NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy in an Integrated Healthcare System in the United States
Protocol number	C3671042
Protocol version identifier	V3.1
Date	03 February 2026
EU Post Authorization Study (PAS) register number	Study will be registered prior to the start of data collection
Active substance	Respiratory Syncytial Virus Vaccine, J07BX05
Medicinal product	ABRYSVO™ (PF-06928316)
Research question and objectives	The overall research question is: what is the risk of preterm birth, hypertensive disorders of pregnancy, and other pre-specified adverse pregnancy, maternal, and neonatal/infant outcomes following exposure to respiratory syncytial virus prefusion F vaccine (RSVpreF) [Brand name: ABRYSVO™] during pregnancy? <u>Primary objective:</u> To estimate the risk of (1) preterm birth, and (2) hypertensive disorders of pregnancy following exposure to ABRYSVO™ during pregnancy <u>Secondary objectives:</u> To estimate the risk of the following safety outcomes of interest following exposure to ABRYSVO™ during pregnancy: • Pregnancy-related outcomes: stillbirth, premature labor (without preterm delivery), premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), cesarean delivery, prolonged maternal

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	length of stay (LOS) after delivery, placental abruption; • Maternal outcomes: thrombocytopenia, Guillain-Barré Syndrome (GBS), other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation, all-cause maternal mortality; and • Neonatal/infant outcomes: small for gestational age (SGA), large for gestational age (LGA), low birth weight (LBW), admission to a neonatal intensive care unit (NICU) and NICU duration of stay, mechanical ventilation in neonatal period, neonatal death
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
BMI	body mass index
CI	confidence interval
EC	Ethics Committee
EMA	European Medicines Agency
EMR	electronic medical record
EU	European Union
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelets
HMA	Heads of Medicines Agencies
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IR	incidence rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ITP	immune thrombocytopenia
KPNC	Kaiser Permanente Northern California
KPVSC	Kaiser Permanente Vaccine Study Center
LGA	large for gestational age

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Abbreviation	Definition
LMP	last menstrual period
LOS	length of stay
LRTD	lower respiratory tract disease
MATISSE	MATernal Immunization Study for Safety and Efficacy
NDI	neighborhood deprivation index
NICU	neonatal intensive care unit
PAS	post-authorization studies
PASS	post-authorization safety study
PMR	postmarketing requirement
PPROM	preterm premature rupture of membranes
PROM	premature rupture of membranes
RR	relative risk
RSV	respiratory syncytial virus
RSVpreF	respiratory syncytial virus prefusion F vaccine
RWD	real world data
SAP	statistical analysis plan
SAS	Statistical Analysis System
SES	socioeconomic status
SGA	small for gestational age
TTP	thrombotic thrombocytopenic purpura
US	United States
USPI	United States Product Information

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3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: A Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy in an Integrated Healthcare System in the United States

Version: 3.1

Date: 03 February 2026

Primary Authors: Sampada Gandhi and Cynthia de Luise, Pfizer, Inc

Rationale and background:

ABRYSVO™ is an unadjuvanted bivalent RSVpreF containing two stabilized prefusion F proteins representing the two major respiratory syncytial vaccine (RSV) subgroups, A and B. RSVpreF was approved in the United States (US) on 31 May 2023 for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older and on 21 August 2023 for active immunization of pregnant individuals at 32 through 36 weeks' gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age.

Additional characterization of safety endpoints in a real-world population of pregnant individuals, including those who may have been ineligible for clinical trials, is valuable and important. This protocol describes a pregnancy post-marketing study to evaluate the real-world safety of RSVpreF in pregnant individuals and their infants using an integrated healthcare system in the US. This non-interventional study is designated as a post-authorization safety study (PASS) and is a post marketing requirement (PMR) to the US Food and Drug Administration (FDA).

Research question and objectives:

The overall research question is: what is the risk of preterm birth, hypertensive disorders of pregnancy, and other pre-specified adverse pregnancy, maternal, and neonatal/infant outcomes following exposure to ABRYSVO™ during pregnancy?

Primary objective:

To estimate the risk of (1) preterm birth, and (2) hypertensive disorders of pregnancy following exposure to ABRYSVO™ during pregnancy.

Secondary objectives:

To estimate the risk of the following safety outcomes of interest following exposure to ABRYSVO™ during pregnancy:

- Pregnancy-related outcomes: stillbirth, premature labor (without preterm delivery), PROM, PPROM, cesarean delivery, prolonged maternal LOS after delivery, placental abruption;

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

- Neonatal/infant outcomes: SGA, LGA, LBW, admission to a NICU and NICU duration of stay, mechanical ventilation in neonatal period, and neonatal death.

Study design: This is a real-world retrospective non-interventional cohort study using electronic health record data from an integrated healthcare system, Kaiser Permanente Northern California (KPNC) in the US during a study period from 22 September 2023 [corresponding to the date when the Advisory Committee on Immunization Practices (ACIP) and American College of Obstetricians and Gynecologists (ACOG) recommended ABRYSVO™ in the US] through 12 January 2028 (corresponding to a 42-day postpartum period after the last eligible pregnancy reaches $42^{0/7}$ completed weeks of gestation).

Population: The study population will include a pregnancy cohort comprising all eligible pregnancies that reach $32^{0/7}$ completed weeks of gestation during a 4-year period from 22 September 2023 to 22 September 2027. The start of follow-up of eligible pregnancies will be at $32^{0/7}$ weeks' gestation consistent with the United States Product information (USPI) and ACIP recommendation. All live born infants from the eligible pregnancies in the pregnancy cohort will be included in the infant cohort.

Variables:

Exposure of interest: exposure to ABRYSVO™ will be identified in the pregnancy cohort using the data from the KPNC electronic medical records (EMR) from the KPNC database, which captures all vaccination data including vaccination date and manufacturer. ABRYSVO™ exposure will be a time-varying variable. Pregnant individuals will contribute unexposed follow-up time starting at $32^{0/7}$ weeks' gestation until they are exposed to ABRYSVO™, at which point they contribute exposed follow-up time to the analysis. Exposure to ABRYSVO™ that occurs after the ACIP-recommended timeframe (i.e., on or after $37^{0/7}$ weeks' gestation) will be censored in the analysis.

Outcomes of interest: the following outcomes will be defined using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes or validated algorithms as available in relevant data sources in the maternal and/or infant EMR:

- Primary outcomes: preterm birth and hypertensive disorders of pregnancy

- Secondary outcomes:

  A. Pregnancy-related outcomes: stillbirth, premature labor (without preterm delivery), PROM, PPROM, cesarean delivery, prolonged maternal LOS after delivery, placental abruption;

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B. Maternal outcomes: thrombocytopenia, GBS, other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation, all-cause maternal mortality; and

C. Neonatal/infant outcomes: SGA, LGA, LBW, admission to a NICU and NICU duration of stay, mechanical ventilation in neonatal period, neonatal death.

Key maternal/infant covariates of interest: the following covariates of interest will be identified within the KPNC EMR and may be considered for inclusion as potential confounders or effect modifiers in the analysis.

- Maternal sociodemographic characteristics, maternal clinical characteristics, pre-existing maternal comorbidities, assisted reproduction in the current pregnancy, excessive stress, documented shortened cervix in the current pregnancy identified after 22 weeks of gestation, early bleeding in pregnancy, short interpregnancy interval of <3 months, prior history of placental disorder, placenta previa or placental abruption, and healthcare utilization prior to the current pregnancy

- Newborn sex, newborn race/ethnicity, gestational age at birth of the newborn

Data source: KPNC is an integrated delivery health care organization with more than 4.5 million members. KPNC has a comprehensive EMR that captures data on all medical services, including immunization and pregnancy related care from before pregnancy, during pregnancy to delivery and beyond. Pregnancies will be identified using the KPNC pregnancy database. This pregnancy database includes pregnancies with a documented and validated pregnancy outcome (e.g., miscarriage, stillbirth, live birth) as recorded in the EMR.

