Study information

Title	A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech COVID-19 Vaccine in the United States
Protocol number	C4591009
Protocol version identifier	1.0
Date	19 August 2021
EU Post-Authorization Study (PAS) register number	Study to be registered
Active substance	Pfizer-BioNTech coronavirus disease 2019 (COVID-19) Vaccine is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine
Research question and objectives	The research question is "What is the incidence (or birth prevalence) of safety events of interest among individuals vaccinated with (or exposed in utero to) Pfizer-BioNTech COVID-19 Vaccine compared with individuals who have not received (or not exposed in utero to) any vaccination for COVID-19 in the United States?" The primary objectives are as follows: • To estimate the relative risk (RR) of safety events of interest following receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine within the overall study population • To estimate the RR of safety events of interest following receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19

	• To estimate the birth prevalence and odds ratio of birth outcomes among pregnant women vaccinated with the Pfizer-BioNTech COVID-19 vaccine compared to unvaccinated pregnant women. The secondary objectives are as follows: • To describe the proportion of individuals receiving at least 1 dose and a complete dose series of Pfizer-BioNTech COVID-19 Vaccine, within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19 • To describe—among individuals who receive a first dose of Pfizer-BioNTech COVID-19 Vaccine—the timing and type of second dose of COVID-19 vaccine (Pfizer-BioNTech COVID-19 Vaccine or other COVID-19 vaccine), within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19 • To describe baseline characteristics (demographics and comorbidities) of individuals who receive at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine and those with no record of COVID-19 vaccination of any type, within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19
Author	Alison Kawai, ScD RTI Health Solutions Waltham, Massachusetts Jeffrey Brown, PhD Department of Population Medicine Harvard Medical School & Harvard Pilgrim Health Care Institute Boston, Massachusetts Cynthia de Luise, MPH, PhD Risk Management and Safety Surveillance Research

	Pfizer Inc. New York, New York

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AEM	adverse event monitoring
BEST	Biologics Effectiveness and Safety
BLA	Biological License Application
BNT162b2	Pfizer-BioNTech COVID-19 vaccine
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CPT	Current Procedural Terminology
CTS	Clinical Trial Services
DCT	data collection tool
DP	data partner
ETL	Extract, Transformation, Load
EUA	Emergency Use Authorization
EU PAS Register	European Union Electronic Register of Post-Authorisation Studies
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act
FU	follow-up
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HHR	Humana Healthcare Research

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPHCI	Harvard Pilgrim Health Care Institute
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, Procedure Coding System
IEC	Independent Ethics Committee
IMEDS	Innovation in Medical Evidence Development and Surveillance
IRB	institutional review board
LNP	lipid nanoparticle
mRNA	messenger RNA
NIS	non-interventional study
NIST	National Institute of Standards and Technology
PASS	post-authorization safety study
PCORnet	The National Patient-Centered Clinical Research Network
PHI	protected health information
Q (1-4)	1st, 2nd, 3rd, or 4th Quarter
QA	quality assurance
QC	quality control
RR	relative risk
RTI-HS	RTI Health Solutions

Abbreviation	Definition
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCDM	Sentinel Common Data Model
SCRI	self-controlled risk interval design
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 infections
US	United States
VSD	Vaccine Safety Datalink
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigators and Contributors to the Protocol

Name, degree(s)	Job title	Affiliation	Address
Cynthia de Luise, MPH, PhD	Senior Director, Epidemiology	Pfizer Inc.	235 E 42nd Street, Mail Stop 219/8/01; Office 61 New York, NY 10017 USA
Alison Kawai, ScD	Senior Research Epidemiologist	RTI Health Solutions	307 Waverley Oaks Rd, Suite 101 Waltham, MA, US 02452
Jeffrey Brown, PhD	Associate Professor in the Department of Population Medicine	Harvard Medical School & Harvard Pilgrim Health Care Institute	401 Park Drive, Suite 401 Boston, MA 02215
Catherine Johannes, PhD	Senior Director, Epidemiology	RTI Health Solutions	307 Waverley Oaks Rd, Suite 101 Waltham, MA, US 02452
J Bradley Layton, PhD	Senior Research Epidemiologist	RTI Health Solutions	3040 East Cornwallis Rd, PO Box 12194 Research Triangle Park, NC US 27709
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, FISPE	Vice President, Epidemiology	RTI Health Solutions	3040 East Cornwallis Rd, PO Box 12194 Research Triangle Park, NC US 27709
Brian Calingaert, MS	Director, Epidemiology Analysis	RTI Health Solutions	3040 East Cornwallis Rd, PO Box 12194 Research Triangle Park, NC US 27709

Data Research Partner Coordinating Investigators

Name, degree(s)	Job title	Affiliation	Address
Cheryl N McMahill-Walraven, MSW, PhD	Director, Safety Surveillance & Collaboration	CVS Health, Clinical Trial Services (CTS)	1425 Union Meeting Road – U21n Blue Bell, PA 19422-0031
Audrey Djibo, PhD	Epidemiologist	CVS Health, Clinical Trial Services (CTS)	1425 Union Meeting Road – U21n Blue Bell, PA 19422-0031
Aziza Jamal-Allial, PhD	Senior Epidemiologist	HealthCore	480 Pleasant Street Suite A100 Watertown, MA 02472
Kevin Haynes, PharmD, MSCE	Principal Scientist	HealthCore	480 Pleasant Street Suite A100 Watertown, MA 02472
Pamala A. Pawloski, PharmD., BCOP, FCCP	Senior Research Investigator	HealthPartners Institute	295 Phalen Blvd; MS41200F St. Paul, MN 55130
Vinit Nair, BPharm, MS, RPh	Principal & Director, Government Research & Consortiums	Humana	515 W. Market St Louisville, KY 40202
Ryan Seals, PhD	Epidemiologist	Optum	1325 Boylston Street, Suite 1100 Boston, MA 02215
Jessica Franklin, PhD	Principal Consultant, Epidemiology	Optum	1325 Boylston Street, Suite 1100 Boston, MA 02215

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

4. ABSTRACT

Title: A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech COVID-19 Vaccine in the United States

Version and Date: Version 1.0, 19 August 2021

Main authors: Alison Kawai, ScD, RTI Health Solutions; Jeffrey Brown, PhD, Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute; Cynthia de Luise, MPH, PhD, Risk Management and Safety Surveillance Research, Pfizer Inc.

Rationale and background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has resulted in a global pandemic. On 11 December 2020, Pfizer-BioNTech COVID-19 Vaccine was authorized for emergency use by the Food and Drug Administration (FDA) to prevent COVID-19 in individuals aged 16 years and older in the United States (US). On 10 May 2021, Pfizer-BioNTech COVID-19 Vaccine was authorized for emergency use in children 12-15 years of age in the US. As of 07 May 2021, Pfizer-BioNTech has initiated a Biological License Application (BLA) for marketing approval of the vaccine for the prevention of COVID-19 in individuals aged 16 years and older.

Post-authorization observational studies using real-world data are needed to assess the association between Pfizer-BioNTech COVID-19 Vaccine and predetermined safety events of interest in individuals administered the vaccine in the general population and in subpopulations of interest (e.g., pregnant women, immunocompromised individuals, and individuals with a history of COVID-19). This protocol describes a proposed observational study of safety events of interest occurring in recipients of Pfizer-BioNTech COVID-19 Vaccine using data from claims and electronic health records (where available) from data research partners participating in the Sentinel System. The safety events of interest in this study are based on those included in COVID-19 vaccine rapid cycle analysis in the FDA's Biologics Effectiveness and Safety (BEST) System and the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink (VSD), with the addition of vaccine-associated enhanced respiratory disease, immune hemolytic anemia, and thrombotic events with thrombocytopenia. Pregnancy safety outcomes (spontaneous abortion, stillbirth, and preterm birth, major congenital malformations, and small size for gestational age) will also be assessed in this study. Additional safety events of interest may be added as new evidence develops during the pandemic and the data sources permit. The proposed non-interventional study is designated as a post-authorization safety study (PASS) and is a commitment to the US FDA.

Research question and objectives

The research question is, "What is the incidence or (or birth prevalence) of safety events of interest among individuals vaccinated with (or exposed in utero to) Pfizer-BioNTech

COVID-19 Vaccine compared with individuals who have not received (or not exposed in utero to) any vaccination for COVID-19 in the United States?"
The primary objectives are as follows:

- To estimate the relative risk (RR) of safety events of interest following receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine within the overall study population

- To estimate the RR of safety events of interest following receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19

- To estimate the birth prevalence and odds ratio of birth outcomes among pregnant women vaccinated with the Pfizer-BioNTech COVID-19 vaccine compared to unvaccinated pregnant women

The secondary objectives are as follows:

- To describe the proportion of individuals receiving at least 1 dose and a complete dose series of Pfizer-BioNTech COVID-19 Vaccine, within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19

- To describe—among individuals who receive a first dose of Pfizer-BioNTech COVID-19 Vaccine—the timing and type of second dose of COVID-19 vaccine (Pfizer-BioNTech COVID-19 Vaccine or other COVID-19 vaccine), within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19

- To describe baseline characteristics (demographics and comorbidities) of individuals who receive at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine and those with no record of COVID-19 vaccination of any type, within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19

Study design

This is a retrospective cohort study comparing vaccinated individuals with unexposed individuals who have not received any COVID-19 vaccine during a concurrent time. Exposed and unexposed individuals will be matched (in a ratio of at least 1:1) within data source on age, state (if feasible, or broader geographic region if not feasible), calendar time, and propensity score (for analysis in the overall population, immunocompromised individuals, and individuals with a history of COVID-19) or on maternal age, state (if feasible), and estimated pregnancy start (for analysis in pregnant women). In analysis of

pregnant women, confounding will be addressed through propensity score matching or through the inclusion of propensity scores in exposure-outcome regression models.

The study period will start on the date that Pfizer-BioNTech COVID-19 Vaccine was granted Emergency Use Authorization (EUA) in the US (11 December 2020) and will end a minimum of 3 years after this date. The study will include vaccinations received under both the EUA and the BLA (once approved).

Population

The source population for this study will be health plan enrollees from 5 data research partners that contribute data from claims and electronic health records to the Sentinel System: CVS Health/Aetna, HealthCore/Anthem, HealthPartners, Humana, and Optum/UnitedHealthcare.

Individuals of all ages will be included in the descriptive analysis of Pfizer-BioNTech COVID-19 Vaccine utilization. Safety analysis is planned to be limited to individuals within the age ranges approved (either under the EUA or the BLA) to receive Pfizer-BioNTech COVID-19 Vaccine, with age-based eligibility criteria changing over the study period as the ages approved for use change. However, if the proportion of Pfizer-BioNTech COVID-19 Vaccine recipients that falls outside of the ages approved for use is greater than 1%, then safety analyses will include individuals of all ages who have received the vaccine at any time during the study period.

Individuals will be eligible for the study if they have continuous medical and pharmacy insurance coverage for at least 12 months before the index date (defined in the next paragraph). Women will be eligible to be included in analysis of the pregnant population if they were pregnant for at least 1 day during the study period (regardless of the timing of estimated pregnancy start relative to the study start date). Analysis of congenital malformations, preterm birth, and small size for gestational age will be limited to pregnancies ending in a live birth.

For exposed individuals in the general population, immunocompromised individuals, and individuals with a history of COVID-19, the index date is the date of receipt of the Pfizer-BioNTech COVID-19 Vaccine, and this date is the start of follow-up (FU); each dose of Pfizer-BioNTech COVID-19 Vaccine will contribute separate index dates. For each individual selected to be an unexposed match, an index date will be assigned to a randomly selected date in close temporal proximity (e.g., within the same calendar month) to the vaccination date of their exposed match.

For analyses of spontaneous abortion, stillbirth, and preterm birth, each dose of Pfizer-BioNTech COVID-19 Vaccine will contribute separate index dates. For each individual selected to be an unexposed match, the index date will be set to the equivalent of the gestational age (in days) at the time of vaccination of their exposed match. For analyses of

small size for gestational age and congenital malformations, the index date in exposed and unexposed individuals is the estimated pregnancy start date.

The following subpopulations will be identified for descriptive and comparative safety analysis: individuals with immunocompromising conditions, pregnant women, and individuals with a history of COVID-19. Additional subgroup analysis will be conducted by age group (<18, 18-64, ≥65 years).

Variables

Safety events

Safety events of interest will be identified in claims and electronic health records (where available, as not all data research partners will have access to electronic health records) using predefined algorithms based on diagnosis codes, with procedure and/or pharmacy dispensing codes as appropriate. Algorithms for select outcomes that may be susceptible to substantial misclassification may be validated through clinician review of medical records or patient profiles (i.e., listings of codes in data from claims or electronic health records in chronological order) to estimate the positive predictive values. The determination of whether each outcome may be susceptible to substantial misclassification will be informed by clinical expert opinion and review of prior validation studies, if available.

The following safety events of interest (referred to as "general safety events") will be assessed in the general population, immunocompromised individuals (e.g., individuals with immunodeficiencies, immunosuppressant medication use, human immunodeficiency virus or other immunocompromising conditions, or receipt of organ or bone marrow transplant), individuals with a history of COVID-19, and pregnant women:

- Neurologic: acute disseminated encephalomyelitis, Bell's palsy, convulsions, encephalomyelitis/encephalitis, Guillain Barré syndrome, narcolepsy, transverse myelitis
- Cardiac: acute myocardial infarction, myocarditis/pericarditis
- 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, vaccine-associated enhanced respiratory disease
- Other system: anaphylaxis, appendicitis, Kawasaki disease, multisystem inflammatory syndrome

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

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

Other emergent safety events of interest may be added as the understanding of the safety profile of Pfizer-BioNTech COVID-19 Vaccine evolves and if the data sources permit their assessment. For general safety events, risk windows will be defined for outcomes that have a hypothesized increased risk during specific time periods following vaccination. For other general safety events, patients will be followed for outcomes for a maximum of 1 year.

