NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Non-Interventional Post-Authorization Safety Study of Pfizer-BioNTech Bivalent COVID-19 Vaccine in the United States (US)
Protocol number	C4591051
Protocol version identifier	2.0
Date	06 December 2023
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	Pfizer-BioNTech COVID-19 Vaccine, Bivalent is a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of severe acute respiratory syndrome coronavirus (SARS-CoV-2) (Original) and the viral spike (S) glycoprotein of SARS-CoV-2 (Omicron BA.4/BA.5)
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Product reference	EMEA/H/C/005735
Procedure number	PAM-MEA-064.1
Marketing Authorization Holder(s) (MAH)	BioNTech Manufacturing GmbH: Pfizer Limited Ramsgate Road, Sandwich, Kent CT13 9NJ United Kingdom
Joint PASS	No
Research question and objectives	Research questions 1. What is the incidence of safety events of interest (including myocarditis/pericarditis) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine as compared with a self-matched control interval?

	2. What is the incidence of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy? 3. What is the prevalence of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy? <u>Primary Study Objectives</u> 1. To estimate the relative risk of safety events of interest (including myocarditis/pericarditis) in a post-vaccination risk interval, compared with a self-matched post-vaccination control interval, among individuals in the overall population who have received Pfizer-BioNTech bivalent COVID-19 Vaccine. 2. To estimate the relative risk of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy. 3. To estimate the prevalence odds ratio (POR) of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy. <u>Secondary Objectives</u> 1. To estimate the relative risk of safety events of interest (including myocarditis/pericarditis) in a post-vaccination risk interval, compared with a self-matched post-vaccination control interval, among individuals who have received Pfizer-BioNTech bivalent COVID-19 Vaccine among the following

	subgroups: pregnant women, immunocompromised individuals, individuals with a recorded history of severe COVID-19, and subgroups defined by age (as appropriate for the outcome). 2. To estimate the relative risk of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy by subgroups of maternal age. 3. To estimate the POR of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy by subgroups of maternal age.
Country(-ies) of study	United States
Authors	Alison Kawai, ScD RTI Health Solutions Waltham, Massachusetts Candace Fuller, PhD Department of Population Medicine Harvard Medical School & Harvard Pilgrim Health Care Institute Boston, Massachusetts Nana Koram, MPH, PhD Safety Surveillance Research Pfizer, Inc. New York, New York

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany
MAH contact person	Constanze Blume

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUA	emergency use authorization
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act of 2002
HIV	human immunodeficiency virus
HPHCI	Harvard Pilgrim Health Care Institute
HR	hazard ratio
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEA	International Epidemiological Association
IEC	independent ethics committee
IRB	institutional review board
IRR	incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
LMP	date of last menstrual period
NBDPN	National Birth Defects Prevention Network
NIST	National Institute of Standards and Technology
PAS	post authorization study
POR	prevalence odds ratio
PPV	positive predictive value
QA	quality assurance

Abbreviation	Definition
QC	quality control
RMP	risk management plan
RP	research partner
RR	risk ratio
RTI	RTI International
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCDM	Sentinel Common Data Model
SCRI	self-controlled risk interval
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TBD	to be determined
TORCH	toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes
US	United States
VSD	Vaccine Safety Database

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job title	Affiliation	Address
Nana Koram, MPH, PhD	Senior Director, Safety Surveillance Research	Pfizer Inc.	66 Hudson Blvd E New York, NY 10001
Alison Kawai, ScD	Director, Epidemiology	RTI Health Solutions	307 Waverley Oaks Road Suite 101 Waltham, MA 02452
Candace Fuller, PhD	Research Scientist in the Department of Population Medicine	Harvard Medical School & Harvard Pilgrim Health Care Institute	401 Park Drive Suite 401 Boston, MA 02215
Alicia Gilsenan, PhD,	Vice President, Epidemiology	RTI Health Solutions	3040 East Cornwallis Road PO Box 12194 Research Triangle Park, NC 27709
Richard Platt, MD, MSc	Department Chair and Professor of Population Medicine	Harvard Medical School & Harvard Pilgrim Health Care Institute	401 Park Drive Suite 401 Boston, MA 02215

4. ABSTRACT

Title: A Non-Interventional Post-Authorization Safety Study of Pfizer-BioNTech Bivalent COVID-19 Vaccine in the US

Version and date: Version 2.0, 06 December 2023

Main authors: Alison Kawai, ScD, Alicia Gilsenan, PhD, RTI Health Solutions; Candace Fuller, PhD, Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute; and Nana Koram, PhD, Safety Surveillance Research, Pfizer Inc.

Rationale and background

On 31 August 2022, the United States (US) Food and Drug Administration (FDA) authorized Pfizer-BioNTech bivalent COVID-19 Vaccine (Original and Omicron BA.4/BA.5) for emergency use as a single booster dose for the prevention of COVID-19 in individuals aged 12 years and older (FDA, 2023b). In April 2023, the FDA amended the emergency use authorization (EUA) for Pfizer-BioNTech COVID-19 Vaccine to simplify the vaccination schedule, such that the current bivalent vaccine is to be used for all initial and subsequent doses administered to individuals 6 months of age and older, as follows. Pfizer-BioNTech monovalent COVID-19 Vaccine is no longer authorized for use (FDA, 2023b). As of 11 September 2023, the Pfizer-BioNTech bivalent COVID-19 Vaccine (Original and Omicron BA.4/BA.5) is no longer authorized for use in the US since the updated (2023–2024 Formula) Pfizer-BioNTech COVID-19 Vaccine has become available (Regan et al., 2023). Since the authorization of Pfizer-BioNTech bivalent COVID-19 Vaccine, no signal for myocarditis/pericarditis has been observed in any age group in the Vaccine Safety Database (VSD), with preliminary data suggesting lower rates of myocarditis/pericarditis following booster vaccination with Pfizer-BioNTech bivalent COVID-19 Vaccine as compared with Pfizer-BioNTech monovalent COVID-19 Vaccine among individuals aged 12-39 years (Shimabukuro, 2023). While a potential safety signal for ischemic stroke for individuals aged 65 years and older was initially observed in the VSD, the signal was not subsequently confirmed(Shimabukuro, 2023).

Post-authorization observational studies using real-world data are needed among the general population and among subpopulations of interest (eg, pregnant people, immunocompromised individuals, and the pediatric population) to assess the association between Pfizer-BioNTech bivalent COVID-19 Vaccine and pre-determined safety events of interest, including myocarditis/pericarditis. This protocol describes a proposed observational study of safety events of interest, including myocarditis/pericarditis, occurring in recipients of the Pfizer-BioNTech bivalent COVID-19 Vaccine using claims data and electronic health records data (where available) from data research partners (RPs) participating in the FDA Sentinel System.

The study is a commitment to the US FDA and is also a Risk Management Plan (RMP) Category 3 commitment to the European Medicines Agency (EMA).

Research question and objectives

Research questions

1. What is the incidence of safety events of interest (including myocarditis/pericarditis) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine as compared with a self-matched control interval?

2. What is the incidence of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy?

3. What is the prevalence of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy?

Primary objectives

1. To estimate the relative risk of safety events of interest (including myocarditis/pericarditis) in a post-vaccination risk interval, compared with a self-matched post-vaccination control interval, among individuals in the overall population who have received Pfizer-BioNTech bivalent COVID-19 Vaccine.

2. To estimate the relative risk of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy.

3. To estimate the POR of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy.

Secondary objectives

1. To estimate the relative risk of safety events of interest (including myocarditis/pericarditis) in a post-vaccination risk interval, compared with a self-matched post-vaccination control interval, among individuals who have received Pfizer-BioNTech bivalent COVID-19 Vaccine for the following subgroups: pregnant women, immunocompromised individuals, individuals with a recorded history of severe COVID-19, and subgroups defined by age (as appropriate for the outcome).

2. To estimate the relative risk of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy by subgroups of maternal age.

3. To estimate the POR of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy by subgroups of maternal age.

Study design

The study will use a self-controlled risk interval (SCRI) design to assess general safety events (ie, non-pregnancy related safety events of interest, including myocarditis/pericarditis) and a cohort design to assess pregnancy outcomes (spontaneous abortion, stillbirth, and preterm birth) and birth outcomes (major congenital malformations and small size for gestational age). The SCRI study design is appropriate for studying acute events with well-defined risk periods and avoids confounding by time-invariant characteristics (eg, age, sex, pre-existing comorbidities).

To assess the feasibility for planned analyses, a monitoring analysis will be conducted to describe vaccine utilization among the overall population, among immunocompromised individuals, among individuals with a history of severe COVID-19, and in subgroups defined by age as well as among women who may have been exposed during pregnancy.

The study period will start on the date that Pfizer-BioNTech bivalent COVID-19 Vaccine was granted EUA in the US (31 August 2022) and will end a minimum of 2 years after this date.

Population

The source population for this study will be health plan enrollees from data RPs that contribute data from claims and electronic health records to the FDA Sentinel System. The planned data sources for the study are CVS Health, Carelon Research (formerly HealthCore, Inc.), Health Partners, Humana, and Optum Research Database; additional data sources may also be added.

Individuals will be eligible for the analysis of general safety events if they are aged ≥ 6 months during the study period and have continuous medical and pharmacy insurance coverage for at least 12 months before their vaccination date or from birth until the vaccination date (for children aged younger than 12 months on the vaccination date). For children aged younger than 12 months on the vaccination date, a delay in enrollment from birth (duration to be specified in the statistical analysis plan (SAP) may be allowed.

Women will be eligible for inclusion in analyses of pregnancy and birth outcomes if they are aged between 12 and 55 years, had a pregnancy outcome recorded during the study period, and had continuous medical and pharmacy coverage from at least 12 months before the vaccination date until the end of pregnancy. Analyses of major congenital malformations and small size for gestational age will be limited to singleton pregnancies ending in a live birth.

The following subgroups will be identified for descriptive and comparative safety analysis: pregnant women, immunocompromised individuals, individuals with a recorded history of severe COVID-19, and subgroups defined by age (as appropriate for the outcome). Subgroup analysis of pregnancy outcomes and birth outcomes will be conducted by maternal age group.

Variables

Safety events

Safety events of interest will be identified in claims and electronic health records (where available, as not all data RPs will have access to electronic health records) using predefined algorithms based on diagnosis codes, and procedure and/or pharmacy dispensing codes as appropriate.

The following general safety events will be assessed. Unless otherwise noted, all general safety events will be assessed in individuals aged ≥ 6 months.