Study size/Power: An estimated 168,000 pregnancies and live births are anticipated to be captured in the KPNC pregnancy database during the 4-year period from 22 September 2023 to 22 September 2027. Conservatively assuming that at least 50% of the total pregnancies/births will be included in the study after applying eligibility criteria and assuming ABRYSVO™ uptake of 20%, a prevalence of 8.5% and 15.9% for preterm birth and hypertensive disorders of pregnancy, respectively, the study will have at least 80% power to detect a minimum relative risk (RR) of 1.07 for preterm birth and 1.06 for hypertensive disorders of pregnancy when comparing pregnant individuals who are exposed to ABRYSVO™ during pregnancy versus those who are not exposed to ABRYSVO™.

Data analysis: The two primary outcomes of interest, pregnancy-related outcomes and maternal outcomes will be examined in the pregnancy cohort and neonatal/infant outcomes will be examined in the infant cohort. Preterm birth will be assessed up to $36^{6/7}$ weeks' gestation. Hypertensive disorders of pregnancy will be assessed until 42-days postpartum. All pregnancy-related outcomes will be ascertained until the end of pregnancy, hospital discharge date after delivery, or gestational age where appropriate. All maternal outcomes will be assessed until 42-days post-vaccination with ABRYSVO™. The following neonatal/infant outcomes will be assessed at birth: SGA, LGA and LBW. The remainder of

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neonatal/infant outcomes, i.e., admission to a NICU, mechanical ventilation, and neonatal death will be assessed between birth up to 28 days after birth.

Interim analysis will include counts of pregnancies meeting the eligibility criteria for the pregnancy cohort. Descriptive summaries of maternal and neonatal/infant covariates of interest among pregnant individuals and infants born to eligible pregnant individuals will be provided. Incidence rates (IRs) and associated 95% confidence intervals (CIs) will be calculated for the primary outcomes of interest, as well as for each pregnancy-related, maternal, and neonatal/infant outcomes of interest in the ABRYSVO™-exposed and unexposed pregnancies.

The final analysis will include a descriptive summary of key maternal and infant covariates of interest among the pregnancy and infant cohorts. For the primary outcomes and pregnancy-related outcomes, Cox regression anchored on gestational age (or time-since-conception for outcomes that are assessed in the postpartum period) will be used to compare the risk of an outcome in pregnant individuals who were exposed to ABRYSVO™ with the risk in similar pregnant individuals who were not exposed to ABRYSVO™ (reference group), adjusting for covariates. The analysis will include ABRYSVO™ exposure as a time-varying variable, whereby pregnant individuals contribute unexposed follow-up time until they are exposed to ABRYSVO™, at which point they contribute exposed follow-up time to the analysis. Cox regression will also be used for analysis of the maternal outcomes with exposure to ABRYSVO™ as a time-varying variable. On each day of the days-since-conception timeline, the risk of a maternal outcome in ABRYSVO™-exposed individuals in the 42-day post-vaccination risk window will be compared to the risk of a maternal outcome in similar ABRYSVO™-unexposed individuals (reference group), adjusting for covariates. For neonatal/infant outcomes, logistic regression, adjusting for key covariates will be fitted to examine the odds of these outcomes among ABRYSVO™-exposed pregnant individuals compared to ABRYSVO™-unexposed individuals (reference group).

An additional exploratory analysis will also be performed in the final analysis, with an objective to capture real-world ABRYSVO™ exposures occurring in all eligible pregnancies that reach $24^{0/7}$ completed weeks of gestation during a 4-year period from 22 September 2023 to 22 September 2027. The study period for the exploratory analysis will end on 08 March 2028.

Milestones: A final protocol will be submitted to the FDA on 29 March 2024 and was revised on 20 June 2024. The estimated start and end of data collection is 30 September 2026 and 08 September 2028, respectively. A statistical analysis plan (SAP) will be submitted to the FDA on 30 June 2025. An interim report is planned for 31 March 2027 and final report is planned for 08 March 2029.

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5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
3.1	03 February 2026	Administrative	Section 9.6: Data Management and Section 9.7: Data Analysis	Updated type and version of software used	To clarify type and version of software used
3.0	09 January 2026	Substantial	Title Page: Author	Added Cynthia de Luise as a protocol author	Addition of author
			Section 4: Abstract / Research Question and Objectives; Variables	Added placental abruption to list of Pregnancy related outcomes	Addition of placental abruption outcome per FDA request
			Section 4: Abstract / Variables	Added prior history of placenta previa and placental abruption to covariates of interest	Supports placental abruption outcome
			Section 8: Research Questions and Objectives	Added placental abruption to list of Pregnancy related outcomes	Addition of placental abruption outcome
			Section 9.3.2.2.1: Pregnancy-related Outcomes	Added placental abruption to list of Pregnancy related outcomes	Addition of placental abruption outcome
			Section 9.3.3: Covariates of Interest	Added history of placenta disorders, placenta previa and placental abruption prior to current pregnancy to covariate list	Supports placental abruption outcome
			Section 16: Appendix 1 – Operationalization	Specified placental abruption on table	Addition of placental

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			of the Primary, Pregnancy-Related, and Maternal Outcomes	of Pregnancy related outcomes	abruption outcome
2.0	14 June 2024	Substantial	9.2.2.1.2. Exclusion Criteria	Revised exclusion criterion 3 to "Exposed to any other RSV vaccine at any time during the pregnancy"	To address the possibility that other RSV vaccines in addition to Arexvy may be available
			3 Responsible Parties	Update name of Pfizer Safety Surveillance Study Lead	Personnel change

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6. MILESTONES

Milestone	Planned Date
Registration in the HMA-EMA Catalogue of RWD studies	Pending (prior to start of data collection)
Start of data collection	30 September 2026
Interim report	31 March 2027
End of data collection	08 September 2028
Final study report	08 March 2029

7. RATIONALE AND BACKGROUND

ABRYSVO™ is a bivalent RSVpreF that is unadjuvanted and composed of two preF proteins to optimize protection against RSV A and B strains. RSVpreF was approved in the US on 31 May 2023 for the prevention of LRTD caused by RSV in individuals 60 years of age and older and on 21 August 2023 for active immunization of pregnant individuals at 32 through 36 weeks' gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age.

RSV is a major cause of severe LRTD in infants and young children. Globally, an estimated 33 million cases of RSV-associated acute lower respiratory infection occur annually among children < 5 year of age, with 6.5 million cases occurring among those 0-6 months of age (Li et al, 2021). Further, the estimated annual incidence rate of RSV-associated hospitalizations is 5 per 1000 children < 5 year of age and 20 per 1000 infants 0-6 months of age (Li et al, 2021). 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 (McLaughlin et al, 2022).

The ongoing Phase 3 clinical trial (NCT04424316), MATISSE (MATernal Immunization Study for Safety and Efficacy), is evaluating the efficacy, immunogenicity, and safety of ABRYSVO when administered to pregnant individuals between $24^{0/7}$ to $36^{6/7}$ weeks gestational age. In this 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. The rate of preterm birth in the full MATISSE population (vaccinated between $24^{0/7}$ and $36^{6/7}$) was 5.7% in the ABRYSVO group versus 4.7% in the placebo group, but the difference was not statistically significant. In a Phase 2, randomized, placebo-controlled, observer-blinded study that investigated the safety of two dose levels (120 mcg and a higher dose) of ABRYSVO administered to pregnant individuals, preterm births occurred in 5.3% (6 out of 114) in the ABRYSVO group and 2.6% (3 out of 116) in the placebo group. A numerical imbalance in preterm births in ABRYSVO recipients compared to placebo recipients was observed in both studies. However, available data are insufficient to establish or exclude a causal

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relationship between preterm birth and ABRYSVO [Package Insert - ABRYSVO (STN 125769/26) (fda.gov)].

Additional characterization of safety endpoints in a real-world population of pregnant individuals, including those who may have been ineligible for clinical trials, is valuable and important. This protocol describes a real-world pregnancy post-marketing study to evaluate the safety of RSVpreF in pregnant individuals and their infants using an integrated healthcare system in the US. This non-interventional study is designated as a PASS and is a PMR to the FDA.