Vaccine exposures

Exposures to Pfizer-BioNTech COVID-19 Vaccine will be identified in data from claims and electronic health records 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 existing linkages with immunization registries are available for use in research studies within the appropriate data research partner databases, the immunization registry data will also be used to assess exposure. The completeness of data on COVID-19 vaccines will be assessed during the monitoring phase of the study. Based on the level of completeness of data on COVID-19 vaccine exposures and its anticipated impact on comparative risk estimates, alternative study designs (eg. self-controlled analyses and/or linkages to immunization registries will be considered.

Covariates

Covariates will be identified in data from claims and electronic health records (where available, as not all data research partners will have access to electronic health records) using administrative health plan enrollee data or codes for diagnoses (with procedures or medications, as appropriate). The following potential variables will be identified in relation

to the index date (i.e., cohort entry date), to be included in descriptive analysis and to be considered as potential confounders in analysis of general safety events.

- Demographics (on the index date, unless otherwise noted): age, sex, geographic region (using the latest information available as of the index date), and race/ethnicity (if feasible)

- Date of Pfizer-BioNTech COVID-19 Vaccine (categorized as appropriate, e.g., by year or month) and dose of vaccine received (1 or 2)

- Medical history:

    - Comorbidities (in the 12 months before or on the index date, unless otherwise noted): history of anaphylaxis (not including the index date), history of allergies, diabetes (type 1, type 2, gestational diabetes in current pregnancy), hypertension, cardiovascular disease, cerebrovascular diseases, chronic respiratory disease, chronic kidney disease, chronic liver disease, cancer, epilepsy, autoimmune disorders, influenza and other respiratory infections (including COVID-19), immunocompromising conditions, gastrointestinal infections, and obesity (capture anticipated to be incomplete)

    - Pregnancy status (on the index date)

    - Medications and non–COVID-19 vaccinations (in the 12 months before or on the index date), including vaccines administered concomitantly with Pfizer-BioNTech COVID-19 Vaccine

    - Healthcare utilization (in the 12 months before or on the index date): any healthcare encounter (including telehealth encounters, if feasible); hospitalizations; emergency department visits; cancer screening(s); skilled nursing facility, nursing home, or extended care facility stay; other preventive healthcare services, as appropriate; and COVID-19 tests

For comparative analysis of pregnancy safety outcomes, the following potential confounders and descriptive variables will be identified in relation to the index date.

- Demographics (on the index date, unless otherwise noted): maternal age, geographic region (using the latest available information on index date), race/ethnicity (if feasible)

- Medical history:
    - Comorbidities (in the 12 months before or on the index date): diabetes mellitus (type 1, type 2), hypertension, connective tissue disorders, thyroid disorders, heart disease, epilepsy and mood disorders, asthma, liver disease, kidney disease, cancer
    - Obesity (in the 12 months before or on the index date; capture anticipated to be incomplete since obesity is not routinely documented via diagnosis or procedure codes in claims data)
    - Alcohol use and smoking (in the 12 months before or on the index date; capture anticipated to be incomplete)
    - Reproductive history (in all available data): gravidity, parity, spontaneous abortions in previous pregnancies, and pregnancy terminations in previous pregnancies (capture anticipated to be incomplete)
    - Pregnancy complications (recorded during the pregnancy): multiple pregnancy, gestational diabetes, preeclampsia/eclampsia, TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes infections); except for multiple pregnancy, only information recorded up to and including the index date will be used to identify potential confounders
    - Teratogenic medications (from 28 days before pregnancy up to and including the end of pregnancy); only information up to and including the index date will be used to identify potential confounders
    - Non–COVID-19 vaccinations, including those administered concomitantly with Pfizer-BioNTech COVID-19 Vaccine (from 28 days before pregnancy up to and including the end of pregnancy); only information up to and including the index date will be used to identify potential confounders

Data sources

This study will use data from 5 data research partners, including data from 4 national insurers (CVS Health/Aetna, HealthCore/Anthem, Humana, and Optum/UnitedHealthcare) and 1 regional insurer (HealthPartners). Each data research partner is a participant in the FDA Sentinel System. This study will use the research eligible population within the most recently available database at each data research partner at the time of analysis. These data sources capture longitudinal medical care information on outpatient medication dispensings, vaccine administrations, and inpatient and outpatient diagnoses and procedures. The data sources also capture member demographic and health plan enrollment information. Each data research partner can request access to full-text medical records for outcome validation for a subset of participants. Where available, maternal data will be linked with infant data to

identify outcomes to be assessed in infants (small size for gestational age and major congenital malformations).

Study size

The size of the exposed population will depend on the use of Pfizer-BioNTech COVID-19 Vaccine, and the size of the comparator population will depend on the proportion of the source population that comprises unvaccinated individuals over time in the data sources. The precision of comparative risk estimates will depend on the background rate and the duration of the risk interval for each safety event of interest. For example, for Bell's palsy (background rate of 25.2 per 100,000 person-years and 28 days at risk per dose), with 1,000,000 exposed individuals, we estimate an 86% probability that the upper bound of the observed RR would be below 2.0, assuming a 1:1 ratio between vaccinated and comparator person-time and that the true RR is 1.0.

Data analysis

All analyses will initially be conducted separately within the data from each data source. Pooled analysis of RR and odds ratio estimates from all data sources will be conducted using privacy-preserving summary-level data sets or, if this is not feasible, meta-analysis.

Descriptive analysis will report on utilization of Pfizer-BioNTech COVID-19 Vaccine during the overall study period and in sequential increments of time (to assess vaccine uptake and patterns of exposure over time). Characteristics (demographics, comorbidities, and other potential covariates) of the matched and unmatched cohorts will be shown in a table.

Vaccinated individuals will be matched to concurrent unexposed comparators (in a ratio of at least 1:1) within data source on age, state (if feasible, or broader geographic region if not feasible), and calendar time–specific propensity scores for analysis in the overall study population, immunocompromised individuals, and individuals with a history of COVID-19. In analyses of pregnant women, pregnant women who are vaccinated will be matched to pregnant concurrent unexposed comparators (in a ratio of at least 1:1) on maternal age, state (if feasible, or broader geographic region if not feasible), and pregnancy start. Confounding will be addressed through propensity score matching or through the inclusion of propensity scores in exposure-outcome regression models.

In each data source, crude measures of incidence or prevalence of the study outcomes with associated 95% confidence intervals (CIs) will be estimated within the matched exposed and unexposed cohorts.

Cox models or Poisson regression will be used to estimate RRs and 95% CIs for general safety events in the overall study population, immunocompromised individuals, individuals with a history of COVID-19 and pregnant women, and to estimate RRs 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 odds ratios and 95% CIs.

To address the potential for misclassification of unexposed status due to incomplete capture of vaccination exposures in claims data, sensitivity analyses will incorporate a self-controlled risk interval design (for outcomes with well-defined onset and risk intervals of no longer than 42 days) or a cohort design with historical comparators in a period before the introduction of COVID-19 vaccines (for outcomes with gradual onset and/or risk intervals longer than 42 days). Additional sensitivity analyses will consider alternative risk intervals for safety events for which the risk interval is not well characterized.

Milestones

The anticipated start of data collection is quarter 2 (Q2) 2022, and the end of data collection is anticipated to be by 30 June 2025. A monitoring report is planned for Q3 2022, an interim study report for Q3 2023, and a final study report no later than Q4 2025, depending on the extent of validation and/or the need for external linkages.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Below is a proposed schedule of milestones.

Milestone	Planned date	Description of milestone
Registration in the EU PAS Register	To be determined (TBD)	To be registered before the start of data collection
Start of data collection, estimated	Q2 2022	Start of data collection is the planned date for the initial data extraction for the purpose of the monitoring analysis
Monitoring analysis report[a,b]	Q3 2022	Vaccine counts and proportions of individuals in the databases who were vaccinated, within the overall study population, in immunocompromised individuals, in individuals with a history of COVID-19, and in subgroups defined by age (< 18, 18-64, 65 years and older)
Interim study report	Q3 2023	Vaccine counts and proportions of individuals in the databases who were vaccinated, within the overall study population, in immunocompromised individuals, in individuals with a history of COVID-19, and in subgroups defined by age (< 18, 18-64, 65 years and older) Distribution of characteristics among exposed and unexposed individuals within the overall study population, in immunocompromised individuals, and in individuals with a history of COVID-19 Incidence rates of safety events of interest, overall, without regard to exposure status, in the overall study population, in immunocompromised individuals, and in individuals with a history of COVID-19 For select safety events of interest that have signaled in other studies or vaccine safety surveillance systems (e.g., myocarditis/pericarditis), additional analysis describing incidence by exposure status and by select covariates of interest may be reported
End of data collection	30 June 2025	End of data collection is the planned date on which the analytical data set will first be completely available The analytical data set is the minimum set of data required to perform the statistical analysis for the study objectives

Milestone	Planned date	Description of milestone
Final study report	Q3 2025[c]	Descriptive analysis of vaccine utilization in the overall study population, in immunocompromised individuals, in individuals with a history of COVID-19, and in pregnant women Comparative safety analysis in the overall study population, in immunocompromised individuals, in pregnant women, and in individuals with a history of COVID-19

a. Includes only data research partners with a data lag of < 6 months.
b. Monitoring counts will not incorporate enrollment or any other study eligibility criterion.
c. Report may be delayed to Q4 2025, depending on the extent of validation and/or the need for external linkages.

7. RATIONALE AND BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has resulted in a global pandemic (WHO, 2020). As of 03 August 2021, approximately 200 million cases of COVID-19 have been reported globally, with over 35 million cases and 618,407 deaths reported in the United States (US) (CSSE, 2021). To date, the incidence of COVID-19 has continued to rise, largely affecting the elderly and middle-aged individuals, with a disproportion of cases occurring in racial and ethnic minority populations (Lee et al., 2021), and with worsening clinical sequelae linked to increasing age and comorbid conditions (e.g., cardiovascular disease, active cancer, obesity, diabetes, and chronic lung disease) (CDC Covid Response Team, 2020; Dorjee et al., 2020; Gupta et al., 2020).

Pfizer and BioNTech have developed a novel messenger RNA (mRNA) vaccine against SARS-CoV-2 for the prevention of COVID-19 (BNT162b2). This is a lipid nanoparticle–formulated, nucleoside-modified mRNA vaccine that directs the host cell to produce the SARS-CoV-2 spike protein, which is expressed on the host cell surface and induces neutralizing antibody and cellular immune responses (Lamb, 2021). The BNT162b2 vaccine is administered intramuscularly in a 2-dose regimen with a recommended interval between doses of 21 days (Lamb, 2021).

Pfizer is conducting Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy studies among healthy individuals (NCT04368728). The Phase 3 clinical trial was initiated on 27 July 2020, with a target enrollment of 43,998 individuals; efficacy and safety results from this ongoing multinational trial were reported in December 2020 for 43,448 individuals aged 16 years or older who received injections (21,720 with BNT162b2 and 21,728 with placebo) and showed that a 2-dose regimen was 95% effective in preventing COVID-19 (Polack et al., 2020). Safety was assessed in 37,706 participants with a median of at least 2 months of data available after the second dose, with most adverse events (AEs) being transient reactogenicity events; the most commonly solicited AEs were pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%) (Pfizer and BioNTech, 2020). The incidence of serious AEs was similar in the vaccine (0.6%) and placebo (0.5%) groups (Polack et al., 2020). An imbalance was noted in the occurrence of Bell's palsy, with 4 cases in the vaccine group and no cases in the placebo group, but the frequency was not in excess of that expected in the general population (Pfizer and BioNTech, 2020).

Efficacy and safety results for the Phase 3 clinical trial were reported in May 2021 for 2,260 adolescents 12 to 15 years of age (1,131 with BNT162b2 and 1,129 with placebo) (Frenck et al., 2021). No COVID-19 cases with onset of 7 or more days after dose 2 occurred among recipients of BNT162b2, and 18 cases occurred among recipients of placebo, for an observed vaccine efficacy of 100% (95% confidence interval [CI], 78.1%-100%). Adverse events were mainly transient, mild to moderate reactogenicity events such as injection site pain (in 79%-86% of study participants), fatigue (in 60%-66% of participants), and headache (in

55%-65% of participants). There were no vaccine-related serious AEs, and severe AEs were very rare (in 0.2% of BNT162b2 recipients).

On 11 December 2020, Pfizer-BioNTech COVID-19 Vaccine was authorized for emergency use by the US Food and Drug Administration (FDA) to prevent COVID-19 in individuals 16 years of age or older (Pfizer, 2020) and on 12 December 2020, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation for use of the vaccine in individuals aged 16 years or older (Oliver et al., 2020). On 10 May 2021, Pfizer-BioNTech COVID-19 Vaccine was authorized for emergency use in children 12-15 years of age (FDA, 2021), and on 12 May 2021, the ACIP issued an interim recommendation for the use of the vaccine in children 12-15 years of age (Wallace et al., 2021). As of 07 May 2021, Pfizer-BioNTech has initiated the submission of a Biological License Application (BLA) approval authorization of Pfizer-BioNTech COVID-19 Vaccine for the prevention of SARS-CoV-2 infection in individuals aged 16 years or older.