- Cardiac: myocarditis/pericarditis, acute myocardial infarction
- Neurologic: acute disseminated encephalomyelitis, Bell's palsy, convulsions (in children aged 6 months to 4 years), encephalomyelitis/encephalitis, Guillain-Barré syndrome, transverse myelitis
- Hematologic: deep vein thrombosis, disseminated intravascular coagulation, immune hemolytic anemia, immune thrombocytopenia, pulmonary embolism, thromboembolic events associated with thrombocytopenia, thrombotic thrombocytopenic purpura, venous thromboembolism, hemorrhagic stroke, ischemic stroke
- Respiratory: acute respiratory distress syndrome
- Other system: anaphylaxis, appendicitis, Kawasaki disease (in children aged 6 months to years), multisystem inflammatory syndrome; multisystem inflammatory syndrome in children (in individuals aged < 21 years)

The following pregnancy and birth outcomes will be assessed in pregnant women or their infants:

- Spontaneous abortion (spontaneous pregnancy loss before 20 completed weeks of gestation)

- Stillbirth (fetal deaths at or after 20 completed weeks of gestation)
- Preterm birth (live birth before 37 completed weeks of gestation)
- Major congenital malformations
- Small size for gestational age

Vaccine exposures

Receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine and other COVID-19 vaccines will be identified in claims and/or electronic health records data via pharmacy dispensing and/or procedure codes. In analyses of pregnant women, exposures occurring within 28 days before the estimated pregnancy start or during pregnancy will be considered. Where quality data from existing linkages with immunization registries are available for use in research studies, immunization registry data will also be used to identify receipt of COVID-19 vaccines.

Covariates

Covariates for analysis of general safety events will include demographics, immunocompromising conditions, pregnancy status, history of severe COVID-19, geographic region, whether vaccination with Pfizer-BioNTech COVID-19 bivalent Vaccine was for a primary or booster dose (if feasible), and formulation type of Pfizer-BioNTech COVID-19 Vaccine (ie, bivalent or multivalent vaccine if additional formulations of Pfizer-BioNTech COVID-19 are authorized during the study observation period) and receipt of other vaccines recommended for routine use on the index date.

The same covariates used to assess general safety events will be also use to assess pregnancy and birth outcomes, as appropriate, in addition to the following descriptive and confounding variables: estimated pregnancy start date; gestational age on the index date (for analysis of pregnancy outcomes only); comorbidities in the 12 months before the index date, including history of anaphylaxis, history of vaccine-related allergies, diabetes (type 1 and type 2), hypertension, cardiovascular disease, cerebrovascular diseases, chronic respiratory disease, chronic kidney disease, chronic liver disease, cancer, epilepsy, infections, connective tissue disorders, thyroid disorders, mood disorders, asthma, obesity, healthcare utilization in the 12 months before or on the index date, history of alcohol abuse and smoking, reproductive history, pregnancy complications recorded during the current pregnancy (i.e. multiple pregnancy, gestational diabetes, preeclampsia/eclampsia, and TORCH infections [toxoplasmosis, other {syphilis, varicella-zoster, parvovirus B19}, rubella, cytomegalovirus, and herpes infections]), and teratogenic medications.

Data sources

The study will use data from data RPs that contribute claims and electronic health records to the Sentinel System. The data sources planned for inclusion in this study are CVS Health (Aetna Research Database), Carelon Research (formerly HealthCore), HealthPartners,

Humana, and Optum Research Database. The participation of these data sources in the general safety events and/or pregnancy and birth outcome analyses will be confirmed before finalizing the SAP; additional data sources may also be added.

Study size

Because an SCRI design will be used, statistical power for general safety events will depend on the total number of events in the risk and control intervals combined, the ratio of the duration of the risk and control intervals, and the incidence rate ratio (IRR). For example, using a 2-sided alpha = 0.05 level test, with risk and control intervals of equal duration, 80 events provide 86% power to detect an incidence rate ratio equal to or greater than 2.0.

Data analysis

Analyses will initially be conducted separately within the data from each data RP. Data RP–specific results will be returned to the study coordinating center, Harvard Pilgrim Health Care Institute(HPHCI), which will aggregate results across the data RPs for reporting. Pooled analysis of incidence rate ratios, hazard ratios (HRs), and POR estimates from all data RPs will be conducted using privacy-preserving summary-level data sets (eg, risk set–level data sets) or another appropriate method.

General safety events

In each event-specific analytic cohort for general safety events (which will be assessed using an SCRI design), demographics and comorbidities and other key characteristics will be described. For each general safety event, conditional Poisson regression or another appropriate statistical method will be used to obtain incidence rate ratios and 95% confidence intervals (CIs) in the risk interval compared with the control interval.

Pregnancy and birth outcomes

Among pregnant women, the distribution of demographics, comorbidities, and other potential confounders will be reported and compared between the matched exposed and unexposed cohorts. Covariate balance in the matched cohorts after inverse probability of treatment weighting will be assessed using standardized differences or other suitable methods.

Vaccinated pregnant women will be matched to pregnant unexposed comparators in a ratio of at least 1:1 on maternal age, US state (if feasible, or broader geographic region if not feasible), and pregnancy start date (to address confounding by calendar time). Confounding by other variables will be addressed using inverse probability of treatment weighting, based on propensity scores estimated in the matched population.

Measures of incidence or prevalence of pregnancy and birth outcomes with associated 95% CIs will be estimated within the matched exposed and unexposed cohorts. Cox models or Poisson regression will be used to calculate adjusted HRs or incidence rate ratios and 95% CIs for spontaneous abortion, stillbirth, and preterm birth. For small size for gestational

age and major congenital malformations, logistic regression will be used to estimate PORs and 95% CIs.

Sensitivity analyses

A sensitivity analysis may be considered for general safety events if signals are observed in other studies or surveillance systems and the risk intervals are not well characterized. Quantitative bias analysis of comparative risk estimates for myocarditis/pericarditis may be performed using outcome algorithm validation results from Study C4591009 or other published studies, if the algorithm for myocarditis/pericarditis has not been demonstrated to have adequate performance in these other studies.

To address the potential for misclassification of exposure status in the analysis of pregnancy and birth outcomes, a sensitivity analysis may be performed among data RPs that have linkages to high-quality immunization registry data available (if feasible), and quantitative bias analysis addressing exposure misclassification of comparative risk estimates of pregnancy and birth outcomes will be considered. To address the potential for confounding due to comparisons between vaccinated and unvaccinated pregnant women, a sensitivity analysis will be performed. This sensitivity analysis will be conducted among pregnant women with a recorded history of any monovalent COVID-19 vaccination before cohort entry, which may serve as a proxy for these health-seeking behaviors and risk factors for pregnancy and birth outcomes. This analysis will also address the potential for misclassification of unexposed status, as women with a recorded history of monovalent COVID-19 vaccine receipt may have more complete data on bivalent COVID-19 vaccines than those who do not have a recorded history of monovalent COVID-19 vaccine receipt.

Milestones

The anticipated start of data collection is no later than 30 September 2024, and the end of data collection is anticipated to be no later than 31 July 2026. A monitoring report is planned for no later than 31 January 2025, and a final study report is planned for no later than 31 January 2027.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	06 December 2023	Abstract, Section 6	Revised milestones to remove the Interim Report and update the end of data collection and final study report	To align with the shortened observation period given that authorization for Pfizer-BioNTech bivalent COVID-19 Vaccine (Original and Omicron BA.4/BA.5) ended on 11 September 2023
1	06 December 2023	Section 6	Added rationale for milestone dates	Included rationale per request from the EMA
1	06 December 2023	Abstract, Section 6, Section 9.1	Updated minimum observation period from 3 years to 2 years	Due to the change in authorization of Pfizer-BioNTech bivalent COVID-19 Vaccine (Original and Omicron BA.4/BA.5) as of 11 September 2023
1	06 December 2023	Abstract, Section 6, Section 9.1, Section 12	Removed all references to interim analysis	Given the shortened observation period, only monitoring and final reports will be implemented
1	06 December 2023	Abstract, Section 7	Added information relating to Pfizer-BioNTech bivalent COVID-19 Vaccine (Original and Omicron BA.4/BA.5) no longer being authorized as of 11 September 2023	To align with regulatory updates
1	06 December 2023	Abstract, Section 9.1, Section 9.3.2.2, Section 9.3.3 Section 9.7	Removed references to analysis relating to exploring other formulations of Pfizer-BioNTech COVID-19 Vaccines	To focus the study on Pfizer-BioNTech bivalent COVID-19 Vaccine (Original and Omicron BA.4/BA.5) only
1	06 December 2023	Abstract, Section 9.1	Added feasibility during the monitoring analysis to assess uptake in women who may have been exposed during pregnancy	To assess potential study size for final analysis
1	06 December 2023	Section 9.1, Section 9.2	Added clarification that washout period would be applied for assessment of safety events	To clarify intent to identify incident cases
1	06 December 2023	Section 9.5	Added study size for pregnancy analyses (this is a newly added section (9.5.2) and the existing wording is now presented under section 9.5.1)	Per request from the EMA

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	06 December 2023	Section 9.9	Minor updates	Minor updates
1	06 December 2023	Abstract, Section 9.7.1	Add "another appropriate statistical method" as option for estimating incidence rate ratios of general safety events	To allow flexibility with method within a distributed network
1	06 December 2023	Sections 10.4 and 12	Minor editorial changes	Minor editorial changes

COVID-19 = coronavirus disease 2019; EMA = European Medicines Agency.

6. MILESTONES

Below is the anticipated schedule of milestones, based on the anticipated data lags and timing of data availability for the planned data sources.

Milestone	Planned date
Registration in the EU PAS Register	Prior to the start of data collection
Start of data collection	30 September 2024
Monitoring analysis report	31 January 2025
End of data collection	31 July 2026
Final study report	31 January 2027

EU PAS Register = European Union electronic register of post-authorization studies

Planned dates for the study milestones are based on anticipated data lag in the data sources and a minimum of 2 years of observation (data through at least 30 August 2024) after the initial EUA of Pfizer-BioNTech bivalent (BNT162b2 and BNT162b2 OMI BA.4/BA.5) COVID-19 Vaccine, which occurred on 31 August 2022 in the US. It is anticipated that the milestone dates would allow for at least 1 year of follow-up for general safety events of interest after the Pfizer-BioNTech bivalent COVID-19 Vaccine was no longer authorized as well as least 1 year of follow-up for infants born to pregnant women receiving the Pfizer-BioNTech bivalent COVID-19 Vaccine.

The start of data collection (30 September 2024) is equivalent to the query distribution by the coordinating center (Harvard Pilgrim Health Care Institute) to participating Research Partners for the monitoring analysis, with a monitoring analysis report milestone date of 31 January 2025. Query distribution for the final analysis is anticipated to occur in the second quarter of 2026. The exact timing of query distribution will take into consideration latest data refreshes for participating research partners, which occur on a regular but staggered basis. The end of data collection (31 July 2026) is anticipated to be the date on which all analysis is complete.

7. RATIONALE AND BACKGROUND

On 31 August 2022, the US FDA authorized Pfizer-BioNTech bivalent COVID-19 Vaccine (Original and Omicron BA.4/BA.5) for emergency use as a single booster dose for the prevention of COVID-19 (coronavirus disease 2019) in individuals aged 12 years and older (FDA, 2023b). On 12 October 2022, the FDA subsequently authorized the vaccine for use as a single booster dose in individuals aged 5-11 years. Additionally, on 08 December 2022, the FDA authorized Pfizer-BioNTech bivalent COVID-19 Vaccine to be used as a third dose in the primary series in children aged 6 months through 4 years, following 2 doses of Pfizer-BioNTech monovalent COVID-19 Vaccine (Original). On 14 March 2023, the FDA authorized Pfizer-BioNTech bivalent COVID-19 Vaccine for use as a single booster dose in children aged 6 months through 4 years who had previously completed a 3-dose primary series of Pfizer-BioNTech monovalent COVID-19 Vaccine (FDA, 2023a).