8. RESEARCH QUESTION AND OBJECTIVES

The overall research question is: what is the risk of preterm birth, hypertensive disorders of pregnancy, and other pre-specified adverse pregnancy, maternal, and neonatal/infant outcomes following exposure to ABRYSVO™ during pregnancy?

- The primary study objective is to estimate the risk of (1) preterm birth, and (2) hypertensive disorders of pregnancy following exposure to ABRYSVO™ during pregnancy.

- The secondary study objective is to estimate the risk of the following safety outcomes of interest following exposure to ABRYSVO™ during pregnancy:

    - Pregnancy-related outcomes: stillbirth, premature labor (without preterm delivery), PROM, PPROM, cesarean delivery, prolonged maternal LOS after delivery, placental abruption;

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

    - Neonatal/infant outcomes: SGA, LGA, LBW, admission to a NICU and NICU duration of stay, mechanical ventilation in neonatal period, neonatal death.

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective real-world non-interventional cohort study using electronic health record data from an integrated healthcare system in the US. A pregnancy cohort will include all eligible pregnancies that reach $32^{0/7}$ completed weeks of gestation and that are identified during a 4-year period from 22 September 2023 [corresponding to the date when ACIP recommended ABRYSVO™ in the US] to 22 September 2027. All live born infants from the eligible pregnancies in the pregnancy cohort will be included in the infant cohort. The incidence of all primary and secondary outcomes of interest will be calculated among eligible ABRYSVO™-exposed and unexposed pregnancies. Cox regression anchored on gestational age (or time-since-conception) will be used to compare the incidence of the two primary

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outcomes, pregnancy-related outcomes, and maternal outcomes of interest between the ABRYSVO™-exposed and ABRYSVO™-unexposed pregnancies, adjusting for key covariates. In addition, logistic regression will be used to compare the odds of neonatal/infant outcomes among infants whose mothers were exposed to ABRYSVO™ versus those who were not exposed, adjusting for key covariates.

9.2. Setting

The study setting is KPNC, an integrated delivery health care organization with more than 4.5 million members. KPNC members are broadly representative of the catchment population in terms of sociodemographic characteristics, except for the extremes of income distribution. KPNC has a comprehensive EMR that captures data on all medical services, including immunization and pregnancy related care from before pregnancy, during pregnancy to delivery and beyond.

9.2.1. Study Period

The study period will begin on 22 September 2023, corresponding to the date when ACIP and ACOG recommended ABRYSVO™ in the US. All eligible pregnancies that reach $32^{0/7}$ completed weeks of gestation between 22 September 2023 and 22 September 2027 will be identified and will comprise the pregnancy cohort. Assuming the last eligible pregnancy(s) of gestational age of $32^{0/7}$ weeks identified on 22 September 2027 reaches $42^{0/7}$ completed weeks of gestation, the delivery is anticipated to occur in 10 weeks, i.e., on 01 December 2027. Table 1 below outlines the latest date of follow-up for the primary, pregnancy-related and maternal outcomes for the pregnancy cohort, and neonatal/infant outcomes for the infant cohort. Thus, the study period will end on 12 January 2028.

Table 1. Latest dates of follow-up for the final analysis of the primary, pregnancy-related and maternal outcomes for the pregnancy cohort, and neonatal/infant outcomes for the infant cohort

Cohort	Eligible pregnancies are estimated to end or a birth would occur by:	Follow-up for outcomes of interest through:
Pregnancy cohort	01 December 2027	12 January 2028 (i.e., 42-day post-partum*)
Infant cohort	01 December 2027	29 December 2027 (i.e., 28-day post-birth†)

* All pregnancy-related outcomes will be ascertained until end of pregnancy, hospital discharge date after delivery, or gestational age where appropriate. Preterm birth will be assessed up to $36^{6/7}$ weeks gestation. Hypertensive disorders of pregnancy which will be assessed until 42-days postpartum. Maternal outcomes will be assessed up to 42-days post-vaccination. † The following neonatal/infant outcomes will be assessed at birth: SGA, LGA and LBW and 28 days is the maximum follow-up time for infants for the outcomes of admission to NICU, whether the infant required mechanical ventilation after birth, and neonatal death.

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9.2.2. Study Population

9.2.2.1. Pregnancy Cohort

Pregnancies will be identified using the KPNC pregnancy database. This pregnancy database includes pregnancies with a documented and validated pregnancy outcome (e.g., miscarriage, stillbirth, live birth) as recorded in the EMR.

Pregnancy onset dates are typically calculated using documented gestational age, estimated delivery date using ultrasound information, or last menstrual period (LMP). The pregnancy end date is either the delivery date (i.e., live birth) or terminal pregnancy outcome date (e.g., fetal death, stillbirth).

The two primary outcomes of interest, pregnancy-related outcomes, and maternal outcomes as described in Section 9.3.2 below will be examined in the pregnancy cohort.

9.2.2.1.1. Inclusion Criteria

Pregnancies must meet all of the following inclusion criteria to be included in the pregnancy cohort.

1. $32^{0/7}$ completed weeks of gestation between 22 September 2023 and 22 September 2027
2. Maternal age 15-54 years at $32^{0/7}$ weeks' gestation
3. Presence of at least 1 prenatal visit between pregnancy onset and <20 weeks' gestation
4. Continuous health plan enrollment of the pregnant individual with medical and pharmacy benefits for a minimum of 90 days prior to pregnancy onset date through the date of delivery/pregnancy outcome, with no more than a 1-month administrative gap in coverage being permitted

9.2.2.1.2. Exclusion Criteria

1. Loss of pregnancy or delivery <32 weeks' gestation
2. Exposed to ABRYSVO™ prior to $32^{0/7}$ weeks of gestation
3. Exposed to any other RSV vaccine at any time during the pregnancy

9.2.2.2. Infant Cohort

All live born infants born from the eligible pregnancies, which meet the inclusion/exclusion criteria outlined in Section 9.2.2.1.1 and Section 9.2.2.1.2 will be included in the infant cohort for examination of the neonatal/infant outcomes as described in Section 9.3.2. There are no exclusion criteria that will be applied to the infant cohort.

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9.3. Variables

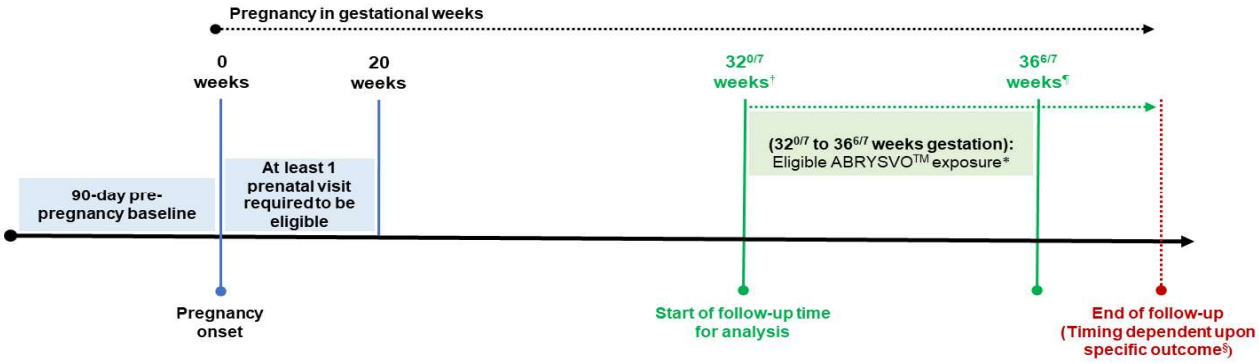
9.3.1. Exposure of Interest

Exposure to ABRYSVO™ will be identified using the data from the KPNC EMR, which captures all vaccination data including vaccination date and manufacturer.

