NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Post-Marketing Safety Study using a Pregnancy Registry to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy
Protocol number	C3671041
Protocol version identifier	3.0
Date	28 October 2025
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 research question is: What is the risk of adverse pregnancy outcomes, including preterm birth, hypertensive disorders of pregnancy, and other maternal and neonatal/infant outcomes, following exposure to ABRYSVO between 32 weeks 0 days and 36 weeks 6 days of gestation)? The primary study objective is to estimate the risk of (1) preterm birth and (2) hypertensive disorders of pregnancy in the ABRYSVO-exposed cohort and the ABRYSVO-unexposed cohort. The secondary study objective is to estimate the risk of the following other safety outcomes of interest in the ABRYSVO-exposed cohort and the ABRYSVO-unexposed cohort: • Pregnancy-related outcomes: stillbirth, preterm labor without preterm delivery, premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), cesarean delivery, prolonged maternal duration of hospital stay • Maternal outcomes: thrombocytopenia, Guillain-Barré Syndrome (GBS), other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation, maternal death • Neonatal/infant outcomes: small for gestational age (SGA), large for gestational age, low birth weight (LBW),

	admission to a neonatal intensive care unit (NICU), NICU length of stay, mechanical ventilation in neonatal period, neonatal death, postnatal growth deficiency at 1 year of age The exploratory study objective is to describe the most frequently reported maternal adverse events (AEs) following exposure to ABRYSVO between 32 weeks 0 days and 36 weeks 6 days of gestation.
Country(ies) of study	United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
ALRI	acute lower respiratory infection
ART	assisted reproductive technology
CDC	Centers for Disease Control and Prevention
CSF	cerebrospinal fluid
DOC	date of conception
EDC	electronic data capture
EDD	expected date of delivery
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
HCP	healthcare provider
HELLP	hemolysis, elevated liver enzymes and low platelets
HIPAA	Health Insurance Portability and Accountability Act
HMA	Heads of Medicines Agencies
IEC	independent ethics committee
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century

Abbreviation	Definition
IPTW	inverse probability of treatment weighting
IRB	institutional review board
LBW	low birth weight
LMP	last menstrual period
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract infection
MAIN	Morbidity Assessment Index for Newborns
MSM	marginal structural model
NI	non-interventional
NICU	neonatal intensive care unit
NIS	non-interventional study
PAS	post-authorization study
PASS	post-authorization safety study
PPROM	preterm premature rupture of membranes
PROM	premature rupture of membranes
PS	propensity score
R-GINDEX	Revised-Graduated Prenatal Care Utilization Index
RSV	respiratory syncytial virus
RSV-PR	CorEvitas RSV Vaccine Pregnancy Registry
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
RWD	real-world data
SAB	spontaneous abortion
SAC	scientific advisory committee

Abbreviation	Definition
SAP	statistical analysis plan
SAS	Statistical Analysis System
SGA	small for gestational age
US	United States
VRCC	CorEvitas Virtual Research Coordinating Center
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

Title: A Post-Marketing Safety Study using a Pregnancy Registry to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy

Version and Date of Protocol: Version 3.0, 28 October 2025

Main authors: Ronna L. Chan, PhD, MPH, PPD, part of Thermo Fisher Scientific, Morrisville, North Carolina, USA; Sarah MacDonald, ScD, Pfizer, Inc, New York, USA

Rationale and background: ABRYSVO™ is an RSV vaccine approved for use in pregnant individuals during late pregnancy (32 weeks 0 days through 36 weeks 6 days of gestation) to prevent lower respiratory tract disease (LRTD) and severe LRTD caused by RSV in infants from birth through 6 months of age.

This NI study (NIS) is designated as a post-authorization safety study (PASS) and is a commitment to the United States (US) Food and Drug Administration (FDA) as a post-marketing requirement to assess the safety of ABRYSVO.

Research question and objectives: The research question is: What is the risk of adverse pregnancy outcomes, including preterm birth, hypertensive disorders of pregnancy, and other maternal and neonatal/infant outcomes, following exposure to ABRYSVO between 32 weeks 0 days and 36 weeks 6 days of gestation?

The primary study objective is to estimate the risk of (1) preterm birth and (2) hypertensive disorders of pregnancy in the ABRYSVO-exposed cohort and the ABRYSVO-unexposed cohort.

The secondary study objective is to estimate the risk of the following other safety outcomes of interest in the ABRYSVO-exposed cohort and the ABRYSVO-unexposed cohort:

- Pregnancy-related outcomes: stillbirth, preterm labor without preterm delivery, PROM, PPROM, cesarean delivery, prolonged maternal duration of hospital stay
- Maternal outcomes: thrombocytopenia, GBS, other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation, maternal death
- Neonatal/infant outcomes: SGA, large for gestational age, LBW, admission to a NICU, NICU length of stay, mechanical ventilation in neonatal period, neonatal death, postnatal growth deficiency at 1 year of age

The exploratory study objective is to describe the most frequently reported maternal AEs occurring within 42 days of ABRYSVO administration between 32 weeks 0 days and 36 weeks 6 days of gestation.

Outcomes occurring before 32 weeks 0 days of gestation, including but not limited to spontaneous abortion and major congenital malformations, will not be evaluated.

Study design: This will be a US-based, observational, secondary database cohort study using primary data collected by the RSV-PR. The study will be designed to evaluate ABRYSVO exposure during weeks 32 through 36 of pregnancy (i.e., 32 weeks 0 days through 36 weeks 6 days) and the risk of subsequent pregnancy, maternal, and neonatal/infant outcomes. For

this study, the index date will be the date of ABRYSVO administration for the exposed cohort and the date of enrollment for the unexposed cohort. The risks of pregnancy-related outcomes, maternal outcomes, and neonatal/infant outcomes for participants exposed and unexposed to ABRYSVO during pregnancy will be estimated.

Population: The study population will include 2 cohorts of individuals enrolled in the RSV-PR: (1) those exposed to ABRYSVO between 32 weeks 0 days and 36 weeks 6 days and (2) those unexposed to ABRYSVO during pregnancy.

Variables: Exposure to ABRYSVO will be defined as receipt of ABRYSVO at any time between 32 weeks 0 days and 36 weeks 6 days of gestation. The primary outcomes are preterm birth and hypertensive disorders of pregnancy. Secondary pregnancy outcomes of interest include stillbirth, preterm labor without preterm delivery, PROM, PPROM, cesarean delivery, and prolonged maternal duration of hospital stay. Maternal outcomes of interest include thrombocytopenia, GBS, other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation, and maternal death. The neonatal/infant outcomes of interest are SGA, large for gestational age, LBW, admission to a NICU, NICU length of stay, mechanical ventilation in neonatal period, neonatal death, and postnatal growth deficiency at 1 year of age. Maternal AEs occurring within 42 days of ABRYSVO administration will be captured for the cohort of ABRYSVO-exposed pregnant individuals.

Variables including demographics, risk factors for the primary outcome of preterm birth, comorbidities, concomitant medications, and predictors of ABRYSVO use will be incorporated into the analyses.

Data source: This study will use data collected as part of the RSV-PR. The RSV-PR will collect data from participants and the healthcare providers (HCPs) involved in their care or the care of their infants via concise data collection forms at pre-defined timepoints during pregnancy, at pregnancy outcome, and up to 1 year of infant age.

Study Size: The study will aim to include 2,062 total participants (1,031 per cohort) to detect a minimum risk ratio of 1.5 or greater for the primary outcome of preterm birth (fewer participants are required to detect hypertensive disorders of pregnancy), assuming equal accrual (1:1) of ABRYSVO-exposed and ABRYSVO-unexposed participants, and accounting for exclusions from the analysis population and loss of effective sample size due to inverse probability of treatment weighting (IPTW).

