NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine in the United States
Protocol number	C4591009
Protocol version identifier	4.0
Date	30 June 2023
EU Post-Authorisation Study (PAS) register number	EUPAS43468
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 BNT162b2 (original monovalent) COVID-19 Vaccine
Marketing Authorization Holder(s) (MAH)	BioNTech Manufacturing GmbH
Joint PASS	No
Research question and objectives	<u>Research questions</u> Among the general population, immunocompromised individuals, pregnant women, and individuals with a history of COVID-19: 1. What is the incidence of safety events of interest, including myocarditis/pericarditis, among individuals receiving at least 1 dose in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with that among individuals who have not received any

	vaccination for COVID-19 in the United States (US)? 2. In individuals aged 5 years and older who have received the first and second dose in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine, what is the incidence of safety events of interest, including myocarditis/pericarditis, among individuals vaccinated with a third dose (either as an additional dose in a primary series[1] or as a booster dose) of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with that among individuals who have not received a third dose of any COVID-19 vaccine in the US? 3. What is the prevalence of birth outcomes of interest (including major congenital malformations and small size for gestational age) in infants born to pregnant women who were exposed to Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine, as compared with that among infants born to pregnant women who were not exposed to any COVID-19 vaccine in the US? <u>Primary study objectives</u> Among the overall study population and subgroups of pregnant women, immunocompromised individuals, and individuals with a history of COVID-19: 1. **In individuals aged 5 years and older:** To estimate the relative risk (RR) of safety events of interest (including myocarditis/pericarditis) following receipt of a first, second, or third (if received within 2 months of the second dose) dose in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with no receipt of any COVID-19 vaccine 2. **In individuals aged 6 months through 4 years:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following

	receipt of a first, second, or third dose in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with that among individuals with no receipt of any COVID-19 vaccine 3. **In individuals aged 5 years and older who have received 2 doses in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following a third dose (as an additional dose in a primary series[1] or as a booster dose) of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine received more than 2 months after the second dose compared with that among individuals without a third dose of any COVID-19 vaccine **Among pregnant women:** 4. To estimate the birth prevalence and prevalence ratio of birth outcomes among infants born to pregnant women vaccinated with Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with that among infants born to unvaccinated pregnant women. <u>Secondary objectives:</u> Among the overall study population and subgroups of pregnant women, immunocompromised individuals, and individuals with a history of COVID-19: 1. To describe the proportion of individuals receiving Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine, stratified by number of doses 2. To describe—among individuals who have received a first dose of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine—the timing and type of second dose of COVID-19 vaccine (Pfizer-BioNTech BNT162b2

	[original monovalent] COVID-19 Vaccine or other COVID-19 vaccine) 3. To describe baseline characteristics (demographics and comorbidities) of individuals who have received at least 1 dose of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine and those with no record of COVID-19 vaccination of any type 4. To describe—among individuals who have received 2 doses of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine—the timing and type of a third dose of COVID-19 vaccine (Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine or other COVID-19 vaccine) 5. To describe—among individuals aged 5 years and older who have received at least 2 doses in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine—baseline characteristics (demographics and comorbidities) of individuals who received a third dose (either as an additional dose in a primary series[1] or as a booster dose) of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine more than 2 months after the second dose and those with no record of a third dose of COVID-19 vaccination of any type 6. **Among pregnant women who have received 2 doses in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following receipt of a third dose (either as an additional dose in a primary series[1] or as a booster dose) received more than 2 months after the second dose of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with that among individuals with no receipt of a third dose of any COVID-19 vaccine

Country(-ies) of study	United States
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1 Primary series vaccination is administered in a 2-dose series in individuals aged 5 years and older who are not immunocompromised, in a 3-dose series in individuals aged 5 years and older who are immunocompromised, and in a 3-dose series in children aged 6 months through 4 years

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AEM	adverse event monitoring
AESI	adverse event of special interest
BEST	Biologics Effectiveness and Safety
BLA	Biological License Application
BNT162b2	Pfizer-BioNTech COVID-19 Original Monovalent Vaccine
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CSSE	Center for Systems Science and Engineering
CTS	Clinical Trial Services
DCT	data collection tool
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
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

Abbreviation	Definition
FU	follow-up
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPHCI	Harvard Pilgrim Health Care Institute
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
ICD-10-PCS	*International Classification of Diseases, 10th Revision, Procedure Coding System*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
IEA	International Epidemiological Association
IEC	independent ethics committee
IMEDS	Innovation in Medical Evidence Development and Surveillance
IRB	institutional review board
LNP	lipid nanoparticle
MAH	Marketing Authorization Holder
mRNA	messenger RNA
NIS	non-interventional study
NIST	National Institute of Standards and Technology
PCORnet	The National Patient-Centered Clinical Research Network
PRAC	Pharmacovigilance Risk Assessment Committee
Q (1-4)	1st, 2nd, 3rd, or 4th Quarter
QA	quality assurance
QC	quality control

Abbreviation	Definition
RR	relative risk
RTI-HS	RTI Health Solutions
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

2. RESPONSIBLE PARTIES

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

3. ABSTRACT

Title: A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine in the United States

Version and Date: Version 4.0, 30 June 2023

Main authors: Alison Kawai, ScD, RTI Health Solutions; Candace Fuller, 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; and Nana Koram, 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 BNT162b2 (original monovalent) COVID-19 Vaccine was authorized for emergency use by the US Food and Drug Administration (FDA) to prevent COVID-19 in individuals aged 16 years and older (FDA, 2023). On 23 August 2021, Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine (Comirnaty®) was fully approved by the FDA for use in this age group (FDA, 2021). Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine was authorized for emergency use in children aged 12 to 15 years on 10 May 2021, in children aged 5 to 11 years on 29 October 2021, and in children aged 6 months through 4 years on 17 June 2022 (FDA, 2023).

Additionally, a third dose in the primary series was previously authorized in individuals aged 5 years and older with certain immunocompromising conditions (FDA, 2023). The Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine was also previously authorized for booster vaccination as (1) a single booster dose in individuals aged 5 to 11 years, (2) a first booster dose in individuals aged 12 years and older, (3) a second booster dose in immunocompromised individuals aged 12 years and older, and (4) a second booster dose in individuals aged 50 years and older (FDA, 2023). As of 18 April 2023, Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine is no longer authorized for use in the US, and the vaccine schedule was simplified to authorize the use of the current bivalent vaccine for all initial and subsequent doses administered to individuals 6 months and older (FDA, 2023).

After the initial authorization of both monovalent messenger RNA (mRNA) COVID-19 vaccines, cases of myocarditis/pericarditis following vaccination were reported to the Vaccine Adverse Events Reporting System and were first discussed by the Advisory Committee on Immunization Practices in June 2021 (Gargano et al., 2021; Shimabukuro, 2021b). A potential increased risk was reported in males aged 12 to 29 years after the second dose. Based on a risk-benefit assessment, the Advisory Committee on Immunization Practices concluded that the benefits of vaccination outweighed the risks and continued to recommend COVID-19 vaccination. The FDA added this safety event to the Emergency Use

Authorization (EUA) factsheet, and the warnings and precautions section of the prescribing information for the Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine states that, "Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age" (Pfizer, 2021).

Post-authorization observational studies using real-world data are needed to assess the association between Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine and predetermined safety events of interest among the general population and among 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 BNT162b2 (original monovalent) 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 include myocarditis/pericarditis and are partially based on those included in COVID-19 Vaccine rapid-cycle analysis in the FDA's Biologics Effectiveness and Safety System and the Centers for Disease Control and Prevention Vaccine Safety Datalink, with the addition of vaccine-associated enhanced respiratory disease, immune hemolytic anemia, and thrombotic events with thrombocytopenia. Pregnancy safety outcomes (i.e., 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 as the data sources permit.

The proposed non-interventional study is designated as a postmarketing requirement to the FDA and a Category 3 commitment to the European Medicines Agency as noted in the risk management plan. The study is intended to evaluate the occurrence of safety events of interest, including myocarditis/pericarditis following administration of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine.