9.3.1.1. ABRYSVO™-Exposed and ABRYSVO™-Unexposed Follow-up Time

ABRYSVO™ exposure will be a time-varying variable. Pregnant individuals will contribute to unexposed follow-up time starting at $32^{0/7}$ weeks' gestation (Figure 1). Those who become exposed to ABRYSVO™ will have a change in exposure status on the date of vaccination, after which they will contribute exposed follow-up time to the analysis. Day 0 will be considered the day of exposure to ABRYSVO™. Individuals who are exposed to ABRYSVO™ after the ACIP-recommended timeframe (i.e., on or after $37^{0/7}$ weeks' gestation) will be censored in the analysis. If an exposure to ABRYSVO™ occurs on day of delivery or terminal pregnancy outcome, the pregnancy will not be counted as 'exposed' but treated as 'unexposed' in the analysis up until the day before exposure.

Figure 1. Study design schematic to depict eligible ABRYSVO™ exposure window and follow-up time for each eligible pregnancy



* ABRYSVO™ exposure is a time-varying variable. Pregnant individuals contribute unexposed follow-up time starting at $32^{0/7}$ weeks. Those who become exposed to ABRYSVO™ will have a change in exposure status on the date of vaccination, after which they contribute exposed follow-up time to the analysis. Follow-up for exposed and unexposed subjects continues until an outcome occurs or delivery (depending on the outcome), death, loss to follow-up, or end of the outcome-specific risk window, whichever comes first.

†Individuals that were exposed prior to $32^{0/7}$ weeks are excluded from the analysis.

¶ Individuals exposed to ABRYSVO™ after the ACIP-recommended timeframe (e.g., on or after $37^{0/7}$ weeks' gestation) will be censored from the day of exposure onward in the analysis.

§ For example, end of follow-up for preterm birth will be at $36^{6/7}$ weeks and end of follow up will be at 42-days post-partum for hypertensive disorders of pregnancy.

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9.3.2. Outcomes of Interest

Outcomes of interest are required to be incident outcomes that did not occur during the pregnancy prior to <$32^{0/7}$ weeks' gestation. For a pregnant individual who is ABRYSVO™ exposed after $32^{0/7}$ weeks' gestation, the outcome must not have occurred prior to exposure. Day 1 will be the first possible day that an outcome will be counted (following Day 0, the day of exposure).

Outcomes will be defined using relevant ICD-10-CM diagnosis codes or validated algorithms as available in relevant data sources in the maternal and/or infant EMR. Please refer to Appendix 1 for a clinical definition of the primary outcomes, pregnancy-related outcomes, and maternal outcomes, a list of ICD-10-CM codes or relevant data sources to be used to identify these outcomes, and the timing of ascertainment. Similarly, Appendix 2 provides clinical definitions of neonatal/infant outcomes, a list of ICD-10-CM codes or relevant data sources to be used to identify these outcomes, and the timing of ascertainment.

9.3.2.1. Primary Outcomes of Interest

- Preterm birth defined as delivery <37 weeks' gestation (including only live births), assessed up to $36^{6/7}$ weeks' gestation (Appendix 1)
- Hypertensive disorders of pregnancy defined as gestational hypertension, preeclampsia, eclampsia, chronic hypertension superimposed with preeclampsia/eclampsia, Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome, and postpartum hypertension (overall and each sub-outcome), assessed up to 42-days postpartum (Appendix 1)

9.3.2.2. Secondary Outcomes of Interest

9.3.2.2.1. Pregnancy-related Outcomes

The following incident pregnancy-related outcomes will be ascertained at the specified timing listed below for each outcome . These will be identified in the EMR using ICD-10-CM codes (Appendix 1):

- Stillbirth, assessed at end of pregnancy
- Premature labor (without preterm delivery), assessed up to $36^{6/7}$ weeks' gestation
- PROM, assessed at end of pregnancy
- PPROM, assessed up to $36^{6/7}$ weeks' gestation
- Cesarean delivery, assessed on the date of delivery
- Prolonged maternal LOS after delivery (defined as >2 days for a vaginal delivery or >4 days for a cesarean delivery), assessed at hospital discharge date

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- Placental abruption, assessed through end of pregnancy

9.3.2.2.2. Maternal Outcomes

The following incident maternal outcomes will be identified in the EMR using ICD-10-CM codes (Appendix 1). All maternal outcomes will be assessed up to 42-days following vaccination with ABRYSVO™:

- Thrombocytopenia (immune thrombocytopenia [ITP], thromboembolic events associated with thrombocytopenia, and thrombotic thrombocytopenic purpura [TTP])
- GBS
- Other immune-mediated demyelinating conditions (acute disseminated encephalitis and encephalomyelitis, acute transverse myelitis in demyelinating disease of central nervous system, optic neuritis, neuromyelitis optica, and other acute demyelinating diseases)
- Polyneuropathies (inflammatory polyneuropathy, serum neuropathy, other inflammatory polyneuropathies, chronic inflammatory demyelinating polyneuritis, multifocal motor neuropathy, other inflammatory polyneuropathies, drug-induced polyneuropathy, other polyneuropathies)
- Atrial fibrillation
- All-cause maternal mortality

9.3.2.2.3. Neonatal/Infant Outcomes

The following neonatal/infant outcomes will be identified within the EMR (Appendix 2):

- SGA based on birthweight and gestational age, percentile on Fenton scale <0.1 (Fenton et al 2003 and Fenton et al 2013) or ICD-10-CM codes, assessed at birth
- LGA based on birthweight and gestational age, percentile on Fenton scale >0.9 (Fenton et al 2003 and Fenton et al 2013), or ICD-10-CM codes, assessed at birth
- LBW based on birthweight <2500 grams, assessed at birth
- Admission to a NICU between birth up to 28-days after birth (categorical variable: yes/no)
- Duration of stay in NICU in number of days, if admitted to NICU in first 28-days after birth (continuous variable)
- Required mechanical ventilation between birth up to 28-days after birth (categorical variable: yes/no)

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- Neonatal death between birth up to 28-days after birth (categorical variable: yes/no)

9.3.3. Covariates of Interest

The following maternal covariates of interest will be identified within the EMR and may be considered for inclusion as potential confounders or effect modifiers in the analysis of the primary, pregnancy-related and/or maternal outcomes. Further details on operationalization of each covariate of interest will be described in the SAP:

- Maternal age in years at $32^{0/7}$ weeks of gestation (continuous [e.g., mean age] and categorical [e.g., 15-<18 years, 18-<25 years, 25-<30 years, 30-<35 years, 35-<40 years, 40-<45 years, 45-<50 years, 50-54 years])
- Self-reported maternal race/ethnicity (e.g., White, Asian, Black, Hispanic, Multiracial, Native American, Pacific Islander, Unknown)
- Maternal KPNC geographic region based upon where the pregnant individual seeks most prenatal care (e.g., Central Valley, Diablo Valley, East Bay, Greater Sacramento Area, Greater San Francisco Bay Area, North Bay, and South Bay)
- Maternal neighborhood deprivation index (NDI) may be used as a proxy for socioeconomic status (SES)
- Maternal insurance type (e.g., subsidized, non-subsidized)
- Neighborhood level of education may be used as a proxy for SES (reported as the percentage of adults with an educational level of high school or less)
- Month and year of pregnancy onset
- Maternal pre-pregnancy BMI (e.g., based on measured height/weight closest to pregnancy onset in the 3 months prior to estimated pregnancy onset, up to the end of the first trimester <14 weeks' gestation)
- Parity (e.g., 1, 2, ≥3 live births and stillbirths)
- Pre-existing hypertensive disorders identified in the 90 days prior to pregnancy onset, up to pregnancy onset
- Hypertensive disorders of pregnancy identified from date of current pregnancy onset until $31^{6/7}$ weeks of gestation
- Gestational diabetes (diagnosed in the current pregnancy)
- History of preterm birth (if available)
- Number of prenatal visits (in the current pregnancy) as a proxy for healthcare utilization during pregnancy
- Early bleeding in pregnancy (to be defined in the SAP)
- Excessive stress (code list to be further refined in the SAP)
- Other vaccines administered during pregnancy (e.g., influenza, Tdap, COVID-19)