Data analysis: Participant characteristics will be summarized with descriptive statistics for each cohort. Comparative analyses will be conducted for each outcome, if sample size permits. Supplementary analyses will be conducted that include pregnant individuals who were excluded from the analysis population (i.e., those lacking HCP confirmation of ABRYSVO exposure, pregnancy, or outcomes of interest). If sample size permits, subgroup and sensitivity analyses will be performed to examine the extent to which changes in certain methods or assumptions affect the results.

Milestones: Twelve semiannual interim progress reports will be submitted to the US FDA. The final study report and analysis is projected for 30 September 2031.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (Substantial or Administrative)	Protocol Section (s) Changed	Summary of Amendment(s)	Reason(s)
2.0	15 May 2024	Substantial	Title page	Revised version and date Updated contact information for a protocol author Added Country(ies) of study and updated footer	CBER request and clarification Study transition Protocol template update
		Substantial	Section 9.4.2 Data Collection	Added clarification regarding weekly data collection	CBER request and clarification
3.0	28 October 2025	Substantial	Title Page Section 4 Abstract Section 8 Research Questions and Objectives Table 1	Revised the terms 'premature labor' and 'premature labor without preterm delivery' to 'preterm labor without preterm delivery' Revised the term 'NICU duration of stay' to 'NICU length of stay'	To align the terms used and use the most accurate terms
		Substantial	Title Page Section 4 Abstract Section 8 Research Questions and Objectives	Added the ABRYSVO-unexposed cohort to the study objectives	To reflect the planned analyses in the unexposed cohort
		Substantial	Section 9.2.1 Inclusion Criteria	Re-categorized the ABRYSVO inclusion criteria as a PASS-specific criterion rather than an RSV-PR criteria	To accurately reflect the RSV-PR eligibility criteria

Version Identifier	Date	Amendment Type (Substantial or Administrative)	Protocol Section (s) Changed	Summary of Amendment(s)	Reason(s)
		Substantial	Section 9.2.1 Inclusion Criteria	Added an inclusion criterion for the PASS, ABRYSVO-unexposed must have a gestational age between 32 weeks 0 days and 36 weeks 6 days at enrollment	To align the risk period between the exposed and unexposed cohorts
		Substantial	Section 9.3.2 Outcomes Table 1	Added 'NICU length of stay' definition	NICU length of stay was missing from the table
		Substantial	Section 9.3.2 Outcomes Table 1	Added column for the analysis population (denominator), and clarified additional restrictions for exclusion for some outcomes including end of follow-up	To further clarify the risk window for study outcomes and to ensure only outcomes that occur after index date are included in the prevalence calculation
		Substantial	Section 9.3.3 Variables	Added the following variables: calendar month or other seasonality variable, gestational age at vaccination, number of fetuses	To add variables that were inadvertently missing from the prior version.
		Substantial	Section 9.5 Study Size	Clarified that the target sample size is among the main analysis population	To clarify the definition of the population for the target sample size
		Substantial	Section 9.5 Study Size	Further clarified the model and software used for the study size calculation	To clarify how Table 2 was generated.

Version Identifier	Date	Amendment Type (Substantial or Administrative)	Protocol Section (s) Changed	Summary of Amendment(s)	Reason(s)
		Substantial	Section 9.7.1 Main Analysis Population Section 9.7.5 Supplementary Analyses	Revised text on the definition of valid participants: • Revised definition of valid criteria for healthcare providers (HCPs) confirmation of outcomes of interest criteria to 'at least one outcome of interest' • Added a criterion for derived gestational age at index date	To further refine definition of valid participants and exclude participants outside the eligibility window for gestational age at index date
		Substantial	Section 9.7.1 Main Analysis Population Section 9.7.5 Supplementary Analyses	Added a summary of the analysis populations (denominators) that will be used for the study outcomes	To further clarify the different denominators used for prevalence calculation of outcomes
		Substantial	Section 9.7.1.1 Participants Lost to Follow-up	Added details for determining when a participant is lost to follow-up	To further refine and clarify the definition of lost to follow-up
		Substantial	Section 9.7.2 Cohort Assignment, Risk Window, Participant Follow-up, and Censoring	Added further details regarding cohort assignment, risk window, follow-up, and censoring to provide a summary of all possible scenarios for participants enrolling in the study and to further clarify cohort assignment, risk window, and follow-up	To align with the edits in the SAP
		Substantial	Section 9.7.4.1 IPTW Derivation	Revised the text on IPTW to further clarify the methods and number of	To clarify the analysis plan

Version Identifier	Date	Amendment Type (Substantial or Administrative)	Protocol Section (s) Changed	Summary of Amendment(s)	Reason(s)
				weights used for estimating weighted risk ratios using IPTW	
		Substantial	Section 9.7.4.2 MSM Methodology	Revised the text on MSM methodology to further clarify the types of models used for comparative analysis	To clarify the analysis plan
		Substantial	Section 9.7.6 Sensitivity Analyses	Clarified analysis details for the sensitivity analysis examining the risk of preterm delivery	To clarify the analysis plan
		Substantial	Section 9.7.6 Sensitivity Analyses	Added the sensitivity analysis excluding prevalent ABRYSVO-exposed participants. Clarified that this analysis will include both descriptive and inferential data	To align with the SAP
		Substantial	Section 9.7.6 Sensitivity Analyses	Added a new sensitivity analysis that will perform time-based matching on gestational age at date of ABRYSVO vaccination	To minimize potential time-related bias
		Substantial	Section 9.9 Limitations of the Research Methods	Added a discussion of time-based biases	To align with the SAP
		Administrative	All	Editorial corrections and clarifications	To improve clarity

6. MILESTONES

Anticipated milestone dates are shown below.

Milestone	Planned Date
Start of data collection[1]	31 July 2024
End of data collection[2]	30 September 2030
Interim report 1	30 November 2024
Interim report 2	31 May 2025
Interim report 3	30 November 2025
Interim report 4	31 May 2026
Interim report 5	30 November 2026
Interim report 6	31 May 2027
Interim report 7	30 November 2027
Interim report 8	31 May 2028
Interim report 9	30 November 2028
Interim report 10	31 May 2029
Interim report 11	30 November 2029
Interim report 12	31 May 2030
Registration in the HMA-EMA Catalogue of RWD studies	Prior to the start of data collection
Final study report	30 September 2031

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

1 The study will use secondary data collected for the RSV-PR. The start of data collection is defined as the date of data extraction for the first interim study report.

2 The end of data collection is defined as the date of data extraction for the final study report.

7. RATIONALE AND BACKGROUND

RSV is an ubiquitous pathogen that poses a substantial public health burden, particularly among infants and young children (Munro et al., 2023). According to global estimates from 2015, there were 33 million episodes of RSV-related acute lower respiratory infections (ALRIs) that resulted in about 3 million hospital admissions and 59,600 in-hospital deaths in children under 5 years of age (Shi et al., 2017). In the first 2 years of life, nearly 100% of children are infected with RSV (Griffin et al., 2020; Li et al., 2022), 10% will go to see a doctor and, of these, 1 in 10 will require hospitalization (Kandeil et al., 2020). While RSV infections typically result in mild-to-moderate respiratory symptoms in healthy individuals, they can lead to severe LRTD and, in some instances, life-threatening respiratory distress (Colosia et al., 2023). This risk is notably heightened among infants with underlying cardiopulmonary conditions or those living in regions with limited access to effective healthcare systems.