Because of the relatively short prelicensure period and limited number of participants in clinical studies, monitoring of the safety of the vaccine will be needed in the US in populations large enough to detect rare possible AEs and with follow-up long enough to evaluate the full safety profile. The clinical study NCT04368728 did not include certain subgroups of individuals for whom safety data about the vaccine is needed. These groups include pregnant women, immunocompromised individuals, and individuals with a history of COVID-19 (ClinicalTrials.gov NCT04368728, 2021). An ongoing clinical study (NCT04754594) is evaluating the safety, tolerability, and immunogenicity of Pfizer-BioNTech COVID-19 Vaccine in pregnant women, but the study is limited to healthy women with uncomplicated pregnancies who were 24 to 34 weeks pregnant at the time of enrollment (ClinicalTrials.gov NCT04754594, 2021). Post-authorization observational studies using real-world data are needed to assess the association between Pfizer-BioNTech COVID-19 Vaccine and predetermined safety events of interest in individuals administered the vaccine in the general population of all ages and in subpopulations of interest (e.g., pregnant women, immunocompromised individuals, and individuals with a history of COVID-19).

This protocol describes a proposed observational study of safety events of interest occurring in recipients of Pfizer-BioNTech COVID-19 Vaccine using data from claims and electronic health records (where available) from data research partners participating in the Sentinel System. The safety events of interest in this study are partially based on those included in COVID-19 vaccine safety surveillance in the FDA Biologics Effectiveness and Safety (BEST) System (Wong et al., 2021) and the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink (VSD) (Shimabukuro, 2021), with the addition of vaccine-associated enhanced respiratory disease, immune hemolytic anemia, and thrombotic events with thrombocytopenia. Pregnancy safety outcomes (spontaneous abortion, stillbirth, and preterm birth, major congenital malformations, and small size for gestational age) will also

be assessed in the study. Additional safety events of interest may be added as new evidence develops during the pandemic and the data sources permit.

The proposed non-interventional study is designated as a post-authorization safety study (PASS) and is a commitment to the US FDA.

8. RESEARCH QUESTION AND OBJECTIVES

The main research question is, "What is the incidence (or birth prevalence) of safety events of interest among individuals vaccinated with (or exposed in utero to) Pfizer-BioNTech COVID-19 Vaccine compared with individuals who have not received (or not exposed in utero to) any vaccination for COVID-19 in the United States?"
Primary objectives

- To estimate the relative risk (RR) of safety events of interest following receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine within the overall study population
- To estimate the RR of safety events of interest following receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19
- To estimate the birth prevalence and odds ratio of birth outcomes among pregnant women vaccinated with the Pfizer-BioNTech COVID-19 vaccine compared to unvaccinated pregnant women

Secondary objectives

- To describe the proportion of individuals receiving at least 1 dose and a complete dose series of Pfizer-BioNTech COVID-19 Vaccine, within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19
- To describe—among individuals who receive a first dose of Pfizer-BioNTech COVID-19 Vaccine—the timing and type of second dose of COVID-19 vaccine (Pfizer-BioNTech COVID-19 Vaccine or other COVID-19 vaccine), within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19
- To describe baseline characteristics (demographics and comorbidities) of individuals who receive at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine and those with no record of COVID-19 vaccination of any type, within the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19

9. RESEARCH METHODS

9.1. Study design

This study will use a retrospective cohort design to compare the incidence or birth prevalence of safety events of interest in individuals who have received Pfizer-BioNTech COVID-19 Vaccine to the incidence or birth prevalence in individuals who have no record of any COVID-19 vaccine during a concurrent time. Vaccinated individuals will be matched to concurrent unexposed comparators (in a ratio of at least 1:1) within data source on age, state (if feasible, or broader geographic region if not feasible), calendar time, and propensity score for analysis in the overall study population, in immunocompromised individuals, and in individuals with a history of COVID-19. In pregnant women, those who are vaccinated will be matched to pregnant concurrent unexposed comparators (in a ratio of at least 1:1) within data source on maternal age, state (if feasible, or broader geographic region if not feasible), and estimated pregnancy start. In analysis of pregnant women, confounding will be addressed through propensity score matching, or through the inclusion of propensity scores in exposure-outcome regression models.

The safety events in this study vary with respect to the onset of the event (well-defined versus gradual) and duration of risk window (short versus long). The strength of the cohort design is that it can handle a wide range of safety events with respect to these characteristics (Baker et al., 2015). Contemporaneous rather than historical unexposed comparators will be used because both healthcare-seeking behaviors and healthcare utilization have changed from the prepandemic period, which may impact outcome ascertainment. Further, COVID-19, which will be used to identify the subpopulation of individuals with history of COVID-19, had been in existence for a relatively short period of time in the US before the start of the study period (i.e., prior to when Pfizer-BioNTech COVID-19 Vaccine became available).

A main limitation of the cohort design with concurrent unexposed comparators is that it may be subject to misclassification of unexposed status, since many vaccinations occurring outside traditional medical care settings without health insurance reimbursement (e.g., mass vaccination campaigns by public health officials) may not be captured in administrative claims data. To address this limitation, sensitivity analysis will incorporate a self-controlled risk interval (SCRI) design for events with a well-defined onset and a short risk interval (Baker et al., 2015) (defined for the purposes of this study as ≤ 42 days after vaccination). If feasible, additional sensitivity analysis may incorporate a cohort design with historical unexposed comparators for events with gradual onset and/or a long risk interval, except for vaccine-associated enhanced respiratory disease (see Section 9.7.3). Additionally, the completeness of exposure information will be assessed during the monitoring phase. If exposure information is deemed incomplete, the primary study design may be switched to the SCRI and cohort design with historical comparators, or linkage with data from immunization registries may be conducted (if feasible). Another limitation of the proposed approach is that outcomes may be misclassified in data from claims and electronic health records. To address this limitation, algorithms for select outcomes that may be susceptible to substantial misclassification may be validated through medical records or review of patient profiles

(i.e., chronological listing of a patient's codes in data from claims and/or electronic health records) (see Section 9.3.2.2). The determination of which outcomes may be susceptible to substantial misclassification will be informed by clinical expert opinion and review of validation studies if available.

9.2. Setting

The study period will start on the date that Pfizer-BioNTech COVID-19 Vaccine was granted EUA in the US (11 December 2020) and will end a minimum of 3 years after this date. The study will include both vaccinations received under the EUA and under the BLA (once approved).

The source population for this study will be health plan enrollees from 5 data research partners that contribute data from claims and electronic health records to the Sentinel System: CVS Health/Aetna, HealthCore/Anthem, HealthPartners, Humana, and Optum/UnitedHealthcare. The data sources are described in more detail in Section 9.4.

9.2.1. Study population

Individuals of all ages will be included in the descriptive analysis of Pfizer-BioNTech COVID-19 Vaccine utilization. Safety analysis is planned to be limited to individuals within the age-approved population for Pfizer-BioNTech COVID-19 Vaccine, with age-based eligibility criteria changing over the study period as the ages approved for use of the vaccine change. However, if the proportion of Pfizer-BioNTech COVID-19 Vaccine recipients that fall outside of the approved age range is greater than 1%, then safety analyses will include individuals of all ages who have received the vaccine at any time during the study period.

Additional eligibility requirements for the general population and subpopulations of interest are described below.

9.2.1.1. General population, immunocompromised individuals, and individuals with history of COVID-19

To be included in the general population, population of immunocompromised individuals (individuals with immunodeficiencies, immunosuppressant medication use, human immunodeficiency virus and other immunosuppressing conditions, and receipt of organ or bone marrow transplant), and population of individuals with history of COVID-19, patients must have continuous medical and pharmacy insurance coverage for at least 12 months before each index date, (as defined in Table 1 and in Table 3 in Section 9.2.1.3).

9.2.1.1.1. Cohorts for analyses of general population, immunocompromised individuals, and individuals with history of COVID-19

Because Pfizer-BioNTech COVID-19 Vaccine is currently recommended in a series of 2 doses given at least 3 weeks apart, a separate exposed cohort will be formed for each of the 2 doses. A separate unexposed cohort will be formed for each of the 2 exposed cohorts to serve as comparator cohorts. If approved in the US, third doses of the Pfizer-BioNTech

COVID-19 Vaccine will be included in the study using methods to be described in the statistical analysis plan (SAP).

The criteria for the cohorts for analyses in the general population, immunocompromised individuals, and individuals with history of COVID-19 is described in Table 1.

Table 1. Cohort definitions for analyses of general population, immunocompromised individuals, and individuals with history of COVID-19

Cohort	Inclusion criteria	Index date	Exclusion criteria
Dose 1 exposed	Record of a first dose of Pfizer-BioNTech COVID-19 Vaccine during study period	Date of vaccination	Record of any COVID-19 vaccine before the index date
Dose 2 exposed	Record of a second dose of Pfizer-BioNTech COVID-19 Vaccine during study period	Date of vaccination	Record of COVID-19 vaccine other than Pfizer-BioNTech COVID-19 Vaccine before the index date
Dose 1 unexposed	No record of any COVID-19 vaccine as of the index date (i.e., cohort entry) and matched individually to individuals in the dose 1 exposed cohort on time-specific propensity score and state (if feasible, or broader geographic region if not feasible)	Randomly selected date in a period within close temporal proximity to the date of vaccination in corresponding exposed individuals (e.g., within the same calendar month)	Record of any COVID-19 vaccine before the index date
Dose 2 unexposed	No record of any COVID -19 vaccine as of the index date (i.e., cohort entry) and matched individually to individuals in the dose 2 exposed cohort on time-specific propensity score and state (if feasible, or broader geographic region if not feasible)	Randomly selected date in a period within close temporal proximity to the date of vaccination in corresponding exposed individuals (e.g., within the same calendar month)	Record of any COVID-19 vaccine before the index date

Individuals in the dose 1 and dose 2 cohorts will be matched to unexposed individuals (in a ratio of at least 1:1) on age, state (if feasible, or broader geographic region if not feasible), and calendar time–specific propensity score, which is described in Section 9.7.2.2.1.1. Individuals who receive 2 doses of the vaccine can contribute to both the dose 1 exposed and dose 2 exposed cohorts. Individuals in the dose 1 unexposed and the dose 2 unexposed cohorts may also contribute to the exposed cohorts if they subsequently receive Pfizer-BioNTech COVID-19 Vaccine. Conversely, individuals in the dose 1 cohort may be eligible for the unexposed cohorts before they receive their first dose of Pfizer-BioNTech COVID-19

Vaccine. However, an individual woman may contribute only once to the dose 1 unexposed cohort and once to the dose 2 unexposed cohort.

As appropriate, data from the dose 1 and dose 2 cohorts and their matched unexposed comparators will be pooled to obtain RR estimates corresponding to receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine.

9.2.1.2. Pregnant women

To be eligible for analysis of the pregnant population, women must have been pregnant for at least 1 day during the study period (regardless of the timing of estimated pregnancy start relative to the study start date) and had a pregnancy outcome (e.g., live birth, stillbirth, spontaneous abortion, ectopic pregnancy) recorded in the data sources during the study period. Pregnant women will be required to be continuously enrolled in their health plan from 12 months before the index date (as defined in Table 3 in Section 9.2.1.3) until the end of pregnancy. An algorithmic approach (to be described in the SAP) will be used to identify pregnancies via their outcomes (e.g., live birth, stillbirth, spontaneous abortion, termination, ectopic pregnancy) in women of reproductive age. The algorithm will use diagnosis and/or procedure codes to identify the final pregnancy outcome of each pregnancy episode, as well as the start and end dates of pregnancy.

In pregnant women, safety events assessed in the general population (hereafter referred to as "general safety events"; see Table 6 in Section 9.3.2.1 for list of outcomes), as well as pregnancy safety outcomes (spontaneous abortion, stillbirth, preterm birth, major congenital malformations, and small size for gestational age), will be assessed.

The eligible populations and exposure windows for analyses in pregnant women differ by safety event and are listed in Table 2. Only Pfizer-BioNTech COVID-19 Vaccine doses administered during the exposure windows will be considered for inclusion in the exposed cohorts. Women who were vaccinated outside the exposure window (e.g., women who were pregnant during the study period but who were vaccinated after they gave birth) will not contribute to the exposed cohorts but may contribute unexposed person-time. Women with Pfizer-BioNTech COVID-19 Vaccine administrations within 4 weeks before the estimated pregnancy start will be considered for inclusion in the exposed cohorts because of the imprecision of estimating pregnancy start date in claims data and because this period may be of etiologic interest for some of these safety events. If published validation studies suggesting that gestational algorithms are precise become available before the start of the study, the start of the exposure window may be redefined to be closer to pregnancy start (to be documented in the SAP).

Table 2. Eligible populations and exposure windows for analyses of pregnant women

Event	Eligible population	Exposure window
General safety events[a]	All eligible pregnancies	4 weeks before estimated pregnancy start to end of pregnancy
Pregnancy safety outcomes		
Spontaneous abortion	All eligible pregnancies	4 weeks before estimated pregnancy start to end of pregnancy or 19-6/7 weeks of gestation, whichever is earlier
Stillbirth	Pregnancies with gestational age ≥ 20 weeks	4 weeks before estimated pregnancy start to end of pregnancy
Preterm birth	Live deliveries	4 weeks before estimated pregnancy start to end of pregnancy or 36-6/7 weeks of gestation, whichever is earlier
Major congenital malformations	Live deliveries with linkage to infant data available	4 weeks before estimated pregnancy start to 13-6/7 weeks of gestation (end of first trimester)
Small size for gestational age	Live deliveries with linkage to infant data available	4 weeks before estimated pregnancy start to end of pregnancy

a. Safety events of interest listed in Table 6 in Section 9.3.2.1.