Research question and objectives

Research questions

Among the general population, immunocompromised individuals, pregnant women, and individuals with a history of COVID-19:

1. What is the incidence of safety events of interest, including myocarditis/pericarditis, among individuals receiving at least 1 dose in a primary series[1] of Pfizer-BioNTech

[1] Primary series vaccination is administered in a 2-dose series in individuals aged 5 years and older who are not immunocompromised, in a 3-dose series in individuals aged 5 years and older who are immunocompromised, and in a 3-dose series in children aged 6 months through 4 years.

BNT162b2 (original monovalent) COVID-19 Vaccine compared with that among individuals who have not received any vaccination for COVID-19 in the US?

2. In individuals aged 5 years and older who have received the first and second dose in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine, what is the incidence of safety events of interest, including myocarditis/pericarditis, among individuals vaccinated with a third dose (either as an additional dose in a primary series[1] or as a booster dose) of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with that among individuals who have not received a third dose of any COVID-19 vaccine in the US?

3. What is the prevalence of birth outcomes of interest (including major congenital malformations and small size for gestational age) in infants born to pregnant women who were exposed to the Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine, as compared with that among infants born to pregnant women who were not exposed to any COVID-19 vaccine in the US?

Primary study objectives

Among the overall study population and subgroups of pregnant women, immunocompromised individuals, and individuals with a history of COVID-19:

1. **In individuals aged 5 years and older:** To estimate the relative risk (RR) of safety events of interest (including myocarditis/pericarditis) following receipt of a first, second, or third (if received within 2 months of the second dose) dose in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with no receipt of any COVID-19 vaccine

2. **In individuals aged 6 months through 4 years:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following receipt of a first, second, or third dose in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with no receipt of any COVID-19 vaccine

3. **In individuals aged 5 years and older who have received 2 doses in a primary series of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following a third dose (as an additional dose in a primary series[1] or as a booster dose) of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine received more than 2 months after the second dose compared with that among individuals without a third dose of any COVID-19 vaccine

Among pregnant women:

4. To estimate the birth prevalence and prevalence ratio of birth outcomes among infants born to pregnant women vaccinated with Pfizer-BioNTech BNT162b2 (original

monovalent) COVID-19 Vaccine compared with that among infants born to unvaccinated pregnant women.

Secondary objectives:

Among the overall study population and subgroups of pregnant women, immunocompromised individuals, and individuals with a history of COVID-19:

1. To describe the proportion of individuals receiving Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine, stratified by number of doses

2. To describe—among individuals who have received a first dose of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine—the timing and type of second dose of COVID-19 vaccine (Pfizer-BioNTech BNT162b2 [original monovalent] COVID-19 Vaccine or other COVID-19 vaccine)

3. To describe baseline characteristics (demographics and comorbidities) of individuals who have received at least 1 dose of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine and those with no record of COVID-19 vaccination of any type

4. To describe—among individuals who have received 2 doses of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine—the timing and type of a third dose of COVID-19 vaccine (Pfizer-BioNTech BNT162b2 [original monovalent] COVID-19 Vaccine or other COVID-19 vaccine)

5. To describe—among individuals aged 5 years and older who have received at least 2 doses in a primary series[1] of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine—baseline characteristics (demographics and comorbidities) of individuals who received a third dose (either as an additional dose in a primary series[1] or as a booster dose) of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine more than 2 months after the second dose and those with no record of a third dose of COVID-19 vaccination of any type

6. **Among pregnant women who have received 2 doses in a primary series of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following receipt of a third dose (either as an additional dose in a primary series[1] or as a booster dose) received more than 2 months after the second dose of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine compared with that among individuals with no receipt of a third dose of any COVID-19 vaccine

Study design

This study will use a retrospective cohort design of individuals with concurrent unexposed comparators. The study will compare the incidence of safety events among individuals who

have received a first, second, or third dose in a primary series of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine with that among individuals who have no record of any COVID-19 vaccine in a concurrent time period. In individuals aged 5 years and older, third doses will only be included in primary series analysis if the third dose is received within 2 months of the second dose.

Additionally, in individuals aged 5 years and older who have received 2 doses in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine, the incidence of safety events among individuals who have received a third dose (either as an additional dose in a primary series or as an initial booster dose) of the vaccine more than 2 months after the second dose will be compared with that among individuals who have not received a third dose of any COVID-19 vaccine.

Finally, the study will compare the prevalence of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to women who have received at least 1 dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine during an exposure window of interest with that among infants born to women who have not received any COVID-19 vaccine during the exposure window of interest.

For analyses in the overall population, as well as in subcohorts of immunocompromised individuals and individuals with a history of COVID-19, individuals in the exposed group will be matched to individuals in the comparator group (in a ratio of at least 1:1) within data source on age, sex, state (if feasible, or broader geographic region if not feasible), calendar time, and propensity score. For analyses in pregnant women, those in the exposed group will be matched to women in the comparator group on maternal age, state (if feasible), and estimated pregnancy start; confounding will be addressed through propensity score matching or through the inclusion of propensity scores in exposure-outcome regression models.

To inform the full implementation of the study, 2 monitoring analyses and an interim analysis will be conducted before the final analysis to describe vaccine utilization in the overall population, among immunocompromised individuals, among individuals with a history of COVID-19, and in subgroups defined by age. The monitoring phase will also describe incidence rates of select events of interest among Pfizer-BioNTech original monovalent COVID-19 Vaccinees (monitoring analysis report 1 and monitoring analysis report 2), incidence rates of safety events of interest overall in matched cohorts without regard to exposure status (overall, and within the subgroups of interest; interim analysis), and incidence of myocarditis/pericarditis by exposure status (overall, and by select covariates of interest; interim analysis). Additional analyses during the monitoring phase will assess feasibility aspects, including the data completeness of COVID-19 vaccines, dose number availability in the data sources, and geographc information granularity that may be incorporated into the analyses.

The study observation period will start on the date that Pfizer-BioNTech original monovalent COVID-19 Vaccine was granted EUA in the US (11 December 2020) and the exposure assessment window will end 18 April 2023 (when the original monovalent vaccine was no

longer authorized). Follow-up to identify outcomes within predefined risk periods will end a minimum of 3 years after the initial authorization date. The study will include vaccinations received under both the EUA and the biologic license application (BLA).

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, Carelon Research (formerly HealthCore/Anthem), HealthPartners, Humana, and Optum.

Individuals of all ages will be included in the descriptive analysis of Pfizer-BioNTech original monovalent 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 original monovalent COVID-19 Vaccine, with age-based eligibility criteria changing throughout the study period. However, if the proportion of Pfizer-BioNTech original monovalent COVID-19 Vaccine recipients whose ages fall outside the approved age range is greater than 1%, then safety analyses will include individuals of all ages who have received the Pfizer-BioNTech original monovalent COVID-19 Vaccine at any time during the study period.

Individuals older than 1 year of age 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) or from the earliest date that they were eligible to receive the vaccine until the index date—whichever period is longer. Children aged younger than 12 months on the index date must be enrolled from birth until the index date. Depending on whether data on vaccine dose number are recorded in the data sources (to be determined during the monitoring phase of the study), additional enrollment may be required from the earliest authorization of Pfizer-BioNTech original monovalent COVID-19 Vaccine (i.e., 11 December 2020) to enable dose number identification. 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). Analyses of congenital malformations and small size for gestational age will be limited to singleton 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 original monovalent COVID-19 Vaccine, and this date is the start of follow-up; each dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine will contribute separate index dates. For each individual selected to be a comparator 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 in pregnant women, each dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine received will contribute

separate index dates. For each individual selected to be a comparator 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 in pregnant women, the index date for 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. Subgroup analysis will be conducted by age group (0-4, 5-11, 12-17, 18-64, and ≥ 65 years), as appropriate for each safety event of interest. Further subgroup analysis of myocarditis/pericarditis will be conducted by additional age categories (0-4, 5-11, 12-17, 18-24, 25-29, 30-39, 40-49, 50-64, and ≥ 65 years), sex, sex and age together (in the aforementioned age categories), dose number, and calendar time.