Despite the significant disease burden posed by RSV, no authorized vaccine had previously been available for the prevention of RSV disease in infants. In the absence of a vaccine, strategies for RSV prevention primarily revolved around the use of humanized monoclonal antibodies, such as palivizumab (Swedish Orphan Biovitrum AB, 2021) and nirsevimab (AstraZeneca, 2023), which are authorized for the prevention of RSV-related LRTD in neonates and infants. However, these interventions have limitations, including the need for multiple doses and cost considerations, thus necessitating alternative preventive approaches.

On August 21, 2023, the US FDA granted approval for ABRYSVO™ to be used in pregnant individuals during late pregnancy (32 weeks 0 days through 36 weeks 6 days of gestation) to prevent LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age (Pfizer, 2023), and on September 22, 2023, the Advisory Committee on Immunization Practices (ACIP) voted to recommend the vaccine for seasonal administration (Centers for Disease Control and Prevention (CDC), 2023a; 2023b). Subsequently, the American Academy of Family Physicians, American College of Nurse-Midwives, American College of Obstetricians and Gynecologists, Association of Women's Health, Obstetric and Neonatal Nurses, National Association of Nurse Practitioners in Women's Health, and the Society for Maternal-Fetal Medicine have collectively supported the Centers for Disease Control and Prevention's (CDC's) recommendations for RSV vaccination during pregnancy to prevent lower respiratory tract infections (LRTIs) in infants (American Academy of Family Physicians (AAFP), 2023; American College of Obstetricians and Gynecologists (ACOG), 2023).

The introduction of ABRYSVO as a preventive measure during late pregnancy raises important questions regarding its safety profile, particularly concerning pregnancy, maternal, and neonatal/infant outcomes. While the FDA's approval represents a pivotal step forward, there is a need for comprehensive and rigorous post-licensure safety assessments. This study protocol, developed in accordance with the FDA 2019 Guidance for Industry: Postapproval Pregnancy Safety Studies (FDA, 2019), outlines a systematic and comprehensive evaluation of the safety of ABRYSVO when administered between 32 weeks 0 days and 36 weeks 6 days of gestation, with a particular focus on assessing the risk of preterm birth, hypertensive disorders of pregnancy, and other adverse outcomes of interest, using data from the RSV-PR.

The successful completion of this study will not only contribute valuable insights into the safety of ABRYSVO, but will also facilitate informed decision-making for HCPs and pregnant individuals considering the use of this vaccine as a preventive strategy against RSV-related severe LRTD in infants. This NIS is designated as a PASS and is a commitment to the US FDA as a post-marketing requirement.

8. RESEARCH QUESTION AND OBJECTIVES

The research question is: what is the risk of adverse pregnancy outcomes, including preterm birth, hypertensive disorders of pregnancy, and other maternal and neonatal/infant outcomes, following exposure to ABRYSVO between 32 weeks 0 days and 36 weeks 6 days of gestation?

The primary study objective is to estimate the risk of (1) preterm birth and (2) hypertensive disorders of pregnancy in the ABRYSVO-exposed cohort and the ABRYSVO-unexposed cohort.

The secondary study objective is to estimate the risk of the following other safety outcomes of interest in the ABRYSVO-exposed cohort and the ABRYSVO-unexposed cohort:

- Pregnancy-related outcomes: stillbirth, preterm labor without preterm delivery, PROM, PPROM, cesarean delivery, prolonged maternal duration of hospital stay
- Maternal outcomes: thrombocytopenia, GBS, other immune-mediated demyelinating conditions, polyneuropathies, atrial fibrillation, maternal death
- Neonatal/infant outcomes: SGA, large for gestational age, LBW, admission to NICU, NICU length of stay, mechanical ventilation in neonatal period, neonatal death, postnatal growth deficiency at 1 year of age

The exploratory study objective is to describe the most frequently reported maternal AEs occurring within 42 days of ABRYSVO administration between 32 weeks 0 days and 36 weeks 6 days of gestation.

Outcomes occurring before 32 weeks 0 days of gestation, including but not limited to spontaneous abortion and major congenital malformations, will not be evaluated.

9. RESEARCH METHODS

9.1. Study Design

This will be a US-based, observational, secondary database cohort study using primary data collected by the RSV-PR. The study will be designed to evaluate the risk of subsequent pregnancy, maternal, and neonatal/infant outcomes among pregnant individuals exposed to ABRYSVO between 32 weeks 0 days through 36 weeks 6 days of gestational age and among pregnant individuals unexposed to ABRYSVO between 32 weeks 0 days through 36 weeks 6 days of gestational age.

The risks of pregnancy-related outcomes, maternal outcomes, and neonatal/infant outcomes will be calculated for participants exposed and unexposed to ABRYSVO during pregnancy.

The RSV-PR will collect data from enrolled pregnant individuals and the HCPs involved in their care or the care of their infants, if applicable. The RSV-PR will be observational in design; the schedule of office visits and all treatment regimens, including vaccinations, will be determined by the patient's treating HCPs. Pregnancy outcomes and exposure information will be assessed throughout pregnancy, and neonatal/infant outcomes will be assessed throughout the infant's first year of life. Maternal outcomes (i.e., hypertensive disorders of pregnancy, thrombocytopenia, GBS, polyneuropathies [excluding GBS], other immune-mediated demyelinating conditions, atrial fibrillation, and maternal death) will be examined up to 6 weeks (42 days) after vaccination (if ABRYSVO-exposed) or enrollment (if ABRYSVO-unexposed). Baseline characteristics will be assessed at enrollment.

9.2. Setting

The RSV-PR will launch after institutional review board (IRB) approval of the RSV-PR protocol. The PASS will use data that are collected as part of the RSV-PR. As described in Section 6, the start of data collection for this PASS, which is defined as the date of data extraction for the interim report, will be in July 2024; the end of data collection, which is defined as the date of data extraction for the final report, will be in February 2030.

9.2.1. Inclusion Criteria

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

1. Enrolled in the RSV-PR, for which the following inclusion criteria apply:
    a. A resident of the US at enrollment
    b. 18 to 50 years of age at enrollment
    c. Self-reported gestational age of ≥32 weeks 0 days at enrollment
    d. Evidence of a personally signed and dated informed consent document or, upon waiver of written consent by the relevant IRB/independent ethics committee (IEC), verbal consent indicating that the individual (or a legally acceptable representative) has been informed of all pertinent aspects of the study
    e. Authorization obtained for the relevant HCP(s) to provide data to the registry
    f. Contact information available (for participant and HCPs)
2. If exposed to ABRYSVO, receipt of ABRYSVO between 32 weeks 0 days and 36 weeks 6 days of gestation
3. If unexposed to ABRYSVO, gestational age at enrollment between 32 weeks 0 days and 36 weeks 6 days of gestation

9.2.2. Exclusion Criteria

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

1. Excluded from the RSV-PR, for which the following exclusion criteria apply:
    a. Receipt of an RSV vaccine during pregnancy before 32 weeks 0 days gestation
    b. Multi-fetal pregnancy
    c. Enrolled in the RSV-PR with a previous pregnancy

9.3. Variables

Variables for the exposures, outcomes, demographics, and clinical characteristics of interest are included below. Data on these variables will be collected via maternal and HCP data collection forms in accordance with the procedures established for the RSV-PR. Details on the collection of each datapoint, including reporter(s), timepoint(s) for collection, and format of question/item, will be outlined in the statistical analysis plan (SAP).

9.3.1. Exposure

The RSV-PR will collect detailed information on exposure to ABRYSVO, including date of vaccination, gestational age at vaccination, and brand of vaccine.

9.3.2. Outcomes

Table 1 presents the definitions of the outcomes of interest. Additional information on outcome ascertainment is provided in the footnotes.