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- Method of delivery (vaginal or cesarean)
- Assisted reproduction in the current pregnancy identified in the 90 days prior to pregnancy onset
- Documented shortened cervix in the current pregnancy identified after 22 weeks of gestation (timing of assessment to be defined in the SAP)
- Short interpregnancy interval of <3 months (pregnant individuals with presence of any pregnancy or delivery related diagnosis or procedure codes occurring within 90 days prior to the current pregnancy onset will be categorized as those with a short interpregnancy interval)
- Healthcare utilization prior to the current pregnancy (e.g., number of weeks with an outpatient visit in the year prior to pregnancy, number of hospital admissions in the year prior to pregnancy)
- History of placental disorder, placenta previa or placental abruption prior to the current pregnancy
- Maternal pre-existing comorbidities as listed below, identified from 90 days prior to and up to pregnancy onset) within the EMR using ICD-10-CM diagnosis and/or procedure codes

    a. Diabetes (Type 1 and Type 2)

    b. Chronic hypertension (i.e., diagnosed prior to LMP, or at least prior to 20 weeks of gestation)

    c. Cardiovascular disease

    d. Cerebrovascular diseases

    e. Chronic respiratory disease, excluding asthma

    f. Asthma

    g. Chronic kidney disease

    h. Chronic liver disease

    i. Cancer

    j. Epilepsy

    k. Connective tissue disorders

    l. Thyroid disorders

    m. Chronic anemia

    n. Antiphospholipid syndrome

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o. Uterine and cervical factors (e.g., leiomyoma, procedures such as cold knife conization, electrosurgical excision, history of procedural abortion)

The following neonatal/infant covariates of interest will be identified within the EMR and will be descriptively summarized:

- Newborn sex (male or female)
- Newborn race/ethnicity (e.g., White, Asian, Black, Hispanic, Multiracial, Native American, Pacific Islander, Unknown)
- Gestational age at birth of the newborn (reported as categorical variable)

9.4. Data Sources

This study will use KPNC EMR data collected as part of routine clinical care. KPNC is an integrated health care delivery system with a membership of over 4.6 million. As one of the earliest sites of the Vaccine Safety Datalink project initiated by the Centers for Disease Control and Prevention, KPNC has provided clinical, methodological, and data expertise to evaluate the safety of vaccines in several large observational studies, including ones in pregnant women and their infants.

Baseline characteristics (e.g., age, race/ethnicity, relevant medical history), vaccination history, outcome event data, and infant birth data will be extracted from the KPNC EMR to create study datasets in the required file format for analysis. These data include demographics, membership information, pre-defined pregnancy-related, maternal, and neonatal/infant outcomes, healthcare encounters (e.g., inpatient, outpatient, hospitalizations, and emergency department), immunization information, clinical outcomes, and diagnoses.

Outcomes will be identified using ICD-10-CM diagnosis codes, measured birthweight (in addition to gestational age, depending on the outcome), and/or healthcare encounter data (e.g., number of days in the NICU). Neonatal deaths will be identified using KPNC's mortality table, which contains validated deaths. Maternal deaths will be identified in the KPNC EMR as well.

9.5. Study Size

There are approximately 42,000 live births every year at KPNC. During the 4-year period from 22 September 2023 to 22 September 2027, an estimated 168,000 total births are anticipated. Since the uptake of ABRYSVO™ is unknown, power is calculated based on 20%, 10% and 5% uptake among pregnant individuals and assumes the risk of preterm birth among the unexposed pregnancies as 8.5% based on the 2019 US preterm birth rate for singleton births (Martin et al 2021) and assumes the risk of hypertensive disorders of pregnancy among the unexposed pregnancies as 15.9% as reported using data from the US National Inpatient Sample for the year 2019 (Ford et al 2022). Additionally, it conservatively assumes that at least 50% of total pregnancies/births will be included in the study after applying eligibility criteria. Assuming a type 1 error of 5%, (two-sided test), the study will have at least 80% power to detect a minimum RR of 1.07 and 1.06 for preterm birth and

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hypertensive disorders of pregnancy, respectively, if 20% of the pregnant individuals are exposed to RSV vaccine (Table 2).

Table 2. Minimum detectable RR comparing ABRYSVO™-exposed pregnant individuals versus unexposed individuals with 80% Power and type 1 error of 5%

Primary Outcome of Interest	Minimum RR by Percentage of ABRYSVO™ Vaccine Uptake in the Pregnancy Cohort		
	20%	10%	5%
Preterm birth	1.07	1.11	1.15
Hypertensive disorders of pregnancy	1.06	1.08	1.11

9.6. Data Management

Data management will be carried out by experienced data analysts in accordance with the standard operating procedures at Kaiser Permanente Vaccine Study Center (KPVSC). Routine procedures include checking electronic files, maintaining security and data confidentiality, and performing quality-control checks of all programming. All data management and statistical analyses will be conducted using software such as Statistical Analysis System (SAS) Version 9.4 (SAS Institute, Cary, NC, USA), R (version 4.3.1 or higher), and/or Python (version 3.11.9 or higher).

9.7. Data Analysis

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

Statistical analyses will be performed using software such as SAS, version 9.4 or higher (SAS Institute Inc., Cary, NC), R (version 4.3.1 or higher), and/or Python (version 3.11.9 or higher).

9.7.1. Interim Analysis

The interim analysis will be descriptive. The descriptive results will be stratified by type of pregnancy, i.e., among singleton pregnancies (and births) and among multiple gestation pregnancies (and births). All eligible pregnancies that have been identified during 22 September 2023 to 10 April 2026 will be included in the interim analysis. Assuming the last eligible pregnancy(s) of gestational age of $32^{0/7}$ weeks identified on 10 April 2026 reaches $42^{0/7}$ completed weeks of gestation, the delivery is anticipated to occur in 10 weeks, i.e., on 19 June 2026. Table 3 below outlines the latest date of follow-up for the interim analysis of the primary, pregnancy-related and maternal outcomes for the pregnancy cohort, and neonatal/infant outcomes for the infant cohort. Thus, the study period for interim analysis will end on 31 July 2026.

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Table 3. Latest dates of follow-up for the interim analysis of the primary, pregnancy-related and maternal outcomes for the pregnancy cohort, and neonatal/infant outcomes for the infant cohort

Cohort	Eligible pregnancies are estimated to end or a birth would occur by:	Follow-up for outcomes of interest through:
Pregnancy cohort	19 June 2026	31 July 2026 (i.e., 42-day post-partum*)
Infant cohort	19 June 2026	17 July 2026 (i.e., 28-day post-birth†)

* All pregnancy-related outcomes will be ascertained until end of pregnancy, hospital discharge date after delivery, or gestational age where appropriate. Preterm birth will be assessed up to $36^{6/7}$ weeks gestation. Hypertensive disorders of pregnancy which will be assessed until 42-days postpartum. Maternal outcomes will be assessed up to 42-days post-vaccination. † The following neonatal/infant outcomes will be assessed at birth: SGA, LGA and LBW and 28 days is the maximum follow-up time for infants for the outcomes of admission to NICU, whether the infant required mechanical ventilation after birth, and neonatal death.

Descriptive results will include the following:

(1) Descriptive summaries of maternal and neonatal/infant covariates of interest for pregnant individuals and infants born to eligible pregnant individuals as listed in Section 9.3.3 will be provided.

(2) Incidence rates (IRs) and 95% CIs will be calculated for the two primary outcomes, all pregnancy-related outcomes, maternal outcomes, and neonatal/infant outcomes among ABRYSVO™-exposed and ABRYSVO™-unexposed pregnancies. The denominator for pregnancy-related outcomes will be the number of pregnancies or person-time at risk. The denominator for neonatal/infant outcomes will be the number of live-born infants.

9.7.2. Final Analysis

The final analysis will include the descriptive analysis as described in Section 9.7.1. In addition to the descriptive analysis, the following comparative analysis depending upon the type of outcome (primary, pregnancy-related, maternal, or neonatal/infant) and an additional exploratory analysis will be undertaken.

