be calculated within strata of both RP site and pre-defined covariates to control for confounding. Covariate stratification may include demographic and clinical factors, which will be described in the SAP. The expected number of outcomes will be calculated by summing the products of numbers of ABRYSVO-exposed pregnancies within the strata in each data cut and the background incidence rate from the historical comparator group within the strata. Observed and expected numbers of outcomes will then be compared using sequential hypothesis testing. For these analyses, either the Poisson maxSPRT (PmaxSPRT) or the conditional PmaxSPRT will be utilized to generate the test statistic which will be measured against a critical value. As before, the critical value

is dynamic over the course of the analysis as data accrue. The choice of a PmaxSPRT or conditional PmaxSPRT depends on the number of outcomes available in the historical data and the projected number of outcomes in the treatment group. If the historical group data has less than 5x the outcome counts expected in the RSV preF-exposed group, then a conditional PmaxSPRT will be utilized to account for additional variability in outcome rates. Log-likelihood ratios are analogous to relative risks but on a different scale. They are calculated as point estimates without CIs to determine presence or absence of a signal. Once an analysis has signaled, sequential monitoring may continue but hypothesis testing will be completed. The SAP will describe signal refinement strategies when a given outcome has a statistically significant finding.

If a concurrent comparator is used for select outcomes, ABRYSVO-exposed outcomes will be compared with outcomes among matched or stratified comparator pregnancies. Based on projected sample size calculations, criteria will be set to detect or rule out a specific effect size at a specific power by the projected end of sequential analysis. For example, one might seek to detect at least a twofold elevated relative risk of a particular outcome at 80% power. For matched analyses, imbalances in outcome occurrence will be continuously evaluated as data accrue using the Binomial-based maxSPRT (BmaxSPRT) method.[31] In the BmaxSPRT, a signal is detected (and the null hypothesis rejected) when the log likelihood ratio exceeds a critical value, which is recalculated at each interim hypothesis test based on the data arrival rate and alpha spending plan. If there is not enough evidence to reject the null hypothesis of no excess risk by the end of the planned study period, then surveillance will end with the accrual of the pre-specified stopping point (ie, usually operationalized in terms of total outcomes accrued). Propensity score methods will be used to control for confounding when using a concurrent comparator, provided sample size is large enough for models to converge (details to be finalized in the SAP).

9.7.2. Cohort Study Analyses

9.7.2.1. Propensity Score Development and Matching

Propensity score development and matching (1:1 matching ratio) will occur within each RP. For all analyses, the unit of analysis will be a pregnancy episode.

The propensity score reflects the conditional probability of an individual being exposed to ABRYSVO during pregnancy given baseline potential confounders. Potential confounders are described in Section 9.3.3. Separate propensity score models will be fit for the cohort of all eligible (live birth and non-live birth) pregnancies (for pregnancy and maternal outcome analyses) and the cohort of all eligible live birth pregnancies linked to an infant (for neonatal/birth outcomes analyses).

For each pregnancy that occurs in the exposed group of the cohort study, one pregnancy in the unexposed group will be matched, without replacement, on RP (health care system), estimated LMP (calendar year and quarter: January-March; April-June; July-September;

October-December), diagnosis of an immunocompromised condition, diagnosis of a hypertensive disorder (pre-existing or pregnancy-associated hypertensive disorder) prior to the index date, and propensity score. Separate matched comparison groups will be identified for all eligible pregnancies (for evaluation of pregnancy and maternal outcomes) and live birth pregnancies linked to an infant (for evaluation of neonatal/infant outcomes in the cohort study).

Matching with a propensity score will minimize confounding bias due to differences between the ABRYSVO-exposed and unexposed group. Matching on RP and estimated LMP, will control for RP differences in ABRYSVO uptake, seasonality, and potential secular trends in ABRYSVO exposure and obstetric and maternal outcomes. Matching on diagnosis of an immunocompromised condition diagnosis will allow for an analysis restricting to individuals with these conditions. Matching on hypertensive disorder prior to the index date will allow for a stratified analysis and also restriction of the sample for identification of specific pregnancy-associated hypertensive orders of interest (Appendix A).

The methodology will be described in the SAP. In addition, the SAP will describe alternative plans and methods, should the proposed matching plan perform poorly in practice (eg, if many unmatched ABRYSVO-exposed pregnancies are excluded); for example, confounding may be addressed using inverse propensity score treatment weighting rather than propensity score matching.

9.7.2.2. Characterization of ABRYSVO Use

Descriptive analyses of baseline characteristics of ABRYSVO-exposed and matched unexposed pregnancies will be performed, overall and among those individuals identified with an immunocompromising condition. The mean follow-up time for all eligible pregnancies/infants will be summarized. Separate analyses will be conducted among all eligible pregnancies (live birth and non-live birth) and among live birth pregnancies linked to an infant.