Table 1. Pregnancy and Neonatal/Infant Outcomes

Outcome	Clinical Definition	Start of Follow-up	Outcome-Specific End of Follow-up[a]	Analysis Population (denominator)
Pregnancy-related Outcomes				
Preterm birth (primary outcome)	Live birth before 37 weeks 0 days of gestation	Index date	Earliest of the following: [a] • Date of occurrence of preterm birth (i,e., live birth before 37 weeks 0 days of gestation) • 36 weeks 6 days of gestation (latest gestational age at which a preterm birth can occur)	Main analysis population (live births)

Table 1. Pregnancy and Neonatal/Infant Outcomes

Outcome	Clinical Definition	Start of Follow-up	Outcome-Specific End of Follow-up[a]	Analysis Population (denominator)
Hypertensive disorders of pregnancy (primary outcome)	See definitions for specific conditions below (gestational hypertension, preeclampsia, eclampsia, hemolysis, elevated liver enzymes and low platelets [HELLP] syndrome, chronic hypertension superimposed with preeclampsia/eclampsia, postpartum hypertension)	Index date	Earliest of the following: [a] • Date of occurrence of either gestational hypertension, preeclampsia/eclampsia, HELLP syndrome, or postpartum hypertension • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of hypertensive disorders of pregnancy during the current pregnancy prior to index date
Gestational hypertension	New-onset hypertension on or after 20 weeks 0 days of gestation	Index date	Earliest of the following: [a] • Date of occurrence of gestational hypertension • Pregnancy outcome date • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of gestational hypertension during the current pregnancy prior to index date
Preeclampsia/ eclampsia	Preeclampsia: New-onset hypertension on or after 20 weeks 0 days of 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	Index date	Earliest of the following: [a] • Date of occurrence of preeclampsia/eclampsia • Pregnancy outcome date • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of preeclampsia/eclampsia during the current pregnancy prior to index date

Table 1. Pregnancy and Neonatal/Infant Outcomes

Outcome	Clinical Definition	Start of Follow-up	Outcome-Specific End of Follow-up[a]	Analysis Population (denominator)
HELLP syndrome	Variant of preeclampsia with hemolysis, elevated liver enzymes, and low platelet count	Index date	Earliest of the following: [a] • Date of occurrence of HELLP syndrome after index date • Pregnancy outcome date • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of HELLP syndrome during the current pregnancy prior to index date
Chronic hypertension superimposed with preeclampsia/ eclampsia	Development of preeclampsia among those with pre-existing hypertension	Index date	Earliest of the following: [a] • Date of occurrence of chronic hypertension superimposed with preeclampsia/eclampsia • Pregnancy outcome date • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of chronic hypertension superimposed with preeclampsia/eclampsia during the current pregnancy prior to index date
Postpartum hypertension	Pregnancy-associated hypertension occurring after delivery	Delivery date	Earliest of the following: [a] • Date of occurrence of postpartum hypertension • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of postpartum hypertension during the current pregnancy prior to index date
Cesarean delivery	Surgical delivery of an infant through incision in the mother's abdomen and uterus	Index date	Earliest of the following: [a] • Pregnancy outcome date	Main analysis population (pregnancies)

Table 1. Pregnancy and Neonatal/Infant Outcomes

Outcome	Clinical Definition	Start of Follow-up	Outcome-Specific End of Follow-up[a]	Analysis Population (denominator)
Preterm labor without preterm delivery	Presence of regular uterine contractions that occur without a live birth/stillbirth delivery before 37 weeks 0 days of gestation	Index date	Earliest of the following: [a] • Date of occurrence of preterm labor without preterm delivery • 36 weeks 6 days of gestation (latest gestational age at which a preterm labor can occur) • Pregnancy outcome date	Main analysis population (pregnancies) excluding pregnancies with preterm labor during the current pregnancy prior to index date
PROM	Rupture of membranes prior to the onset of labor	Index date	Earliest of the following: [a] • Date of occurrence of PROM • Pregnancy outcome date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of PROM during the current pregnancy prior to index date
PPROM	Rupture of membranes prior to the onset of labor that occurs before 37 weeks 0 days of gestation	Index date (<37 weeks 0 days of gestation)	Earliest of the following: [a] • Date of occurrence of PPROM • Pregnancy outcome date • 36 weeks 6 days of gestation (latest gestational age at which PPROM can occur)	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of PPROM during the current pregnancy prior to index date
Stillbirth	Spontaneous pregnancy loss on or after 20 weeks 0 days of gestation	Index date	Earliest of the following: [a] • Date of occurrence of stillbirth • Pregnancy outcome date	Main analysis population (pregnancies)

Table 1. Pregnancy and Neonatal/Infant Outcomes

Outcome	Clinical Definition	Start of Follow-up	Outcome-Specific End of Follow-up[a]	Analysis Population (denominator)
Prolonged maternal duration of hospital 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	Delivery admission date	• Delivery hospitalization discharge date	Main analysis population (pregnancies)
Maternal Outcomes				
Thrombocytopenia	<150,000/µL of circulating blood	Index date	Earliest of the following: [a] • Date of occurrence of thrombocytopenia • 42 days after index date[b]	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of thrombocytopenia any time prior to index date
GBS	Findings on cerebrospinal fluid (CSF) analysis include albuminocytologic dissociation (elevation in CSF protein [>0.55 g/L]) without an elevation in white blood cells	Index date	Earliest of the following: [a] • Date of occurrence of GBS • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of GBS any time prior to index date
Polyneuropathies, excluding GBS	Symmetric distal sensory loss, burning sensations, or weakness	Index date	Earliest of the following: [a] • Date of occurrence of polyneuropathies, excluding GBS • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of polyneuropathies (excluding GBS) any time prior to index date

Table 1. Pregnancy and Neonatal/Infant Outcomes

Outcome	Clinical Definition	Start of Follow-up	Outcome-Specific End of Follow-up[a]	Analysis Population (denominator)
Other immune-mediated demyelinating conditions	Including: acute disseminated encephalitis and encephalomyelitis, acute transverse myelitis in demyelinating disease of central nervous system, optic neuritis, neuromyelitis optica, and other acute demyelinating diseases	Index date	Earliest of the following: [a] • Date of first occurrence of other immune-mediated demyelinating conditions[c] • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of other immune-mediated demyelinating conditions any time prior to index date
Atrial fibrillation	Confirmation by 12-lead electrocardiogram	Index date	Earliest of the following: [a] • Date of occurrence of atrial fibrillation after index date • 42 days after index date	Main analysis population (pregnancies) excluding pregnancies with a diagnosis of atrial fibrillation any time prior to index date
Maternal death	Maternal death	Index date	Earliest of the following: [a] • Date of maternal death • 42 days after index date	Main analysis population (pregnancies)
Most frequently reported maternal AEs (exploratory outcome)	Maternal AEs reported in at least 10% of the ABRYSVO-exposed cohort (descriptive outcome)	Index date	• 42 days after index date	Main analysis population (pregnancies)
Neonatal/Infant Outcomes				
SGA	<10th percentile of birth weight for gestational age[d]	Birth	• Date of birth	Main analysis population (live births)
Large for gestational age	Birthweight >90th percentile for gestational age	Birth	• Date of birth	Main analysis population (live births)
LBW	Birth weight <2,500g	Birth	• Date of birth	Main analysis population (live births)