On 18 April 2023, the FDA amended the EUA for Pfizer-BioNTech COVID-19 Vaccine to simplify the vaccination schedule, such that the current bivalent vaccine was to be used for all initial and subsequent doses administered to individuals aged 6 months and older. At the same time, the original Pfizer-BioNTech monovalent COVID-19 Vaccine was no longer authorized for use (FDA, 2023b). Updates to simplify the vaccination schedule were as follows:

- For unvaccinated individuals, Pfizer-BioNTech bivalent COVID-19 Vaccine was authorized as a 3-dose series in individuals aged 6 months through 4 years and as a single dose in individuals aged 5 years and older.

- For individuals aged 6 months through 4 years who had previously received 1 dose of monovalent vaccine, Pfizer-BioNTech bivalent COVID-19 Vaccine was authorized to be used as 2 additional doses; for individuals aged 6 months through 4 years who had received 2 or 3 doses of monovalent vaccine, Pfizer-BioNTech bivalent COVID-19 Vaccine was authorized to be used as a single dose.

- For individuals aged 5 years and older who had previously received 1 or more doses of monovalent COVID-19 vaccine, a single dose of Pfizer-BioNTech bivalent COVID-19 Vaccine was authorized.

- For individuals aged 65 years and older and immunocompromised individuals aged 5 years and older, a single additional dose of Pfizer-BioNTech bivalent COVID-19 Vaccine was authorized after receipt of a first dose of bivalent COVID-19 vaccine.

- Additional doses of Pfizer-BioNTech bivalent COVID-19 Vaccine were authorized to be administered, at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances.

Additionally, on 28 April 2023, the FDA authorized the use of a fourth dose of Pfizer-BioNTech COVID-19 bivalent COVID-19 Vaccine for immunocompromised individuals aged 6 months through 4 years who had previously received 3 doses of Pfizer-BioNTech monovalent COVID-19 Vaccine or Pfizer-BioNTech bivalent COVID-19 Vaccine. Myocarditis and pericarditis were included in the warnings and precautions of the EUA factsheet for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), stating "Post-marketing safety data with Pfizer-BioNTech COVID-19 Vaccine are relevant to Pfizer-BioNTech COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process. Post-marketing data with authorized or approved monovalent mRNA COVID-19 vaccines demonstrate increased risks of myocarditis and pericarditis, particularly within the first week following vaccination. For the Pfizer-BioNTech COVID-19 Vaccine, the observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae" (FDA, 2023a).

As of 11 September 2023, the Pfizer-BioNTech bivalent COVID-19 Vaccine (Original and Omicron BA.4/BA.5) is no longer authorized for use in the US (since the updated [2023–2024 Formula] COVID-19 Pfizer-BioNTech COVID-19 Vaccine became available) (Regan et al., 2023). Since the authorization of Pfizer-BioNTech bivalent COVID-19 Vaccine, no safety signal for myocarditis/pericarditis has been observed with this vaccine in any age group in the VSD, with preliminary data suggesting lower rates of myocarditis/pericarditis following booster vaccination with Pfizer-BioNTech bivalent COVID-19 Vaccine compared with rates of myocarditis/pericarditis following receipt of Pfizer-BioNTech monovalent COVID-19 Vaccine among individuals aged 12-39 years (Shimabukuro, 2023). While a potential safety signal for ischemic stroke for individuals aged 65 years and older was initially observed in the VSD, the signal was not subsequently confirmed (Shimabukuro, 2023).

Post-authorization observational studies using real-world data are still needed among the general population and among subpopulations of interest (eg, pregnant people, immunocompromised individuals, and the pediatric population) to assess the association between Pfizer-BioNTech bivalent COVID-19 Vaccine and pre-determined safety events of interest, including myocarditis/pericarditis. This protocol describes a proposed observational study of safety events of interest, including myocarditis/pericarditis, occurring in recipients of the Pfizer-BioNTech bivalent COVID-19 Vaccine using claims data and electronic health records data (where available) from data RPs participating in the FDA Sentinel System.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the US FDA and is also a RMP Category 3 commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

Research questions

1. What is the incidence of safety events of interest (including myocarditis/pericarditis) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine as compared with a self-matched control interval?

2. What is the incidence of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy?

3. What is the prevalence of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy?

Primary objectives

1. To estimate the relative risk of safety events of interest (including myocarditis/pericarditis) in a post-vaccination risk interval, compared with a self-matched post-vaccination control interval, among individuals in the overall population who have received Pfizer-BioNTech bivalent COVID-19 Vaccine.

2. To estimate the relative risk of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy.

3. To estimate the POR of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy.

Secondary objectives

1. To estimate the relative risk of safety events of interest (including myocarditis/pericarditis) in a post-vaccination risk interval, compared with a self-matched post-vaccination control interval, among individuals who have received Pfizer-BioNTech bivalent COVID-19 Vaccine for the following subgroups: pregnant women, immunocompromised individuals, individuals with a recorded history of severe COVID-19, and subgroups defined by age (as appropriate for the outcome).
2. To estimate the relative risk of pregnancy outcomes (including spontaneous abortion, stillbirth, and preterm birth) following receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with no receipt of any COVID-19 vaccine during pregnancy by subgroups of maternal age.
3. To estimate the POR of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to women who were not exposed to any COVID-19 vaccine during pregnancy by subgroups of maternal age.

9. RESEARCH METHODS

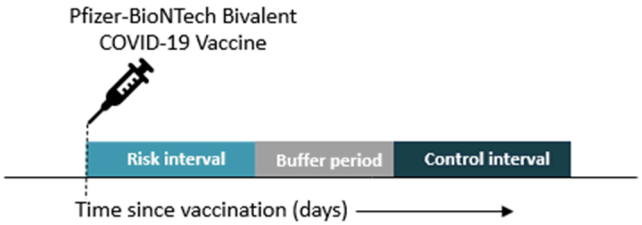
9.1. Study design

The study will use a SCRI design to assess general safety events (ie, non-pregnancy related safety events of interest, including myocarditis/pericarditis; see Section 9.3.2.1 for list of specific events) among the general population and specific subpopulations of interest (immunocompromised individuals, pregnant women, and the pediatric population). A cohort design will be used to assess pregnancy and birth outcomes.

For general safety events, the SCRI design (Figure 1) will compare the incidence of safety events of interest in a predefined post-vaccination risk interval with that in a self-matched post-vaccination control interval, among individuals who have received Pfizer-BioNTech bivalent COVID-19 Vaccine. A buffer period (in which incidence will not be assessed) will be incorporated between the risk and control intervals to avoid any carry over effects from the risk interval into the control interval. Control intervals for each outcome will be defined to reflect the baseline risk of the outcome, and buffer and control intervals will take into consideration the duration of the risk interval, potential seasonality of the outcome, and the recommended timing between the initial bivalent vaccine dose and additional COVID-19

vaccine doses. Additionally, as an eligibility criterion for each specific safety event of interest, a set period of time prior to the event date (washout period) in which the individual may not have experienced the safety event of interest will be defined to more plausibly identify incident cases.

Figure 1. Self-controlled risk interval design to assess general safety events

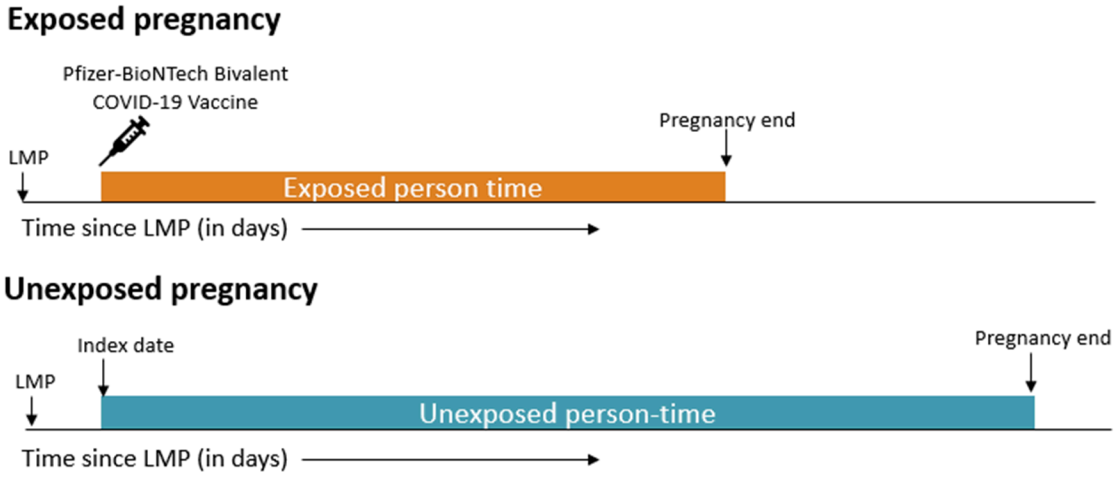


COVID-19 = coronavirus disease 2019.

This study design is appropriate for studying acute events with well-defined risk periods. A strength of the SCRI design is that it avoids confounding due to time-invariant confounders (including prior history of COVID-19 vaccination, which may be challenging to identify in claims administrative data). Additionally, because the SCRI design only includes vaccinated individuals, it avoids misclassification of unexposed status arising from incomplete capture of COVID-19 vaccination in claims data.

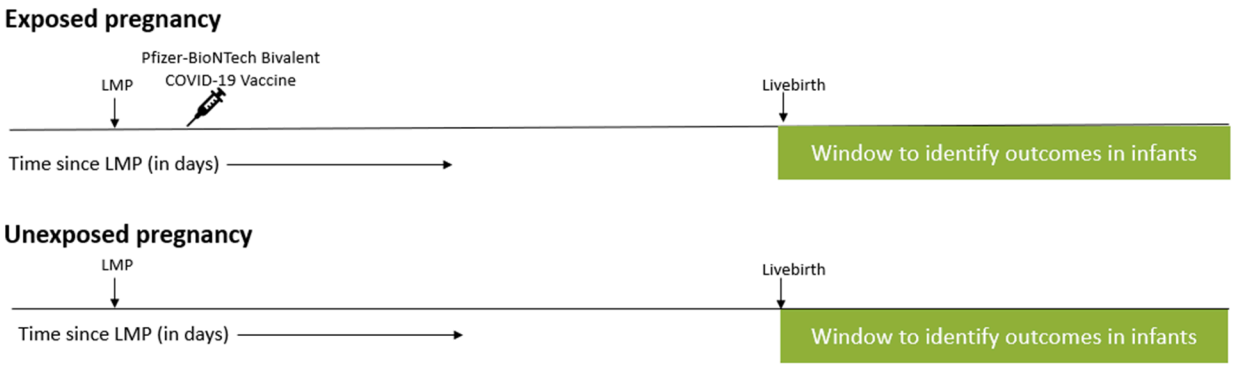
Among pregnant women, a cohort design will be used to compare the incidence of pregnancy outcomes (spontaneous abortion, stillbirth, and preterm birth) among those who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that among those who were unexposed to any COVID-19 vaccine during pregnancy (Figure 2). Similarly, a cohort design will be used to compare the prevalence of birth outcomes (major congenital malformations and small size for gestational age) in infants who were born to pregnant women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during pregnancy compared with that in infants born to pregnant women who were unexposed to any COVID-19 vaccine during pregnancy (Figure 3). Exposed and unexposed pregnant women will be matched on estimated pregnancy start (date of last menstrual period [LMP]), gestational age at cohort entry (for pregnancy outcomes only), maternal age, and US state (if feasible, or broader geographic region if not feasible). Inverse probability of treatment weighting will be used to account for additional confounders.