9.7.2.3. Risks of Pregnancy, Maternal and Neonatal/Infant Outcomes

Risks of study outcomes (with 95% CIs) will be estimated among ABRYSVO-exposed and matched unexposed pregnancies, overall and among those individuals identified with an immunocompromising condition. Survival analysis methods (eg, Kaplan Meier curve) will also be used to describe the risk (cumulative incidence) for particular periods from administration in ABRYSVO-exposed and matched ABRYSVO-unexposed pregnancies.

Pending sample size feasibility for each specific outcome (see Section 9.5), comparative analyses will be conducted to compare the risks of those outcomes between the ABRYSVO-exposed and ABRYSVO-unexposed pregnancies, adjusting for confounding factors. Potential residual confounding after propensity score matching will be addressed by covariate adjustment.

Cox models will be used to calculate adjusted HRs and 95% CIs for pregnancy outcomes and maternal outcomes. For the primary outcomes of interest (preterm birth and pregnancy-associated hypertensive disorders), analyses will also be stratified by prior hypertensive disorder (preexisting/ pregnancy-associated hypertension) status.

For neonatal/infant outcomes, conditional logistic regression will be used to estimate prevalence odds ratios and 95% CIs.

Multivariable regressions will be employed for covariate adjustment to address confounding by variables other than those matching factors and potential residual confounding after propensity score matching.

9.7.2.4. Secondary Analyses

The following secondary and exploratory analyses will be conducted:

1. Among those identified preterm births in the ABRYSVO-exposed and matched ABRYSVO-unexposed groups, the frequency of characteristics and risk factors will be described.

2. Among those identified with preterm labor (without delivery) in the ABRYSVO-exposed and matched ABRYSVO-unexposed groups, the frequency of those with preterm labor prior to the index date and other characteristics will be described.

3. The risk of preterm delivery, including both live births and stillbirths, will be examined in the ABRYSVO-exposed pregnant individuals and the ABRYSVO-unexposed pregnant individuals.

4. Evaluation of the risk of GBS using a risk window of 1-21 days following vaccination will be conducted.

5. Characteristics and outcomes of pregnant individuals who received ABRYSVO outside the recommended gestational ages (32 0/7 through 36 6/7 weeks) will be described. For this evaluation, select study exclusion and censoring criteria will not be implemented, specifically pregnant individuals with receipt of ABRYSVO before 32 0/7 weeks gestation and pregnancies ending before 32 0/7 weeks gestation will not be excluded.

6. For all live births linked to an infant, frequencies of categories of MFMU Neonatal Morbidity Index[19] will be described (death, major morbidity, minor morbidity) in ABRYSVO-exposed and matched ABRYSVO-unexposed.

7. The prevalence of ABRYSVO >7 days after the index vaccination and before 37 weeks will be reported in the ABRYSVO-exposed pregnant individuals. If that

number is higher than 5%, a sensitivity analysis [to omit these pregnancies] will be considered and the SAP will be amended accordingly.

8. Among those identified with PPROM in the ABRYSVO-exposed and ABRYSVO-unexposed groups, the frequency of characteristics and risk factors will be described.

9. The prevalence of chorioamnionitis will be examined in the ABRYSVO-exposed pregnant individuals and the ABRYSVO-unexposed pregnant individuals.

These analyses will be conducted in the overall eligible populations and among those individuals identified with an immunocompromising condition.

9.7.2.5. Sensitivity Analyses

To assess the robustness of the results, sensitivity analyses will be conducted to address the potential misclassifications for outcomes, exposure, and important confounders. For example, a quantitative bias analysis of comparative risk estimates of pregnancy and birth outcomes will be performed to assess the potential impact of outcome misclassification. The criteria for the eligible population will also be varied to include those with receipt of ≥ 1 vaccine recommended for adults[f] within 1 year prior to the date of estimated LMP for a more restrictive proxy for healthcare (vaccine)-seeking behavior.

Another sensitivity analysis will include stratification by race (Asian, Black/African American, Other, Unknown, and White) at all participating data RPs and separately at the Medicaid RP. This analysis has been implemented because race is an important confounder to the potential relationship between ABRYSVO vaccination during pregnancy and the primary outcomes[32-34] but is also poorly captured in administrative claims data and differentially captured at each RP.[35,36]

Detailed sensitivity analyses and assessment of potential biases will be documented in the SAP.