Table 1. Pregnancy and Neonatal/Infant Outcomes

Outcome	Clinical Definition	Start of Follow-up	Outcome-Specific End of Follow-up[a]	Analysis Population (denominator)
Admission to a NICU	Admission to a neonatal intensive (critical) care unit	Birth	Earliest of the following (for the infant): [a] • Date of NICU admission • 28 days after date of birth	Main analysis population (live births)
NICU length of stay	Number of days of stay in the NICU	NICU admission date	Earliest of the following (for the infant): [a] • NICU discharge date	Main analysis population (live births) that were admitted to the NICU
Mechanical ventilation in the neonatal period	Use of an external device to assist/control breathing	Birth	Earliest of the following (for the infant): [a] • Date of first mechanical ventilation • 28 days after date of birth	Main analysis population (live births)
Neonatal death	Infant death during the 28 days after birth	Birth	Earliest of the following (for the infant): [a] • Date of neonatal death • 28 days after date of birth	Main analysis population (live births)
Postnatal growth deficiency at 1 year of age	Weight, length, or head circumference in <10th percentile for sex and chronological age using standard growth[e] charts	Birth	• 12 months after date of birth	Main analysis population (live births with follow-up data at 12 months of age)

a. See Section 9.7.2 for additional censoring events.
b. With the exception of "thromboembolic events associated with thrombocytopenia" and "thrombotic thrombocytopenic purpura," which will be assessed up to 28 days after the index date, per published literature and the BEST Initiative (FDA, 2021; Struyf et al., 2023).
c. With the exception of "acute disseminated encephalitis and encephalomyelitis", which will be assessed between 5 days after the index date and 28 days after the index date, per prior literature and Brighton Collaboration recommendations (Rowhani-Rahbar et al., 2012; Sejvar et al., 2011).
d. For the determination of SGA, the registry will utilize the sex-specific international growth reference standards from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) for those born between 24 weeks 0 days and 42 weeks 6 days gestational weeks (Villar et al., 2016; Villar et al., 2014). The INTERGROWTH-21st standards are the latest-available global reference standards, representing contemporary information from an international, multiethnic, diverse population, and have been specifically developed for modern research.

Table 1. Pregnancy and Neonatal/Infant Outcomes

Outcome	Clinical Definition	Start of Follow-up	Outcome-Specific End of Follow-up[a]	Analysis Population (denominator)

e. Postnatal growth deficiency, as part of routine care, will be evaluated at 12 months of infant age; deficiencies in weight, length, and head circumference will be evaluated separately. For the determination of postnatal growth deficiency, the registry will utilize the sex-specific international growth reference standards from the World Health Organization (WHO) for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age (Centers for Disease Control and Prevention (CDC), 2010).

9.3.3. Variables

In accordance with the FDA and the Agency for Healthcare Research and Quality (AHRQ) guidance (FDA, 2019; Gliklich et al., 2020), potential confounders and other covariates collected as part of the RSV-PR will include maternal age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, and prenatal tests.

The following variables will be collected (or derived from collected data):

- Geographic region
- Calendar year at conception
- Calendar month or other seasonality variable (season at enrollment)
- Maternal age at conception
- Maternal race
- Maternal ethnicity
- Marital status
- Maternal insurance status (commercial insurance, Medicaid insurance, or uninsured)
- Proxies for maternal socioeconomic status, including maternal education, employment status, and income
- Maternal pre-pregnancy body mass index, calculated from pre-pregnancy weight and height
- Maternal stress rating
- Gestational age at registry enrollment
- Gestational age at vaccination

- Gestational age at pregnancy outcome
- Method of conception
- Proxies for maternal prenatal care, including number of prenatal care visits and timing of first prenatal care visit
- Assisted reproductive technology (ART) in 12 months prior to pregnancy
- Short interpregnancy interval (<6 months)
- Previous gynecological procedures (e.g., cold knife conization, electrosurgical excision, procedural abortion)
- Fetal/infant sex and race/ethnicity
- Concurrent maternal medical conditions, including chronic anemia, antiphospholipid syndrome, thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune/inflammatory diseases, depression and other psychiatric disorders, hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (e.g., congenital uterine abnormalities, leiomyoma)
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including gestational diabetes, hypertensive disorders of pregnancy (gestational hypertension, preeclampsia/eclampsia, HELPP), preterm labor, placental abruption, incompetent cervix, early bleeding, and shortened cervix after 22 weeks of gestation
- Prenatal testing in current pregnancy, including whether any prenatal tests have been performed, name of test (e.g., ultrasound, amniocentesis, maternal serum screening including maternal serum alpha-fetoprotein, chorionic villus sampling, fetal fibronectin, insulin-like growth factor-binding protein 4, and sex hormone-binding protein), type of test (diagnostic or screening), gestational age at test, and whether the test indicated any abnormal findings
- The Revised-Graduated Prenatal Care Utilization Index (R-GINDEX) (Alexander, 2001)
- The Morbidity Assessment Index for Newborns (MAIN) score (Verma et al., 2005)
- Characteristics of previous pregnancies:
    - Number of previous pregnancies
    - Number of fetuses

  - Previous pregnancy outcomes (spontaneous abortion [SAB], stillbirth, elective termination, live birth)
  - Previous pregnancy complications
  - Characteristics of previous live births (preterm birth, SGA)
  - Previous fetus/infant with congenital malformations (major and minor)

- Family history of congenital malformations (major and minor)
- Maternal exposure to other drugs or biological products, including prescription and non-prescription drugs, dietary supplements, and vaccines during pregnancy and gestational age at exposure
- Maternal exposure to prenatal vitamins and folic acid during pregnancy
- Maternal exposure to tobacco, alcohol, marijuana, and recreational or illicit drugs during pregnancy and timing of exposure

Of note, the SAP will outline the methods and indexes used to derive variables from the collected data; this includes how certain data points will be used to derive composite index scores using validated tools.

9.3.4. Pregnancy Period

As per the American College of Obstetricians and Gynecologists (ACOG), gestational age and the expected date of delivery (EDD) should be determined by the obstetric HCP as soon as data are obtained regarding the last menstrual period (LMP), first accurate ultrasound, or both. ACOG considers ultrasound measurement of the embryo or fetus in the first trimester (up to and including 13 weeks 6 days of pregnancy) to be the most accurate method to establish or confirm gestational age and discourages against changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before 22 weeks 0 days of pregnancy to confirm or revise the EDD should be considered suboptimally dated. If the pregnancy resulted from ART, the obstetric HCP should use the ART-derived gestational age (e.g., based on the age of the embryo and the date of transfer) to determine EDD. ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes (American College of Obstetricians and Gynecologists (ACOG), 2017).

Based on ACOG's recommendations, the RSV-PR will collect the EDD from the obstetric HCP, and the HCP will report whether the EDD was calculated based on LMP, ultrasound, or ART data. If ultrasound-based, it will be recorded whether the ultrasound was performed before 14 weeks 0 days, before 22 weeks 0 days, or at 22 weeks 0 days of pregnancy or later. EDD data will be collected on each data collection form throughout pregnancy. If the HCP reports a corrected EDD on subsequent forms that is different from the EDD initially reported, the registry will evaluate whether a correction is appropriate, based on the timing of

the correction and the methods used to determine the corrected EDD, and will follow-up with the HCP, if needed.

The RSV-PR will conform to ACOG recommendations for determining the "best" EDD, and that EDD will be used to calculate first day of LMP, gestational age, and date of conception (DOC), as follows:

- First day of LMP, defined as 0 weeks 0 days of gestation, will be calculated as EDD minus 280 days (40 weeks).
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP:
  - 0 weeks 0 days to 13 weeks and 6 days of gestation will be considered the first trimester.
  - 14 weeks 0 days to 27 weeks and 6 days of gestation will be considered the second trimester.
  - 28 weeks 0 days of gestation to pregnancy outcome will be considered the third trimester.
- DOC, defined as 2 weeks 0 days of gestation, will be calculated as first day of LMP plus 14 days (2 weeks).