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 myocarditis/pericarditis will be validated. Algorithms for other outcomes that have signaled in other studies or surveillance systems may also be validated if the outcomes could be susceptible to substantial misclassification. The determination of whether an outcome may be susceptible to substantial misclassification will be informed by clinical expert opinion and review of prior validation studies, if available. Outcome validation will be conducted 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 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:

- Cardiac: myocarditis/pericarditis, acute myocardial infarction
- Neurologic: acute disseminated encephalomyelitis, Bell’s palsy, convulsions, encephalomyelitis/encephalitis, Guillain-Barré syndrome, narcolepsy, transverse myelitis
- Hematologic: deep vein thrombosis, disseminated intravascular coagulation, immune hemolytic anemia, immune thrombocytopenia, pulmonary embolism, thromboembolic events associated with thrombocytopenia, thrombotic thrombocytopenic purpura, venous thromboembolism, hemorrhagic stroke, ischemic stroke

- Respiratory: acute respiratory distress syndrome, 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 (singleton pregnancies only)

- Small size for gestational age (singleton pregnancies only)

Other emergent safety events of interest may be added as the understanding of the safety profile of Pfizer-BioNTech original monovalent 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, individuals will be followed for outcomes for a maximum of 1 year.

Vaccine exposures

Exposures to Pfizer-BioNTech original monovalent 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 (e.g., 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 original monovalent COVID-19 Vaccine (categorized as appropriate, e.g., by year or month) and dose of vaccine received (e.g., 1, 2, 3)

- Medical history:

    - Comorbidities (in the 12 months before, not including the index date): history of anaphylaxis, 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 original monovalent 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 analyses of pregnancy safety outcomes among pregnant women, 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 and not including the index date): diabetes mellitus (type 1, type 2), hypertension, gestational hypertension, connective tissue

disorders, thyroid disorders, heart disease, epilepsy and mood disorders, asthma, liver disease, kidney disease, cancer

- Obesity (in the 12 months before 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)

- 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 original monovalent 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, Carelon Research [formerly HealthCore/Anthem], Humana, and Optum) and 1 regional insurer (HealthPartners). Each data research partner is a participant in the FDA Sentinel System. This study will focus on the research-eligible population within each partner's Sentinel Distributed Database and will use the most recent data available 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 individuals. For safety analyses of birth outcomes (i.e., small size for gestational age and major congenital malformations) following maternal prenatal vaccination, maternal data in pregnant women will be linked with infant data to identify outcomes.

Study size

The size of the exposed population will depend on the use of Pfizer-BioNTech original monovalent COVID-19 Vaccine, and the size of the comparator population will depend on the proportion of the source population that comprises unvaccinated individuals (or

individuals not receiving a third dose) 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 the primary series analysis of myocarditis/pericarditis, with 5,000,000 exposed individuals and an estimated background rate of 10 per 100,000 person-years, we estimate a 92% probability that the upper bound of the observed RR would be below 2.5, assuming a 1:1 ratio between vaccinated and comparator person-time, and that the true RR is 1.4.

Data analysis

Analyses will initially be conducted separately within the data from each data source. Data source–specific results will be returned to the study coordinating center, which will aggregate results across the data sources for reporting. Pooled analysis of RR and prevalence 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 original monovalent 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 (i.e., 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 (or comparators who have not received a third dose of COVID-19 vaccine, in the case of third dose analysis) in a ratio of at least 1:1 within data source on age, sex, 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, vaccinated pregnant women will be matched to pregnant concurrent unexposed comparators (or comparators who have not received a third dose of COVID-19 vaccine in the case of third dose analysis) 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. For pregnancy outcomes, hazard ratios and 95% CIs will be estimated using Fine-Gray subdistribution proportional hazards models (using gestational age as the time scale) to account for competing risks of other end-of-

pregnancy events. For small size for gestational age and major congenital malformations, Poisson regression will be used to estimate prevalence 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 acute onset and risk intervals of no 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 September 2025. Two monitoring reports are planned for Q3 2022 and Q3 2024, as well as an interim study report for Q3 2023 and a final study report no later than 31 March 2026.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Version 4.0		Global	• Clarified objectives and focus for this protocol is to assess safety of the Pfizer-BioNTech **original monovalent** COVID-19 Vaccine	To distinguish from other formulations of Pfizer-BioNTech COVID-19 Vaccines
Version 4.0		Title page, abstract, Section 7, and Section 8.7	• Changed terminology “odds ratio” to “prevalence ratio” to clarify measure of association for birth outcomes	To align with planned analyses for birth outcomes (small size for gestational age and major congenital malformations)
Version 4.0		Section 2	• Updated Pfizer Investigators • Updated Data Research Partner Coordinating Investigators for Humana and Optum	Staff update at Pfizer and Research Partners
Version 4.0		Section 2, abstract, Section 8.2.1, Section 8.4, and Section 8.4.2	• Changed HealthCore, Inc to Carelon Research	Name change for Data Research Partner
Version 4.0		Section 5	• Added “0-4” as subgroup to be included in the interim analysis to assess vaccine counts and proportions	To align with planned interim analyses

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Version 4.0		Abstract, Section 6	• Revised background to describe regulatory updates for Pfizer-BioNTech original monovalent COVID-19 Vaccine, including that the original monovalent vaccine is no longer authorized as of 18 April2023	To accommodate new emergency use authorizations of the Pfizer-BioNTech COVID-19 Vaccine since Version 3.0 of the protocol
Version 4.0		Abstract, Section 8.1	• Added end date (18 April 2023) for exposure assessment window	To align with date original monovalent vaccine was no longer authorized
Version 4.0		Abstract, Section 8.1, Section 8.2.2, Section 8.7.2	• Added "sex" as matching criterion for comparative analysis of general safety outcomes	To include matching variable inadvertently omitted previously
Version 4.0		Abstract, Section 8.2.2	• Clarified eligibility criteria for individuals older than 1 year of age versus children 12 months or younger	To accommodate reduced enrollment criteria (birth to index date) in children 12 months or younger
Version 4.0		Abstract, Section 8.2.3, Table 3, Section 8.7.2	• Added language to clarify outcomes of major congenital malformations and small size for gestational age will be assessed only in singleton pregnancies	To minimize impact of confounding by multiple pregnancy on these birth outcomes
Version 4.0		Abstract, Section 8.3.3	• Changed comorbidity assessment period to 12 months before the index date, not including the index date	To exclude assessment of relevant comorbidities on the date, as exposed individuals are more likely to have an outpatient or inpatient healthcare encounter on the index date relative to comparators, which could lead to imbalance in the 2 groups
Version 4.0		Abstract, Section 8.3.3	• Added preeclampsia/eclampsia and gestational hypertension as covariate potential confounding variables	To allow for additional potential confounding variables among pregnant

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			• Removed reproductive history including gravity, parity, spontaneous abortions, and pregnancy terminations from prior pregnancies as a covariate	women and remove reproductive history, which is incomplete in claims data
Version 4.0		Abstract, Section 8.7.2.2	• Added measure of association and planned analyses for pregnancy outcomes (i.e., hazard ratios using Fine-Gray subdistribution proportional hazards models) and birth outcomes (i.e., Poisson regression to estimate prevalence ratios)	Clarify planned analyses for pregnancy and birth outcomes
Version 4.0		Abstract, Section 8.1, Section 8.7.3	• Removed sensitivity analyses using historical comparator to assess potential misclassification for outcomes with gradual onset and/or risk intervals longer than 42 days and clarified historical comparator analysis will be used for pregnancy and birth outcomes	This analysis would be relevant for only one adverse event of special interest (AESI) (narcolepsy) and this AESI has not been listed as an AESI in the pharmacovigilance plan. This outcome will still be included in primary analyses.
Version 4.0		Section 8.2.3 and Section 8.2.4	• Updated eligible population in Table 3 for stillbirth and preterm birth to include all eligible pregnancies • Updated follow-up time to remove requirement to reach 20 weeks gestation	To avoid selection bias
Version 4.0		Section 8.2.3	• Updated Tables 3-5 for clarity and consistency regarding inclusion and exclusion criteria • Added criteria to Table 5 for Dose 3 analysis of pregnancy outcomes	Clarifications
Version 4.0		Section 8.3.1	• Removed Table displaying codes for COVID-19 vaccines available in the United States as of 29 June 2022	Table was outdated, and available vaccines are evolving. Codelists for vaccines relevant at time of final analysis will be appended to the final statistical analysis plan