Analyses of major congenital malformations and small size for gestational age will require pregnancies to be linked to infants who have health plan enrollment from birth until age 3 months (or from birth until death if the infant dies before age 3 months). Where available, the Sentinel mother-infant linkage table (see Section 9.4) included in the most recently approved ETL (Extract, Transform, Load) at the time of the data extraction will be used for this study. Mother-infant linkage algorithms differ by data source and may use subscriber identification numbers and/or names and addresses; these algorithms will be described in the SAP.

9.2.1.3. Cohorts for analyses of pregnant women

In pregnant women, different cohorts will be formed to assess specific groups of outcomes (Table 3). For analysis of pregnant women (similar to the analytic approach in the general population), separate cohorts will be formed for each dose of Pfizer-BioNTech COVID-19 Vaccine to assess general safety events, spontaneous abortion, stillbirth, and preterm birth. For analysis of small size for gestational age and major congenital malformations, separate cohorts of women exposed to Pfizer-BioNTech COVID-19 Vaccine and women not exposed to any COVID-19 vaccine during the exposure window (without regard to dose number) will be formed.

Table 3. Cohort definitions for analyses of pregnant women

Cohort	Inclusion criteria	Index date	Exclusion criteria
Analysis of general safety events[a], spontaneous abortion, stillbirth, and preterm birth			
Dose 1 exposed	Record of a first dose of Pfizer-BioNTech COVID-19 Vaccine during the exposure window[b]	Date of vaccination	Record of any COVID-19 vaccine other than Pfizer-BioNTech COVID-19 Vaccine before the index date (or during the exposure window before the index date in analyses of spontaneous abortion, stillbirth, and preterm birth)
Dose 2 exposed	Record of a second dose of Pfizer-BioNTech COVID-19 Vaccine during the exposure window. For analysis of general safety events, the first dose is *not* required to have been administered during the exposure window. For analysis of spontaneous abortion, stillbirth, and preterm birth, the first dose must also have been administered during the exposure window.	Date of vaccination	Record of any COVID-19 vaccine other than Pfizer-BioNTech COVID-19 Vaccine before the index date (or during the exposure window before the index date in analyses of spontaneous abortion, stillbirth, and preterm birth)
Dose 1 unexposed	No record of any COVID-19 vaccine as of the index date (or no record of any COVID-19 vaccine during the exposure window before the index date in analyses of spontaneous abortion and stillbirth) Individually matched to women in dose 1 cohort on maternal age and pregnancy start	Equivalent of the gestational age (in days) at the time of the exposed individual's vaccination[c]	Record of any COVID-19 vaccine as of the index date
Dose 2 unexposed	Same criteria as dose 1 unexposed cohort, but matched individually to women in dose 2 exposed cohort	Same criteria as dose 1 unexposed cohort	Same criteria as dose 1 unexposed cohort
Analysis of small size for gestational age and major congenital malformations			
Exposed	Record of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine during the exposure window	Estimated pregnancy start	No record of Pfizer-BioNTech COVID-19 Vaccine during the exposure window
Unexposed	No record of any COVID-19 vaccine during the exposure window, individually matched to women in exposed cohort on maternal age and pregnancy start	Estimated pregnancy start	Record of any COVID-19 Vaccine during the exposure window

Table 3. Cohort definitions for analyses of pregnant women

Cohort	Inclusion criteria	Index date	Exclusion criteria

a. Safety events of interest listed in Table 6 in Section 9.3.2.1.
b. Pregnant women who have received their first dose of the Pfizer-BioNTech COVID-19 Vaccine before the exposure window and their second dose of Pfizer-BioNTech COVID-19 Vaccine during the exposure window may contribute (via their second doses) to the exposed cohorts if all other eligibility criteria are met. For analyses of general safety events, their second dose could contribute to the dose 2 exposed cohort, whereas for analyses of spontaneous abortion, stillbirth, and preterm birth, their second dose could contribute to the dose 1 exposed cohort (in this situation, the first dose would be excluded from analysis).
c. Following exposed and unexposed women for the same duration will ensure that women have equal opportunity to be exposed during pregnancy. Furthermore, starting follow-up at the same gestational age in exposed and unexposed women will ensure that both groups have a comparable at-risk period with respect to gestational age.
Note: Individuals in the dose 1 unexposed and dose 2 unexposed cohorts may contribute to the dose 1 and/or dose 2 exposed cohorts if they subsequently receive the Pfizer-BioNTech COVID-19 Vaccine during the exposure window. Conversely, pregnant women in the dose 1 cohort may be eligible to contribute to the dose 1 unexposed or dose 2 unexposed cohorts before they receive their first dose of Pfizer-BioNTech COVID-19 Vaccine. However, an individual woman may contribute only once to the dose 1 unexposed cohort and once to the dose 2 unexposed cohort.

9.2.2. Follow-up

Events that can define the start and end of follow-up are provided in Table 4. Follow-up will end at the earliest of all possible events that define the end of follow-up.

Table 4. Events defining the start and end of follow-up

Safety event of interest	Events defining the start of follow-up	Events defining the end of follow-up[a]
General safety events[b]	• Index date (if the risk interval starts on day 0), or • One day after the index date (if the risk interval starts on day 1; see Table 6 in Section 9.3.2.1 for outcome-specific risk windows)	• End of the study period • End of data availability • Disenrollment from the health plan • Death • Occurrence of the safety event of interest • End of duration of the outcome-specific risk window (maximum of 1 year; see Table 6 in Section 9.3.2.1 for outcome-specific risk windows) • Receipt of a dose of the Pfizer-BioNTech COVID-19 Vaccine or any other COVID-19 vaccine[c]
Pregnancy safety outcomes		
Spontaneous abortion	• One day after the index date (if the index date is on or after estimated pregnancy start), or • Estimated pregnancy start	• End of pregnancy • 20 weeks of gestation • Receipt of a dose of Pfizer-BioNTech COVID-19 Vaccine or any other COVID-19 vaccine[c]
Stillbirth	• One day after the index date (if the index date is on or after 20 weeks of gestation), or • 20 weeks of gestation	• End of pregnancy • Receipt of a dose of Pfizer-BioNTech COVID-19 Vaccine or any other COVID-19 vaccine[3]
Preterm birth	• Index date (if the index date is on or after 20 weeks of gestation), or • 20 weeks of gestation	• End of pregnancy • 36 6/7 weeks of gestation • Receipt of a dose of Pfizer-BioNTech COVID-19 Vaccine or any other COVID-19 vaccine[c]
Major congenital malformations[d]	• Day of birth	• End of study period • End of data availability • Disenrollment from the health plan • Death • Diagnosis of major congenital malformation • Age 1 year
Small size for gestational age[d]	• Day of birth	• Predefined period shortly after birth (specific period to be defined in the SAP)

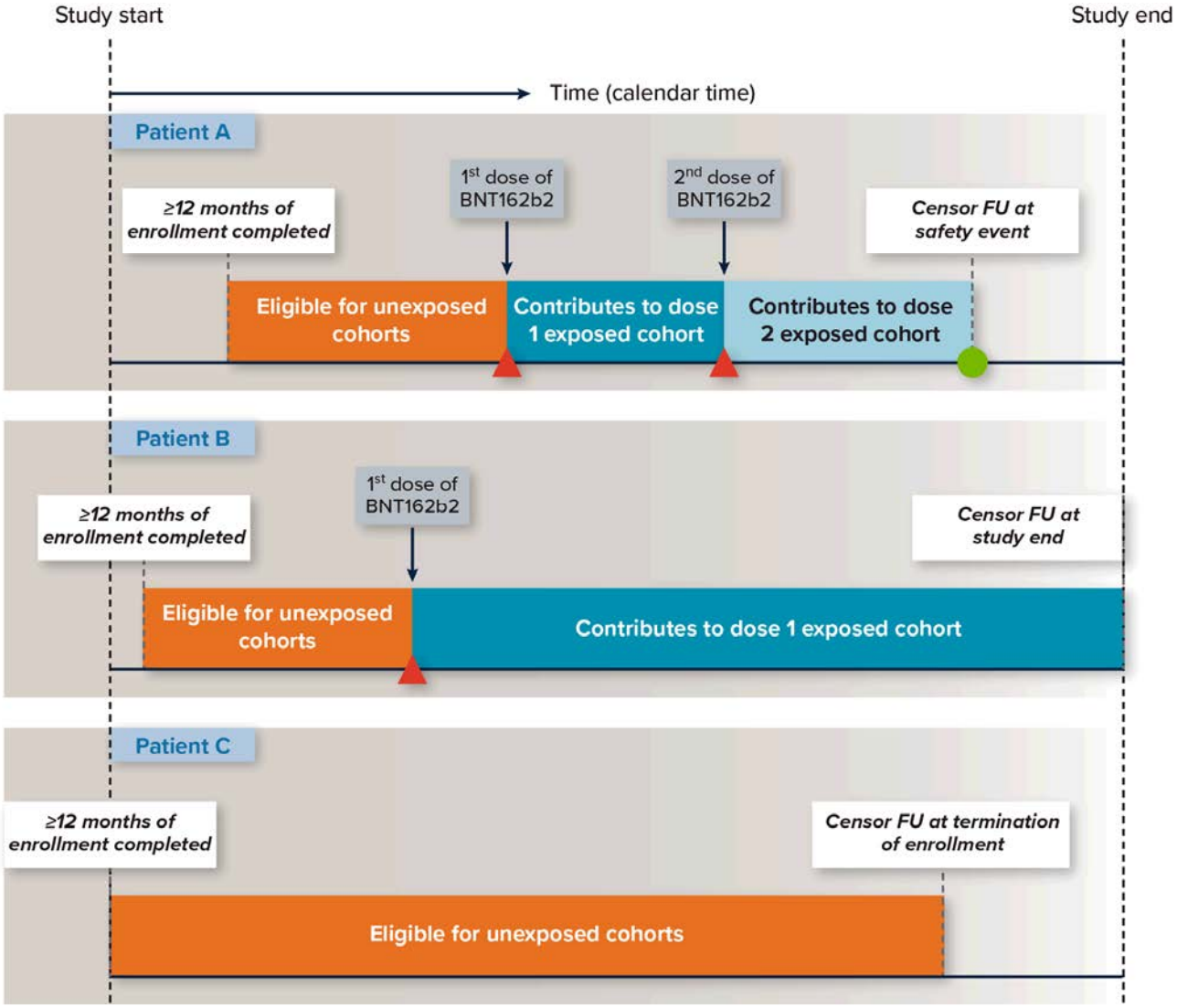
Table 4. Events defining the start and end of follow-up

Safety event of interest	Events defining the start of follow-up	Events defining the end of follow-up[a]

a. The earliest of the listed events will mark the end of follow-up for each outcome. If follow-up ends due to the occurrence of a particular safety event of interest, follow-up will continue for all other safety events.
[b] Safety events of interest are listed in Table 6 in Section 9.3.2.1.
c. If dose 2 is Pfizer-BioNTech COVID-19 Vaccine, individuals will stop follow-up in the dose 1 cohort and may start follow-up in the dose 2 cohort. When the risk interval for dose 1 overlaps with the risk interval for dose 2 and the risk interval definition includes day 0, the date of receipt of dose 2 will be included in follow-up of dose 1. Otherwise, the date of receipt of dose 2 will be included in follow-up of dose 2.
d. Major congenital malformations and small size for gestational age will be assessed in the infant.

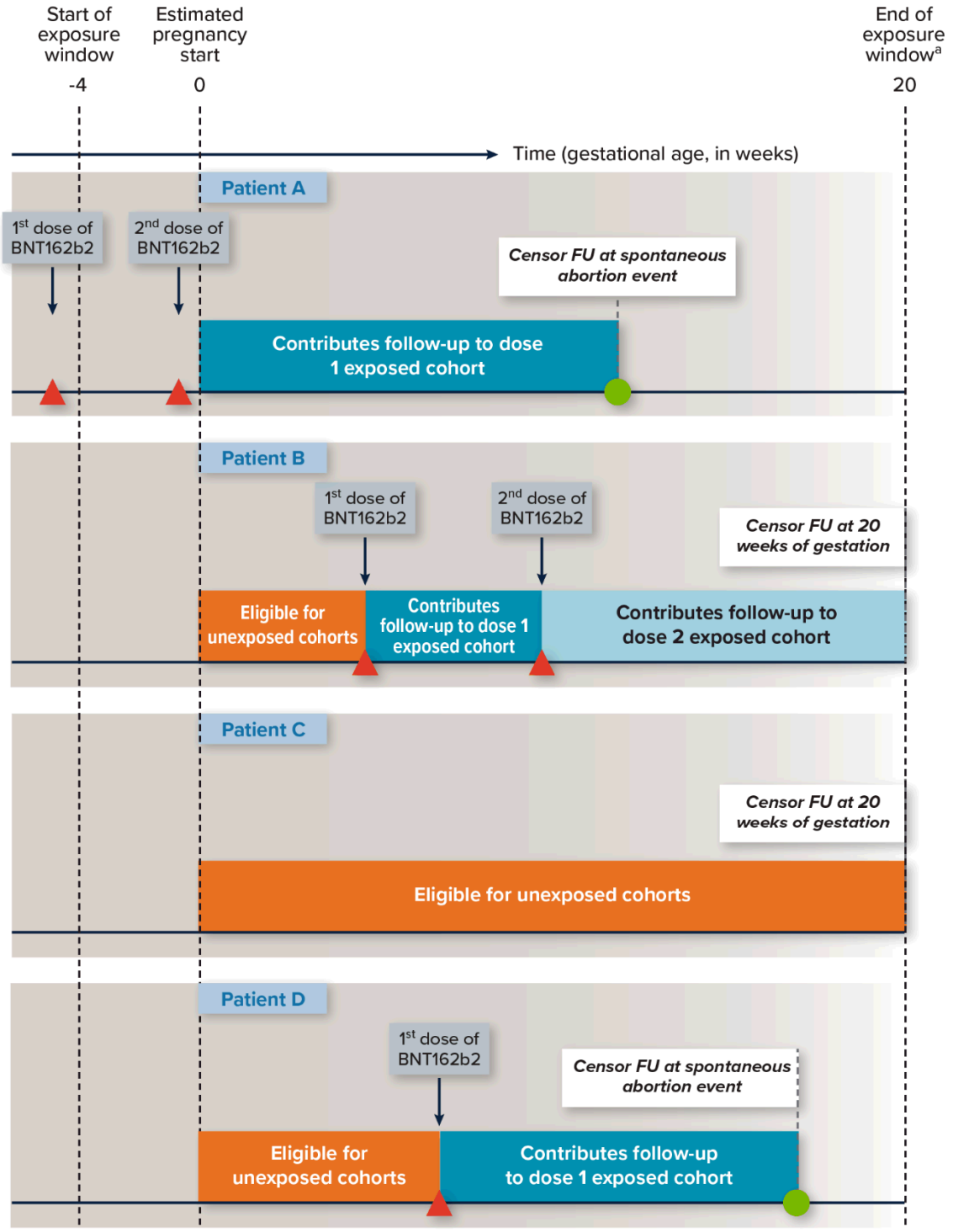
For illustrative purposes, Figure 1 depicts the timelines of hypothetical patients to show the concepts of eligibility for study cohorts and follow-up in analysis of general safety events in the general population, immunocompromised individuals, or individuals with history of COVID-19. Figure 2 depicts the timelines of hypothetical patients to illustrate eligibility for the study cohorts and follow-up, using analysis of spontaneous abortion as an example.