If the EDD is not reported by the HCP but LMP data are available, the RSV-PR will use first day of LMP to calculate EDD, gestational age, and DOC.

9.4. Data Source

This study will use data that are collected as part of the RSV-PR. The RSV-PR will be established in 2024 and will be a US-based, prospective, observational cohort study designed to evaluate RSV vaccine exposure during pregnancy and risk of subsequent pregnancy, maternal, and neonatal/infant outcomes, among other research objectives.

9.4.1. Enrollment

Enrollment in the RSV-PR will be voluntary and will require informed consent by the pregnant individual. Eligible individuals will initiate self-enrollment using the RSV-PR website or the toll-free number. To increase data validity, specific efforts will be made to enroll pregnant individuals as soon as possible beginning at 32 weeks 0 days of gestation. The study information, informed consent form, and data collection forms will be available in English and Spanish. Active recruitment strategies will also be used, including direct mailings to HCPs, advertisements on social media, and dissemination of study results in professional meetings. In addition, approximately 10 prominent birthing centers in the US will be involved to support awareness activities for the RSV-PR. Participants will be able to enroll regardless of whether they or their HCPs are affiliated with one of these sites.

9.4.2. Data Collection

The RSV-PR will collect data from participants and the HCPs involved in their care or the care of their infants via concise data collection forms at pre-defined timepoints at: enrollment, 42 days post index date, during pregnancy (weekly from participants), at pregnancy outcome, and up to 1 year of infant age. Participants and their HCPs may provide data to the registry online, via phone, or via fax/email. Data collection procedures will be standardized for all enrolled pregnant individuals irrespective of their ABRYSVO exposure and study cohort assignment. HCPs who serve as reporters to the registry will be instructed to transcribe data that are readily available in the participants' medical records into the data collection forms.

The RSV-PR will conduct active monitoring for study outcomes through the data collection forms at each designated timepoint.

It is anticipated that the majority of obstetric data will be collected from the pregnant individual's obstetric HCP (e.g., obstetrician, family practitioner, general practitioner who provides care during pregnancy), and that the majority of pediatric data will be collected from the infant's pediatric HCP (e.g., pediatrician, family practitioner, general practitioner who provides pediatric care). The registry may also request data from other HCPs involved in the participant's or infant's care (e.g., prescriber, specialist) or from additional HCPs who were not identified at enrollment (e.g., if a participant does not know who their pediatric HCP will be at the time of enrollment) after appropriate medical release is obtained from the participant.

In cases where participants or their offspring experience a safety event of interest, additional data may be provided by participants and/or HCPs through targeted data collection forms.

9.4.3. Scientific Advisory Committee (SAC)

An important aspect of the RSV-PR will be the SAC, which will be composed of experts in maternal-fetal medicine, infectious diseases, epidemiology, and biostatistics. The SAC will operate according to the stipulations and guidelines established in the SAC Charter. SAC members will receive interim RSV-PR reports. Each year, completion of one of these reports may be followed by an annual SAC meeting. The SAC responsibilities will include, among others, to assist the RSV-PR study team in resolving operational issues and to suggest strategies for increased registry awareness and participant engagement. However, the SAC will not receive ABRYSVO-specific interim reports nor the ABRYSVO-specific final study report, unless specifically requested by the SAC Chairperson and approved by Pfizer.

9.5. Study Size

Table 2 presents the sample sizes that will be required to detect various minimum detectable risk ratios of the primary outcomes. These sample sizes, which represent the main analysis population, were estimated using the procedures to estimate sample sizes for mixed models. As shown in the table, 1,650 total participants (825 per cohort) will be needed to detect a minimum risk ratio of 1.5 or greater for the primary outcome of preterm birth (fewer participants are required to detect hypertensive disorders of pregnancy), assuming equal accrual (1:1) of ABRYSVO-exposed and ABRYSVO-unexposed participants. To account for exclusions from the analysis population and loss of effective sample size due to IPTW

weighting, a 20% inflation factor was applied. As a result, it is predicted that 2,062 total participants (1,031 per cohort) will need to be included in the main analysis population for the study to detect a minimum risk ratio of 1.5 or greater.

Table 2. Total Sample Size (ABRYSVO-exposed + ABRYSVO-unexposed) Needed to Detect a Range of Risk Ratios

Primary Outcome	Reference Risk	Minimum Detectable Risk Ratio*		
		1.5	2.0	3.0
Preterm birth (Martin et al., 2021)	8.5%	1650	484	152
Hypertensive disorders of pregnancy (Ford et al., 2022)	13.0%	1016	290	88

*Alpha 0.05, 80% power, equal number of exposed and unexposed patients. Binomial family generalized linear mixed model with a logit-link. Sample sizes shown are before the 20% inflation factor that is used to account for the reduction in effective sample size due to IPTW weighting. PASS version 16 was used, with the Mixed Models Test for Two Proportions in a 2-Level Hierarchical Design.

9.6. Data Management

The study will be conducted using data collected for the RSV-PR. Data will be collected through streamlined data collection forms submitted by participants and HCPs. The database will be designed and maintained according to CorEvitas' standard data management procedures.

For this study, statistical analyses will be conducted using SAS®.

9.7. Data Analysis

Detailed methodology for the 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 analyses outlined in the SAP may be modified versions of those outlined in this protocol; any major modifications of primary outcome definitions or their analyses would be reflected in a protocol amendment. Details will also be provided in the SAP on the collection of each datapoint, including reporter(s), timepoint(s) for collection, and format of question/item.

9.7.1. Main Analysis Population

The main analysis population will include participants who meet the following criteria:

- Are valid,[1] defined as:
    - HCP confirmation of exposure status, pregnancy status, and at least 1 outcome of interest; and
    - Have a derived gestational age at index between 32 week 0 days and 36 weeks 6 days, based on HCP report of EDD, or LMP if EDD is not available.
- Are not lost to follow-up (Section 9.7.1.1)

[1] Invalid participants will be included in supplementary analyses (Section 9.7.5)

Within the Main Analysis Population, the following three subsets of participants will be evaluated, depending on the outcome of interest:

- Pregnancies
- Live births
- Live births with 12 months of follow-up

Within each of these subsets, outcome-specific exclusions may also be applied (see Table 1).

9.7.1.1. Participants Lost to Follow-up

An enrolled participant will be considered lost to follow-up if HCP confirmation of the pregnancy outcome (e.g., live birth, stillbirth) follow-up information is never obtained or is unavailable within 3 months after all HCP follow-up attempts have been exhausted.

Further, if a pregnancy is missing HCP confirmation of a study outcome that the participant self-reported (e.g., atrial fibrillation), they will be excluded from the main analysis for that outcome, but will be included in a supplementary analysis (see Section 9.7.5)

Infants will be defined as lost to follow-up if the HCP-reported infant outcomes are never obtained or are unavailable within 3 months after all HCP follow-up attempts have been exhausted. Infants who are lost to follow-up will not contribute to the analysis of infant outcomes after the point when they were lost to follow-up, but will still have their pregnancy-related information included in the main analysis population of pregnancies.

9.7.2. Cohort Assignment, Risk Window, Participant Follow-up and Censoring

The cohorts will be assigned as follows:

- Participants who receive ABRYSVO on enrollment date will contribute to the exposed cohort starting at the date of vaccination (index date). They will be followed until the end of the outcome specific risk window or censoring event. Depending on time of index date and date of delivery, follow-up may extend past delivery for some outcomes (see Table 1 for outcome-specific end of follow-up).