9.8. Quality Control

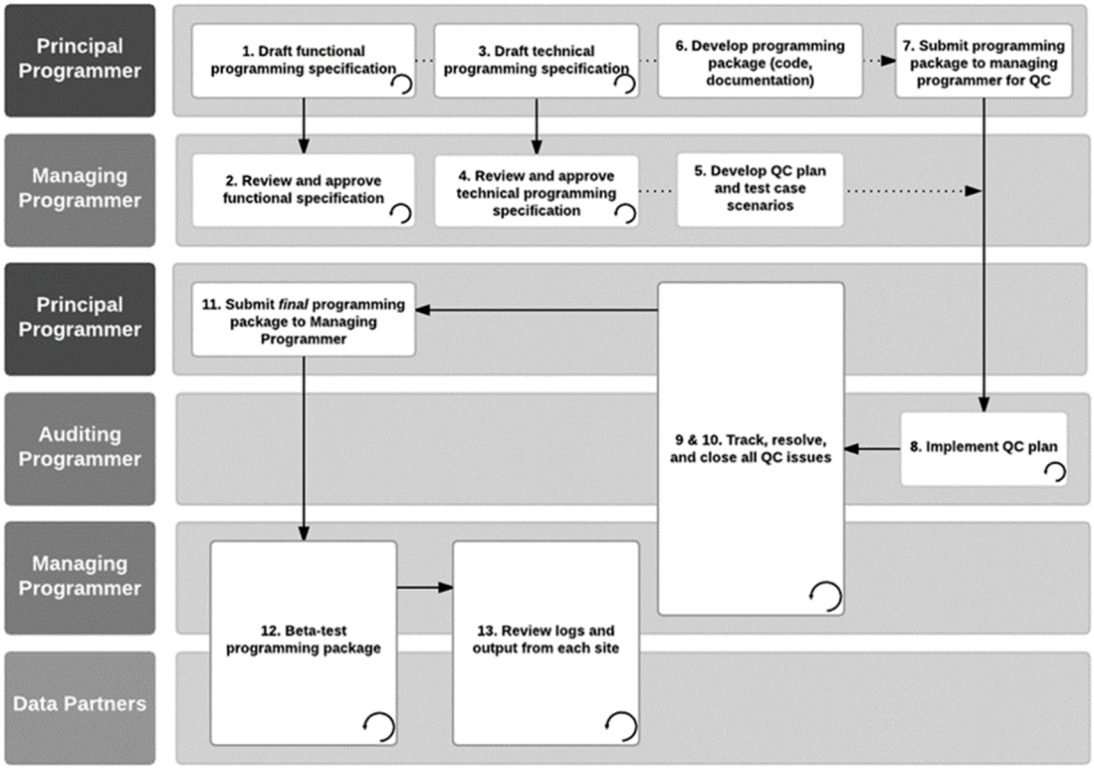
The data RPs that will contribute aggregate data for this study are participants in the Sentinel System. The study will use the same data QA procedures as the Sentinel System and the same curated datasets used by the FDA to conduct Sentinel analyses. The QA approach assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across data RPs. The QA approach assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across RPs. Full QA processes and details on the Sentinel

[f] https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

data curation approach are documented on the Sentinel website.[37] The data curation approach is consistent with guidance set forth by the FDA in its current recommendations for data QA, specifically, "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (Guidance), section IV.E "Best Practices – Data Sources: QA and Quality Control (QC)", published in May 2013.[38] This Guidance describes best practices that particularly apply to observational studies designed to assess the risk associated with a drug exposure using electronic healthcare data.

In addition to QA of data elements, HPHCI adopts standard SAS programming QA and QC processes used by the Sentinel System to check SAS programs and deliverables. Figure 5 illustrates the standard operating procedures for SAS programming QA and QC in the Sentinel System.

Figure 5. Standard operating procedure for SAS programming QA and QC in the Sentinel System



9.9. Strengths and Limitations of the Research Methods

9.9.1. Limitations

Several limitations are inherent in the conduct of studies of pharmacologic exposures during pregnancy using electronic healthcare databases. The algorithms used to define data study

variables may be imperfect as these rely on the accuracy and precision of coding for these items. As a result, misclassification of exposures, outcomes, potential confounders, and the study's eligibility criteria can occur. To minimize the potential for outcome misclassification, highly specific outcome definitions from validated claims-based algorithms will be used when possible. In addition, validation of the algorithms for preterm birth (primary outcome), preterm labor (without preterm delivery), and pregnancy-associated hypertensive disorders (primary outcome) will be conducted through review of medical records for a sample of potential cases. Sensitivity analyses will also be conducted to assess the potential impact of misclassifications of outcomes, exposure, and important confounders. For example, sensitivity analyses including stratification on race at all data RPs and separately at the Medicaid RP will be included because race is an important confounder to the potential relationship between ABRYSVO vaccination during pregnancy and the primary outcomes[32-34] yet is also generally poorly captured in administrative claims data sources such as those provided by the RPs.[35,36] Analyses related to some outcomes (eg, admission to NICU, mechanical ventilation, neonatal death) will be considered exploratory, given the expected low capture or high misclassification of the variables using claims data. In addition, while death (including maternal death) will be used to censor follow-up when it is available in the data, death data are not consistently captured across participating RPs. Given the unreliability of recording of maternal death in the study database, it is not proposed as an outcome for evaluation.