Figure 1. Hypothetical patients to illustrate eligibility for study cohorts and follow-up of general safety events in the general population, immunocompromised individuals, or individuals with history of COVID-19



Note: If follow-up ends due to the occurrence of a particular safety event of interest, follow-up will continue for all other safety events.

Figure 2. Hypothetical patients to illustrate eligibility for study cohorts and follow-up of spontaneous abortion events in pregnant women



a. End of exposure window is 20 weeks of gestation or pregnancy end, whichever is earlier.

9.3. Variables

9.3.1. Vaccine exposures

The primary exposure of interest is Pfizer-BioNTech COVID-19 Vaccine (receipt of Pfizer-BioNTech COVID-19 Vaccine versus no receipt of any COVID-19 vaccine). Receipt of Pfizer-BioNTech COVID-19 Vaccine will be identified in data from claims and electronic health records (where available, as not all data research partners will have access to electronic health records) via pharmacy dispensing and/or procedure codes (Table 5). Where existing linkages with immunization registries are available for use in research studies within the appropriate participating research databases, immunization registry data will be combined with data from claims and electronic health records to identify vaccine exposures.

Receipt of other COVID-19 vaccines available in the US will be identified in a similar manner. The vaccines in Table 5 are those that have received authorization in the US as of the time of writing of this protocol. Other COVID-19 vaccines that are authorized during the study period will be added, as needed. Rules to handle de-duplication of codes and/or implausible spacing of doses (e.g., 2 codes for COVID-19 vaccine within 2 days) will be described in the SAP.

Table 5. Codes for COVID-19 vaccines available in the United States as of 28 July 2021

COVID-19 Vaccine	Role of variable	Vaccine codes	Vaccine administration codes	National Drug Codes
Pfizer-BioNTech COVID-19 Vaccine	Primary exposure, used to define exposed cohorts	91300 (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA/lipid nanoparticle(LNP), spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted, for intramuscular use)	001A (first dose) 002A (second dose)	59267-1000-1 59267-1000-01 59267-1000-02 59267-1000-03
Moderna COVID-19 Vaccine	Exclusion variable before index date; censoring variable during follow-up	91301 (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA/LNP, spike protein, preservative free, 100 mcg/0.5mL dosage, for intramuscular use)	0011A (first dose) 0012A (second dose)	80777-273-10 80777-0273-10 80777-0273-99
Janssen COVID-19 Vaccine	Exclusion variable before index date; censoring variable during follow-up	91303 (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5 x 10^{10} viral particles/0.5mL dosage, for intramuscular use)	0031A (single dose)	59676-580-05 59676-0580-05 59676-580-15

Sources: AMA (2021); DailyMed (2021).

If COVID-19 vaccines are administered without reimbursement from health insurers, there is the potential that they will not be recorded in claims and electronic health records. This situation may lead to misclassification of truly exposed individuals as "unexposed" comparators, which will underestimate vaccine coverage rates and may bias comparative risk estimates for the cohort design with concurrent unexposed comparators. The completeness of exposure data will be assessed in monitoring analyses before the final analyses are conducted by comparing study data with publicly available estimates of vaccine coverage and/or estimates based on immunization registry data from select states (if available); if the coverage estimates differ meaningfully from the "benchmarking" estimates (based on to-be-defined criteria in the SAP), then modifications to the study approach may be considered. If this happens, the SCRI and the cohort design with historical unexposed comparators may be designated as the primary study designs and/or linkage to immunization registries may be considered if feasible.

9.3.2. Outcomes

9.3.2.1. Safety events of interest

Safety events of interest to be assessed in the general population, immunocompromised individuals, individuals with a history of COVID-19, and pregnant women, and their risk interval definitions, are listed in Table 6. Throughout the protocol, these safety events are referred to as "general safety events."

These events comprise outcomes being monitored in rapid-cycle analysis of COVID-19 vaccines in the FDA's BEST System (Wong et al., 2021) and the CDC's VSD (Wong et al., 2021), with the addition of vaccine-associated enhanced respiratory disease (Munoz et al., 2021), immune hemolytic anemia, and thromboembolic events with thrombocytopenia. Other safety events of interest may be added as the understanding of the safety profile of Pfizer-BioNTech COVID-19 Vaccine evolves and feasibility of their assessment permits in the data sources.

Table 6. General safety events to be assessed in the general population, immunocompromised individuals, individuals with a history of COVID-19, and pregnant women

Organ system	Safety event of interest	Risk window (days following receipt of Pfizer-BioNTech COVID-19 Vaccine)[a]
Neurologic	Acute disseminated encephalomyelitis	1-42
	Bell's palsy	1-42
	Convulsions	1-42
	Encephalomyelitis/encephalitis	1-42
	Guillain-Barré syndrome	1-42
	Narcolepsy	1-180
	Transverse myelitis	1-42
Cardiac	Acute myocardial infarction	1-28
	Myocarditis/pericarditis	1-21[b]

Table 6. General safety events to be assessed in the general population, immunocompromised individuals, individuals with a history of COVID-19, and pregnant women

Organ system	Safety event of interest	Risk window (days following receipt of Pfizer-BioNTech COVID-19 Vaccine)[a]
Hematologic	Deep vein thrombosis	1-28
	Disseminated intravascular coagulation	1-28
	Immune hemolytic anemia	1-42
	Immune thrombocytopenia	1-42
	Pulmonary embolism	1-28
	Thromboembolic events associated with thrombocytopenia	1-28
	Thrombotic thrombocytopenic purpura	1-28
	Venous thromboembolism	1-28
	Hemorrhagic stroke	1-28
	Ischemic stroke	1-28
Respiratory	Acute respiratory distress syndrome	1-28
	Vaccine-associated enhanced respiratory disease	1-365
Other system	Anaphylaxis	0-1
	Appendicitis	1-42
	Kawasaki disease	1-42
	Multisystem inflammatory syndrome	1-42

a. Time interval following vaccination when patients will be followed for safety events of interest. Day 0 refers to the day of vaccination.
b. Sensitivity analysis will assess alternative risk interval definitions of 1-7 and 1-14 days.

The following pregnancy safety outcomes will be assessed in pregnant women or their infants based on diagnosis codes because clinical information, such as gestational age estimates and ultrasound results, will not be available in electronic data:

- Spontaneous abortion: spontaneous pregnancy loss before 20 completed weeks gestation
- Stillbirth: fetal deaths at or after 20 completed weeks gestation
- Preterm birth: live birth before 37 completed weeks gestation
- Major congenital malformations: major congenital malformations will be identified in live-born infants using code lists from the National Birth Defects Prevention Network (NBDPN, 2021a), which defines 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, 2021b)
- Small size for gestational age: less than 10th percentile of weight for gestational age, based on diagnosis codes for small size for gestational age or combinations of diagnosis codes for birthweight (in categories) and gestational age (in categories)

9.3.2.2. Outcome identification and validation

Safety events of interest will be identified with a date of diagnosis in data from claims or electronic health records (where available, as not all data research partners will have access to electronic health records) using predefined algorithms based on codes for diagnoses (with codes for procedures and/or treatments if appropriate for the outcome). As possible, validated algorithms will be used. Detailed algorithm definitions (including washout periods to define incident events and the medical care settings in which safety events will be identified) and code lists will be included in the SAP.

Algorithms for select outcomes that are susceptible to substantial misclassification may be validated. The determination of whether each outcome is susceptible to substantial misclassification will be informed by clinical expert opinion and review of prior validation studies, if available. For the outcomes selected for validation, clinician review of medical records or patient profiles (i.e., listings of codes in data from claims or electronic health records in chronological order) will be conducted on a sample of cases to estimate the positive predictive values of case-finding algorithms and to estimate the proportion of cases that were accurately identified as occurring during the risk interval. To the greatest extent possible, such reviews will be conducted without knowledge of vaccination status. Clinical definitions of safety events of interest will be based on Brighton Collaboration definitions, where available, or other clinical definitions from published literature if medical record review is implemented.

For safety events of interest selected for algorithm validation, a sampling strategy that considers the rarity of events will be used to identify cases that will undergo clinician review. If the outcome algorithm performs adequately (using predefined criteria to be defined in a separate data validation plan), then all algorithm-identified cases will be included in the final analysis. If the algorithm does not perform adequately, then the validation results will be used to inform or adjust RRs or odds ratios that were estimated from electronic data (e.g., in quantitative bias analyses). The sampling strategy, selection of safety events for which algorithms will be validated and rationale for the selection, details on the methods for validation (including criteria for determining whether algorithms have performed adequately), and the plan for integrating the validation results into final analysis will be described separately in a data validation plan.

9.3.3. Covariates

Covariates will be identified in claims and electronic health records (where available, as not all data research partners will have access to electronic health records) using administrative health plan enrollee data or codes for diagnoses (with procedures or medications, as appropriate). Detailed algorithms and code lists to identify each covariate will be included in the SAP.

9.3.3.1. Potential confounding variables

The following variables will be used to describe the overall study population, immunocompromised individuals, individuals with a history of COVID-19, and pregnant women and will be considered as potential confounding variables to be included in propensity score models for analysis of general safety events.

- Demographics will be evaluated at the index date of each patient, unless otherwise noted.
    - Age: Individuals of all ages will be included in the study; for descriptive analyses, age categories will be 0-4, 5-11, 12-15, 16-20, 21-29, 30-49, 50-64, 65-80, and greater than 80 years.
    - Sex
    - Geographic region (zip code where available, state or census region; evaluated using the latest information available on the index date)
    - Race/ethnicity: Data on race/ethnicity are anticipated to be incomplete, and the feasibility of including this variable in the analyses will be assessed before study start.
- Date of Pfizer-BioNTech COVID-19 Vaccine (categorized as appropriate, e.g., by year or month)
- Dose of vaccine received (1 or 2)
- Comorbidities, identified in the 12 months before and including the index date (unless otherwise noted) in claims or electronic health records using diagnosis codes (with procedure and/or pharmacy dispensing codes as appropriate)
    - History of anaphylaxis (not including the index date)
    - History of allergies
    - Diabetes mellitus (type 1, type 2, or gestational diabetes in current pregnancy)
    - Hypertension
    - Cardiovascular disease
    - Cerebrovascular disease
    - Chronic respiratory disease
    - Chronic kidney disease

- Chronic liver disease
- Cancer
- Epilepsy
- Autoimmune disorders
- Influenza and other respiratory infections (including COVID-19)
- Gastrointestinal infections
- Immunocompromising conditions, including the following (to be defined in more detail in the SAP):
  - Immunodeficiencies
  - Immunosuppressant medication use
  - Human immunodeficiency virus and other immunosuppressing conditions
  - Receipt of organ or bone marrow transplant
- Obesity (to be identified with proxies using diagnosis and procedure codes; capture anticipated to be incomplete)
- Pregnancy status (on the index date), identified using an algorithm as described in Section 9.2.1.2

- Medications in the 12 months before and including the index date, identified in data from claims or electronic health records via procedure and/or pharmacy dispensing codes
  - Analgesics
  - Antibiotics
  - Antiviral medications
  - Corticosteroids
  - Nonsteroidal anti-inflammatory drugs
  - Psychotropics
  - Statins

  - Novel oral anticoagulants
  - Warfarin
- Non–COVID-19 vaccinations (including those administered concomitantly with Pfizer-BioNTech COVID-19 Vaccine) in the 12 months before or on the index date, identified in data from claims or electronic health records with procedure and/or pharmacy dispensing codes
  - Influenza
  - Pneumococcal disease
  - Diphtheria, tetanus, and pertussis
  - Polio
  - Measles, mumps, and rubella
  - Haemophilus influenzae type b
  - Hepatitis B virus
  - Human papillomavirus
  - Meningitis
  - Rotavirus
  - Varicella
  - Herpes zoster
- Healthcare utilization (including telehealth encounters, if feasible) in the 12 months before or on the index date
  - Any healthcare encounter
  - Hospitalizations
  - Emergency department visits
  - Skilled nursing facility, nursing home, or extended care facility stay
  - Cancer screening(s)

- Other preventive healthcare services, as appropriate
- COVID-19 tests

The following variables will be used to describe the population of pregnant women and will be considered as potential confounders to be included in propensity score models for analysis of pregnancy safety outcomes. Except where noted, only information up to and including the index date will be used to identify potential confounders.