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Version 4.0		Section 8.3.2	• Removed reference to "combinations of diagnosis codes for birthweight and gestational age" for definition of small size for gestational age	Updated to align with available information from data sources
Version 4.0		Section 8.3.2.2 and	• Clarified validation of myocarditis/pericarditis will be limited to individuals aged 12 years and older • Added description of planned sensitivity analyses following validation	To align with population most at risk for myocarditis/pericarditis and allow flexibility for identifying cases to validate during the interim analysis and clarify planned sensitivity analyses will be specified in the statistical analysis plan (SAP)
Version 4.0		Section 8.7.3.5	• New section added to describe how outcome misclassification will be handled	Additional detail provided regarding quantitative bias analysis
Version 3.0	07 July 2022	Title page, abstract, Section 2	• Added additional author/investigator for Pfizer	Staff update for main author at Pfizer
Version 3.0	07 July 2022	Abstract and Section 5	• Updated dates for end of data collection and final study report	To allow time for data on the 0-4 years age group to accrue
Version 3.0	07 July 2022	Abstract and Section 6	• Revised background to describe new emergency use authorizations for Pfizer-BioNTech COVID-19 Vaccine since Version 2.0 of the protocol, including primary series vaccination in children aged 6 months through 4 years, as well as use of the vaccine as a single booster dose in individuals aged 5-11 years, a first booster dose in individuals aged 12 years and older, a second booster dose in individuals aged 50 years and older, and a second booster dose in immunocompromised	To accommodate new emergency use authorizations of the Pfizer-BioNTech COVID-19 Vaccine since Version 2.0 of the protocol

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			individuals aged 12 years and older	
Version 3.0	07 July 2022	Title page, abstract, and Sections 7, 8.2.2.1, 8.2.2.2, 8.7.2.3.1, 8.7.2.3.1.1, 8.7.2.3.1.2	• Added a research objective to assess risk of safety events following primary series vaccination (dose 1, dose 2, or dose 3) in individuals aged 6 months through 4 years • Revised existing objective regarding dose 1 and dose 2 (in individuals aged 5 years and above) to now include dose 1, dose 2, and dose 3 if the third dose in the primary series is received within 2 months of the second dose • Revised existing objective regarding dose 3 (received as an additional dose or booster dose in individuals aged 5 years and above) such that it only includes third doses received more than 2 months after the second dose • Section 8.2.2 reordered such that all study population descriptions of the general population, immunocompromised individuals, and individuals with a history of COVID-19 are grouped together (separately from descriptions of pregnant women)	Request from CBER to incorporate the age group newly approved for the vaccine (6 months through 4 years) To accommodate variable timing between second and third primary series doses in individuals aged 5 years and above who are recommended to receive a third dose
Version 3.0	07 July 2022	Abstract and Section 8.2.2.1	• Revised enrollment criteria for primary series analysis, such that individuals aged younger than 12 months on the index date must be enrolled from birth through the index date	Request from CBER to incorporate the age group newly approved for the vaccine (6 months through 4 years)
Version 3.0	07 July 2022	Section 8.3.1	• Added codes for Pfizer-BioNTech COVID-19 Vaccine in children aged 6 months through 4 years • Added codes for third dose and booster dose of Pfizer-BioNTech COVID-19 Vaccine in children aged 5-11 years • Added codes for primary series of Moderna COVID-19 vaccine in	To accommodate new emergency use authorizations of COVID-19 vaccines since Protocol version 2.0.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			children aged 6 months through 5 years • Removed pharmacy dispensing codes, which will be specified in the SAP	
Version 3.0	07 July 2022	Section 8.3.3.2	• Shortened the period for identifying immunocompromised status to 12 months before the index date (from all available data)	To reflect that an individual's immunocompromised status may vary over time
Version 3.0	07 July 2022	Title page, abstract, and Sections 7, 8.2.3, and 8.7.2.3.2	• Combined existing objectives on birth outcomes in pregnant women such that risk will be assessed following receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine, as compared with no receipt of any COVID-19 vaccine. • Revisions were made to the descriptions of cohort identification and analysis to accommodate the above changes. • Section 8.2.3 reordered such that all study population descriptions of pregnant women are grouped together	To reflect that for the analysis of birth outcomes, the exposure of interest is receipt of at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine
Version 2.0	16 December 2021	Title page, abstract, and Section 7	• Revised existing research question to clarify that the comparison of incidence/prevalence of safety events of interest between exposed and unexposed individuals applies to the analysis of first and second doses of Pfizer-BioNTech COVID-19 Vaccine • Added an additional research question to assess the relative prevalence/incidence of safety events following a third dose of Pfizer-BioNTech COVID-19 Vaccine, among individuals who have received 2 doses of the Vaccine • Revised primary objectives to explicitly include myocarditis/pericarditis among the safety events of interest • Added new primary objectives to assess the RR of safety events of	Updates requested by CBER

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			interest following a third dose of Pfizer-BioNTech COVID-19 Vaccine, within the overall population and among immunocompromised individuals and individuals with a history of COVID-19 • Added to existing secondary objective to assess the proportion of individuals receiving Pfizer-BioNTech COVID-19 Vaccine, stratified by number of doses; added a new secondary objective to describe the timing and type of third dose of Pfizer-BioNTech COVID-19 Vaccine overall and in subpopulations • Added a new secondary objective to describe baseline characteristics of individuals who receive a third dose of Pfizer-BioNTech COVID-19 Vaccine vs. those who do not • Added secondary objectives to assess the RR of safety events of interest and odds ratio of birth outcomes among pregnant women receiving a third dose of Pfizer-BioNTech COVID-19 Vaccine	
Version 2.0	16 December 2021	Title page, abstract, Section 2	Updated main author affiliated with Harvard Pilgrim Health Care Institute	Staff change for main author at Harvard Pilgrim Institute
Version 2.0	16 December 2021	Section 2	Revised data research partner coordinating investigators	Staff departure for principal scientist at HealthCore
Version 2.0	16 December 2021	Abstract and Section 5	• Added additional monitoring report for Q32024 • Included analysis for incidence rates of myocarditis/pericarditis and select safety events of interest for Pfizer-BioNTech vaccinees to each monitoring report • Updated age categories for analysis of vaccine counts and proportions of individuals in the databases who were vaccinated	Additional monitoring report and incidence for myocarditis/pericarditis added per PRAC request. Clarification of final report timeline.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			• Explicitly stated that incidence of myocarditis/pericarditis by exposure status, dose number, age and will be reported in the interim study report • Emphasis added in footnote that the report may be delayed to December 2025, contingent on validation activities	
Version 2.0	16 December 2021	Abstract and Section 6	• Updated rationale and background section to include updated regulatory approvals since Version 1.0 for BLA in individuals aged ≥ 16 years, EUA in ages 12-15 and 5-11 years, 3rd dose in primary series, and booster doses • Added information related to myocarditis/pericarditis safety signal and regulatory commitments to the FDA and EMA	Alignment of rationale and background with current state of approvals and safety information
Version 2.0	16 December 2021	Abstract and Section 8.1	• Updated study design section to include description of monitoring analyses and interim analyses • Clarified that the study observation period (rather than follow-up period) will be a minimum of 3 years (i.e., December 2020 to December 2023)	Clarification regarding planned analyses and study observation period
Version 2.0	16 December 2021	Abstract, Section 8.2, and Section 8.3.3	• Specified more granular age groups for subgroup analysis in children, as appropriate for safety events of interest • Added subgroup analysis in individuals aged ≥ 30 years and < 12 years (with more granular age categories) and revised the 12-29 year category with more granular age categories • Added subgroup analysis for myocarditis by calendar time, sex, age and sex together, and dose number	• CBER and PRAC request for more granular age/sex categories for myocarditis/pericarditis; to account for different doses in younger age groups • CBER request to provide estimates of incidence attributable to vaccination by sex, age, and dose number • CBER request to account for the