Although appropriate methodologies (eg, 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. To address the potential for unmeasured confounding related to health care (vaccine)-seeking behavior in the cohort study, eligible pregnant individuals will be required to have a record of ≥ 1 administration of a vaccine recommended for adults any time prior to the date of estimated LMP (during all available claims/EHR history), and a sensitivity analysis is proposed to further restrict the study population to those with a record of ≥1 administration of a recommended vaccine in the 1 year prior to the date of estimated LMP.

Depending on the number of events observed, the ability to include additional covariate information in regression models (ie, using multivariable adjustment) will be limited. Some potential covariates are incompletely captured in the health plan data, such as alcohol use, tobacco use, and history of preterm birth. This limitation is common to all claims data and it is not expected that capture of these variables will be differential among the exposed and unexposed pregnancies. A sensitivity analysis (to be described in the SAP) will be conducted to estimate the magnitude of unmeasured confounding needed to change the statistical inference.

Similar to other claims and EHR databases in the US, an additional limitation of the data sources proposed for this study is the proportion of individuals with long-term health plan enrollment. Within the Sentinel Distributed Database, only 46% of individuals have ≥ 2 years

continuous database enrollment, with 39% of individuals enrolled for at least 2.5 years.[g] While implementing long-term enrollment criteria will likely reduce sample size, differential effects between the treatment and comparator groups would not be expected.

An important potential limitation of the study is that an adequate sample size might be difficult to achieve for some of the comparative analyses, particularly for many of the rare secondary outcomes of interest (eg, GBS and other maternal outcomes). If an inadequate number of exposed pregnancies are identified for a specific outcome (see Section 9.5), only descriptive analyses of that outcome will be conducted. The sample size will be monitored and the feasibility of comparative analyses will be discussed in interim monitoring reports.

Limitations specific to RCA also include the potential for incomplete data for assessment and inability to conduct chart reviews to confirm outcomes in order to provide data in a timely manner. In addition, potential bias may exist with use of historical comparators (for rare outcomes) due to secular trends; however, historical comparators are necessary when evaluating rare outcomes to reduce the time to declare a statistical signal and/or reach a stopping boundary. A concurrent ABRYSVO-unexposed group (individuals not administered ABRYSVO during pregnancy but administered other vaccinations) will be considered for outcomes that are not rare but may be impractical if pregnant individuals are often dually exposed to both ABRYSVO and other routine vaccinations.

9.9.2. Strengths

To mitigate 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. In addition, review of medical records will allow validation of the algorithms for the primary outcomes of interest.

The proposed RCA will allow faster detection of potential associations between ABRYSVO and safety events (signal detection) due to the interim hypothesis testing, with a cohort study approach for a more comprehensive evaluation of the risks of safety outcomes.

Selection of an appropriate comparator group for a cohort study on vaccine safety in a pregnant population has challenges. Using a cohort design with a concurrent unexposed group will allow evaluation of safety events for which the risks may vary over time or during the course of pregnancy/perinatal period. As noted in Section 9.2.4.1, while other comparators were considered, they were ultimately disregarded due to key limitations.

A major strength of this study is the use of claims and EHR data collected as part of routine medical care, which will avoid recall bias and provides access to a large sample of insured

[g] https://www.sentinelinitiative.org/about/key-database-statistics#length-of-member-enrollment-spans-in-the-sentinel-distributed-database

individuals in the US. This approach minimizes the potential for selection bias that might occur in primary data collection studies, as the study population includes all individuals in the participating databases who meet eligibility criteria for research rather than individuals who have volunteered to participate in the study. The ability to access medical record data will also allow assessment of the validity of algorithms to identify the primary outcomes 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 PARTICIPANTS

This study involves use of existing structured data and will include human review of unstructured data for the subset of patient charts that may be reviewed for validation purposes. Each data RP will obtain appropriate reviews and determinations from respective institutional review boards (IRBs) according to its site requirements or cede authority to HPHCI's IRB, if possible.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

10.1. Patient Information

All data analyzed for this study, with the exception of review of medical records for chart validation, will exist as structured data.