- Demographics: maternal age (on the index date), geographic region (using the latest information available as of the index date), race/ethnicity (if feasible, on the index date)
- Comorbidities, identified in the 12 months before and including the index date in claims or electronic health records using diagnosis codes (with procedure and/or pharmacy dispensing codes as appropriate).
  - Diabetes mellitus (type 1, type 2)
  - Hypertension
  - Connective tissue disorders
  - Thyroid disorders
  - Heart disease
  - Epilepsy and mood disorders
  - Asthma
  - Liver disease
  - Kidney disease
  - Cancer
- Obesity, identified in the 12 months before or on the index date with proxies based on diagnosis and procedure codes (capture anticipated to be incomplete since documentation via diagnosis or procedure codes is not routinely done in claims data)
- Alcohol use, identified in the 12 months before or on the index date with proxies based on diagnosis and procedure codes (capture anticipated to be incomplete)
- Smoking, identified in the 12 months before or on the index date with proxies based on diagnosis and procedure codes (capture anticipated to be incomplete)

- Reproductive history identified in all available data (capture anticipated to be incomplete because data will be limited by duration of enrollment before index date)
    - Gravidity, identified via diagnosis codes
    - Parity, identified via diagnosis or procedure codes for deliveries or C-sections
    - Spontaneous abortions in previous pregnancies, identified via diagnosis codes
    - Pregnancy terminations in previous pregnancies, identified via diagnosis codes
- Multiple pregnancy, identified during pregnancy via diagnosis codes. Information recorded after the index date will be used to identify potential confounders.
- Gestational diabetes, identified during pregnancy via diagnosis codes
- Preeclampsia/eclampsia, identified during pregnancy via diagnosis codes
- TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, and herpes infections), identified during pregnancy via diagnosis codes
- Teratogenic medications from 28 days before pregnancy up to and including the end of pregnancy, identified via pharmacy dispensing and procedure codes
- Vaccinations other than COVID-19 vaccinations (including those administered concomitantly with Pfizer-BioNTech COVID-19 Vaccine) from 28 days before pregnancy up to and including the end of pregnancy, identified via pharmacy dispensing and procedure codes

9.3.3.2. Variables for identifying subcohorts

Three subcohorts will be identified from the general population cohort in which descriptive and comparative analyses of general safety events will be conducted: individuals with immunocompromising conditions, pregnant women, and individuals with a history of COVID-19. Comparative safety analyses of pregnancy safety outcomes will also be conducted in pregnant women. These 3 subcohorts will be identified as follows:

- Immunocompromising conditions will be identified using diagnosis, procedure, and medication dispensing codes in all available data before the index date for immunodeficiencies, immunosuppressant medication use, human immunodeficiency

virus and other immunosuppressing conditions, and receipt of organ or bone marrow transplant.

- Pregnancy status will be identified using an algorithm as described in Section 9.2.1.2.
- History of COVID-19 (in all available data) will be identified in data from claims or electronic health records via ICD-10-CM (International Classification of Diseases, 10th Revision, Clinical Modification) diagnosis codes for COVID-19 (U07.1), personal history of COVID-19 (Z86.16), or pneumonia due to coronavirus disease 2019 (J12.82). If feasible, a positive laboratory test result for SARS-CoV-2 will be incorporated into the definition.

9.3.3.3. Subgroup analysis

Subgroup analysis will be conducted in the following age categories: 0-17, 18-64, 65 years and older.

In additional analyses, the following safety events will be studied among individuals of specific ages if sufficient numbers of exposures are identified within these age groups:

- Multisystem inflammatory syndrome in children: ages 0-20 years
- Convulsions: ages 0-4 years
- Kawasaki disease: ages 0-4 years
- Myocarditis/pericarditis: ages 12-29 years

Additional subgroup analysis (e.g., stratified by other demographic variables or calendar time) may be conducted for specific safety events of interest that have signaled in other studies or vaccine safety surveillance systems (e.g., myocarditis/pericarditis).

Additionally, analysis to identify risk factors for postvaccine outcomes may be conducted for specific safety events of interest (e.g., myocarditis/pericarditis).

These analyses will be described in the SAP.

9.4. Data sources

This study will use data from 5 data research partners, including data from 4 national insurers (CVS Health/Aetna, HealthCore/Anthem, Humana, and Optum/UnitedHealthcare) and 1 regional insurer (HealthPartners). Each data research partner is a participant in the FDA Sentinel System. The Sentinel System is an active surveillance system that uses routine querying and analytical tools to evaluate electronic healthcare data from a distributed data network for monitoring the safety of regulated medical products in the US, established under the Sentinel Initiative (Behrman et al., 2011; Platt et al., 2018). All of these data research

partners update their curated Sentinel database multiple times per year. This study will use the research-eligible population within the most recently available database at each data research partner at the time of analysis.

These data sources capture longitudinal medical care information on outpatient medication dispensings, vaccine administrations, and inpatient and outpatient diagnoses and procedures. The data sources also capture member demographic and health plan enrollment information. Each data research partner can request access to full-text medical records for outcome validation for a subset of participants. All data research partners are able to link to external data sources (e.g., state immunization registries) and can collect additional information via surveys in at least a subset of members. As part of their participation in the Sentinel System, 3 data research partners (CVS Health, HealthCore, and Optum) maintain a mother-infant linkage table to support studies of medication exposures during pregnancy. All of the national insurers contribute claims data, while the regional insurer (HealthPartners) contributes data from both claims and electronic health records to the Sentinel database. As all data research partners contribute data to the Sentinel System, this study will leverage the Sentinel database and distributed querying infrastructure, including quality-checked and curated data formatted to the Sentinel Common Data Model (SCDM) and the publicly available Sentinel analytic tools (Curtis et al., 2012; Sentinel, 2018).

The data research partners use the SCDM (Curtis et al., 2012; Sentinel, 2018) to standardize demographic and clinical data elements. Publicly available routine analytical tools (i.e., reusable, modular SAS programs) designed to be executed against the SCDM permit rapid and standardized queries across data from different partners, including descriptive analyses and complex methodologies (e.g., comparative analyses).

Specific information in the SCDM includes, but is not limited to, the following types of data:

- Enrollment data, including 1 record per covered individual per unique enrollment span. The average enrollment length for patients across data sources in the Sentinel System is similar to that in other claims databases of members with medical and pharmacy coverage; approximately 25% of patients have over 3 years of enrollment, and patients with chronic conditions such as diabetes and older members typically have longer than average enrollment periods within these databases.

- Individuals are assigned a unique identifier by their insurer that is linkable to other data in the SCDM. Each record in the enrollment file indicates the patient identifier, enrollment start and end dates, and whether the patient was enrolled in medical coverage, pharmacy coverage, or both during that enrollment.

- Demographic data, including birth date, sex, race/ethnicity, and zip code of their most recently recorded primary residence.

- Outpatient pharmacy dispensing data, including the date of each vaccination or prescription dispensing, the National Drug Code identifier associated with the dispensed

product, the nominal days' supply, and the number of individual units (e.g., pills, tablets, vials) dispensed. Products purchased over the counter or at some cash-only retail locations selling prescription drug products (e.g., through the Walmart Prescription Program) are not consistently captured.

- Medical encounter data, including the healthcare provider most responsible for the encounter, as well as the facility at which the encounter occurred and its zip code. Admission and discharge dates (if applicable) are also included, in addition to the encounter type (i.e., an ambulatory visit, emergency department visit, inpatient hospital stay, nonacute inpatient stay, or otherwise unspecified ambulatory visit). Discharge disposition (i.e., alive, expired, or unknown) and discharge status (i.e., where a patient was discharged) are also included for acute and nonacute inpatient hospital stays.

- Diagnosis data, including the date of diagnosis, its associated encounter identifier, admission date, provider identifier, and encounter type. Diagnoses are recorded with ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) and ICD-10-CM codes. For acute and nonacute inpatient stays, the SCDM includes both principal and nonprincipal discharge diagnoses.

- Procedure data, including the procedure date (e.g., date of vaccination), its associated encounter identifier, admission date, provider identifier, and encounter type, are coded as ICD-9-CM procedure and ICD-10-PCS (ICD-10 Procedure Coding System) codes; CPT (Current Procedural Terminology) categories II, III, or IV codes; revenue codes and Healthcare Common Procedure Coding System levels II and III codes.

The following subsections include brief descriptions of each individual data source.

9.4.1. CVS Health, Aetna

Aetna, a CVS Health company, is one of the nation's leading healthcare benefits companies, currently serving 38 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 median (range) age of 45 (0-119) years (based on patients' most recent available data).

9.4.2. HealthCore

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 February 2021, there were 79 million unique individuals with medical coverage and approximately 60 million with

medical and pharmacy coverage available for research, covering all ages, with median (Q1, Q3) age of 40 (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 median (range) age of 39 (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 (HHR) 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/HHR is an active collaborator and data research partner in the Sentinel System. The Humana research-eligible database represents geographic coverage for the entire US population (Puerto Rico excluded), and as of 31 March 2021 has 32.7 million unique individuals, covering all ages, with median (Q1, Q3) age of 67 (48, 76) years.

9.4.5. Optum Research Database

The Optum Research Database is a proprietary research database that contains eligibility data and medical claims and includes 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 median (Q1, Q3) age of 36 (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

The size of the exposed population will depend on the use of Pfizer-BioNTech COVID-19 Vaccine, and the size of the comparator population will depend on the proportion of the source population that comprises unvaccinated individuals over time in the data sources. The precision of comparative risk estimates will depend on the background rate and the duration of the risk interval for each safety event of interest.

Assuming a matching ratio of 1:1, Table 7 presents the probability that the upper limit of the 95% CI for the observed RR will be below 1.5, 2.0, 2.5, and 3.0 for assumed true RRs of 1.0, 1.2, 1.4 and study sizes ranging from 500,000 to 20,000,000 vaccinated individuals (1,000,000 doses to 40,000,000 doses, under the assumption that each individual will receive 2 doses). The estimates in the table on the following page reflect a cohort analysis. These estimates are presented to cover a range of safety events of interest with respect to rareness, based on background rates in the general population.

For example, for Bell's palsy, with 1,000,000 exposed individuals we estimate an 86% probability that the upper bound of the observed RR would be below 2.0, assuming a 1:1 ratio between vaccinated and comparator person-time and that the true RR is 1.0.

Table 7. Study size calculations

Assumed true RR	Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021)	Number of individuals vaccinated	Probability that the upper confidence limit of RR will be below the following thresholds[a] :			
				1.5	2.0	2.5	3.0
1.0	Guillain-Barré syndrome	1.68	500,000	0.06	0.10	0.14	0.19
			1,000,000	0.08	0.16	0.25	0.33
			2,500,000	0.14	0.33	0.52	0.68
			5,000,000	0.24	0.58	0.81	0.93
			10,000,000	0.43	0.86	0.98	1.00
			20,000,000	0.71	0.99	1.00	1.00
	Bell's palsy	25.2	500,000	0.24	0.58	0.81	0.93
			1,000,000	0.43	0.86	0.98	1.00
			2,500,000	0.80	1.00	1.00	1.00
			5,000,000	0.98	1.00	1.00	1.00
			10,000,000	1.00	1.00	1.00	1.00
			20,000,000	1.00	1.00	1.00	1.00
	Myocardial infarction	208	500,000	0.95	1.00	1.00	1.00
			1,000,000	1.00	1.00	1.00	1.00
			2,500,000	1.00	1.00	1.00	1.00
			5,000,000	1.00	1.00	1.00	1.00
			10,000,000	1.00	1.00	1.00	1.00
			20,000,000	1.00	1.00	1.00	1.00
1.2	Guillain-Barré syndrome	1.68	500,000	0.04	0.08	0.11	0.15
			1,000,000	0.05	0.11	0.19	0.26
			2,500,000	0.07	0.22	0.39	0.56
			5,000,000	0.11	0.38	0.66	0.85
			10,000,000	0.17	0.65	0.92	0.99
			20,000,000	0.30	0.91	1.00	1.00
	Bell's palsy	25.2	500,000	0.11	0.38	0.66	0.85
			1,000,000	0.17	0.65	0.92	0.99
			2,500,000	0.37	0.96	1.00	1.00
			5,000,000	0.63	1.00	1.00	1.00
			10,000,000	0.90	1.00	1.00	1.00
			20,000,000	1.00	1.00	1.00	1.00
	Myocardial infarction	208	500,000	0.55	1.00	1.00	1.00
			1,000,000	0.84	1.00	1.00	1.00
			2,500,000	1.00	1.00	1.00	1.00
			5,000,000	1.00	1.00	1.00	1.00
			10,000,000	1.00	1.00	1.00	1.00

Table 7. Study size calculations

Assumed true RR	Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021)	Number of individuals vaccinated	Probability that the upper confidence limit of RR will be below the following thresholds[a] :			
				1.5	2.0	2.5	3.0
			20,000,000	1.00	1.00	1.00	1.00
1.4	Guillain-Barré syndrome	1.68	500,000	0.03	0.06	0.09	0.12
			1,000,000	0.03	0.08	0.14	0.21
			2,500,000	0.04	0.13	0.28	0.44
			5,000,000	0.04	0.22	0.49	0.73
			10,000,000	0.05	0.40	0.79	0.95
			20,000,000	0.07	0.67	0.97	1.00
	Bell's palsy	25.2	500,000	0.04	0.22	0.49	0.73
			1,000,000	0.05	0.40	0.79	0.95
			2,500,000	0.07	0.76	0.99	1.00
			5,000,000	0.11	0.97	1.00	1.00
			10,000,000	0.18	1.00	1.00	1.00
			20,000,000	0.31	1.00	1.00	1.00
	Myocardial infarction	208	500,000	0.10	0.93	1.00	1.00
			1,000,000	0.15	1.00	1.00	1.00
			2,500,000	0.32	1.00	1.00	1.00
			5,000,000	0.56	1.00	1.00	1.00
			10,000,000	0.85	1.00	1.00	1.00
			20,000,000	0.99	1.00	1.00	1.00

a. Estimates in this table assume a risk window duration of 42 days for Guillain-Barré syndrome and 28 days for Bell's palsy and myocardial infarction.