Figure 2. Cohort design to assess pregnancy outcomes



COVID-19 = coronavirus disease 2019; LMP = date of last menstrual period.

Figure 3. Cohort design to assess birth outcomes



COVID-19 = coronavirus disease 2019; LMP = date of last menstrual period.

A strength of a cohort design with concurrent unexposed comparators is that, unlike the SCRI design, it can be used to study safety events for which the risk varies substantially over time (such as spontaneous abortion) and/or for which the timing of onset is unknown (such as major congenital malformations and small size for gestational age). The use of a contemporaneous comparator rather than a historical comparator avoids bias due to temporal trends in coding for outcomes. Limitations of the cohort approach include the potential for bias due to misclassification of exposed individuals as "unexposed" comparators and bias due to confounding when comparing exposed with unexposed pregnant women. Confounding will be handled by matching and inverse probability of treatment weighting.

To assess the feasibility for planned analyses, a monitoring analysis will be conducted to describe vaccine utilization among the overall population, among immunocompromised

individuals, among individuals with a history of severe COVID-19, and in subgroups defined by age, as well as among women who may have been exposed during pregnancy (based on pregnancy markers in the 200 days before the index date).

The study period will start on the date that Pfizer-BioNTech bivalent COVID-19 Vaccine was granted EUA in the US (31 August 2022) and will end a minimum of 2 years after this date.

9.2. Setting

The source population will be health plan enrollees from data RPs that contribute data from claims and electronic health records to the FDA Sentinel System. The planned data sources for the study are CVS Health (Aetna Research Database), Carelon Research (formerly HealthCore), HealthPartners, Humana, and Optum Research Database. The participation of these data sources will be confirmed before the SAP is finalized, and additional data sources may be added.

9.2.1. Study population eligibility criteria

9.2.1.1. Population to assess general safety events

Individuals will be eligible for analysis of general safety events (which will use an SCRI design) if they meet the following criteria:

1. Aged ≥ 6 months for at least 1 day during the study observation period.
2. Have received a dose of Pfizer-BioNTech bivalent COVID-19 Vaccine. Note that individuals will be eligible regardless of the brand(s) of any COVID-19 vaccines received before Pfizer-BioNTech bivalent COVID-19 Vaccine.
3. Have had continuous medical and pharmacy insurance coverage for at least 12 months before receipt of the Pfizer-BioNTech bivalent COVID-19 Vaccine, or from birth until receipt of the Pfizer-BioNTech bivalent COVID-19 Vaccine (for individuals aged younger than 12 months at the time of receipt of the vaccine). For children aged younger than 12 months at the time of vaccination, a delay in enrollment (duration to be specified in the SAP) from birth will be allowed.

Additionally, for analysis of each safety event, individuals will be required to meet the following criteria:

4. Have experienced the event of interest during the risk or control intervals (see Section 9.3.2.1 for event-specific risk interval definitions; event-specific control intervals will be defined in the SAP)
5. Did not experience the specific safety event of interest during the pre-event washout period (the event-specific washout periods will be defined in the SAP)
6. Have continuous health plan enrollment from the start of the event-specific risk interval until the end of the event-specific control interval (for individuals who live until the end of the control interval) or until death (for individuals who die before the end of the control interval)

7. Have received no additional doses of COVID-19 vaccine other than Pfizer-BioNTech bivalent COVID-19 Vaccine during the risk interval and no additional doses of COVID-19 vaccine of any brand through the end of the control interval. Additional doses of Pfizer-BioNTech bivalent COVID-19 Vaccine will be allowed during the risk interval to enable the capture of more than 1 dose administered in a short timeframe, as the vaccine is currently approved for use as more than 1 dose in the primary series.

The index date (ie, date of cohort entry) will be the date of receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine.

All individuals receiving Pfizer-BioNTech bivalent COVID-19 Vaccine will be assumed to have met the eligibility criteria to receive the vaccine under the FDA authorization (see Section 7 for summary of FDA authorizations of Pfizer-BioNTech bivalent COVID-19 Vaccine, which have changed over the course of the study period). This assumption will be made because requiring the prerequisite number and types of COVID-19 vaccine doses before receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine is anticipated to require health plan enrollment from the date of an individual's initial eligibility for COVID-19 vaccination, which would severely reduce the number of individuals eligible for the study and potentially lead to imprecise comparative risk estimates and selection bias.

Given the FDA authorizations of Pfizer-BioNTech bivalent COVID-19 Vaccine, it is anticipated that some individuals may contribute more than 1 dose of Pfizer-BioNTech bivalent COVID-19 Vaccine to the analyses. Details on how subsequent doses of Pfizer-BioNTech bivalent COVID-19 Vaccine will be handled in the analysis will be described in the SAP.

9.2.1.2. Population to assess pregnancy and birth outcomes

Pregnant women aged between 12-55 years will be eligible for inclusion in the final analysis of pregnancy and birth outcomes if they had a recorded pregnancy outcome (eg, live birth, stillbirth, spontaneous abortion, ectopic pregnancy, pregnancy termination) during the study period. As pregnancy status is not directly recorded in Sentinel data sources, an algorithm (to be defined in the SAP) that incorporates diagnosis and/or procedure codes will identify pregnancy episodes and pregnancy outcomes as well as the estimated start (estimated LMP) and end of pregnancy. Livebirth pregnancies identified in maternal data will be linked with infant data to identify birth outcomes during the first year of life (Sentinel, 2019). Additional cohort eligibility criteria are described below for each of the pregnancy and birth outcomes.

9.2.2. Pregnancy outcomes (spontaneous abortion, stillbirth, and preterm birth)

Separate cohorts of pregnant women exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine (exposed cohort) and pregnant women not exposed to any COVID-19 vaccine (unexposed cohort) will be formed for the final analysis of pregnancy outcomes (Table 1). To be eligible for either cohort, pregnant women must be enrolled from 12 months before cohort entry (ie, the index date) until the end of pregnancy.

Table 1. Cohort definitions for analysis of pregnancy outcomes

Cohort	Eligibility criteria	Index date
Exposed cohort	• Receipt of a dose of Pfizer-BioNTech bivalent COVID-19 Vaccine in the exposure window (as defined in Table 3) • Continuous enrollment in the 12 months before the index date until end of pregnancy	• Date of vaccination
Unexposed cohort	• No receipt of any COVID-19 vaccine in the exposure window (as defined in Table 3) • Continuous enrollment in the 12 months before the index date until end of pregnancy • Matched individually (in a ratio of at least 1:1) to exposed women on estimated pregnancy start (LMP, within pre-specified calendar intervals), maternal age, and US state (if feasible, or broader geographic region if not feasible)	• Equivalent of the gestational age at vaccination (in days) in the exposed match. For example, if an exposed individual was vaccinated at 28 weeks and 3 days of gestation, the index date for unexposed matches would be set to 28 weeks and 3 days after their LMP.

COVID-19 = coronavirus disease 2019; LMP = date of last menstrual period; US = United States.

9.2.3. Birth outcomes (major congenital malformations and small size for gestational age)

Separate cohorts of pregnant women exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine (exposed cohort) and pregnant women not exposed to any COVID-19 vaccine (unexposed cohort) will be formed for the analysis of birth outcomes (Table 2). To be eligible for either cohort, women must have had a singleton pregnancy ending in a livebirth and must have had continuous enrollment from 12 months before the index date until birth. The index date in both exposed and unexposed women will be the LMP date. Analyses will be limited to pregnant women whose singleton pregnancies have ended in a livebirth and who have been successfully linked to an infant.

Table 2. Cohort definitions for analysis of birth outcomes

Cohort	Eligibility criteria
Exposed cohort	• Pregnancy ending in a livebirth, with continuous enrollment in the 12 months before the index date (LMP) until birth • Pregnancy linked to at least 1 infant • Receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine during the outcome-specific exposure window (as defined in Table 3)
Unexposed cohort	• Pregnancy ending in a livebirth, with continuous enrollment in the 12 months before the index date (LMP) until birth • Pregnancy linked to at least 1 infant

Table 2. Cohort definitions for analysis of birth outcomes

Cohort	Eligibility criteria
	• No receipt of any COVID-19 vaccine during the outcome-specific exposure window (as defined in Table 3) • Matched individually (in a ratio of at least 1:1) to exposed women on LMP, maternal age, and US state (if feasible, or broader geographic region if not feasible)

COVID-19 = coronavirus disease 2019; LMP = date of last menstrual period. US = United States

9.2.3.1. Exposure windows for analyses in pregnant women

Outcome-specific exposure windows are provided in Table 3. For pregnancy and birth outcomes, only women who were exposed to Pfizer-BioNTech bivalent COVID-19 Vaccine during outcome-specific exposure windows will be eligible for the exposed cohorts. For each pregnancy and birth outcome, the exposure window will be from 28 days before pregnancy start until the end of the outcome-specific risk period (as defined in Section 9.3.2.2).

Table 3. Exposure windows for analysis of pregnancy outcomes and birth outcomes

Type of safety event	Safety event of interest	Exposure window
Pregnancy outcomes	Spontaneous abortion	From 28 days before LMP until 19 weeks and 6 days of gestation
	Stillbirth	From 28 days before LMP until pregnancy end
	Preterm birth	From 28 days before LMP until 36 weeks and 6 days of gestation
Birth outcomes	Major congenital malformations	From 28 days before LMP until the last day of the first trimester
	Small size for gestational age	From 28 days before LMP until pregnancy end

LMP = date of last menstrual period.

9.2.4. Follow-up

9.2.4.1. General safety outcomes

Individuals will be followed from the start of the risk interval (the index date or day after the index date, depending on the outcome) until the end of the control interval (to be defined in the SAP).

9.2.4.2. Pregnancy and birth outcomes

For analysis of pregnancy outcomes, pregnant women will be followed from the index date until the earliest of the following: end of pregnancy, latest gestational age at which an outcome can occur (applies only to stillbirth and preterm birth), or receipt of another dose of any COVID-19 vaccine other than Pfizer-BioNTech bivalent COVID-19 Vaccine (Table 4).

For analysis of birth outcomes, infants will be followed for events from birth until 12 months after birth (for major congenital malformations) or until 1 month after birth (for small size for gestational age) (Table 4).