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
				changing incidence of myocarditis/pericarditis following receipt of Pfizer-BioNTech COVID-19 Vaccine over time
Version 2.0	16 December 2021	Section 8.2.1	Clarified that the cohorts described are for analysis of first and second doses	Clarification to accommodate third dose analyses
Version 2.0	16 December 2021	Section 8.2.2	• Clarified that the cohorts described are for analysis of first and second doses • Added a feasibility assessment for identifying dose number in the data sources	Clarification and addition of feasibility assessment to accommodate third dose analyses
Version 2.0	16 December 2021	Section 8.2.2.1	Added new text to describe eligibility criteria for analyses related to third dose	Per CBER request to add analyses for booster doses
Version 2.0	16 December 2021	Section 8.3.1	Table 8 updated to include current codes for COVID-19 vaccines	Alignment with new codes for COVID-19 vaccines
Version 2.0	16 December 2021	Abstract and Section 8.3.2	Specified explicitly that validation will be performed for myocarditis/pericarditis and may be performed for outcomes that have signaled in other studies or surveillance systems, if the outcomes could be susceptible to substantial misclassification	Given the focus of myocarditis/pericarditis, explicitly confirmed performing validation for this outcome
Version 2.0	16 December 2021	Abstract and Section 8.4	Clarified plan to use each data research partner's most recent data in the Sentinel Distributed Database at the time of monitoring, interim, and final analyses	Clarification
Version 2.0	16 December 2021	Abstract and Section 8.5	Added study size estimates for myocarditis/pericarditis	Added since myocarditis/pericarditis has generated a safety signal

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Version 2.0	16 December 2021	Section 8.5	Updated sample size calculation for Bell's palsy	Corrected sample size for Bell's palsy to reflect risk window of 42 days
Version 2.0	16 December 2021	Abstract and Section 8.7	Clarified that the data analysis will initially be performed at individual data partners and that aggregated data across data sources will be used for reporting	Clarification
Version 2.0	16 December 2021	Section 8.7.1	• Added third doses and additional doses (if authorized and available in the data sources) to descriptive analysis on utilization of Pfizer-BioNTech COVID-19 Vaccine • Added new descriptive analysis to examine the proportion of myocarditis/pericarditis cases with subsequent serious cardiovascular conditions for individuals vaccinated with Pfizer-BioNTech COVID-19 Vaccine and in individuals not vaccinated with a COVID-19 vaccine • Added new analysis to describe—among individuals who receive 2 doses of Pfizer-BioNTech COVID-19 Vaccine—the proportion of individuals by type of third dose of COVID-19 vaccine and time between the second and third doses	Per CBER request to capture long-term outcomes of myocarditis/pericarditis and to accommodate booster doses
Version 2.0	16 December 2021	Section 8.7.2	• Clarified that the analysis described addresses confounding for first and second doses (Sections 8.7.2.3.1.1 and Sections 8.7.2.3.2.1) • Added new text to describe analysis for third dose (Sections 8.7.2.3.1.2 and 8.7.2.3.2.2)	Clarifications and new text added to accommodate third dose analyses
Version 2.0	16 December 2021	Section 8.9	Added limitations relating to third dose analyses	Added to accommodate the addition of third dose analyses

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Version 2.0	16 December 2021	Section 11	Updated to clarify that the final report will be uploaded to the EU PAS Register and that manuscript reporting results will be submitted to a peer-reviewed journal	Per PRAC request

BLA = biologic license application; CBER = Center for Biologics Evaluation and Research; EMA = European Medicines Agency; EU PAS = European Union Electronic Register of Post-Authorisation Studies; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; PRAC = Pharmacovigilance Risk Assessment Committee; RR = relative risk.

5. MILESTONES

Below is a proposed schedule of milestones.

Milestone[a]	Planned date	Description of milestone
Registration in the EU PAS Register	19 October 2021	To be registered before the start of data collection.
Start of data collection, estimated (for monitoring analysis report 1)	Q2 2022	Start of data collection is the planned date for the initial data extraction (query execution) for the purpose of the monitoring analysis.
Monitoring analysis report 1	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 (5-11, 12-17, 18-64, and ≥ 65 years). Incidence rates of myocarditis/pericarditis and other select safety events of interest among Pfizer-BioNTech vaccinees.
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 (0–4, 5-11, 12-17, 18-64, and ≥ 65 years). 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

Milestone[a]	Planned date	Description of milestone
		immunocompromised individuals, and in individuals with a history of COVID-19. Analysis describing incidence of myocarditis/pericarditis by exposure status, dose number, age, and sex will be reported.
Monitoring analysis report 2	Q3 2024	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 (0-4, 5-11, 12-17, 18-64, and ≥ 65 years). Incidence rates of myocarditis/pericarditis and other select safety events of interest among Pfizer-BioNTech vaccinees.
End of data collection	30 September 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.
Final study report	31 March 2026	Descriptive analysis of vaccine utilization in the overall study population, in immunocompromised individuals, in individuals with a history of COVID-19, in pregnant women, and in subgroups defined by age (0-4, 5-11, 12-17, 18-64, ≥ 65 years). Comparative safety analysis in the overall study population, in immunocompromised individuals, in pregnant women, in individuals with a history of COVID-19, and for select safety events of interest, in subgroups defined by age. For myocarditis/pericarditis, analyses will be stratified in the following age groups: 0-4, 5-11, 12-17, 18-24, 25-29, 30-39, 40-49, 50-64, ≥ 65 years).

COVID-19 = coronavirus disease 2019; Q = quarter; TBD = to be determined.
a. Monitoring analysis 1 and 2, the interim analysis, and the final analysis will use the most recent data available within the Sentinel Common Data Model at the time of each analysis.

6. 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). As of 13 December 2021, approximately 270 million cases of COVID-19 have been reported globally, with over 49.9 million cases and 797,350 deaths reported in the United States (US) (CSSE, 2021). To date, the incidence of COVID-19 has continued to rise, largely affecting individuals who are elderly and middle aged, with a disproportion of cases occurring among 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, 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 (BNT162b2) against SARS-CoV-2 for the prevention of COVID-19. BNT162b2 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).

Pfizer is conducting a phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy studies among healthy individuals aged 18 years and above (phase 1) and individuals aged 12 years and above (phases 2/3) (NCT04368728). Initial 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 reported 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 across 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 among the general population (Pfizer and BioNTech, 2020).

Efficacy and safety results for 2,260 children aged 12 to 15 years were initially reported in May 2021 (1,131 who received BNT162b2 and 1,129 who received 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). No vaccine-related serious AEs occurred, and severe AEs were very rare (in 0.2% of BNT162b2 recipients).

Pfizer is also conducting a phase 1, open-label, dose-finding study to evaluate safety, tolerability, and immunogenicity and a phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of BNT162b2 in healthy children and young adults aged 6 months to 30 years (NCT04816643). Initial efficacy and safety results for the phase 2/3 study were reported in November 2021 for 2,268 children aged 5 to 11 years (1,517 who received BNT162b2 and 751 who received placebo) (Walter et al., 2021). Three cases with an onset 7 or more days after the second dose occurred among recipients of BNT162b2, and 16 cases occurred among recipients of placebo, for an observed vaccine efficacy of 90.7% (95% CI, 67.4-98.3%). The reactions and events reported in BNT162b2 recipients were

generally mild to moderate, lasting 1 to 2 days. The most common local reaction was injection site pain, occurring in 71% to 74% of BNT162b2 recipients. Severe injection site pain after the first or second dose was reported in 0.6% of BNT162b2 recipients and in no placebo recipients. The most frequently reported systemic events were fatigue and headache, with severe fatigue, headache, chills, and muscle pain reported after the first or second dose in 0.9%, 0.3%, 0.1%, and 0.1% of BNT162b2 recipients, respectively. From the first dose through 1 month after the second dose, AEs were reported by 10.9% of BNT162b2 recipients and 9.2% of placebo recipients. Severe AEs were reported in 0.1% of BNT162b2 recipients and in 0.1% of placebo recipients.

Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine (Comirnaty®) was previously approved by the FDA for individuals aged 16 years and older in a series of 2 doses administered 3 weeks apart (FDA, 2023). Pfizer-BioNTech original monovalent COVID-19 Vaccine was also previously authorized for emergency use by the FDA in individuals aged 6 months through 4 years in a series of 3 doses, with the first and second doses administered 3 weeks apart and the second and third doses administered at least 8 weeks apart; and in individuals aged 5 to 15 years in a series of 2 doses administered 3 weeks apart (FDA, 2023). Additionally, in individuals aged 5 years and older with certain types of immunocompromising conditions, a third dose in the primary series, to be administered at least 28 days after the second dose was previously authorized (FDA, 2023). A summary of FDA emergency use authorization (EUA) and full approval for primary series vaccination with Pfizer-BioNTech original monovalent COVID-19 Vaccine is provided below.

- On 11 December 2020, the Pfizer-BioNTech original monovalent COVID-19 Vaccine was authorized for emergency use in a 2-dose series by the FDA to prevent COVID-19 in individuals aged 16 years or older (FDA, 2023). On 12 December 2020, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation (which the CDC Director endorsed) for use of the vaccine in individuals aged 16 years and older (Oliver et al., 2020).

- On 10 May 2021, Pfizer-BioNTech original monovalent COVID-19 Vaccine was authorized for emergency use in children aged 12 to 15 years in a 2-dose series in the US (FDA, 2023), and on 12 May 2021, the ACIP issued an interim recommendation for the use of the vaccine in children aged 12 to 15 years (Wallace et al., 2021).

- On 23 August 2021, Pfizer-BioNTech original monovalent COVID-19 Vaccine (Comirnaty®) was fully approved by the FDA for the prevention of COVID-19 in individuals aged 16 years and older (FDA, 2021). On 30 August 2021, the ACIP revised its interim recommendation (which the CDC Director adopted) to a standard recommendation for use of Pfizer-BioNTech original monovalent COVID-19 Vaccine in individuals aged 16 years and older for the prevention of COVID-19 (Dooling et al., 2021).

- On 12 August 2021, the FDA authorized emergency use of the Pfizer-BioNTech original monovalent COVID-19 Vaccine as a third dose in a primary series at least 28 days

following completion of the 2-dose regimen of Pfizer-BioNTech original monovalent COVID-19 Vaccine in individuals aged 12 years or older who have undergone solid organ transplantation or individuals aged 12 years or older who have been diagnosed with conditions that are considered to confer an equivalent level of immunocompromise (FDA, 2023). On 13 August 2021, the ACIP issued an interim recommendation (which the CDC Director adopted) for use of a single dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine at least 28 days following completion of the 2-dose series of the vaccine in moderately to severely immunocompromised individuals aged 12 years and older (Mbaeyi, 2021).

- On 29 October 2021, the Pfizer-BioNTech original monovalent COVID-19 Vaccine was authorized for emergency use in children aged 5 to 11 years in a 2-dose series (FDA, 2023), and on 02 November 2021, the ACIP issued an interim recommendation (which the CDC Director endorsed) for use of the vaccine in children aged 5 to 11 years (Woodworth, 2021).

- On 03 January 2022, the FDA authorized a third dose in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine administered at least 28 days following the 2-dose regimen of this vaccine aged 5 to 11 years who have undergone solid organ transplantation or in individuals aged 5 to 11 years who have been diagnosed with conditions that are considered to have an equivalent level of immunocompromise (FDA, 2023). Shortly thereafter, the CDC recommended that moderately to severely immunocompromised children aged 5 to 11 years should receive a third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine at least 28 days after completion of doses 1 and 2 in the primary series (HHS, 2022a).

- On 17 June 2022, the Pfizer-BioNTech original monovalent COVID-19 Vaccine was authorized for emergency use in children aged 6 months through 4 years in a 3-dose series in the US (FDA, 2023). On 18 June 2022, the ACIP issued an interim recommendation for the use of the Vaccine in children aged 6 months through 4 years, which the CDC adopted shortly thereafter (HHS, 2022c).

The Pfizer-BioNTech original monovalent COVID-19 Vaccine was previously authorized for booster vaccination as (1) a single booster dose in individuals aged 5 to 11 years, (2) a first booster dose in individuals aged 12 years and older, (3) a second booster dose in immunocompromised individuals aged 12 years and older, and (4) a second booster dose in individuals aged 50 years and older (FDA, 2023). A chronological history of FDA EUA of Pfizer-BioNTech original monovalent COVID-19 Vaccine for booster vaccination is summarized below.

- On 22 September 2021, the FDA authorized emergency use of a single booster dose of the Pfizer-BioNTech original monovalent COVID-19 Vaccine to be administered at least 6 months after completion of a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine in individuals aged 65 years and older; individuals aged 18 through 64 years at high risk of severe COVID-19; and individuals aged 18 through 64 years

whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications from COVID-19, including severe COVID-19 (FDA, 2023). On 23 September 2021, the CDC Director issued an interim recommendation that individuals aged 65 years and older, residents of long-term care settings who are aged 18 years and older, and individuals aged 50 to 64 years with certain underlying medical conditions should receive a booster dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine at least 6 months after completing the primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine. The CDC Director's recommendation also stated that individuals aged 18 to 49 years with certain underlying medical conditions and individuals aged 18 to 64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting may receive a booster dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine at least 6 months after completing the primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine.

- On 20 October 2021, the FDA authorized emergency use of the Pfizer-BioNTech Vaccine as a single heterologous booster dose after completion of primary vaccination with another COVID-19 vaccine brand. (FDA, 2023; Mbaeyi, 2021). On 21 October 2021, ACIP issued interim recommendations (which the CDC Director endorsed) for the Pfizer-BioNTech original monovalent COVID-19 Vaccine to be used as a single booster dose in certain populations who had completed their primary vaccine series, regardless of the primary vaccination brand. The eligible population(s) and dosing interval for the heterologous booster dose of Pfizer-BioNTech Vaccine were the same as those authorized for a booster dose of the vaccine used for primary vaccination. Specifically, individuals aged 65 years and older, residents of long-term care settings who are aged 18 years and older, and individuals aged 50 to 64 years with certain underlying medical conditions who had received Pfizer-BioNTech original monovalent COVID-19 Vaccine or Moderna COVID-19 vaccine for their primary series should receive a single COVID-19 vaccine booster dose at least 6 months later. According to the ACIP's recommendations, individuals aged 18 to 49 years with certain underlying medical conditions and individuals aged 18 to 64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting who had completed a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine or Moderna COVID-19 vaccine may receive a single COVID-19 booster dose at least 6 months later, based on individual benefits and risks of vaccination. Individuals aged 18 years and older who received Janssen for their vaccine primary series should receive a single COVID-19 vaccine booster dose at least 2 months later (Mbaeyi, 2021).

- On 19 November 2021, the FDA authorized emergency use of the Pfizer-BioNTech original monovalent COVID-19 Vaccine as a single booster dose in individuals aged 18 years and older at least 6 months after completing the primary series of this vaccine and emergency use of the vaccine as a single booster dose following completion of primary vaccination with another authorized COVID-19 vaccine in individuals aged 18 years and older (FDA, 2023). The dosing interval for the heterologous booster dose was

the same as that authorized for a booster dose of the vaccine used for primary vaccination. On 19 November 2021, the ACIP issued interim recommendations (which the CDC Director adopted) that all individuals aged 18 years and older who are not otherwise recommended to receive a COVID-19 booster dose may receive one at least 6 months after completion of a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine or Moderna COVID-19 vaccine, based on individual benefits and risks of vaccination (CDC, 2021). The ACIP continued to recommend that individuals aged 18 to 49 years with certain underlying medical conditions and individuals aged 18 to 64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting who had completed a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine or Moderna COVID-19 vaccine may receive a single COVID-19 booster dose at least 6 months later, based on individual benefits and risks of vaccination. On 29 November 2021, the CDC revised its recommendations such that all individuals aged 18 years and older who have completed a primary series of COVID-19 vaccine should receive a single booster dose.

- On 9 December 2021, the FDA amended the EUA to authorize the use of the Pfizer-BioNTech original monovalent COVID-19 Vaccine as a single booster dose in individuals aged 16 and 17 years, at least 6 months after completing the primary series of this vaccine (FDA, 2023). Shortly thereafter, the CDC revised its recommendations such that individuals aged 16 and 17 years may receive a single booster dose of Pfizer-BioNTech COVID-19 at least 6 months after completion of the primary series, based on their individual benefits and risks (CDC, 2021).