10.1.1. Structured Data Analysis: Main Analyses

The main analyses of this study (including both the RCA and cohort study) involve data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.1.2. Human Review of Unstructured Data: Chart Validation

During chart validation, data RPs will remove and redact all direct patient identifiers as delineated in the Privacy Rule of HIPAA (Health Insurance Portability and Accountability Act of 1996). A limited data set of PHI—including date of birth, date of vaccination, date of death, visit date, and diagnosis date—may be collected.

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

HPHCI will maintain a secure web-based portal to enable secure data transfer and document storage. The system will match the FDA Sentinel System and will comply with all FDA Sentinel System security standards. A study identification number will also be used in place of direct patient identifiers to minimize risk. Patients' personal data will be stored at the individual data RP or at HPHCI in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. No individual patient data will be sent to Pfizer, unless related to AE reporting described in Section 11. Each data RP and HPHCI will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, each data RP and HPHCI shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural individuals with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, data RP results will be aggregated. For the RPs who have agreed to sharing their individual-level data with HPHCI and Pfizer, only individual patient data that is related to AE reporting described in Section 11 will be transferred to Pfizer. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the research agreement and applicable privacy laws.

For the RPs that will not share individual level data including any PHI data, the above agreement is not applicable and no data will be transferred to HPHCI, Pfizer, or other RPs.

10.2. Patient Consent

10.2.1. Structured Data Analysis: Main Analyses

As the main analyses of this study (both the RCA and cohort study) involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.2.2. Human Review of Unstructured Data: Chart Validation

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

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

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

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

10.4. Ethical Conduct of the Study

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

- FDA Draft Guidance for Industry: Postapproval Pregnancy Safety Studies[39]
- EMA Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations III: Pregnant and breastfeeding women[40]
- Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE)[41]
- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-ISPE Special Task Force on real-world evidence in health care decision making[42]
- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)[43]
- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology[44]
- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment[45]
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data[38]
- International Ethical Guidelines for Health-related Research Involving Humans issued by the CIOMS in collaboration with the World Health Organization (WHO)[46]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis: Main Analyses

The main study analyses involve data that exist as structured data by the time of study start. In these data sources, it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Human Review of Unstructured Data: Chart Validation

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS AE monitoring (AEM) Report Form to Pfizer Safety are as follows:

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

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

- For exposure during pregnancy in studies of pregnant individuals, data on the exposure to ABRYSVO during pregnancy, are not reportable unless associated with serious or non-serious AEs.

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

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least 1 patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "DrugName" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

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

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training statements must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current YRR with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within 60 calendar days of issuance by Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of analysis and interpretation will be delivered in the form of reports. RCA reports, interim study reports, an extended interim study report, and a final study report are planned per the milestones scheduled in Section 6. The RCA, interim, and final study reports will be submitted to the FDA. Final study results will be disseminated at scientific conferences and a manuscript of the study will be submitted to a peer reviewed journal for publication. Interim data may also be presented at scientific conferences. Additionally, the final report will be posted to the EU PAS Register.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

APPENDIX A. ALGORITHMS FOR IDENTIFICATION OF OUTCOMES: COHORT STUDY

Pregnancy, maternal, and neonatal/infant outcomes will be identified in the mother's and/or infant's electronic healthcare data using diagnosis, procedure, and revenue codes, and hospital discharge disposition data. The index date is defined as the date of receipt of ABRYSVO for the exposed group. For the unexposed group, the index date will be the equivalent of the gestational age at vaccination administration (in days) in the exposed match. Code lists may be modified based upon future studies to validate algorithms using claims data. Algorithms may be modified for RCA.

Pregnancy outcomes

Outcome	Operational Definition[a] Defined by the presence of any of the following ICD-10-CM codes (inclusive)	Setting (Inpatient [IP], emergency department [ED], outpatient [OP])	Washout Window	Measurement characteristics of algorithm	Source
Preterm birth (primary outcome)	Gestational age <37 0/7 weeks: Pregnancy algorithm under development at Sentinel	IP	Not applicable (NA)	Published studies indicate ICD-10-CM gestational age codes within 7 days of those in medical record for 78%-84% for live births and for 67%-90% for stillbirths. Chomistek et al, 2023[7] also found codes for preterm labor and delivery: PPV=92%.	Sentinel pregnancy algorithm is based upon validated algorithms from Sentinel and non-Sentinel studies.[6,7,9,10]