Table 4. Follow-up for pregnancy outcomes and birth outcomes

Safety event	Start of follow-up	End of follow-up
Pregnancy outcomes		
Spontaneous abortion	Index date (as defined in Table 1)	Earliest of the following: • Occurrence of spontaneous abortion • 20 weeks of gestation (latest gestational age at which a spontaneous abortion can occur) • Other event marking the end of pregnancy (ectopic pregnancy or pregnancy termination); to be treated as competing events • Receipt of another dose of COVID-19 vaccine other than Pfizer-BioNTech bivalent COVID-19 Vaccine
Stillbirth	Index date (as defined in Table 1)	Earliest of the following: • Occurrence of stillbirth • Other event marking the end of pregnancy (ectopic pregnancy, spontaneous abortion, pregnancy termination, or livebirth); to be treated as competing events • Receipt of another dose of COVID-19 vaccine other than Pfizer-BioNTech bivalent COVID-19 Vaccine
Preterm birth	Index date (as defined in Table 1)	Earliest of the following: • Occurrence of preterm birth (ie, livebirth before 37 completed weeks of gestation) • 37 weeks of gestation (latest gestational age at which a preterm birth can occur) • Other event marking the end of pregnancy (ectopic pregnancy, spontaneous abortion, pregnancy termination, stillbirth); to be treated as competing events • Receipt of another dose of COVID-19 vaccine other than Pfizer-BioNTech bivalent COVID-19 Vaccine
Birth outcomes		
Major congenital malformations	Birth	Earliest of the following (in the infant): • Diagnosis of major congenital malformation • End of the study period • End of data availability • Death • 12 months after birth
Small size for gestational age	Birth	Earliest of the following (in the infant): • Diagnosis of small size for gestational age • End of the study period • End of data availability • Death • 1 month after birth

COVID-19 = coronavirus disease 2019.

9.3. Variables

9.3.1. Vaccine exposures

Receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine and other COVID-19 vaccines will be identified in claims and/or electronic health records data via pharmacy dispensing and/or procedure codes. Where quality data from existing linkages with immunization registries are available for use in research studies, immunization registry data will also be used to identify receipt of COVID-19 vaccines.

9.3.2. Safety events

All safety events of interest (ie, general safety events, pregnancy outcomes, and birth outcomes) will be identified in claims and electronic health records (where available, as not all data RPs may have access to structured electronic health records data) using diagnosis codes, with procedure and/or pharmacy dispensing codes as appropriate. Detailed definitions will be included in the SAP.

To the greatest extent possible, validated algorithms will be used for the study, if available. There are currently no plans for medical record or clinical validation of study outcomes, as validation of myocarditis/pericarditis (the primary outcome of interest) is being conducted in study C4591009 and in other studies led by other research groups.

If the algorithm for myocarditis/pericarditis has demonstrated adequate performance characteristics in other relevant validation studies (using predefined criteria, eg, a minimum positive predictive value [PPV], that will be defined in the SAP), then all algorithm-identified cases will be included in the final analysis without additional analysis to adjust for outcome misclassification. If the algorithm has not demonstrated adequate performance in prior validation studies, then the validation results (eg, PPVs) from other studies will be used to inform or adjust risk ratios (RRs) in sensitivity analysis.

9.3.2.1. General safety events

General safety events (which will be assessed using a SCRI design) are listed along with their risk interval definitions in Table 5. Event-specific risk intervals have been defined to reflect a period of potentially increased risk following vaccination. Event-specific control intervals will be defined in a pre-specified period (to be specified in the SAP) following the risk interval. Buffer and control intervals for each outcome will be defined to reflect the baseline risk of the outcome and will take into consideration the duration of the risk interval, the potential seasonality of the outcome, and the recommended timing between the initial bivalent vaccine dose and additional COVID-19 vaccine doses.

Table 5. General safety events

Organ system	Safety event of interest	Risk interval (days following vaccination [Day 0])	Ages to be included in analyses[a]
Cardiac	Myocarditis/pericarditis	1-7	Ages ≥ 6 months
	Acute myocardial infarction	1-28	Ages ≥ 6 months
Neurologic	Acute disseminated encephalomyelitis	1-42	Ages ≥ 6 months
	Bell's palsy	1-42	Ages ≥ 6 months
	Convulsions	1-42	6 months through 4 years
	Encephalomyelitis/encephalitis	1-42	Ages ≥ 6 months
	Guillain-Barré syndrome	1-42	Ages ≥ 6 months
	Transverse myelitis	1-42	Ages ≥ 6 months
Hematologic	Deep vein thrombosis	1-28	Ages ≥ 6 months
	Disseminated intravascular coagulation	1-28	Ages ≥ 6 months
	Immune hemolytic anemia	1-42	Ages ≥ 6 months
	Immune thrombocytopenia	1-42	Ages ≥ 6 months
	Pulmonary embolism	1-28	Ages ≥ 6 months
	Thromboembolic events associated with thrombocytopenia	1-28	Ages ≥ 6 months

Table 5. General safety events

Organ system	Safety event of interest	Risk interval (days following vaccination [Day 0])	Ages to be included in analyses[a]
	Thrombotic thrombocytopenic purpura	1-28	Ages ≥ 6 months
	Venous thromboembolism	1-28	Ages ≥ 6 months
	Hemorrhagic stroke	1-28	Ages ≥ 6 months
	Ischemic stroke	1-28	Ages ≥ 6 months
Respiratory	Acute respiratory distress syndrome	1-28	Ages ≥ 6 months
Other system	Anaphylaxis	0-1	Ages ≥ 6 months
	Appendicitis	1-42	Ages ≥ 6 months
	Kawasaki disease	1-42	Ages 6 months through 4 years
	Multisystem inflammatory syndrome	1-42	Ages ≥ 6 months
	Multisystem inflammatory syndrome in children	1-42	Ages < 21 years

COVID-19 = coronavirus disease 2019.
a. Subgroup analysis will also be performed among pregnant women, immunocompromised individuals, individuals with a recorded history of severe COVID-19, and in subgroups defined by age, and for myocarditis/pericarditis, by subgroups defined jointly by age and sex; additional subgroup analysis may be performed by vaccine formulation and receipt of the bivalent vaccine as a primary series vs booster dose if feasible in the data sources. See Sections 9.7.4 and 9.7.5 for further details.

9.3.2.2. Pregnancy and birth outcomes

Pregnancy outcomes and birth outcomes, including clinical definitions, method for identification in the data sources, and the period at risk are provided in Table 6.

Table 6. Pregnancy outcomes and birth outcomes

Outcome type	Safety event of interest	Clinical definition and method for identification in the data sources	Period at risk
Pregnancy outcomes	Spontaneous abortion	Defined as spontaneous pregnancy loss before 20 completed weeks of gestation; to be identified via diagnosis codes	From pregnancy start until 19 weeks and 6 days of gestation
	Stillbirth	Defined as spontaneous pregnancy loss on or after 20 completed weeks of gestation; to be identified via diagnosis codes	From 20 weeks of gestation until pregnancy end
	Preterm birth	Defined as live birth before 37 completed weeks of gestation; to be identified via diagnosis codes	< 37 weeks of gestation
Birth outcomes	Major congenital malformations	Defined a major defect as a congenital abnormality that requires medical or surgical treatment, has a serious adverse effect on health and development, or has significant cosmetic impact (NBDPN, 2021); to be identified in live-born infants using diagnosis codes based on the National Birth Defects Prevention Network case definitions (NBDPN, 2023)	First trimester of pregnancy[a]
	Small size for gestational age	Defined as less than 10th percentile of weight for gestational age; to be identified using diagnosis codes for small size for gestational age or combinations of diagnosis codes for birthweight (in categories) and gestational age (in categories)	Any time during pregnancy[a]

a. Although the etiologic period for major congenital malformations is the first trimester and for small size for gestational age is any time during pregnancy, these events can only be reliably observed in infants after birth.

9.3.3. Covariates

Table 7 presents variables that will be used for descriptive analysis in analyses of general safety events as well as variables that will be used for descriptive analysis, matching, and

propensity score estimation in analysis of pregnancy and birth outcomes. These variables will be identified using claims or electronic health records data (where available).

Table 7. Covariates used for descriptive analysis, matching or propensity score estimation

Variable	General safety events	Pregnancy and birth outcomes		
	Descriptive	Descriptive	Matching	Propensity scores
Age (as of the index date or LMP[a])	X	X	X	
Sex	X			
Geographic region (based on the most recent information at the time of data refresh)	X	X	X	
Immunocompromising conditions (in the 12 months before the index date) • Including immunodeficiencies, immunosuppressant medication use, HIV and other immunosuppressing conditions, and receipt of organ or bone marrow transplants	X	X		X
Pregnancy status as of the index date	X			
History of severe COVID-19 disease (as of the index date) • Defined with inpatient diagnoses in the principal diagnosis position or in pregnant women, with inpatient claims with a principal diagnosis of viral diseases complicating pregnancy and a diagnosis of COVID-19 in another position	X	X		X
Receipt of the index Pfizer-BioNTech COVID-19 bivalent Vaccine as a primary series dose vs booster dose; only to be assessed if feasible to identify in the data sources; anticipated to be incomplete	X	X		
Other vaccines recommended for routine use (on the index date or from 28 days before pregnancy until end of pregnancy)[b]	X	X		X
Estimated pregnancy start date (LMP)		X	X	
Gestational age on the index date[c]		X		

Table 7. Covariates used for descriptive analysis, matching or propensity score estimation

Variable	General safety events	Pregnancy and birth outcomes		
	Descriptive	Descriptive	Matching	Propensity scores
Comorbidities (in the 12 months before the index date); separate variables for the following conditions: • History of anaphylaxis • History of vaccine-related allergies • Diabetes (type 1 and type 2) • Hypertension • Cardiovascular disease • Cerebrovascular diseases • Chronic respiratory disease • Chronic kidney disease • Chronic liver disease • Cancer • Epilepsy • Infections • Connective tissue disorders • Thyroid disorders • Mood disorders • Asthma • Obesity (capture anticipated to be incomplete in the data sources)		X		X
Healthcare utilization in the 12 months before or on the index date		X		X
Alcohol abuse and smoking in the 12 months before or on the index date (capture anticipated to be incomplete)		X		X
Reproductive history (in all data available before the index date; if feasible in the data sources): • Spontaneous abortions in previous pregnancies • Pregnancy terminations in previous pregnancies		X		X
Pregnancy complications during the current pregnancy[d]: • Multiple pregnancy • Gestational diabetes • Preeclampsia/eclampsia • TORCH infections		X		X
Teratogenic medications (from 28 days before pregnancy start until end of pregnancy[d])		X		X

Table 7. Covariates used for descriptive analysis, matching or propensity score estimation

Variable	General safety events	Pregnancy and birth outcomes		
	Descriptive	Descriptive	Matching	Propensity scores

COVID-19 = coronavirus disease 2019; LMP = date of last menstrual period; TORCH = toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes infections.
a. To be assessed on the index date for general safety events and on LMP for pregnancy and birth outcomes.
b. To be assessed on the index date for analysis of general safety events and from 28 days before LMP until end of pregnancy for pregnancy and birth outcomes. Only information up to and including the index date will be included in propensity scores.
c. Applies only to pregnancy outcomes analysis.
d. Except for multiple pregnancy, only information up to and including the index date will be included in propensity scores.

9.4. Data sources

The study will use data from data RPs that contribute claims and electronic health records to the Sentinel System. The data sources planned for inclusion in this the study are CVS Health (Aetna Research Database), Carelon Research (formerly HealthCore), HealthPartners, Humana, and Optum Research Database. The participation of these RPs in the general safety and/or pregnancy and birth outcome analyses will be confirmed before finalizing the SAP; additional data sources may be added.