- On 3 January 2022, the FDA authorized the use of Pfizer-BioNTech original monovalent COVID-19 Vaccine as a single booster dose in individuals aged 12 to 15 years and lowered the authorized dosing interval of the homologous booster dose to at least 5 months after completion of the primary series (FDA, 2023). On 3 January 2022, the CDC recommended that individuals aged 18 years and older should receive a single homologous Pfizer-BioNTech original monovalent COVID-19 Vaccine booster dose (or heterologous as authorized for another COVID-19 vaccine for those aged 18 years and older) 5 months after completion of a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine, 6 months after completion of a primary series of Moderna COVID-19 vaccine, or 2 months after completion of a single-dose primary series of Janssen COVID-19 vaccine (HHS, 2022a). Furthermore, the CDC recommended that individuals aged 16 to 17 years may receive a Pfizer-BioNTech original monovalent COVID-19 Vaccine booster dose 5 months after completion of a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine. On 5 January 2022, the CDC adopted the ACIP's recommendation that children aged 12 to 17 years should receive a Pfizer-BioNTech original monovalent COVID-19 Vaccine booster dose 5 months after completion of a primary series of the Pfizer-BioNTech original monovalent COVID-19 Vaccine.

- On 29 March 2022, the FDA authorized a second booster dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine at least 4 months after receipt of a first booster dose of any FDA-authorized or approved COVID-19 vaccine to individuals aged 50 years and older, individuals aged 12 years or older who have undergone solid organ transplantation, or individuals aged 12 years or older who have been diagnosed with conditions that are considered to have an equivalent level of immunocompromise (FDA, 2023). Shortly thereafter, the CDC updated its COVID-19 vaccination guidance to allow certain immunocompromised individuals and people over age 50 years who received an initial booster dose at least 4 months prior to be eligible for another mRNA booster to increase their protection against severe disease from COVID-19 (CDC, 2022).

- On 17 May 2022, the FDA authorized the administration of a single booster dose of the Pfizer-BioNTech original monovalent COVID-19 Vaccine in individuals aged 5 to 11 years, at least 5 months after completing a primary series with this vaccine (FDA, 2023). On 19 May 2022, the ACIP recommended a single Pfizer-BioNTech original monovalent COVID-19 Vaccine booster dose for individuals aged 5 to 11 years after completion of a Pfizer-BioNTech original monovalent COVID-19 Vaccine primary series (HHS, 2022b). The CDC shortly thereafter endorsed this recommendation, stating that individuals aged 50 years and over and individuals aged 12 to 49 years with moderate to severe immunocompromise should receive an mRNA COVID-19 vaccine second booster dose at least 4 months after their first COVID-19 vaccine booster dose. This recommendation replaced an earlier recommendation that such individuals who wish to increase their individual protection may receive the second booster dose.

As of 18 April 2023, Pfizer-BioNTech original monovalent COVID-19 Vaccine is no longer authorized for use in the US, and the vaccine schedule was simplified to authorize the use of the current bivalent vaccine for all initial and subsequent doses administered to individuals aged 6 months and older (FDA, 2023). Following authorization of both mRNA vaccines, several passive and active surveillance systems have monitored the safety of the Pfizer-BioNTech original monovalent COVID-19 Vaccine and other COVID-19 vaccines in the US. In June 2021, the ACIP reported that a potential safety signal for myocarditis/pericarditis through the national spontaneous reporting system, the Vaccine Adverse Event Reporting System, after receipt of both authorized mRNA vaccines (Pfizer-BioNTech original monovalent COVID-19 Vaccine and Moderna COVID-19 Vaccine). As of 11 June 2021, approximately 300 million doses of mRNA COVID-19 vaccines had been administered, and 1,226 cases of myocarditis or pericarditis following receipt of any mRNA COVID-19 vaccine had been reported to the Vaccine Adverse Events Reporting System (Gargano et al., 2021; Shimabukuro, 2021b). The median (range) age of cases following dose 1 was 30 years (12-94 years) and following dose 2 was 24 years (12-87 years). These individuals were predominantly male, and most cases occurred after the second dose. Median (range) onset of symptoms was 4 days (0-61 days) for dose 1 and 3 days (0-98 days) for dose 2. The number of observed cases was greater than the number of expected cases (based on US population–based background incidence rates), especially after the second dose in individuals aged 12 to 39 years.

Based on data through 12 June 2021, the Vaccine Safety Datalink (VSD) observed in analyses based on 22 cases in the risk interval, that the age- and site-adjusted rate ratio for risk of myocarditis/pericarditis in the 7 days following mRNA vaccination in individuals aged 12 to 39 years was 10.0 (95% CI, 2.9-46.5). The corresponding rate ratio for Pfizer-BioNTech original monovalent COVID-19 Vaccine was 2.4 (95% CI, 0.4-24.9). In individuals aged 12 to 39 years, the incidence rate of myocarditis/pericarditis in the 21 days following mRNA vaccination was greater in males than in females and was greater following the second dose than following the first dose (12.6 cases per million second doses vs. 4.4 cases per million first doses). Additionally, a temporal clustering of myocarditis/pericarditis occurred within the week following vaccination, with the most likely cluster occurring 0 to 5 days following vaccination. Based on these data and a benefit-risk assessment, on 23 June 2021, the ACIP concluded that the benefits of vaccinating all recommended age groups with mRNA COVID-19 vaccine clearly outweighed the risks of vaccination, including the risk of developing myocarditis after vaccination. The ACIP emphasized the need to continue monitoring outcomes of myocarditis cases after COVID-19 vaccination and that providers and the public should be informed about these myocarditis cases and the use of COVID-19 vaccines. Based on the ACIP's conclusions, COVID-19 vaccination continued to be recommended for all individuals aged ≥ 12 years under the FDA's EUA. The FDA added this safety event to the EUA factsheet, and the warnings and precautions section of prescribing information for Pfizer-BioNTech original monovalent COVID-19 Vaccine states that, "Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age" (Pfizer, 2021).

Because of the relatively short prelicensure period and limited number of participants in clinical studies, vaccine safety monitoring will be needed in the US in populations large enough to detect myocarditis/pericarditis and other rare possible AEs and with follow-up (FU) 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 are 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 original monovalent 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 original monovalent COVID-19 Vaccine and predetermined safety events of interest among the general population and among subpopulations of interest (e.g., pregnant women, immunocompromised individuals, 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 original monovalent 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 include myocarditis/pericarditis and are partially based on those included in COVID-19 vaccine safety surveillance in the FDA's Biologics Effectiveness and Safety (BEST) System (Wong et al., 2021) and the CDC's VSD (Shimabukuro, 2021a), 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 postmarketing requirement to the FDA and a Category 3 commitment to the European Medicines Agency (EMA) as indicated in the risk management plan. The study is intended to evaluate the occurrence of safety events of interest, including myocarditis/pericarditis following administration of Pfizer-BioNTech original monovalent COVID-19 Vaccine.

7. RESEARCH QUESTION AND OBJECTIVES

Research questions

Among the general population, immunocompromised individuals, pregnant women, and individuals with a history of COVID-19:

1. What is the incidence of safety events of interest, including myocarditis/pericarditis, among individuals receiving at least 1 dose in a primary series[1] of Pfizer-BioNTech original monovalent COVID-19 Vaccine compared with that among individuals who have not received any vaccination for COVID-19 in the US?

2. In individuals aged 5 years and older who have received the first and second dose in a primary series[1] of Pfizer-BioNTech original monovalent COVID-19 Vaccine, what is the incidence of safety events of interest, including myocarditis/pericarditis, among individuals vaccinated with a third dose (either as an additional dose in a primary series or as a booster dose) of Pfizer-BioNTech original monovalent COVID-19 Vaccine compared with that among individuals who have not received a third dose of any COVID-19 vaccine in the US?