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (Inpatient [IP], emergency department [ED], outpatient [OP])	Washout Window	Measurement characteristics of algorithm	Source
Pregnancy-associated hypertensive disorders[b] (primary outcome) – overall and by specific condition, as defined below: for analyses of pregnancy-associated hypertensive disorders overall, identify new-onset occurrence of any of the specific conditions ≤ 6 weeks after index date					
Gestational hypertension	O13.* Gestational [pregnancy-induced] hypertension without significant proteinuria Identified by searching mother's claims for ≥1 IP code or ≥2 OP and/or ED codes from 20 0/7 weeks' gestation through the hospital delivery admission	IP, ED, OP	Exclude if diagnosis of pre-existing or other pregnancy-associated hypertensive disorder recorded during current pregnancy prior to or on index date	Labgold et al, 2021[47] (US hospital billing discharge codes against gold standard of medical records): PPV for O13.1, O13.2, O13.3, O13.4, O13.5, O13.9) = 88.9% (86.4% – 91.1%) Pace et al, 2017[48]: systematic review for 1 IP code for hypertension or 2 OP codes within 1 year (excluded pregnancy-associated hypertension)	Labgold et al, 2021[47] adapted to include OP, ED codes

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (Inpatient [IP], emergency department [ED], outpatient [OP])	Washout Window	Measurement characteristics of algorithm	Source
				PPV ranges 79-88%	
Preeclampsia/eclampsia	O14.* Preeclampsia Identified by searching the mother's claims for ≥1 IP code or ≥2 OP and/or ED codes from 20 0/7 weeks' gestation through the hospital admission for delivery	IP, ED, OP	Exclude if diagnosis of preeclampsia/eclampsia, chronic hypertension superimposed with preeclampsia/eclampsia, HELLP recorded during current pregnancy prior to index date	Chomistek et al, 2023:[7] using IP, ED, OP codes for O14.* and O11.*: PPV=78.3%; using IP PPV=85.7% Labgold et al, 2021[47] using IP codes: PPVs ranging from 89-99%	Chomistek et al, 2023;[7] adapted to include ≥OP, ED codes
	O15.* Eclampsia Identified by searching the mother's claims from 20 0/7 weeks' gestation through the hospital admission for delivery	IP	Exclude if diagnosis of eclampsia recorded during current pregnancy prior to index date	Labgold et al, 2021[47]: PPV=100.0% (95% CI, 39.8%, 100%) – note that only 4 potential cases identified	Labgold et al, 2021[47]
HELLP syndrome	O14.2, O14.20, O14.22, O14.23, O14.24, O14.25	IP	Exclude those diagnosed with HELLP during current	Labgold et al, 2021[47]:	Labgold et al, 2021[47]

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (Inpatient [IP], emergency department [ED], outpatient [OP])	Washout Window	Measurement characteristics of algorithm	Source
	Identified by searching the mother's claims from 20 0/7 weeks' gestation through the hospital admission for delivery		pregnancy prior to index date	PPV= 88.2% (63.6%, 98.5%)	
Chronic hypertension superimposed with preeclampsia/ eclampsia	O11.* Pre-existing hypertension with pre-eclampsia Identified by searching the mother's claims for ≥1 IP code or ≥2 OP and/or ED codes from 20 0/7 weeks' gestation through the hospital admission for delivery	IP, ED, OP	Exclude if diagnosis of preeclampsia/eclampsia, chronic hypertension superimposed with preeclampsia/eclampsia, HELLP recorded during current pregnancy prior to index date	Chomistek et al, 2023[7]: using IP, ED, OP for O14.* and O11.*: PPV=78.3%; using IP PPV=85.7% Labgold et al, 2021[47]: PPV= 83.3% (74.9%, 89.8%)	Labgold et al, 2021;[47] adapted to include OP, ED codes
Postpartum hypertension	New-onset pregnancy-associated hypertensive disorders (using codes/algorithms above[b]) identified from the day after delivery through ≤ 6 weeks (42 days) after the index date	See algorithms above	Exclude if diagnosis of pre-existing or pregnancy-associated hypertensive disorders recorded during current pregnancy or if	See algorithms above	See algorithms above

Outcome	**Operational Definition**[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	**Setting (Inpatient [IP], emergency department [ED], outpatient [OP])**	**Washout Window**	**Measurement characteristics of algorithm**	**Source**
			index date >6 weeks before the delivery date		
Stillbirth	Pregnancy algorithm under development at Sentinel	IP, ED, OP	NA	PPV estimates range from 66%-83% for stillbirth	Sentinel pregnancy algorithm is based upon validated algorithms from Sentinel and non-Sentinel studies[6,7,9,10]
Preterm labor without delivery	O60.0 Preterm labor without delivery	IP, ED, OP	NA	Goueslard et al, 2020 (French database):[49] O60.0 in IP setting PPV: 57.5% (95% CI 55.8% to 59.2%)	Goueslard et al, 2020[49]
PROM	O42.* Premature rupture of membranes	IP	NA	Goueslard et al, 2020[49] (French database): codes for PROM (O42) or the code for delayed delivery after spontaneous or unspecified	