Inclusion of data sources for specific analyses will be based on the following:

- Anticipated number of Pfizer-BioNTech bivalent COVID-19 vaccinees
- Coverage of special populations of interest (eg, pregnant women, pediatric population, individuals aged ≥ 65 years)
- Ability to identify pregnant women and link them to their infants
- Lag in claims and/or structured electronic health records data
- Availability, quality, and timing (frequency and lag) of data from immunization registries

The FDA Sentinel System is an active surveillance system that uses routine querying and analytical tools to evaluate electronic healthcare data from a distributed data network for monitoring the safety of regulated medical products in the US, established under the Sentinel Initiative (Behrman et al., 2011; Platt et al., 2018). Sentinel data RPs typically update their curated Sentinel database on a routine (tri-annually or annually) basis. This study will focus on the research-eligible populations from each of the RPs participating in the study and will use the most recent data available within each participating partner's Sentinel Distributed Database at the time of analysis.

All data RPs that participate in Sentinel capture longitudinal medical care information on outpatient medication dispensings, vaccine administrations, and inpatient and outpatient diagnoses and procedures. The data RPs also capture member demographic and health plan enrollment information. Each data RP can request access to full-text medical records for outcome validation for a subset of participants in the Sentinel Distributed Database. Data RPs use the Sentinel Common Data Model (SCDM) (Curtis et al., 2012; Sentinel, 2022) to standardize demographic and clinical data elements. Publicly available routine analytical tools (ie, reusable, modular SAS [SAS Institute Inc.; Cary, North Carolina] programs) designed to be executed against the SCDM permit standardized queries across data from different partners, including descriptive analyses and complex methodologies (eg, comparative analyses).

9.4.1. CVS Health, Aetna

Aetna, a CVS Health company, is one of the US's leading healthcare benefits companies, currently serving 39 million people. Aetna became part of the Sentinel System in 2008. Aetna's SCDM captures longitudinal information on dispensed prescriptions, inpatient and outpatient diagnoses, inpatient and outpatient treatments and procedures, and outpatient laboratory results. The healthcare experience for over 34 million individuals is available for research, covering all ages, with a median (range) age of 45 (0-119) years (based on individuals' most recent available data).

9.4.2. Carelon Research (formerly HealthCore, Inc.)

Carelon Research (formerly HealthCore, Inc.) became a participant in the Sentinel System in 2008 and contributes both by submitting data to the Sentinel database and as a collaborator. As of June 2022, there were 80 million unique individuals with medical coverage and approximately 62 million with medical and pharmacy coverage available for research, covering all ages, with a median age of 40 years and an interquartile range of 26-57 years.

9.4.3. HealthPartners

HealthPartners is the largest consumer-governed nonprofit healthcare organization in the US, providing care, insurance coverage, research, and education to its members and patients. HealthPartners operates primarily in the Midwest and serves more than 1.8 million medical and dental health plan members and more than 1.2 million patients, covering all ages, with a median age of 39 years and a range of 0-110 years. HealthPartners and its associated research team, HealthPartners Institute, became a member of the Sentinel System in 2008.

9.4.4. Humana

Humana Healthcare Research is a health economics and outcomes research subsidiary of Humana, which focuses on treatment effectiveness, drug safety, adherence, medical and pharmacy benefit design, disease management programs, and other healthcare services based on the Humana health plan member population. Humana Healthcare Research is an active collaborator and data RP in the Sentinel System. The Humana research-eligible database represents geographic coverage for the entire US population (Puerto Rico excluded) and as of 31 Dec 2022 has 31 million unique individuals, covering all ages, with a median age of 67 years and a mean continuous enrollment of 55.3 months.

9.4.5. Optum Research Database

The Optum Research Database is a proprietary research database that includes data drawn from a large US health plan affiliated with Optum. It contains eligibility data and medical and pharmacy claims for health plan members who are geographically diverse across the US. The Optum Research Database comprises approximately 3% to 4% of the US population, covering all ages, with a median age of 36 years and an interquartile range of 21-51 years. Optum has curated and quality-checked data formatted to the SCDM available for use and is a longtime participant in the Sentinel System.

9.5. Study size

9.5.1. Self-controlled Risk Interval (SCRI) Design

Because an SCRI design will be used, statistical power for general safety events depends on the total number of events in the risk and control intervals combined, the ratio of the duration of the risk and control intervals, and the IRR. Table 8 presents the statistical power that can be obtained for a range of incidence rate ratios and sample sizes, for a 2-sided alpha = 0.05 level test, using an SCRI design with risk and control intervals of equal duration (Musonda et al., 2006). For example, 80 events will provide 86% power to detect incidence rate ratios equal to or greater than 2.0.

Table 8. Study size calculations for self-controlled risk interval design

Total events	Incidence rate ratio	Power
20	1.4	0.11
	1.6	0.17
	1.8	0.25
	2.0	0.32
	2.2	0.39
	2.4	0.46
40	1.4	0.18
	1.6	0.31
	1.8	0.44
	2.0	0.57
	2.2	0.68
	2.4	0.76
80	1.4	0.32
	1.6	0.55
	1.8	0.73
	2.0	0.86
	2.2	0.93
	2.4	0.97
100	1.4	0.39
	1.6	0.64
	1.8	0.83
	2.0	0.93
	2.2	0.97
	2.4	0.99

9.5.2. Study size for the pregnancy cohort

Table 9 provides power calculations for pregnancy outcomes assuming a log-rank test at a 2-sided alpha = 0.05 level for various hazard ratios and numbers of pregnant women (1:1 matching ratio) for each birth outcome assuming the incidence of each outcome is 0.5% for stillbirths, 10% for preterm, and 12% for spontaneous abortion.

Table 9. Power for varying hazard ratios and study size for pregnancy outcomes

Outcome (incidence)	Number of pregnant women per group	Hazard ratio			
		1.2	1.6	2	2.4
Stillbirths (0.5%)	20,000	0.269	0.959	1.000	1.000
	40,000	0.475	0.999	1.000	1.000
	60,000	0.642	1.000	1.000	1.000
	80,000	0.765	1.000	1.000	1.000
	100,000	0.851	1.000	1.000	1.000
Preterm (10%)	20,000	1.000	1.000	1.000	1.000
Spontaneous abortion (12%)	20,000	1.000	1.000	1.000	1.000

For example, assuming the true HR = 1.2, an outcome (eg, stillbirth) with a rate of 0.5% during follow-up, and a sample size of 100,000 per group, there would be 85% power to reject a null hypothesis of HR = 1.0. A sample size of 20,000 per group provides a power of 100% for preterm and spontaneous abortion if the true HR is 1.2 or higher.

For the birth outcomes (i.e., small size for gestational age and major congenital malformations), assuming the true odds ratio = 1.2, an outcome rate of 3% in the unexposed group and a sample size of 20,000 per group, there would be 90% power to reject (at p = 0.05 level for a 2-sided test) a null hypothesis that the prevalence odds ratio = 1.0.

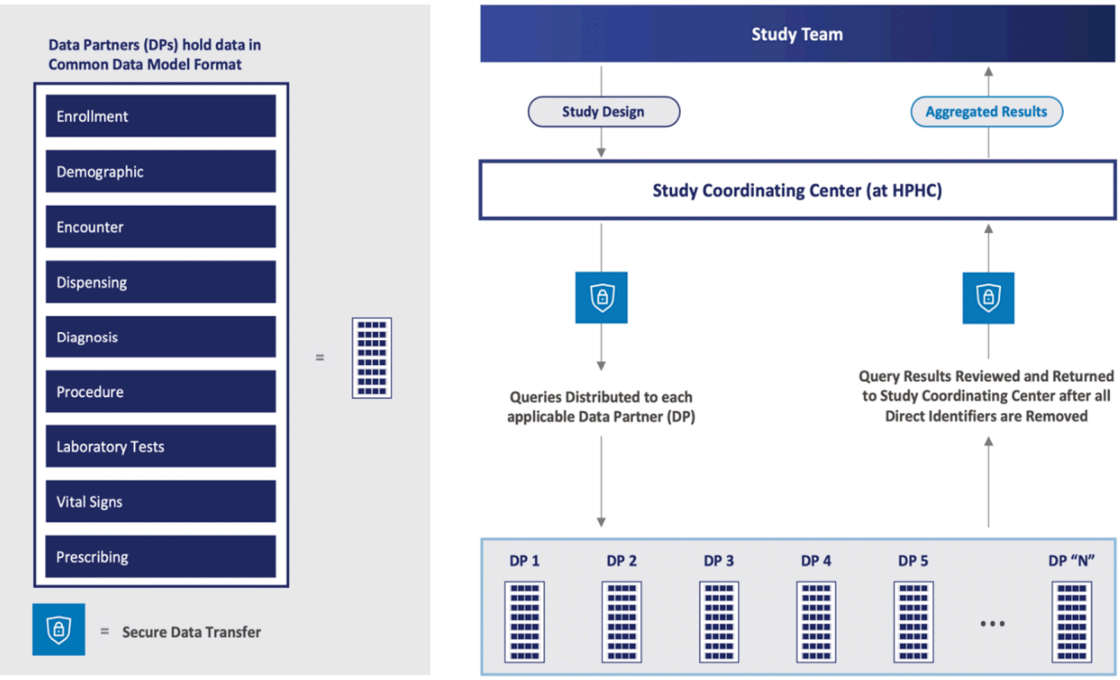
9.6. Data management

HPHCI, located in Boston, Massachusetts, will serve as the coordinating center for the study. HPHCI staff or contractors will be responsible for writing and distributing SAS programs that can be used to evaluate the data included in databases at participating data RPs. The distributed network will allow data RPs to maintain physical and operational control of their data while allowing use of the data to meet the study needs. HPHCI will maintain a secure, distributed, querying web-based portal to enable secure distribution of analytic queries, data transfer, and document storage. The system will meet all required state and federal security guidelines for health data (eg, Federal Information Security Management Act of 2002 [FISMA], Health Insurance Portability and Accountability Act of 1996) and will be specifically FISMA compliant for FISMA security controls as specified in the National Institute of Standards and Technology (NIST) Special Publication 800-53 (NIST, 2020).

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

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

Figure 4. General analytic workflow



HPHCI = Harvard Pilgrim Health Care Institute.

9.7. Data analysis

Analyses will initially be conducted separately using data from each RP. RP–specific aggregated results will be sent to the study coordinating center, which will combine aggregated results across the RPs for reporting. Pooled analysis of incidence rate ratios, HRs, and odds ratio estimates from all RPs will be conducted using privacy-preserving summary-level data sets (eg, risk set–level data sets) or another appropriate method.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Table 10 presents a summary of planned analyses. Analyses are described in more detail in Sections 9.7.1, 9.7.2, 9.7.3, 9.7.4, and 9.7.5.