- Participants who receive ABRYSVO prior to enrollment will contribute to the exposed cohort starting at the date of vaccination (index date). Their follow-up time will include pre-enrollment time and will continue until the end of the outcome specific risk window or censoring event. These participants are prevalent users and will be included in the primary analysis but excluded in a sensitivity analysis (see Section 9.7.6)

- Participants who do not receive ABRYSVO will contribute to the unexposed cohort starting at the date of enrollment (index date) until the end of the outcome specific risk window or censoring event (e.g., receipt of non-ABRYSVO RSV vaccine or receipt of ABRYSVO outside of the indexing period).

- Participants who are unexposed to ABRYSVO at enrollment (index date) but who later receive ABRYSVO prior to 37 weeks 0 days of gestation will contribute to both the exposed cohort and unexposed cohorts:
  - They will contribute to the unexposed cohort starting with the date of enrollment (index date 1) and will be censored at 1 day prior to the date of vaccination (index date 2).
  - They will contribute to the exposed cohort starting with the date of vaccination (index date 2).
  - They will be followed until the end of the outcome specific risk window or censoring event.

Finally, since this study aims to evaluate the potential effect of ABRYSVO vaccine on the outcomes of interest, and not the cumulative effect of the vaccine, the risk window for the outcomes of interest for participants who switch exposure status (enroll as unexposed and become exposed) will be reset on the second index date (vaccination date).

Censoring events for end-of-cohort contribution include:

- For maternal and pregnancy-related outcomes:
  - Maternal death
  - Pregnancy lost to follow-up
  - Receipt of a non-ABRYSVO RSV vaccine
  - For participants who enroll as ABRYSVO-unexposed: receipt of ABRYSVO after 36 weeks 6 days of gestation
  - For participants who enroll as ABRYSVO-unexposed: post-enrollment vaccination with ABRYSVO (described above)[2]
- For neonatal/infant outcomes:
  - Infant death
  - Infant lost to follow-up

In addition, for each outcome of interest, additional outcome-specific censoring criteria apply (see Table 1).

[2] Participants who enroll as RSV-vaccine-unexposed and subsequently receive ABRYSVO prior to week 37 will have both episodes used in the analysis. The unexposed episode will end on the day before the ABRYSVO vaccination and will be considered censored. The exposed episode will start on the day of the vaccination.

9.7.3. Descriptive Characteristics

Participant characteristics (including the covariates listed in Section 9.3.3) will be summarized with descriptive statistics for each cohort. Characteristics will be described for the overall enrolled population as well as those included and excluded from the main analysis population (overall and by reason for exclusion).

The number of observations, median, mean, standard deviation, minimum, and maximum will be reported for each continuous variable. The frequency and percentage per category will be reported for each categorical variable.

In addition, baseline, obstetrical, and neonatal clinical characteristics will be described for preterm and full-term infants.

9.7.4. Comparative Analyses

Comparative analyses will be conducted for all primary outcomes and any secondary outcomes where there is adequate power to compare the risk between ABRYSVO-exposed and the unexposed cohort. Adjusted risk ratios between cohorts will be estimated using inverse probability-weighted marginal structural models (MSMs) including time-varying exposure (Bodnar et al., 2004; Desai and Franklin, 2019; Hernán and Robins, 2020).

For secondary outcomes, adequate power for comparative analyses will be assessed at the time of the analyses. This will be done by using the observed risks for the comparator cohort and assessing if there is adequate sample size to detect the target minimal detectable risk ratio of 2.0 for each outcome. If the sample size is adequate to detect this magnitude of effect, the comparative analysis for the given outcome will be performed. If not, only descriptive analyses will be conducted. A target of 2.0 was chosen given that associations with a risk ratio 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 (Guyatt 2011).

9.7.4.1. IPTW Derivation

IPTW will be calculated using model-based propensity scores (PSs) (Desai and Franklin, 2019). Each individual's person-day score (a time-varying PS that accounts for the probability of being in the exposed cohort, given membership in the study population [either cohort] during specified periods of observation) will be estimated using a single logistic regression model with exposure status as the outcome (dependent variable). Gestational day at index date will be included in the PS model. In addition, the variables listed in Section 9.3.3 will be considered for inclusion in the model as independent (predictor) variables. Each variable will be carefully considered by the investigators to ensure that only potential risk factors (and therefore potential confounders) for the study outcomes are included in the final PS model. Variable selection may be affected by model convergence issues and model performance. The investigators will provide a priority ordering of the variables prior to the estimation; if model convergence issues arise, the variables will be dropped in the order pre-selected by the investigators.

Stabilized weights will be estimated with trimming at the first and 99th percentiles to minimize the impact of any extreme weights (Hernán and Robins, 2020; Stuart, 2010). An initial PS model will be developed that includes all participants in the study cohorts (i.e.,

ABRYSVO-exposed and ABRYSVO-unexposed). Participants who contribute to both the exposed cohort and unexposed cohorts (i.e., participants who are unexposed at enrollment but who later receive ABRYSVO prior to 37 weeks gestation) will have 2 weights calculated within the same logistic regression model: (1) at the time of enrollment as an unexposed participant and (2) at the new index date (time of receiving ABRYSVO) as an exposed participant. The additional weight will take into account the updated ABRYSVO exposure status and their gestational age and updated baseline characteristics at the new index date.

Balance between the cohorts will be assessed by calculating the standardized mean differences for all covariates, comparing the ABRYSVO-exposed and ABRYSVO-unexposed cohorts. These standardized mean differences will be presented before and after IPTW.

9.7.4.2. MSM Methodology

For the second step of the MSM analysis, a weighted repeated measures model will be created. Since a participant's exposure status can change after enrollment (ie start as ABRYSVO-unexposed at index and subsequently receive ABRYSVO after index but before week 37) exposure status will be included as a time-dependent variable. Participants whose exposure status changed will contribute to analyses for both the unexposed and exposed group. All analyses for binary primary and secondary outcomes will use log-binomial regression models to estimate risk ratios. If these models fail to converge, a logistic regression model will be fit and the odds ratio will be presented instead of risk ratio. Analyses of continuous outcomes will use negative-binomial regression models to estimate rate ratios.

Stratified Analyses

If sample size permits, stratified analyses for all outcomes will be conducted that consider:

- Timing of exposure (i.e., 32 weeks, 33 weeks, 34 weeks , 35 weeks, 36 weeks)
- Maternal age group at conception (18 to <35, 35 to <45, and ≥45 years)
- A subgroup analysis for the outcome of preterm birth will be conducted that considers type of labor (induced labor/planned cesarean section or spontaneous labor). This stratified analysis will account for differences in preterm risk in these subgroups (since their risks may differ across labor type).

9.7.5. Supplementary Analyses

Supplementary analyses will be conducted that include pregnant individuals who were excluded from the analysis population due to being invalid from lacking at least one HCP confirmation of enrollment criteria:

- Lack of HCP confirmation of ABRYSVO exposure
- Lack of HCP confirmation of pregnancy
- Lack of HCP confirmation of at least one outcome of interest

- Lack of HCP confirmation of gestational age at index that is between 32 weeks 0 days and 36 weeks 6 days (based on HCP-reported EDD or LMP if EDD is not available).

9.7.6. Sensitivity Analyses

A sensitivity analysis will be conducted to examine the risk of preterm *delivery*, which includes both live births and stillbirths delivering prior to 37 weeks 0 days of gestation. The results will be presented in the final study report. The method undertaken will be identical to that of the primary analysis of preterm birth with the exception that stillbirths prior to 37 weeks 0 days will also be considered an event. The analysis will be run using the binary outcome of preterm delivery. If the log-binomial model fails to converge, logistic regression will be run and the odds ratio will be presented instead of risk ratio.