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (Inpatient [IP], emergency department [ED], outpatient [OP])	Washout Window	Measurement characteristics of algorithm	Source
				rupture of membranes (O75.6) during the delivery stay: PPV=54.9% (53.2 to 56.6), sensitivity= 57.0% (55.3 to 58.7).	
PPROM	ICD-10-CM codes O42.01*, O42.11*, O42.91* Preterm premature rupture of membranes plus a gestational age < 37 weeks based upon the Sentinel pregnancy algorithm	IP	NA	NA	Algorithm including diagnosis codes adapted to include gestational age information (based upon review of RCA patient profiles). Details on pregnancy algorithm can be found at: (https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse/files/file150-type04-pregepi.md)
Placental abruption	O45.* Premature separation of placenta (placental abruption)	IP, ED, OP	NA	NA	

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (Inpatient [IP], emergency department [ED], outpatient [OP])	Washout Window	Measurement characteristics of algorithm	Source
	Identified by searching the mother's claims for ≥1 IP, OP, or ED code from 20 0/7 weeks' gestation through the hospital admission for delivery				
Prolonged maternal length of stay	Days of stay for delivery hospital admission (descriptive) categorized by 1) vaginal delivery ≤2 days vs >2 days or 2) caesarean delivery ≤4 days vs >4 days	IP (ED and OP also if not IP delivery)	NA	NA	Blumenfeld et al, 2015;[50] Kuklina et al, 2009;[51] Horner-Johnson et al, 2020[52]
Caesarean section	ICD-10-CM codes: O82, O75.82, P03.4, Z38.01 CPT 59510, 59514, 59515, 59618, 59620, 59622	IP	NA	NA	

a Codes will be identified in the mothers' claims data

b The algorithms cited for identification of pregnancy-associated hypertensive disorders have not validated the use of O16* ICD-10-CM codes for "Unspecified maternal hypertension," including the more specific O16.5 to identify postpartum hypertension, as the cited studies have found these codes are not of diagnostic utility.

Maternal outcomes

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (IP, ED, OP)	Washout Window	Measurement characteristics of algorithm	Source
Thrombocytopenia					
ITP	D69.3	IP, ED, OP	365 days	Mezaache et al, 2017[53] (French database): PPV=79.5% (incident ITP); Heden et al, 2009[54] (Danish data): PPV=93% for IP setting (chronic ITP); Segal et al, 2004[55] (US data): sensitivity=100%, percent agreement=92% for inpatient ICD-9-CM code 287.3	BEST 2021[15]
Thromboembolic events associated with thrombocytopenia	G08, I63.6, I67.6, I74.0*, I74.1*, I74.3, I74.5, I74.8, I74.9, I81, I82.0, I82.890, K55.0*, N28.0 (codes from Klein et al, 2021[5]) plus a code for thrombocytopenia Diagnosis code for thrombotic event AND a first diagnosis code for thrombocytopenia ≤ 14 days apart (event date is later diagnosis code date)	IP, ED, OP	365 days	NA	Adaptation of BEST 2021[15]

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (IP, ED, OP)	Washout Window	Measurement characteristics of algorithm	Source
TTP	M31.1 (Klein et al, 2021[5] also incorporates exclusionary codes for specific conditions)	IP, ED	365 days	NA	Adaptation of Klein et al, 2021[5]
HELLP syndrome	See above (Pregnancy outcomes)	See above	See above	See above	See above
GBS	G61.0, Guillain-Barre syndrome A diagnosis code of GBS in any setting within 7 days prior to the IP primary diagnosis will define the date of GBS event	IP, primary position	6 months	PPV=71% (US Medicare data)	Arya et al, 2019[56]
Other immune-mediated demyelinating conditions					
ADEM	G04.00, G04.02, Acute disseminated encephalitis and encephalomyelitis, unspecified	IP, ED, or OP	6 months	Boesen et al, 2018 (Danish pediatric population):[57] 1 IP code PPV=15% using codes G04.0, G04.8, G04.9	Klein et al, 2021[5]
Transverse myelitis (TM)	G37.3, Acute transverse myelitis in demyelinating disease of central nervous system	IP or ED	6 months	Boesen et al, 2018 (Danish pediatric population):[57] 1 IP code PPV=64%	
Optic neuritis (ON)	H46.00, Optic papillitis, unspecified eye H46.01, Optic papillitis, right eye H46.02, Optic papillitis, left eye H46.03, Optic papillitis, bilateral H46.10, Retrobulbar neuritis, unspecified eye H46.11, Retrobulbar neuritis, right eye H46.12, Retrobulbar neuritis, left eye H46.13, Retrobulbar neuritis, bilateral H46.3, Toxic optic neuropathy	IP, ED, or OP	6 months	Hamedani et al, 2020 systematic review:[58] 2 studies (data from Denmark, Canada) using single or ≥2 codes PPV 25–88% Boesen et al, 2018 (Danish pediatric	