Table 10. Summary of planned analyses

Type of safety event	Analysis	Study design	Results	Notes on main purpose of analysis/difference from primary analysis
General safety events	Primary analysis	SCRI	Descriptive, IRRs	N/A
	Subgroup analyses in populations of interest: immunocompromised individuals, pregnant women, individuals with severe COVID-19, and subgroups defined by age; additional analysis to be performed in subgroups defined jointly by sex and age (for myocarditis/pericarditis only)	SCRI	Descriptive, IRRs	Subgroup analyses
	Subgroup analysis: by receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine as a primary series vs booster dose	SCRI	Descriptive, IRRs	Exploratory subgroup analysis; only to be performed if feasible
	Sensitivity analysis: alternative risk periods	SCRI	IRRs	Sensitivity analysis to address potential risk interval misspecification; to be performed for general safety events that have signaled in other studies and for which risk intervals are not well characterized
	Sensitivity analysis: quantitative bias analysis to correct comparative risk estimates for outcome misclassification	SCRI	IRRs	Sensitivity analysis to address potential misclassification of outcomes in claims data; to be implemented for myocarditis/pericarditis, if the algorithm is demonstrated to have inadequate performance in other validation studies. Such analysis may also be considered for other general safety events that have signaled in other studies.

Table 10. Summary of planned analyses

Type of safety event	Analysis	Study design	Results	Notes on main purpose of analysis/difference from primary analysis
Pregnancy and birth outcomes	Primary analysis	Cohort: exposed vs unexposed	Descriptive; IRRs or HRs; PORs	N/A
	Subgroup analyses in populations of interest (immunocompromised individuals, individuals with history of severe COVID-19, and among subgroups defined by age)	Cohort	Descriptive, IRRs or HRs; PORs	Subgroup analyses
	Sensitivity analysis: restrict to population with linkages to immunization registries	Cohort: exposed vs unexposed	IRRs, PORs	Sensitivity analysis to address potential misclassification of unexposed status due to incomplete capture of COVID-19 vaccines in claims data; only to be performed if feasible
	Sensitivity analysis: quantitative bias analysis to correct comparative risk estimates for exposure misclassification	Cohort: exposed vs unexposed	IRRs, PORs	Sensitivity analysis to address potential misclassification of unexposed status due to incomplete capture of COVID-19 vaccines in claims data; to be considered if exposure misclassification is not sufficiently addressed in other analyses
	Sensitivity analysis: restrict to pregnant women who have a recorded history of monovalent COVID-19 vaccine before the index date	Cohort: exposed vs unexposed	IRRs, PORs	Sensitivity analysis to address potential confounding and misclassification of unexposed status in claims data
	Sensitivity analysis: quantitative bias analysis to correct comparative risk estimates for outcome misclassification	Cohort: exposed vs unexposed	IRRs, PORs	Sensitivity analysis to address potential misclassification of outcomes in claims data; analysis to be considered for pregnancy and birth outcomes that have signaled in other studies.

COVID-19 = coronavirus disease 2019; IRR = incidence rate ratio; N/A = not applicable; POR = prevalence odds ratio; SCRI = self-controlled risk interval.

9.7.1. Analysis of general safety events

For analysis of general safety events (which will be assessed using an SCRI design), Pfizer-BioNTech bivalent COVID-19 vaccinees within each outcome-specific analysis set will be described using demographics, comorbidities, and other key characteristics. For each general safety event, conditional Poisson regression or another appropriate statistical method will be used to obtain incidence rate ratios and 95% CIs in the risk interval compared with the control interval.

9.7.2. Analysis of pregnancy and birth outcomes

Among pregnant women, the distribution of demographics, comorbidities, and other potential confounders will be reported and compared between the matched exposed and unexposed cohorts. Covariate balance in the matched and weighted cohorts will be assessed using standardized differences or other suitable methods.

Vaccinated pregnant women will be matched to pregnant unexposed comparators in a ratio of exposed:unexposed of at least 1:1 on maternal age, US state (if feasible, or broader geographic region if not feasible), and pregnancy start (to address confounding by calendar time). Confounding by other variables will be addressed using inverse probability of treatment weighting, based on propensity scores estimated in the matched population.

In each data RP, measures of incidence or prevalence of pregnancy and birth outcomes and associated 95% CIs will be estimated within the matched exposed and unexposed cohorts.

Cox models or Poisson regression will be used to calculate adjusted HRs or incidence rate ratios and 95% CIs for spontaneous abortion, stillbirth, and preterm birth. For major congenital malformations and small size for gestational age, logistic regression will be used to estimate PORs and 95% CIs.

9.7.3. Sensitivity analysis

9.7.3.1. Risk interval misspecification

The SCRI design approach proposed in this protocol requires that risk intervals be specified correctly. If risk intervals are too long, comparative risk estimates may be attenuated. A sensitivity analysis with alternative risk interval definitions will be considered for general safety events if signals are observed in other studies or surveillance systems and if the risk interval is not well characterized.

9.7.3.2. Exposure misclassification

In the analysis of pregnancy and birth outcomes, the potential for lack of recording of COVID-19 vaccines in claims and electronic health records during the exposure window may lead to misclassification of exposed individuals as “unexposed” individuals, which will bias comparative risk estimates. If feasible, a sensitivity analysis will be considered to restrict analyses among data RPs that have linkages to high-quality immunization registry data available for some or all of their population. Additionally, quantitative bias analysis of comparative risk estimates of pregnancy and birth outcomes will be considered to assess the potential impact of exposure misclassification. If such analysis is performed, external vaccine coverage rates and estimates for sensitivity and specificity of COVID-19 vaccine capture in

claims data (based on the published literature if available, or a plausible range) will be used to obtain comparative risk estimates corrected for exposure misclassification.

9.7.3.3. Confounding

Comparisons between vaccinated and unvaccinated pregnant women may be confounded, as unvaccinated women may differ substantially with respect to health-seeking behaviors and other risk factors for pregnancy and birth outcomes. For pregnancy and birth outcomes, a sensitivity analysis will be performed among pregnant women with a recorded history of monovalent COVID-19 vaccination before cohort entry, which may serve as a proxy for these health-seeking behaviors. This sensitivity analysis will also address potential misclassification of unexposed status, as women with a recorded history of monovalent COVID-19 vaccination may have more complete data on bivalent COVID-19 vaccination.

Confounding by time-invariant characteristics is not a concern in the SCRI design because it is self-controlled.

9.7.3.4. Outcome misclassification

Outcome misclassification is possible due to the use of claims and structured electronic health records to identify safety events of interest. If the performance of the algorithm for myocarditis/pericarditis has not been demonstrated to be adequate in prior validation studies, quantitative bias analysis (as described in Section 9.3.2) will be performed on comparative risk estimates for myocarditis/pericarditis using algorithm validation results from Study C4591009 if the results are applicable to this study; if the results from Study C4591009 are not applicable to this study, then algorithm validation results from other studies may be used.

Quantitative bias analysis of comparative risk estimates for other study outcomes may be considered if safety signals are observed in other surveillance systems or studies.

9.7.4. Secondary objectives (subgroups of interest)

Subgroup analysis of general safety events will be conducted among pregnant women, immunocompromised individuals, individuals with a recorded history of severe COVID-19 (defined as an inpatient diagnosis in the principal diagnosis position, or in pregnant women, an inpatient claim with a primary diagnosis of viral diseases complicating pregnancy and diagnosis of COVID-19 in another position), and among subgroups defined by age. For myocarditis/pericarditis, age will be categorized as 6 months through 4 years, 5-11, 12-17, 18-24, 25-29, 30-39, 40-49, 50-64, and ≥ 65 years. For all other general safety events, age will be categorized as 6 months through 4 years, 5-11, 12-17, 18-64, and ≥ 65 years. Additionally, if at least 5 events are observed in a given subgroup, analysis for myocarditis/pericarditis will be performed in subgroups defined jointly by sex and age (in the above categories).

9.7.5. Additional subgroup analysis

If feasible in the data sources, analysis will be stratified by receipt of the bivalent vaccine as a primary series vaccine vs booster dose among eligible individuals. These analyses are considered to be exploratory and will require the availability of codes distinguishing between receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine as a primary series vs booster dose in the data sources. Alternatively, if feasible, receipt of the bivalent vaccine as a primary

series vs booster dose may be identified using an individual's recorded history of COVID-19 vaccination; however, such an analysis may not be feasible due to insufficient subgroup sizes, as it would require the study population to be limited to individuals with health plan enrollment from the initial date of becoming eligible for primary series vaccination (to enhance capture of COVID-19 vaccine doses before receipt of Pfizer-BioNTech bivalent COVID-19 Vaccine in administrative claims data).

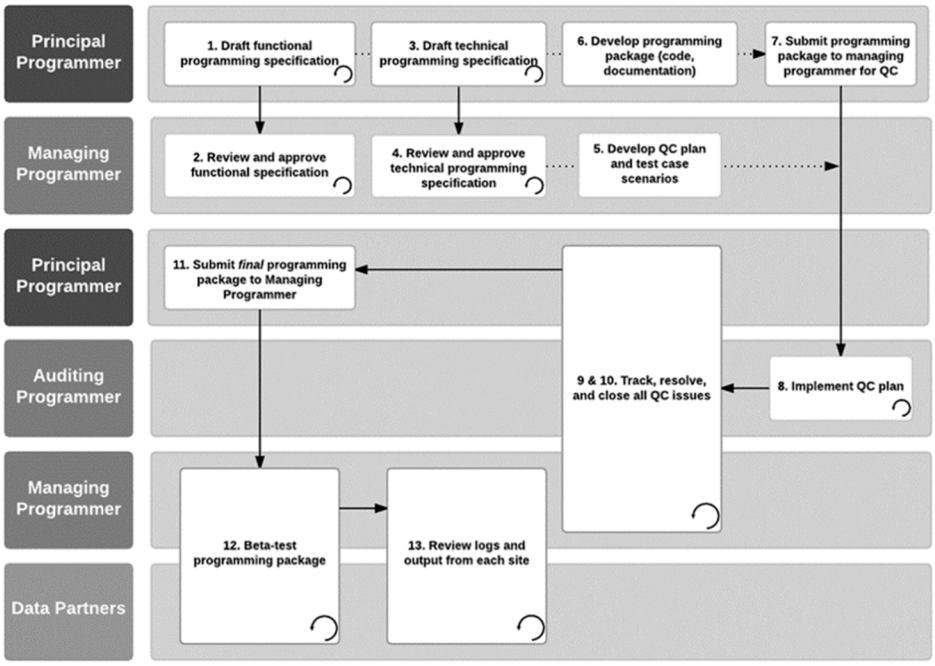
Additional subgroup analyses may be performed for other clinically relevant variables, as appropriate for the outcome.

9.8. Quality control

The data RPs that will contribute aggregate data for this study are all participants in the Sentinel System. The study will use the same data quality assurance (QA) procedures as the Sentinel System and the same curated datasets used by the FDA to conduct Sentinel analyses. The QA approach assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across data RPs. Full QA processes and details on the Sentinel database curation approach are documented on the Sentinel website (Sentinel, 2023a; Sentinel, 2017). The data curation approach is consistent with guidance set forth by the US FDA in its current recommendations for data QA, Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, Section IV.E Best Practices – Data Sources: Quality Assurance (QA) and Quality Control (QC), published in May 2013 (FDA, 2013; Sentinel, 2017). This Guidance describes best practices that particularly apply to observational studies designed to assess the risk associated with a drug exposure using electronic healthcare data.

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

Figure 5. Standard operating procedure for SAS programming quality assurance and quality control in the Sentinel System



QC = quality control.