9.6. Data management

9.6.1. Data collection tools (DCTs)

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

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A DCT is required and should be completed for each patient included in the chart validation activities. The completed original DCT are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or

appropriate regulatory authorities, without written permission from Pfizer. Harvard Pilgrim Health Care Institute (HPHCI) shall ensure that the DCTs shared with HPHCI are securely stored at HPHCI in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

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

The source documents are the hospital or the physician's chart. In these cases, data collected on the DCTs must match those charts.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, HPHCI as the coordinating center agrees to keep all study-related records, including programming specifications, aggregate data reports submitted by data research partners, final study reports, and any related materials. The records should be retained by HPHCI according to local regulations or as specified in the research agreement with Pfizer, whichever is longer. HPHCI must ensure that the records continue to be stored securely for so long as they are retained.

If HPHCI becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

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

HPHCI must obtain Pfizer’s written permission before disposing of any records, even if retention requirements have been met.

9.6.3. Data oversight

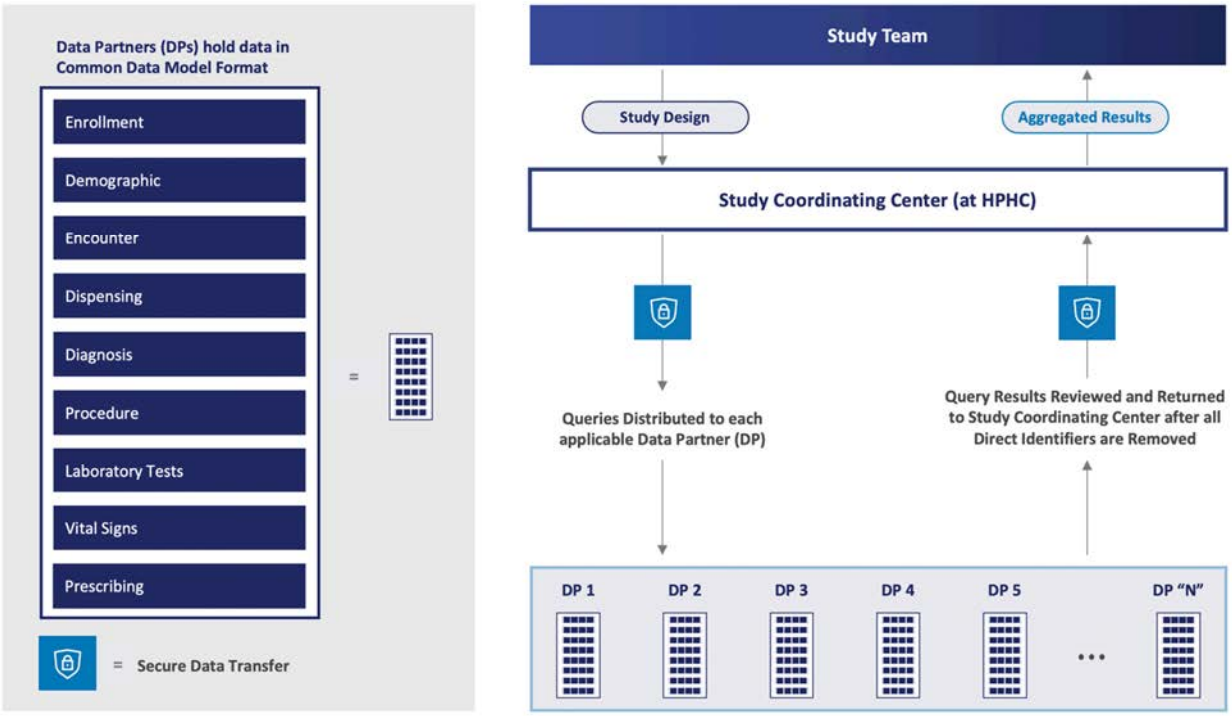
HPHCI, located in Boston, Massachusetts, will serve as the coordinating center for the proposed study. HPHCI staff or contractors will be responsible for writing and distributing SAS programs that can be used to evaluate the data included in databases at participating data research partners. The distributed network will allow data research partners to maintain physical and operational control of their data while allowing use of the data to meet the study

needs. HPHCI will maintain a secure, distributed, querying web-based portal to enable secure distribution of analytic queries, data transfer, and document storage. The system will meet all required state and federal security guidelines for health data (e.g., Federal Information Security Management Act [FISMA], Health Insurance Portability and Accountability Act of 1996) 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).

HPHCI brings expertise in conducting multisite evaluations using disparate electronic healthcare data systems, including work with the Health Care Systems Research Network, the VSD, the National Institutes of Health, Health Care Systems Research Collaboratory, IMEDS (Innovation in Medical Evidence Development and Surveillance), the Biologics and Biosimilars Collective Intelligence Consortium, PCORnet (the National Patient-Centered Clinical Research Network), and the Sentinel System. HPHCI will oversee all project activities, including scientific leadership, management of the partnership, coordination of activities with the data research partners and other participants, oversight of the project plan and budgets, establishment of secure infrastructure used for collaboration, and training related to use of the data sources and associated analytic tools. In collaboration with RTI Health Solutions (RTI-HS), HPHCI will also oversee all activities related to implementation of any potential medical record reviews. HPHCI will develop standard operating procedures and processes to guide any potential linkages to state registries or implementation of medical chart reviews in collaboration with RTI-HS and the data research partners. The data research partners will establish and maintain the administrative, hardware, and software capabilities and capacity to respond to data requests in a timely manner. Data research partners will also provide data science support with epidemiologic review.

Figure 3 summarizes the general analytic workflow. Based on the study design developed by the study team, the study coordinating center first submits through a secure portal a computer program designed to meet the needs of the study. Next, the participating data research partners receive and run the computer program behind their firewalls, using data that is formatted to the SCDM. Then, the data research partners review the analysis results and return them to the study coordinating center through a secure portal. The study coordinating center then reviews and aggregates the results across the data research partners. In the final step, the aggregated results are transferred to the study team.

Figure 3. General analytic workflow



9.7. Data analysis

All analyses will initially be conducted separately within the data from each data source. Pooled analysis of RR and odds ratio estimates from all data sources will be conducted using privacy-preserving summary-level data sets (e.g., risk set–level data sets) or if this is not feasible, meta-analysis. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary outcome definitions or their analyses will be reflected in a protocol amendment.

9.7.1. Descriptive analysis

Descriptive analysis will report on utilization of Pfizer-BioNTech COVID-19 Vaccine during the overall study period and during the study period, stratified in 12-week increments (to assess vaccine uptake and patterns of exposure over time). The proportion of individuals receiving at least 1 dose and a complete dose series of Pfizer-BioNTech COVID-19 Vaccine will be estimated within the overall study population, in immunocompromised individuals, in individuals with a history of COVID-19, and in pregnant women. Among patients who receive a first dose of Pfizer-BioNTech COVID-19 Vaccine, the proportion of patients will

be reported by type of second dose of COVID-19 vaccine and time between the 2 doses will be described.

The number and proportion of patients with a convulsion event who have a history of epilepsy will be reported separately in each of the matched exposed and matched unexposed cohorts. The length of follow-up in the exposed and unexposed cohorts contributing to analyses of vaccine-associated enhanced disease will be output. Characteristics (demographics, comorbidities, and other potential covariates) of the matched and unmatched cohorts will be shown in a table. No statistical tests are planned for this comparison, but the balance of variables in the matched cohorts will be assessed using standardized differences or other suitable methods.

Additional descriptive analysis may be conducted for safety events that have signaled in other studies or vaccine safety surveillance systems (e.g., myocarditis/pericarditis). These analyses will be described in the SAP.

9.7.2. Measures of disease frequency and association

All eligible individuals in each study cohort will be included in analysis of disease frequency and measures of association. However, in analysis of some safety events, individuals who have experienced the outcome in the recent past will be excluded from the analysis. This will be done to distinguish between follow-up care for events that have happened in the past from incident events occurring during follow-up. The washout periods for defining incident events will depend on the outcome and will be specified in the SAP.

9.7.2.1. Measures of disease frequency

In each data source, crude measures of incidence (for all outcomes except congenital malformations and small size for gestational age) or birth prevalence (for congenital malformations and small size for gestational age) with associated 95% CIs will be estimated within the matched exposed and unexposed cohorts. Prevalence will be estimated for major congenital malformations because the outcome is identified after birth without the ability to determine its true timing of onset during pregnancy. Prevalence will be estimated for small size for gestational age because the outcome is identified at a single timepoint (at birth).

9.7.2.2. Measures of association

For comparative analyses of general safety events, spontaneous abortion, stillbirth, and preterm birth, Cox models or Poisson regression will be used to estimate RRs and 95% CIs within the matched cohorts.

For comparative analysis of small size for gestational age and major congenital malformations, logistic regression will be used to estimate odds ratios and 95% CIs within the matched cohorts.

For comparative analysis of outcomes identified separately in dose 1 and dose 2 cohorts, comparative risks will be estimated separately by dose number. If comparative risk estimates

are similar by dose number, then data from the dose 1 exposed/dose 1 unexposed cohorts and the dose 2 exposed/dose 2 unexposed cohorts will be combined to obtain comparative risk estimates associated with any dose of the vaccine.

For the dose 1 comparative risk estimation, when a second dose of vaccine is administered before the risk interval following dose 1 is complete, the risk interval will be truncated at the time of dose 2, and follow-up after dose 2 will be excluded from the dose 1 risk estimation. In this situation, for the dose 2 comparative risk estimation, the risk interval will start on the date of the second vaccine dose and will extend for the duration of the risk interval for dose 2.

Because each dose of vaccine within the same individual will be considered a separate observation when combined in analysis and because some individuals may contribute to both the exposed and unexposed cohorts, the correlation between dose 1 and dose 2 will be accounted for when estimating the variance, using appropriate statistical methods to be detailed in the SAP.

9.7.2.2.1. Methods for addressing confounding

9.7.2.2.1.1. General population, immunocompromised individuals, and individuals with a history of COVID-19

Analysis of nonpregnant populations will use matching on age, state (if feasible, or broader geographic region if not feasible), and time-specific propensity scores within the data from each data research partner to account for confounding. The propensity score is the predicted probability of an individual being in the exposed cohort rather than in the corresponding unexposed cohort, given a set of observed covariates.

Estimation of propensity scores will be performed for the dose 1 and 2 cohorts combined, but matching of exposed to unexposed individuals will be done separately for the dose 1 exposed cohort and for the dose 2 exposed cohort, within narrow time periods to account for changing predictors of vaccination over time, seasonality of circulating infections, and changes in healthcare utilization over time. Matching will occur by age and state (if feasible, or broader geographic region if not feasible) within each time period and dose number. The matching and propensity score estimation process will be done first for the general population and then will be repeated separately for immunocompromised individuals and for individuals with a history of COVID-19. Propensity score estimation will be conducted within each data research partner. The steps for propensity score modeling and matching are as follows.

a. Within each data research partner, the study period will be divided into 1-month intervals of calendar time ("time intervals"). All individuals who received a vaccine dose, either dose 1 or dose 2, during the considered month would contribute vaccinated index dates during the time interval—if a patient received 2 doses during a calendar month, both index dates will be included as independent observations in the propensity score model. All individuals with at least 1 unexposed person-day in the time interval will have an unvaccinated index date randomly assigned during the time interval. In this context,

"unexposed person-day" refers to a day in which the patient has no record of COVID-19 vaccine on or before that day.

b. Within each time interval, the propensity to be vaccinated will be estimated among all individuals with index dates within the time interval using logistic regression. The dependent variable for the logistic regression model will be vaccination status, and the independent variables will be baseline covariates (i.e., individual characteristics as described in Section 9.3.3). The model will combine dose 1 and dose 2 index dates, which assumes that the factors influencing an individual's likelihood of being vaccinated does not change between dose 1 and dose 2.

c. Within each data research partner, the distribution of propensity scores in each dose cohort in each time interval will be plotted to evaluate the comparability of the 2 exposure groups. Greater overlap of the propensity score distributions will indicate greater exchangeability.

d. After the comparability of the treatment groups is confirmed, unexposed individuals will be matched on propensity scores to exposed individuals (in a ratio of at least 1:1) within each data research partner. The matching will be done separately for the dose 1 exposed cohort and for the dose 2 exposed cohort and will be done by age, state (or geographic region) within each time interval.

e. The matching procedure within each dose cohort will be executed chronologically from 1 time interval to the next time interval. An individual may only be selected once for the dose 1 unexposed cohort and once for the dose 2 unexposed cohort. Individuals who match as an unvaccinated index date in 1 time interval will not be considered for the same unvaccinated cohort (i.e., dose 1 unexposed cohort or dose 2 unexposed cohort) in future time intervals. However, if an individual becomes vaccinated after being selected as an unexposed match, he or she may be eligible for the dose 1 and/or dose 2 exposed cohorts.

f. The matched exposed and unexposed individuals from each time interval will be combined into the overall matched analytic cohorts.