Additionally, a sensitivity analysis will be conducted to exclude prevalent ABRYSVO-exposed individuals, that is individuals who were exposed to ABRYSVO prior to enrollment. This analysis will repeat the same methods used for the analyses of the primary outcomes of preterm birth and any hypertensive disorder of pregnancy (composite outcome). The presentation will include descriptive statistics for time to preterm birth, weighted percentage of participants experiencing preterm birth, and the adjusted risk ratio of preterm birth between cohorts. The presentation will also include the number and percentage of participants experiencing any hypertensive disorder of pregnancy within 42 days post index date, weighted percentage of participants experiencing any hypertensive disorder of pregnancy within 42 days post index date, and the adjusted risk ratio between cohorts. For preterm birth, the denominator will be the number of live births, and for hypertensive disorders of pregnancy, the denominator will be pregnancies. Participants who were enrolled in the study in the unexposed cohort and then became exposed to ABRYSVO prior to 37 weeks will be counted in the denominator of each cohort, depending on timing of exposure relative to the index date, as in the main analysis.

A sensitivity analysis will also be conducted that uses time-based matching for the outcome of preterm birth. Participants who receive ABRYSVO will be matched with 1 or more unexposed participants. The matching will be based on the gestational date of ABRYSVO exposure for the exposed participants. The exposed participants will be matched with participants who were unexposed at the time of ABRYSVO exposure in the matched pair. Follow-up for each set of matched participants will start on the gestational age (to the day) of ABRYSVO exposure. Preterm births that occur in either group prior to the match date will not be used in this sensitivity analysis. If the main analysis set contains equal percentages of exposed and unexposed participants, 1:1 matching will be used. If the ratios vary by more than 67:33 (or 33:67), 2:1 or 1:2 matching will be used. If the ratios vary by more than 75:25 (or 25:75), 3:1 (or 1:3) matching will be used. If an unexposed match is vaccinated prior to 37 weeks 0 days and becomes part of the exposed group, they will then be matched to a new unexposed participant, and the new pair will be followed through the end of follow-up for preterm birth (36 weeks 6 days). The original exposed participant in the pair (whose unexposed match became exposed) will be followed through the end of follow-up as well. MSM with the same weights described for main analyses in Section 9.7.4.1 will be used in

these models, as calculating new weights among subgroups is unlikely to produce different results than using weights calculated for the full sample (Rassen et al., 2012).

9.7.7. Missing Data

For critical data points, missing values are expected to be minimal, thereby negating the need for imputation. The registry will make multiple attempts to obtain missing data for critical data points. The frequency and percentage of patients with missing data for each data point will be presented.

For the start and end dates of medical conditions or exposures, if the month and year are known but the day is missing, then the day will be imputed for analyses: missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month.

If there is a high degree of missing covariate data (>10%), imputations may be considered to minimize the loss of observations in the analysis. Further details will be provided in the SAP.

9.8. Quality Control

This study will use data collected as part of the RSV-PR. The RSV-PR will ensure the data collected are of high quality via an ongoing, multi-step process involving automatic programming of edit checks for critical data variables in the electronic data capture (EDC) system, as well as visual review for completeness, logic, consistency, and accuracy by the CorEvitas Virtual Research Coordinating Center (VRCC) staff. As recommended in regulatory guidance documents, the data collection forms will be carefully designed to ensure data quality and integrity.

9.9. Limitations of the Research Methods

The sponsor acknowledges several limitations to the study, which are inherent to and commonly encountered in observational studies. These limitations encompass the risk of random findings arising from multiple comparisons, the potential for failing to detect a true association due to limited sample size, and biases related to self-selection, misclassification, and generalizability (Lobo et al., 2006).

Observational studies that involve comparisons of participants who receive a vaccine prior to the start of data collection can be subject to immortal time bias, as some members of the vaccinated group (who were vaccinated prior to enrollment) will have an interval during which the outcome cannot occur (i.e., they must ‘survive’ without delivering up until the date of enrollment in order to be enrolled). Additionally, this time between vaccination and enrollment may be more likely to have missing outcome information, as data collection does not begin until date of enrollment (although HCPs and participants are asked about events occurring prior to enrollment). These biases are reduced by the relatively short maximum possible interval between when vaccination can occur (beginning 32 weeks 0 days gestation) and the end of the enrollment period (ending at 36 weeks 6 days). Additionally, we have proposed to further evaluate these biases using a sensitivity analysis that will exclude individuals vaccinated prior to enrollment.

Index date in the primary analysis of this study is not matched on gestational age, thus, if individuals tend to be vaccinated earlier than they are enrolling, the exposed cohort may be

more likely to have earlier (or vice versa, later) index dates than the unexposed cohort. Because risks of most of the study outcomes increase as pregnancy progresses, these differential index dates and subsequent follow-up time between cohorts may cause bias. We minimize this bias by utilizing analytical methods with time-varying exposure status and by allowing participants to contribute to both unexposed and exposed cohorts.

Additionally, to address these challenges, the study will implement IPTW methods to mitigate imbalances in participant characteristics between groups and reduce differential risk. Given that ABRYSVO is a novel vaccine, participants receiving it may exhibit distinct risk profiles compared to those who do not. However, comparing these trends with contemporaneous internal comparators will help clarify these patterns. Comparative analyses will also be conducted, adjusting for key participant characteristics.

Although the RSV-PR will make all possible efforts to retain participants in the registry, some participants will be lost during follow-up. It could be possible that participants lost during follow-up may be different than those with complete follow-up data. Characteristics of those lost to follow-up will be described and, should there be a substantial number of participants lost follow-up (above 10%), efforts will be made to compare the characteristics of those lost to follow-up with those who are not to evaluate this potential source of bias.

One strength of the study design is the opportunity to incorporate the comprehensive information collected by the RSV-PR, allowing for incorporation of numerous potential covariates to be evaluated as confounders. This information will be collected prospectively at predetermined intervals, which will reduce the risk of measurement error associated with poor recall.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Participant Consent

As this study will involve 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.

10.3. IRB/IEC

It is the responsibility of the RSV-PR to have prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC will be retained. Copies of IRB/IEC approvals will be forwarded to Pfizer.

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 International Society for Pharmacoepidemiology "Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States" (Public Policy Committee and International Society of Pharmacoepidemiology, 2016), Health Insurance Portability and Accountability Act (HIPAA) (Andrews et al., 1996), FDA regulatory requirements including the Draft Guidance "Postapproval Pregnancy Safety Studies Guidance for Industry" (FDA, 2019), and the ethical principles of the Declaration of Helsinki (World Medical Association, 2013).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study will involve data derived from the RSV-PR that exist as structured data by the time of study start. In this structured pregnancy database, individual patient data will not be retrieved or validated by Pfizer, and it will not be possible for Pfizer to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

In addition, CorEvitas will inform Pfizer immediately of any urgent safety measures taken by CorEvitas to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol of which the investigator becomes aware of.

The study will produce a final comprehensive study report that will be submitted to the relevant regulatory authorities. The report will include a presentation of the registry design, methodology, results to date, and an interpretive discussion of the statistical analysis results. In addition, interim progress reports presenting enrollment and outcome metrics will be produced every 6 months. Conference abstracts and manuscripts based on specific endpoints of interest may be developed for publication purposes. Additionally, this study will be disclosed and registered in the HMA-EMA Catalogues of RWD Studies.

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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	C3671041_PROTOCOL AMENDMENT 2 VERSION 3.0_28OCT2025
Document Title:	C3671041_PROTOCOL AMENDMENT 2 VERSION 3.0_28OCT2025

Signed By:	Date(GMT)	Signing Capacity
Koram, Nana	05-Nov-2025 16:44:16	Manager Approval
De Bernardi, Barbara	06-Nov-2025 09:17:25	EUQPPV Approval