9.7.2.1. Analysis of the Primary Outcomes and Pregnancy-related Outcomes

This analysis will use a days-since-conception timeline, which reflects the gestational age in days starting at pregnancy onset up to the end of the pregnancy period, plus any follow-up time that extends into the post-partum period (for example, the start of follow-up is on $32^{0/7}$ weeks, i.e., 224^{th} days-since-conception). For the primary outcomes and pregnancy-related outcomes, Cox regression anchored on gestational age (or time-since-conception for outcomes that are assessed in the postpartum period) will be used to compare the risk of an outcome in pregnant individuals who were exposed to ABRYSVO™ with the risk in similar pregnant individuals who were unexposed to ABRYSVO™, adjusting for covariates. The

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details on which covariates of interest will be adjusted for in the final analysis will be described in the SAP. The analysis will include ABRYSVO™ exposure as a time-varying variable whereby pregnant individuals contribute unexposed follow-up time until they are exposed to ABRYSVO™, at which point they contribute exposed follow-up time to the analysis. On every day of gestational age (or in the postpartum follow-up period) that an outcome occurs in an ABRYSVO™-exposed pregnant individual, a risk set is formed in which the risk among ABRYSVO™-exposed individuals who are still in follow-up (i.e., the outcome has not occurred), will be compared to the risk among ABRYSVO™-unexposed individuals who are still in follow-up.

The analysis will compare pregnant individuals who are exposed to ABRYSVO™ during the ACIP recommended timeframe of $32^{0/7}$ weeks' gestation to pregnant individuals who are not (yet) exposed to ABRYSVO™ on or after $32^{0/7}$ weeks' gestation. Pregnant individuals will be excluded from this analysis if they are exposed to ABRYSVO™ before $32^{0/7}$ weeks' gestation. Incident outcomes will be captured starting at $32^{1/7}$ weeks' gestation (Day 1 after the first possible day of vaccination on Day 0 [$32^{0/7}$ weeks' gestation]) up until an occurrence of an outcome (or delivery), death, end of KPNC membership, loss to follow-up, or end of the outcome-specific risk window, whichever occurs first.

If a statistically significant association is observed between ABRYSVO™ exposure during pregnancy and preterm birth, additional descriptive results may be provided that stratify preterm births by timing of preterm birth (e.g., 32-<34 weeks, 34-<35 weeks, 35-$36^{6/7}$ weeks), method of delivery, time interval between vaccination and preterm birth, and other characteristics and risk factors, as relevant. In addition, if statistically significant risk is observed for preterm birth, a descriptive analysis may be conducted for all preterm birth outcomes to evaluate neonatal morbidity/mortality using available data from the infant EMR, as feasible in the KPNC database. The details will be included in the SAP.

For the analysis of hypertensive disorders of pregnancy, which includes follow-up to 42 days in the postpartum period, the Cox regression analysis will also include a time-varying covariate that indicates whether the pregnancy has ended (binary 0/1) to control for the possibility that any hypertensive outcome is associated with being pregnant or not.

9.7.2.2. Analysis of Maternal Outcomes

Cox regression will also be used for the analyses of the maternal outcomes. ABRYSVO™ exposure will be treated as a time-varying variable. For ABRYSVO™-exposed individuals, the start of exposed follow-up will be from Day 1, i.e., the day following the day of exposure to ABRYSVO™ or Day 0 (i.e., exposure day is Day 0). The end of exposed follow-up will be on Day 42 after exposure. For ABRYSVO™-unexposed individuals, the start of unexposed follow-up will be from $32^{0/7}$ weeks' gestation. The end of unexposed follow-up will be up to a maximum of 42 days after $36^{6/7}$ weeks' gestation, which is the latest possible timing for ABRYSVO™ exposure.

On each day of the days-since-conception timeline, the risk of a maternal outcome in exposed individuals (in the risk window) will be compared to the risk of a maternal outcome in unexposed individuals (reference group), adjusting for covariates. Further details will be included in the SAP.

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For the analysis of maternal outcomes that may include follow-up in the postpartum period, the Cox regression analysis will also include a time-varying covariate that indicates whether the pregnancy has ended (binary 0/1) to control for the possibility that any outcome is associated with being pregnant or not.

If potential safety signals are identified in the analysis of maternal outcomes, these may be further assessed using various methods, such as assessment of temporal clustering of outcomes in relation to days subsequent to exposure to ABRYSVO™ among ABRYSVO™-exposed pregnant individuals.

9.7.2.3. Analysis of Neonatal/Infant Outcomes

All infants born to eligible unexposed and exposed pregnant individuals will be followed from birth until the occurrence of neonatal/infant outcome of interest, death, end of KPNC membership or the end of follow-up, whichever occurs first. For neonatal/infant outcomes, logistic regression, adjusting for key covariates will be fitted to examine the risk among exposed pregnant individuals compared to unexposed individuals.

Additional details on all analyses will be provided in the SAP.

9.7.2.4. Additional Exploratory Analysis

An additional exploratory analysis will be performed in the final analysis in an expanded pregnancy cohort with an objective to capture real-world ABRYSVO™ exposures occurring in pregnant individuals at or after $24^{0/7}$ completed weeks of gestation (i.e., 8 weeks earlier than the lower limit of the ACIP and ACOG recommended timeframe). In addition, pregnant individuals who are exposed to ABRYSVO™ after the ACIP and ACOG recommended timeframe (i.e., on or after $37^{0/7}$ weeks' gestation) will not be censored in the analysis. This expanded pregnancy cohort will include all eligible pregnancies that reach $24^{0/7}$ completed weeks of gestation during a 4-year period from 22 September 2023 to 22 September 2027. The inclusion and exclusion criteria as described in Section 9.2.2.1.1 and Section 9.2.2.1.2 aligned to $24^{0/7}$ completed weeks of gestation will be applied. Assuming the last eligible pregnancy(s) of gestational age of $24^{0/7}$ weeks identified on 22 September 2027 reaches $42^{0/7}$ completed weeks of gestation, the delivery is anticipated to occur in 18 weeks, i.e., on 26 January 2028. Thus, the study period for the exploratory analysis will end on 08 March 2028, corresponding to a 42-day postpartum period after the last eligible pregnancy reaches $42^{0/7}$ completed weeks of gestation. All live born infants from the eligible pregnancies in this expanded pregnancy cohort will be included in the infant cohort. The descriptive analysis as described in Section 9.7.1 will be conducted in this pregnancy cohort. In addition to the descriptive analysis, comparative analysis will be conducted for Primary Outcomes and Pregnancy-related Outcomes, maternal outcomes and neonatal/infant outcomes as outlined in Sections 9.7.2.1, 9.7.2.2 and 9.7.2.3, respectively. Additional details on this analysis will be provided in the SAP.

9.7.3. Sensitivity Analyses

In addition to examining the risk of preterm birth (which includes only live births) in the primary analysis, the risk of preterm delivery, which includes preterm live births and stillbirths that occur prior to 37 weeks will be examined in ABRYSVO™-exposed

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pregnancies compared to ABRYSVO™-unexposed pregnancies in a sensitivity analysis. Additional sensitivity analyses may be proposed in the SAP as deemed necessary.

9.8. Quality Control

Standard operating procedures at KPVSC will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, and standards for writing analysis plans.

All work will be subject to quality-control and documentation procedures to make certain that the final report is accurate and thorough, and the analyses can be reproduced. All key study documents, such as the protocol, SAP, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

Validation of code and output will occur throughout the data management process utilizing multiple types of discrepancy checks such as internal consistency checks, external data checks, checks against source data, and/or error checks written for specific databases. The latter approaches will be well documented in a structured manner, including the use of tools to systematically document programming code review and analytic decision-making/assumptions. Deliverables also undergo peer review by both PIs and a biostatistician; all source code and output are reviewed by a second programmer, and any inconsistencies or potential errors identified are discussed and resolved, and necessary changes are made to the original programs. All programs, logs and output will be saved, and the coding/programming/analysis process will be well documented for transparency.

9.9. Strengths and Limitations of the Research Methods

9.9.1. Limitations of the Research Methods

This study may have the following limitations:

First, the uptake of the ABRYSVO™ vaccine in the KPNC pregnant population is currently unknown. However, assuming a conservative vaccine uptake of 5%, the study would have sufficient sample size to detect a minimum RR of 1.15 for preterm birth and of 1.11 for hypertensive disorders of pregnancy. Smaller minimum RRs for these outcomes would be detectable with a higher vaccine uptake.