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (IP, ED, OP)	Washout Window	Measurement characteristics of algorithm	Source
	H46.8, Other optic neuritis H46.9, Unspecified optic neuritis			population):[57] 1 IP code PPV=71%	
Neuromyelitis optica (NMO)	G36.0, Neuromyelitis optica [Devic]	IP, ED, or OP	6 months	Boesen et al, 2018 (Danish pediatric population):[57] 1 IP code PPV=43%	
Other acute demyelinating diseases	G37.1, Central demyelination of corpus callosum G37.2, Central pontine myelinolysis G37.8, Other specified demyelinating diseases of central nervous system G37.9, Demyelinating disease of central nervous system, unspecified G61.81, Chronic inflammatory demyelinating polyneuritis	IP, ED, or OP	6 months	NA	
Polyneuropathies					
Acute polyneuropathies excluding GBS	G61, Inflammatory polyneuropathy G61.1, Serum neuropathy G61.8, Other inflammatory polyneuropathies G61.81, Chronic inflammatory demyelinating polyneuritis G61.82, Multifocal motor neuropathy G61.89, Other inflammatory polyneuropathies G61.9, Inflammatory polyneuropathy, unspecified G62, Other polyneuropathies G62.0, Drug-induced polyneuropathy G62.8, Other specified polyneuropathies G62.89, Other specified polyneuropathies G62.9, Polyneuropathy, unspecified	IP, ED, or OP	6 months	NA	

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (IP, ED, OP)	Washout Window	Measurement characteristics of algorithm	Source
Atrial fibrillation	I48.0, Paroxysmal atrial fibrillation I48.11, Longstanding persistent atrial fibrillation I48.19, Other persistent atrial fibrillation I48.20, Chronic atrial fibrillation, unspecified I48.91, Unspecified atrial fibrillation	IP or OP	1 year	Chamberlain et al, 2022:[59] ICD-10 I48* PPV for 1 code=67.5%. PPV for 1 IP or 2 OP ≥1 day apart=71.1%	

a Codes will be identified in the mothers' claims data

Neonatal/infant outcomes

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (IP, ED, OP)	Washout Window	Measurement characteristics of algorithm	Source
SGA	P05.0* Newborn light for gestational age P05.1* Newborn small for gestational age identified by searching the infant and mother claims for up to the first 30 days from the infant's date of birth	IP, ED, OP	NA	Watson et al 2021[60] (international data) PPV=70.4% - algorithm not specified (P05) Phiri et al 2015:[61] PPV=86.8% for ICD-9 656.X on day of delivery He et al 2020:[62] ≥1 maternal or infant ICD-9-CM diagnostic code 656.5x, 764.0x, 764.1x, 764.9x recorded in inpatient or other therapy claims from delivery to delivery + 30 days has a PPV of 92% (82%-97%) in claims (Medicaid)-linked EHR data	
LGA	P08.0 Exceptionally large newborn baby P08.1 Other heavy for gestational age newborn identified by searching the infant and mother claims for up to the first 30 days from the infant's date of birth	IP, ED, OP	NA	NA	
LBW	P07.0* Extremely low birth weight newborn P07.1* Other low birth weight newborn	IP, ED, OP	NA	Chomistek et al, 2023:[7] PPV=96.3%	Chomistek et al, 2023[7]

Outcome	Operational Definition[a] Defined by the presence of any of the following **ICD-10-CM** codes (inclusive)	Setting (IP, ED, OP)	Washout Window	Measurement characteristics of algorithm	Source
	identified by searching the infant and mother claims for up to the first 30 days from the infant's date of birth				(adapted to include time window of interest and mothers' claims data)
NICU admission (exploratory outcome)	CPT codes 99468, 99469, revenue code 0174 identified by searching both the infant and mother claims for up to the first 30 days after the infant's date of birth	IP	NA	Andrade et al 2013:[63] CPT codes for NICU PPV=92% (CPT codes not available at all sites)	Andrade et al, 2013[63] (adapted to include revenue code)
Mechanical ventilation in neonatal period (exploratory outcome)	Algorithm described in more detail here: https://www.sentinelinitiative.org/methods-data-tools/methods/master-protocol-development-covid-19-natural-history Identified by searching the infant claims for up to the first 30 days of life	IP	NA	NA	Sentinel Initiative 2020[64]
Neonatal death (exploratory outcome)	identified in hospital discharge disposition data included in the health plan claims files Identified by searching the infant claims for up to the first 30 days of life	IP	NA	NA	NA

a Codes will be identified in the mothers' and infants' claims data, unless otherwise specified

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