9.9. Limitations of the research methods

A major strength of this study is the use of claims and electronic health records data (where available) collected as part of routine medical care, which will avoid recall bias and provides access to a large sample of commercially insured individuals in the US. This approach also minimizes the potential for selection bias that might occur in primary data collection studies, as the source population for the study includes all individuals in the participating databases who are eligible for research rather than individuals who have volunteered to participate in the study. The SCRI design, which will be used to analyze general safety events, avoids confounding due to time-invariant confounders (including history of COVID-19 vaccination) and misclassification of unexposed status due to incomplete capture of COVID-19 vaccines in claims data.

Nevertheless, this study is subject to limitations arising from the data sources and the selected study designs. Limitations related to the data sources include the potential for lack of recording in claims and electronic health records of COVID-19 vaccines administered without reimbursement from health insurers. For the cohort design, among pregnant women, this situation may lead to misclassification of exposed individuals as “unexposed” comparators, which would bias comparative risk estimates towards the null. If feasible, a sensitivity analysis will be performed among pregnant women with linkages to immunization registry data. Additionally, a quantitative bias analysis of comparative risk estimates of pregnancy and birth outcomes will be performed to assess the potential impact of exposure misclassification.

Similar to other claims and electronic health records databases in the US, an additional limitation of the data sources proposed for this study is that a substantial proportion of individuals may lack enrollment from the initial authorization of COVID-19 vaccines (on 10 December 2020) until the index date; long-term enrollment would be necessary to definitively assess prior completion of a primary vaccine series based on a patient's recorded history of COVID-19 vaccines in claims/administrative data. Within the Sentinel Distributed Database, only 47% of individuals have ≥ 2 years continuous database enrollment, with 36% of individuals enrolled for at least 2.5 years (Sentinel, 2023b). This may severely limit the ability to identify receipt of the bivalent vaccine as a primary series versus booster dose.

Another data source–related limitation is that the identification of outcomes and covariates in claims data and electronic health records data is based on algorithms and is subject to misclassification (eg, false positives, false negatives). There have been limited validation studies of *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM)-based algorithms for safety events of interest, and the accuracy of algorithms for many safety events of interest is unknown. When possible, validated algorithms will be used. However, some events, such as spontaneous abortion, are particularly at risk of misclassification, because early pregnancy losses may not be recognized in claims or even by the individual. If prior studies have not demonstrated adequate performance of the algorithm for myocarditis/pericarditis, a quantitative bias analysis will be performed to assess the potential impact of outcome misclassification on comparative risk estimates for myocarditis/pericarditis based on ongoing validation studies. Capture of non-severe and asymptomatic COVID-19 is anticipated to be substantially incomplete due to the high prevalence of at-home testing, non-medically attended COVID-19, and incomplete capture of laboratory results in the Sentinel Distributed Database. History of COVID-19 (which is a covariate and subgroup of interest for the study) will therefore be limited to severe COVID-19, defined using inpatient diagnoses of COVID-19.

A study design–related limitation is that the SCRI design (which is planned to assess general safety events) is more sensitive than a cohort design to misspecification of risk and control intervals. However, the SCRI design presents a strong alternative to a cohort design because it inherently adjusts for time-invariant confounders, including prior history of COVID-19 vaccination, which may be difficult to assess in claims data. While the SCRI design can generally be subject to time-varying confounding, the buffer and control intervals for each general safety event will be defined (in the SAP) to minimize this potential source of bias by minimizing each person's total duration of observation. Sensitivity analyses with alternative risk intervals will be considered for outcomes for which signals have been observed in other safety surveillance systems or studies and risk intervals that are not well characterized.

A limitation of the cohort design, which will be used to assess pregnancy and birth outcomes, is the potential for residual or unmeasured confounding, because it is unlikely that the data RPs will have information on all potential confounders. However, the cohort design presents a viable alternative to the SCRI design; unlike the SCRI design, it is suitable to assess safety events for which the risk varies substantially over time (such as spontaneous abortion) and/or the timing of onset is unknown (such as major congenital malformations and small size for gestational age). To address the potential for unmeasured confounding, sensitivity analysis will be performed among pregnant women with a history of monovalent COVID-19 vaccine

receipt, which may serve as a proxy for health-seeking behaviors and risk factors for pregnancy outcomes.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

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

10.2. Patient consent

As this study involves 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. Institutional review board (IRB)/Independent ethics committee (IEC)

Each data RP, as well as HPHCI, will follow its local requirements and data custodian requirements to access the data. As the coordinating center, HPHCI will seek approval from its local IRB. There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB or IEC and applicable documentation will be retained as part of the study materials. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

This is a post-authorization study of vaccine safety and will comply with the definition of the non-interventional (observational) study referred to in the International Council for Harmonisation tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004).

The study will be registered in the EU PAS Register (ENCePP, 2021) before data collection commences.

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor, and will follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (ISPE, 2015) issued by the International Society for Pharmacoepidemiology and Good Epidemiological Practice guidelines issued by the International Epidemiological Association (IEA, 2007).

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 the data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of analysis and interpretation will be delivered in the form of reports. A monitoring analysis report and final study report are planned per the milestone scheduled in Section 6. Results from the final report will be posted to the EU PAS Register. A manuscript reporting the results from the final analysis will also be submitted to a relevant peer-reviewed journal. Pfizer will notify the EMA 2 weeks after receiving the journal's notification of acceptance of the final manuscript for publication.

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2023). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (von Elm et al., 2008). Independent publication rights will be granted to the research team in line with Section VIII.B.5., Publication of Study Results, of the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies (EMA, 2017).

Communication via appropriate scientific venues will be considered.

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 the participant is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System—a national resource for evidence development. N Engl J Med. 2011 Feb 10;364(6):498-9. doi:http://dx.doi.org/10.1056/NEJMp1014427.

Curtis LH, Weiner MG, Boudreau DM, Cooper WO, Daniel GW, Nair VP, et al. Design considerations, architecture, and use of the Mini-Sentinel distributed data system. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:23-31. doi:http://dx.doi.org/10.1002/pds.2336.

EMA. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies (Rev 3). 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf. Accessed 27 October 2023.

ENCePP. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. The European Union Electronic Register of Post-Authorisation Studies (EU PAS Register). 2021. http://www.encepp.eu/encepp_studies/indexRegister.shtml. Accessed 27 October 2023.

FDA. Fact sheet for healthcare providers administering vaccine: emergency use authorization of Pfizer-BioNTech COVID-19 vaccine, bivalent (original and omicron BA.4/BA.5) April 2023a. https://www.fda.gov/media/167211/download. Accessed 13 November 2023.

FDA. Guidance for industry and FDA staff. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data. May 2013. https://www.fda.gov/media/79922/download. Accessed 27 October 2023.

FDA. Pfizer-BioNTech COVID-19 Vaccine EUA Letter. 11 September 2023b. https://www.fda.gov/media/150386/download. Accessed 27 October 2023.

ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Pharmacovigilance planning. E2E. 2004. https://database.ich.org/sites/default/files/E2E_Guideline.pdf. Accessed 27 October 2023.

ICMJE. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. May 2023. http://www.icmje.org/recommendations. Accessed 27 October 2023.

IEA. International Epidemiological Association. Good epidemiological practice: IEA guidelines for proper conduct of epidemiological research. 2007. https://ieaweb.org/IEAWeb/Content/IEA_Publications.aspx. Accessed 27 October 2023.

ISPE. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. June 2015. https://www.pharmacoepi.org/resources/policies/guidelines-08027. Accessed 27 October 2023.

Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. Stat Med. 2006 Aug 15;25(15):2618-31. doi:http://dx.doi.org/10.1002/sim.2477.

NBDPN. National Birth Defects Prevention Network. ICD10-CM and birth defects. 2023. https://www.nbdpn.org/icd10.php. Accessed 27 October 2023.

NBDPN. National Birth Defects Prevention Network. NBDPN guidelines for conducting birth defects surveillance. Chapter 3: Case definition. 2021. https://www.nbdpn.org/docs/SGSC_-_Ch3_Case_Definition_-_final_draft_2016DEC20.pdf. Accessed 27 October 2023.

NIST. National Institute of Standards and Technology. Security and privacy controls for information systems and organizations. NIST special publication 800-53, revision 5. 2020. https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.800-53r5.pdf. Accessed 27 October 2023.

Platt R, Brown JS, Robb M, McClellan M, Ball R, Nguyen MD, et al. The FDA Sentinel Initiative—an evolving national resource. N Engl J Med. 2018 Nov 29;379(22):2091-3. doi:http://dx.doi.org/10.1056/NEJMp1809643.

Regan JJ, Moulia DL, Link-Gelles R, Godfrey M, Mak J, Najdowski M, et al. Use of Updated COVID-19 Vaccines 2023-2024 Formula for Persons Aged ≥6 Months: Recommendations of the Advisory Committee on Immunization Practices - United States, September 2023. MMWR Morb Mortal Wkly Rep. 2023 Oct 20;72(42):1140-6. doi:http://dx.doi.org/10.15585/mmwr.mm7242e1.

Sentinel. US Food and Drug Administration. Data quality review and characterization programs. 23 February 2023a. https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model/data-quality-review-and-characterization-programs. Accessed 27 October 2023.

Sentinel. Length of member enrollment spans in the Sentinel Distributed Database. 8 February 2023b. https://www.sentinelinitiative.org/about/key-database-statistics#length-of-member-enrollment-spans-in-the-sentinel-distributed-database. Accessed 27 October 2023.

Sentinel. US Food and Drug Administration. Sentinel Common Data Model. 3 June 2022. https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model/sentinel-common-data-model. Accessed 27 October 2023

Sentinel. Sentinel Common Data Model: Mother Infant Linkage Table. 2019. https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model/mother-infant-linkage-table. Accessed 27 October 2023.

Sentinel. Food and Drug Administration. Sentinel data quality assurance practices. 23 March 2017. https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model/sentinel-data-quality-assurance-practices. Accessed 27 October 2023.

Shimabukuro T. Advisory Committee on Immunization Practices Meeting: COVID-19 MRNA Bivalent Booster Vaccine Safety. 24 February 2023. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/COVID-02-Shimabukuro-508.pdf. Accessed 13 November 2023.

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344-9. doi:http://dx.doi.org/10.1016/j.jclinepi.2007.11.008.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Not applicable	17 May 2023	Full Investigator List (available upon request)
2	Not applicable	30 Jun 2023	C4591009 Non-Interventional Study Protocol, Version 4.0

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A Non-Interventional Post-Authorization Safety Study of Pfizer-BioNTech Bivalent COVID-19 Vaccine in the United States

EU PAS Register® number: To be registered before the start of data collection
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				6
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	8, 9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1, 9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.1, 9.7

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

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

Section 3: Study design		Yes	No	N/A	Section Number
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

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

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.1, 9.3, 9.7
5.3	Is exposure categorized according to time windows?	☒	☐	☐	9.2
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1, 9.2

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQOL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3, 9.7
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1, 9.3, 9.7

Comments:

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3, 9.7

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

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

Comments:

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

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.7, 9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.7, 9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.1

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

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

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

Document Name:	C4591051_PROTOCOL AMENDMENT 1_V2.0_06DEC2023
Document Title:	C4591051_PROTOCOL AMENDMENT 1_V2.0_06DEC2023

Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	13-Dec-2023 14:13:18	Manager Approval
De Bernardi, Barbara	14-Dec-2023 13:35:52	EUQPPV Approval