Second, it is likely that pregnant individuals who choose to receive the ABRYSVO™ vaccine will be different from those who do not in some demographic characteristics, healthcare seeking behaviors, etc. To reduce potential confounding due to these differences, the analysis will carefully control for covariates including prenatal care, comorbidities, SES, etc. However, information on lifestyle factors such as use of alcohol, tobacco, and recreational drug use available in KPNC database is based on self-reported data by patients and is likely to be incomplete. Hence, potential residual confounding by these lifestyle factors and any other unknown confounding factors cannot be controlled in the analysis.

Third, this study will identify outcomes based on ICD-10-CM diagnostic codes; no medical chart reviews are planned to be conducted to validate study outcomes. However, the study

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will use well-recognized validated algorithms to identify outcomes of interest, as have been used in previous safety studies of vaccination in pregnancy conducted by KPNC (Zerbo et al 2017, Vazquez-Benitez et al 2016), hence outcome misclassification is expected to be minimal.

Fourth, there is a possibility of missing data for some covariates of interest, for example, if a pregnant woman receives care for assisted reproduction in the current pregnancy outside of KPNC, may not be well recorded in the KPNC EMR.

Lastly, this study population consists of individuals who are members of an integrated healthcare system, which may limit the generalizability of the findings to uninsured populations. Additionally, while the study population is representative of Northern California's racial/ethnic composition, it may not be representative of the entire California population or other US geographic regions.

9.9.2. Strengths of the Research Methods

The study has several strengths. The study design allows use of the entire eligible pregnancy cohort, which increases study power. Cox regression analysis also allows to finely control for gestational age while adjusting for other covariates of interest. Since the study employs ABRYSVO™ exposure as a time-varying variable, it accounts for immortal time bias, which is a bias introduced in pregnancy studies if unexposed follow-up time prior to the exposure of interest is included in the denominator of the calculation of the risk in the exposed group. Another major strength of this study is the use of EMR data collected as part of routine medical care, which avoids recall bias and provides access to a large sample of insured individuals from Northern California. The study approach also minimizes the potential for selection bias that might occur in primary data collection studies, as the study population includes all pregnant individuals in the database who meet eligibility criteria for research rather than individuals who have volunteered to participate in a study.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that will be delivered to Pfizer by KPVSC in deidentified/anonymized structured format and contain no patient personal information. This study does not involve the collection, use, or transmittal of individually-identifiable patient/subject data.

10.2. Patient Consent

As this 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.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer. This study is approved by the KPNC IRB on 14 November 2023 with a waiver of informed consent.

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 the FDA's industry guidance, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (FDA, 2005), FDA Draft Guidance for Industry: Postapproval Pregnancy Safety Studies (FDA, 2019), the International Society for Pharmacoepidemiology's (ISPE's) *Guidelines for Good Pharmacoepidemiology Practices* (ISPE Guidelines, 2016), STROBE guidelines (von Elm et al, 2007), and the principles of the Declaration of Helsinki (World Medical Association, 2001).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered in the HMA-EMA Catalogue of RWD studies. An interim report (reflecting data from the study period from 22 September 2023 to 31 July 2026), and a final report (reflecting data from the entire study period extending from 22 September 2023 to 12 January 2028 for the analysis of exposures occurring in the ACIP and ACOG recommended timeframe and from 22 September 2023 to 08 March 2028 for the additional exploratory analysis) will be submitted by Pfizer to the US FDA communicating the study results. Some or all data from this study may be developed into abstracts for presentation at scientific conferences, and/or developed into manuscripts for external publication purposes.

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 party responsible for collecting data from participant 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

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

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16. APPENDIX 1. OPERATIONALIZATION OF THE PRIMARY, PREGNANCY-RELATED, AND MATERNAL OUTCOMES

The primary, pregnancy-related, and maternal outcomes will be identified in the mother's and/or infant's EMR using the proposed codes below. These codes may be further refined in the SAP. All outcomes must be incident outcomes during pregnancy (and including the postpartum period where applicable).

Type of Outcome	Outcome	Sub-Outcome/Clinical Definition	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)/Sensitivity	Timing of Ascertainment
Primary outcomes	Preterm birth	Not applicable (NA)	Gestational age (GA) <37 weeks recorded in EMR (includes only live births)	NA	NA	Start of follow-up to GA<37 weeks
	Hypertensive disorders of pregnancy	Gestational hypertension	O13.*	Gestational hypertension	Labgold et al, 2021, PPV for O13.1, O13.2, O13.3, O13.4, O13.5, O13.9 = 88.9% (95% CI: 86.4%- 91.1%)	Start of follow-up to 42-days postpartum
		Preeclampsia	O14.*	Preeclampsia	Chomistek et al, 2023: using IP, ED, OP codes for O14.* and O11.*: PPV=78.3%; using IP PPV=85.7%; Labgold et al, 2021, PPVs ranging from 89%-99%	
		Eclampsia	O15.*	Eclampsia	Labgold et al, 2021, PPV=100.0% (95% CI: 39.8% -100%)	
		HELLP syndrome	O14.2*	HELLP syndrome	Labgold et al, 2021, PPV= 88.2% (95% CI: 63.6%-98.5%)	
		Pre-existing hypertension with pre-eclampsia	O11.*	Pre-existing hypertension with pre-eclampsia	Chomistek et al, 2023: using IP, ED, OP for O14.* and O11.*: PPV=78.3%; using IP PPV=85.7%; Labgold et al, 2021: PPV= 83.3% (95% CI: 74.9%- 89.8%)	

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Type of Outcome	Outcome	Sub-Outcome/Clinical Definition	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)/Sensitivity	Timing of Ascertainment
		Postpartum hypertension	Any of above codes for hypertensive disorders of pregnancy diagnosed in the 42-days postpartum	Postpartum hypertension	See algorithms above	
Pregnancy-related outcomes	Stillbirth	Spontaneous pregnancy loss on or after 20 completed weeks of gestation (in the study, only stillbirths occurring at or after $32^{0/7}$ weeks will be included).	Pregnancy database which uses an algorithm for validating still births	NA	NA	Start of follow-up to end of pregnancy
	Premature labor without preterm delivery	Presence of regular uterine contractions that occur without a livebirth/stillbirth delivery before 37 completed weeks of gestation.	O60.0* coded before GA 37 weeks	Preterm labor without delivery	Goueslard et al, 2020; O60.0 in IP setting PPV: 57.5% (95% CI: 55.8% - 59.2%)	Start of follow-up to GA<37 weeks
	Premature rupture of membranes (PROM)	Rupture of membranes prior to the onset of labor	O42.*	Premature rupture of membranes	Goueslard et al, 2020; codes for PROM (O42) or the code for delayed delivery after spontaneous or unspecified rupture of membranes (O75.6) during the delivery stay: PPV=54.9% (95% CI: 53.2% -56.6%), sensitivity= 57.0% (95% CI: 55.3% - 58.7%).	Start of follow-up to end of pregnancy
			P01.1	Newborn affected by premature rupture of membranes	NA	At birth (infant)
	Preterm premature rupture of membranes (PPROM)	Rupture of members prior to the onset of labor that occurs before 37 weeks gestation	O42.* coded before GA 37 weeks	Premature rupture of membranes	See algorithm above for PROM	Start of follow-up to GA<37 weeks

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Type of Outcome	Outcome	Sub-Outcome/Clinical Definition	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)/Sensitivity	Timing of Ascertainment
	Cesarean delivery	Surgical delivery of an infant through incision in the mother's abdomen and uterus	KPNC pregnancy database, which contains information on a validated variable, cesarean delivery-Yes/No	NA	NA	At delivery
	Prolonged maternal LOS after delivery	Defined as >2 days for a vaginal delivery or >4 days for cesarean delivery	Hospital discharge date minus date of delivery from KPNC EMR	NA	NA	At hospital discharge date
	Placental abruption	Premature separation of placenta before childbirth	O45.*	Premature separation of placenta [abruptio placentae]	NA	Start of follow-up to end of pregnancy
Maternal outcomes	Thrombocytopenia	Immune thrombocytopenia (ITP)	D69.3	Immune thrombocytopenic purpura	Mezaache et al, 2017; PPV=79.5% (Incident ITP); Heden et al, 2009, PPV=93% for IP setting (Chronic ITP); Segal et al, 2004, Sensitivity=100% and Percent agreement =92% for ICD-9-CM code 287.3	Start of follow-up to end of follow-up[†]
		Thromboembolic events associated with thrombocytopenia	G08	Intracranial and intraspinal phlebitis and thrombophlebitis	NA	Start of follow-up to end of follow-up[†]; Diagnosis of thrombocytopenia must occur within 14 days of thrombotic event
			I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic	NA	