Further details on the matching process and estimation of propensity scores will be described in the SAP.

9.7.2.2.1.2. Pregnant women

To minimize confounding by seasonality and maternal age, within the data from each data research partner, exposed pregnant women will be matched to unexposed pregnant women on estimated pregnancy start date (+/- 14 days), state (if feasible, or broader geographic region if not feasible), and maternal age. Propensity scores will be estimated within the matched population and incorporated into regression analysis for exposure-outcome associations (e.g., through weighting or stratification) to address confounding by other variables. The matching and propensity score estimation process will be done first for the

overall population of pregnant women. The process will then be repeated for the subsets of pregnant women eligible for analyses of the different safety events of interest (e.g., pregnancies surviving beyond 20 completed weeks of pregnancy for analysis of stillbirth; live births for analysis of preterm birth and small size for gestational age; and live births that can be linked to infants for analysis of major congenital malformations).

The steps for matching and propensity score analysis are as follows.

a. Unexposed individuals will be matched on estimated pregnancy start date, state (or broader geographic region, as feasible), and maternal age to exposed individuals within each data research partner (in a ratio of at least 1:1). When applicable (when separate dose 1 and dose 2 exposed cohorts are formed), the matching will be done separately for the dose 1 exposed cohort and for the dose 2 exposed cohort.

   An individual may be selected for each unexposed cohort (i.e., dose 1 unexposed, dose 2 unexposed cohort, or unexposed cohort) only once. However, if an individual becomes vaccinated after being selected as an unexposed match, he or she may be eligible for the exposed cohort(s).

b. The propensity to be vaccinated will be estimated among all individuals with eligible index dates. The dependent variable for the logistic regression model will be vaccination status, and the independent variables will be baseline covariates (i.e., individual characteristics as described in Section 9.3.3). When applicable (when separate dose 1 and dose 2 exposed cohorts are formed), the model will combine dose 1 and dose 2 index dates.

c. The distribution of propensity scores in each cohort will be plotted to evaluate the comparability of the 2 exposure groups. Greater overlap of the propensity score distributions will indicate greater exchangeability.

d. After the comparability of the treatment groups is confirmed, propensity scores will be incorporated into regression modeling for exposure-outcome associations through weighting or stratification.

Further details on the matching process and estimation of propensity scores will be described in the SAP.

9.7.3. Sensitivity analysis

9.7.3.1. Exposure misclassification

During the early stages of the roll out of COVID-19 vaccines, many vaccinations may have occurred outside traditional medical care settings without reimbursement from health insurers. The potential for lack of recording of COVID-19 vaccines in claims and electronic health records may lead to misclassification of exposed individuals as “unexposed” individuals, which will underestimate vaccine coverage rates and bias comparative risk

estimates for the cohort design with concurrent unexposed individuals as comparators. To address this potential bias in comparative risk estimates, sensitivity analysis will be performed using a SCRI design or a cohort design with historical comparators, depending on the safety event of interest.

9.7.3.1.1. Self-controlled risk interval design

Sensitivity analyses incorporating a SCRI design will be implemented for outcomes with a well-defined onset and risk intervals no longer than 42 days (specific outcomes to be named in the SAP) in the overall study population, in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19. The SCRI design will not be considered for pregnancy safety outcomes. Only vaccinated individuals will be included in the SCRI analysis; the rate of a specific safety event in a post-vaccination risk interval will be compared with the rate in a control interval within the same individual.

For individuals who receive 2 doses of the vaccine, the risk interval will combine person-time in the risk intervals after the first dose and after the second dose. The control interval will be outcome specific, with the duration and timing relative to vaccination specified in more detail in the SAP. Control intervals will be defined during specific periods following vaccination (up to a maximum of 183 days); prevaccination periods will not be used to avoid bias due to healthy vaccinee effects. For outcomes with risk intervals shorter than the recommended spacing between dose 1 and dose 2 (e.g., anaphylaxis), the control interval may comprise person-time between the first and second doses. For outcomes with risk intervals longer than the recommended spacing between dose 1 and dose 2, the control interval will comprise person-time after the second dose. A washout period between the risk and control intervals may be incorporated for safety events for which the risk interval is not well characterized.

Because of the self-controlled nature of the design, bias of comparative risk estimates arising from differences in the distribution of time-constant confounding factors between vaccinated and unvaccinated individuals is avoided with the SCRI design. Furthermore, as the design only includes vaccinated individuals, it avoids the potential for misclassification of unexposed status due to incomplete capture of COVID-19 vaccinations in data from claims or electronic health records.

9.7.3.1.2. Cohort design with historical unexposed comparators

If feasible, sensitivity analysis of events not meeting criteria for the SCRI design (i.e., outcomes with gradual onset and/or risk intervals longer than 42 days, except for vaccine-associated enhanced respiratory disease; specific outcomes to be named in the SAP) will incorporate historical unexposed individuals as comparators. The comparator cohorts will be identified and followed in a time period before the introduction of COVID-19 vaccines. The index date in historical unexposed individuals will be 2 or more years prior to the date of vaccination in exposed individuals. Exposed and unexposed individuals will be

matched on age and propensity score, using similar methods as for the cohort design with concurrent unexposed comparators.

The use of historical unexposed individuals as comparators avoids the potential for misclassification of unexposed status due to incomplete capture of COVID-19 vaccinations in data from claims or electronic health records. The feasibility of this analysis will depend on the absence of trends in coding for each safety event of interest over time in the historical comparator period and the study period. Further details on the composition of the cohorts, methods to address confounding, and criteria used to determine whether this design is feasible will be specified in the SAP.

9.7.3.2. Risk intervals

The study 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.

Sensitivity analysis of myocarditis/pericarditis will be conducted using alternative risk interval definitions of 1-7 and 1-14 days.

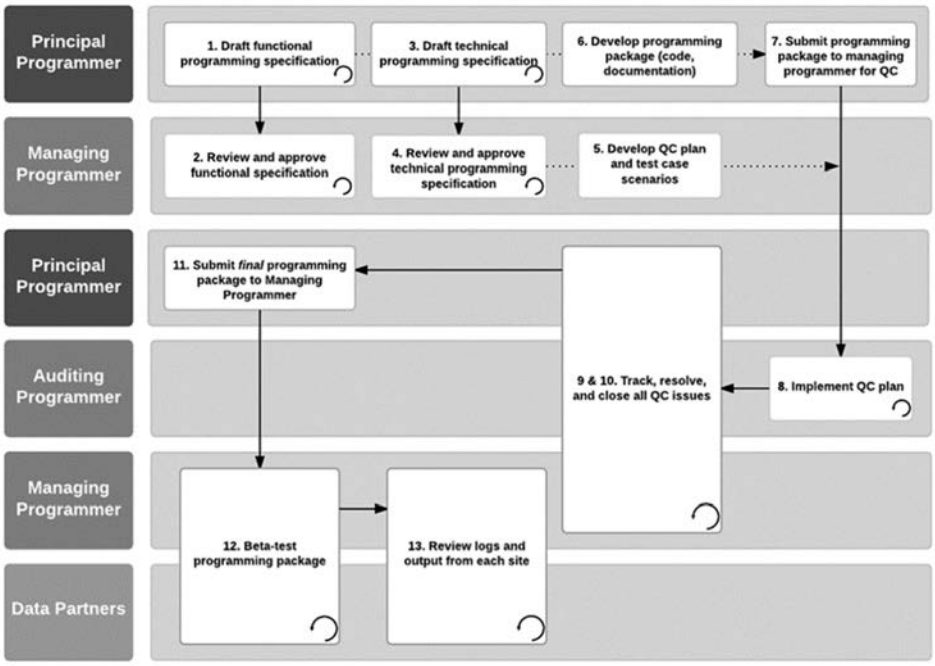
For events for which the risk intervals are not well characterized (to be defined in the SAP), descriptive analyses of the timing of events relative to vaccination will be conducted. If they are identified, temporal clusters will be used to define alternative risk intervals that will be used in sensitivity analyses.

9.8. Quality control

The data research partners that will contribute 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 data sets 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 research partners. Full QA processes and details on the Sentinel database curation approach are documented on the Sentinel website (Sentinel, 2021; 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 quality control (QC) processes used by the Sentinel System to check SAS programs and deliverables. Figure 4 illustrates the standard operating procedures for SAS programming QA and QC in the Sentinel System.

Figure 4. Standard operating procedure for SAS programming quality assurance and quality control in the Sentinel System



9.9. Strengths and limitations of the research methods

A major strength of this study is that it will include a very sizeable source population in the US, as the participating data research partners together collect data on more than 100 million individuals. The use of secondary data will enable the efficient assessment of many safety events of interest identified by the CDC's VSD and the FDA's BEST Initiative, in addition to pregnancy safety outcomes, while using robust study design and analytic approaches to adjust for potential confounding. Moreover, the secondary use of administrative data collected as part of routine medical care avoids selection bias that might occur in primary data collection studies, as a patient's inclusion in this study is not voluntary.

Nevertheless, this study is subject to limitations arising from the use of secondary data 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. If the data appear to be substantially incomplete in monitoring analyses, then the primary study design may be reconsidered. If this happens, the SCRI and the cohort design with historical unexposed comparators may be designated as the primary study designs; and/or linkage to immunization registries may be considered. Additionally, the use of data from claims and electronic health records may lead to some misclassification of outcomes (e.g., false positives and false negatives). Some events, such as spontaneous abortion, will be incompletely captured in existing databases. Conversely, validation studies of ICD-10-CM–based algorithms for many of the safety events of interest have been limited, and the accuracy of algorithms for many safety events of

interest are unknown. When possible, validated algorithms will be used, and outcomes that are likely to be misclassified (based on prior validation studies and clinical expert input) may be validated through review of medical records or claims profiles, depending on the safety event of interest.

A study design-related limitation is that any uncertainty regarding risk periods will lead to misclassification and attenuation of risk estimates. Sensitivity analyses with alternative risk intervals will be considered for outcomes for which the risk interval is not well characterized.

A limitation of the cohort design with concurrent unexposed comparators is the potential for residual or unmeasured confounding because it is unlikely that the data sources will have information on all potential confounders. To address potential confounding, the SCRI, which automatically adjusts for time-invariant confounders, will be used as a secondary approach where feasible. However, the SCRI is not well suited to study outcomes with gradual onset, long risk intervals, or risk periods that are not well characterized.

A limitation specific to the cohort design with concurrent unexposed comparators is that unvaccinated individuals may become exposed to COVID-19 vaccine at any time during the study; if this situation occurs frequently, the amount of unexposed person-time in the unexposed comparator group will be reduced substantially, which will limit the precision of comparative risk estimates and could potentially lead to substantial imbalances in seasonality between exposed individuals and unexposed individuals, particularly for outcomes with long risk intervals. Forming 2 separate exposed cohorts by dose number and matching unexposed to exposed at the time of each vaccine will minimize the loss of unexposed person-time due to receipt of vaccine in these individuals between the first and second doses. Additionally, the sensitivity analyses with the historical unexposed comparator cohort and the SCRI design will not be subject to this limitation. However, it is anticipated that even with separate matching of doses that follow-up time will be substantially longer in analyses of vaccine-associated enhanced respiratory disease in individuals in the vaccinated cohorts than in the unvaccinated comparator cohorts, since the risk interval is 365 days long. Further, the SCRI design and historical unexposed comparator cohort design are not feasible to study this outcome.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

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

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

10.1. Patient information

This study mainly involves data that exist in anonymized structured format and contain no patient personal information. If chart validation is required, during this component of this study, data research partners will remove and redact all direct patient identifiers as delineated in the Privacy Rule of HIPAA (Health Insurance Portability and Accountability Act of 1996). A limited data set of protected health information (PHI)—including date of birth, date of vaccination, date of death, visit date, and diagnosis date—may be collected. Dates related to the individual (date of birth, date of death, visit date, and diagnosis date) are required in order to investigate the safety of COVID-19 vaccines.

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

HPHCI will maintain a secure web-based portal to enable secure data transfer and document storage. The system will be FISMA compliant (FISMA Moderate Risk security controls, as specified in the NIST Special Publication 800-53). The system will comply with relevant FISMA, HIPAA, and NIST requirements. A study identification number will also be used in place of direct patient identifiers to minimize risk. Patient personal data will be stored at the individual data research partner or at HPHCI in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. Each data research partner and HPHCI will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, each data research partner and HPHCI shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will

maintain high standards of confidentiality and protection of patients' personal data consistent with the research agreement and applicable privacy laws.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients is not required.

10.3. Institutional review board/Independent ethics committee (IEC)

Each data research partner, 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 (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB or independent ethics committee 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 Conference on 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 follow generally accepted research practices described in *Guidelines for Good Pharmacoepidemiology Practices* (GPP) (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. If validation of algorithms for identifying outcomes is conducted, the study may also involve human review of unstructured data.

11.1. Structured data analysis

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

11.2. Human review of unstructured data

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

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

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

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

- For the analysis of the subpopulation in pregnant women, data on the exposure to the Pfizer-BioNTech COVID-19 Vaccine during pregnancy, as well as pregnancy safety outcomes, will be included in the analytic data set. For pregnant women whose charts are reviewed for outcome algorithm validation purposes, exposure during pregnancy cases are not reportable unless associated with serious or nonserious adverse events.

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

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

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

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

- Your Reporting Responsibilities (YRR) Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators).

These trainings must be completed by research staff members that will have access to copies of medical records prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current YRR training materials.

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 an interim study report are planned for the first and second year of follow-up. After the end of the third year of follow-up, the final report will be produced, including the analysis and interpretation of each outcome including pregnancy safety outcomes.

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2019). 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 (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator 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.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

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