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Type of Outcome	Outcome	Sub-Outcome/Clinical Definition	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)/Sensitivity	Timing of Ascertainment
			I67.6	Nonpyogenic thrombosis of intracranial venous system	NA	
			I74.0*	Embolism and thrombosis of abdominal aorta	NA	
			I74.1*	Embolism and thrombosis of other and unspecified parts of aorta	NA	
			I74.3	Embolism and thrombosis of arteries of the lower extremities	NA	
			I74.5	Embolism and thrombosis of iliac artery	NA	
			I74.8	Embolism and thrombosis of other arteries	NA	
			I74.9	Embolism and thrombosis of unspecified artery	NA	
			I81	Portal vein thrombosis	NA	
			I82.0	Budd-Chiari syndrome	NA	
			I82.890	Acute embolism and thrombosis of other specified veins	NA	
			K55.0*	Acute vascular disorders of intestine	NA	
			N28.0	Ischemia and infarction of kidney	NA	
		Thrombotic thrombocytopenic purpura (TTP)	M31.1	Thrombotic microangiopathy	NA	Start of follow-up to end of follow-up†
	Guillain-Barré Syndrome (GBS)	NA	G61.0	Guillain-Barre syndrome	Arya et al 2019: PPV of an inpatient diagnosis of GBS in ICD-10 of 71.21% (95% CI:	Start of follow-up to end of follow-up†

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Type of Outcome	Outcome	Sub-Outcome/Clinical Definition	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)/Sensitivity	Timing of Ascertainment
					63.49%, 78.94%) for the 2015–16 season	
	Other immune-mediated demyelinating conditions	Acute disseminated encephalitis and encephalomyelitis	G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified	Boesen et al, 2018 (Danish pediatric population): 1 IP code PPV=15% using codes G04.0, G04.8, G04.9	Start of follow-up to end of follow-up†
			G04.02	Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis	Boesen et al, 2018 (Danish pediatric population): 1 IP code PPV=15% using codes G04.0, G04.8, G04.9	
		Acute transverse myelitis in demyelinating disease of central nervous system	G37.3	Acute transverse myelitis in demyelinating disease of central nervous system	Boesen et al, 2018 (Danish pediatric population): 1 IP code PPV=64%	Start of follow-up to end of follow-up†
		Optic neuritis	H46.00	Optic papillitis, unspecified eye	Hamedani et al, 2020 systematic review: two studies (data from Denmark, Canada) using single or ≥ 2 codes PPV= 25%–88% Boesen et al, 2018 (Danish pediatric population): 1 IP code PPV=71%	Start of follow-up to end of follow-up†
			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		
			H46.8	Other optic neuritis		
			H46.9	Unspecified optic neuritis		
		Neuromyelitis optica	G36.0	Neuromyelitis optica	Boesen et al, 2018 (Danish pediatric population): 1 IP code PPV=43%	Start of follow-up to end of follow-up†

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Type of Outcome	Outcome	Sub-Outcome/Clinical Definition	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)/Sensitivity	Timing of Ascertainment
		Other acute demyelinating diseases	G37.1	Central demyelination of corpus callosum	NA	Start of follow-up to end of follow-up[†]
			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		
	Polyneuropathies	Inflammatory polyneuropathy, serum neuropathy, other inflammatory polyneuropathies, chronic inflammatory demyelinating polyneuritis, multifocal motor neuropathy, other inflammatory polyneuropathies, drug-induced polyneuropathy, other polyneuropathies	G61	Inflammatory polyneuropathy	NA	Start of follow-up to end of follow-up[†]
			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 and unspecified polyneuropathies		
			G62.0	Drug-induced polyneuropathy		
			G62.8	Other specified polyneuropathies		
			G62.89	Other specified polyneuropathies		

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Type of Outcome	Outcome	Sub-Outcome/Clinical Definition	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)/Sensitivity	Timing of Ascertainment
			G62.9	Polyneuropathy, unspecified		
	Atrial fibrillation	NA	I48.0	Paroxysmal atrial fibrillation	Chamberlain et al, 2022: ICD-10 I48* PPV for 1 code=67.5%. PPV for 1 IP or 2 OP ≥ 1 day apart=71.1%	Start of follow-up to end of follow-up†
			I48.11	Longstanding persistent atrial fibrillation		
			I48.19	Other persistent atrial fibrillation		
			I48.20	Chronic atrial fibrillation, unspecified		
			I48.91	Unspecified atrial fibrillation		
	All-cause maternal mortality	NA	KPNC EMR	NA	NA	Start of follow-up to end of follow-up†

Abbreviations: IP, Inpatient; ED, Emergency department; OP, Outpatient; PPV, Positive predictive value; EMR, electronic medical record.
'*' symbol following an ICD-10-CM code indicates inclusion of all subcodes under the main category of codes, for example, O15.* includes all subcodes under O15, i.e., O15.0, O15.1, O15.2, and O15.9.
† For all maternal outcomes: For ABRYSVO™-exposed individuals, the start of exposed follow-up will be from Day 1, i.e., the day following the day of exposure to ABRYSVO™ or Day 0 (i.e., exposure day is Day 0). The end of exposed follow-up will be on Day 42 after exposure. For ABRYSVO™-unexposed individuals, the start of unexposed follow-up will be from $32^{0/7}$ weeks' gestation. The end of unexposed follow-up will be up to a maximum of 42 days after $36^{6/7}$ weeks' gestation, which is the latest possible timing for ABRYSVO™ exposure.

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17. APPENDIX 2. OPERATIONALIZATION OF NEONATAL/INFANT OUTCOMES

Neonatal/infant outcomes will be identified in the mother's and/or infant's EMR using the proposed codes or data source below. These codes may be further refined in the SAP.

Outcome	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)	Timing of Ascertainment
Small for gestational age (SGA)	Birth percentile on Fenton scale <0.1 based on birthweight and gestational age as recorded in infant electronic medical records	Not applicable (NA)	NA	At birth
	P05.0*	Newborn light for gestational age	-Watson et al 2021 (international data) PPV=70.4% - algorithm not specified (P05) -Phiri et al 2015: PPV=86.8% for ICD-9 656.X on day of delivery -He 2020: ≥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% (95% CI: 82%-97%) in claims (Medicaid)-linked EHR data	At birth (only used if birth percentile is not present)
	P05.1*	Newborn small for gestational age		
Large for gestational age (LGA)	Birth percentile on Fenton scale >0.9 based on birthweight and gestational age as recorded in infant EMR	NA	NA	At birth
	P08.0*	Exceptionally large newborn baby	NA	At birth (only used if birth percentile is not present)
	P08.1*	Other heavy for gestational age newborn	NA	
Low birth weight (LBW)	Birthweight <2,500 g as recorded in infant EMR	NA	NA	At birth
Admission to neonatal intensive care unit (NICU)	NICU admission as recorded in infant EMR	NA	NA	At birth through day 28 of life

Outcome	ICD-10-CM or Data Source as applicable	ICD-10-CM Description	Reference for Validated Algorithm and Positive Predictive Value (PPV)	Timing of Ascertainment
Duration of stay in NICU	NICU admission as recorded in infant EMR	NA	NA	At birth through day 28 of life
Mechanical ventilation	As recorded in infant EMR	NA	NA	At birth through day 28 of life
Neonatal death	KPNC mortality table	NA	NA	At birth through day 28 of life

Footnote: '*' symbol following an ICD-10-CM code indicates inclusion of all subcodes under the main category of codes.

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