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

Primary study objectives

Among the overall study population and subgroups of pregnant women, immunocompromised individuals, and individuals with a history of COVID-19:

1. **In individuals aged 5 years and older:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following receipt of a first, second, or third (if received within 2 months of the second dose) dose in a primary series[1] of Pfizer-BioNTech original monovalent COVID-19 Vaccine compared with that among individuals with no receipt of any COVID-19 vaccine

2. **In individuals aged 6 months through 4 years:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following receipt of a first, second, or third dose in a primary series[1] of Pfizer-BioNTech original monovalent COVID-19 Vaccine compared that among individuals with no receipt of any COVID-19 vaccine

3. **In individuals aged 5 years and older who have received 2 doses in a primary series[1] of Pfizer-BioNTech original monovalent COVID-19 Vaccine:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following a third dose (as an additional dose in a primary series[1] or as a booster dose) of Pfizer-BioNTech original monovalent COVID-19 Vaccine received more than 2 months after the second dose compared with that among individuals without a third dose of any COVID-19 vaccine

Among pregnant women:

4. To estimate the birth prevalence and prevalence ratio of birth outcomes among infants born to pregnant women vaccinated with Pfizer-BioNTech original monovalent COVID-19 Vaccine compared with that among infants born to unvaccinated pregnant women.

Secondary objectives:

Among the overall study population and subgroups of pregnant women, immunocompromised individuals, and individuals with a history of COVID-19:

1. To describe the proportion of individuals receiving Pfizer-BioNTech original monovalent COVID-19 Vaccine, stratified by number of doses

2. To describe—among individuals who have received a first dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine—the timing and type of second dose of COVID-19 vaccine (Pfizer-BioNTech original monovalent COVID-19 Vaccine or other COVID-19 vaccine)

3. To describe baseline characteristics (demographics and comorbidities) of individuals who have received at least 1 dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine and those with no record of COVID-19 vaccination of any type

4. To describe—among individuals who have received 2 doses of Pfizer-BioNTech original monovalent COVID-19 Vaccine—the timing and type of a third dose of COVID-19 vaccine (Pfizer-BioNTech original monovalent COVID-19 Vaccine or other COVID-19 vaccine)

5. To describe—among individuals aged 5 years and older who have received at least 2 doses in a primary series[1] of Pfizer-BioNTech original monovalent COVID-19 Vaccine—baseline characteristics (demographics and comorbidities) of individuals who received a third dose (either as an additional dose in a primary series[1] or as a booster dose) of Pfizer-BioNTech original monovalent COVID-19 Vaccine more than 2 months after the second dose and those with no record of a third dose of COVID-19 vaccination of any type

6. **Among pregnant women who have received 2 doses in a primary series[1] of Pfizer-BioNTech original monovalent COVID-19 Vaccine:** To estimate the RR of safety events of interest (including myocarditis/pericarditis) following receipt of a third dose (either as an additional dose in a primary series[1] or as a booster dose) received more than 2 months after the second dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine compared with that among individuals with no receipt of a third dose of any COVID-19 vaccine

8. RESEARCH METHODS

8.1. Study design

This study will use a retrospective cohort design with concurrent unexposed comparators. The study will compare the incidence of safety events among individuals who have received a first, second, or third dose in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine with that among individuals who have no record of any COVID-19 vaccine in a concurrent time period. In individuals aged 5 years and older, third doses will only be included in primary series analysis if the third dose is received within 2 months of the second dose.

Additionally, in individuals aged 5 years and older who have received 2 doses in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine, the incidence of safety events in individuals who have received a third dose (either as an additional dose in a primary series or as an initial booster dose) of the vaccine more than 2 months after the second dose will be compared with that among individuals who have not received a third dose of any COVID-19 vaccine.

Finally, the study will compare the prevalence of birth outcomes (including major congenital malformations and small size for gestational age) in infants born to pregnant women who

have received at least 1 dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine during an exposure window of interest with that among infants born to pregnant women who have not received any COVID-19 vaccine during the exposure window of interest.

For analyses in the overall population, as well as in subcohorts of immunocompromised individuals and individuals with a history of COVID-19, individuals in the exposed group will be matched to individuals in the comparator group (in a ratio of at least 1:1) within data source on age, sex, state (if feasible, or broader geographic region if not feasible), calendar time, and propensity score. For analyses in pregnant women, those in the exposed group will be matched to women in the comparator group on maternal age, state (if feasible), and estimated pregnancy start; confounding will be addressed through propensity score matching or through the inclusion of propensity scores in exposure-outcome regression models.

To inform full study implementation, 2 monitoring analyses and an interim analysis will be conducted before the final analysis to describe vaccine utilization in the overall population, in immunocompromised individuals, in individuals with a history of COVID-19, and in subgroups defined by age. The monitoring phase will also describe incidence rates of select events of interest among Pfizer-BioNTech original monovalent COVID-19 Vaccinees (monitoring analysis reports 1 and 2), incidence rates of safety events of interest overall in the matched cohorts without regard to exposure status (overall, and within the subgroups of interest; interim analysis), and incidence of myocarditis/pericarditis by exposure status (overall, and by select covariates of interest; interim analysis). Additional analyses during the monitoring phase will assess feasibility aspects, including the data completeness of COVID-19 vaccines, dose number availability in the data sources, and geographic information granularity that may be incorporated into analyses.

The safety events in this study vary with respect to event onset (acute vs. gradual) and risk window duration (short vs. 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 pre-pandemic period, which may impact outcome ascertainment. Furthermore, 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 original monovalent 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 an acute onset and a short risk interval (Baker et al., 2015) (defined for the purposes of this study as ≤ 42 days after vaccination). If exposure information is deemed incomplete based on feasibility analysis during the monitoring phase,

the primary study design may be switched to the SCRI design 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 8.3.2.2). 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.

The study observation period will start on the date that Pfizer-BioNTech original monovalent COVID-19 Vaccine was granted EUA in the US (11 December 2020) and will end a minimum of 3 years after this date. Although only exposures identified through 18 April 2023 (the date that authorization of Pfizer-BioNTech original monovalent COVID-19 Vaccine ended) will be included in the study, outcomes occurring in the predefined risk period will be assessed after this date. The study will include both vaccinations received under the EUA and under the biologic license application (BLA).

8.2. Setting

8.2.1. Study 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, Carelon Research, HealthPartners, Humana, and Optum. The data sources are described in more detail in Section 8.4.

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

Additional eligibility requirements for the general population and subpopulations of interest are described below for (1) safety analyses in the general population, immunocompromised individuals, and individuals with a history of COVID-19 and (2) safety analyses in the pregnant population.

8.2.2. Safety analyses in the general population, immunocompromised individuals, and individuals with a history of COVID-19

8.2.2.1. Primary series analysis

Primary series analyses in children aged 6 months through 4 years will include doses 1, 2, and 3. Details for handling the timing between individual doses in this age group will be described in the statistical analysis plan (SAP). Primary series analyses in individuals aged 5 years and older will include dose 1 and 2 as well as dose 3 if received within 2 months of dose 2.

To be included in the primary series analysis of Pfizer-BioNTech original monovalent COVID-19 Vaccine receipt among the general population, the population of immunocompromised individuals (individuals with immunodeficiencies, immunosuppressant medication use, HIV and other immunosuppressing conditions, and/or receipt of organ or bone marrow transplant), and the population of individuals with a history of COVID-19, individuals older than 1 year of age must have had continuous medical and pharmacy insurance coverage for at least 12 months before each index date (as defined in Table 1 below and Table 2 in Section 8.2.2.2) or from the earliest date that they were eligible to receive the vaccine until the index date—whichever period is longer. Children aged younger than 12 months on the index date must be enrolled from birth until the index date.

Depending on whether data on vaccine dose number are recorded in the data sources, additional enrollment may be required from the earliest authorization of the Pfizer-BioNTech original monovalent COVID-19 Vaccine (i.e., 11 December 2020) to enable dose number identification. The feasibility of determining dose number based on vaccine codes will be confirmed during the monitoring phase of the study, and all eligibility criteria will be fully documented in the SAP.

A separate exposed cohort will be formed for each dose. A separate unexposed cohort will be formed for each of the exposed cohorts to serve as comparator cohorts. The criteria for the cohorts for primary series analyses of the general population, immunocompromised individuals, and individuals with a history of COVID-19 are described in Table 1.

Table 1. Cohort definitions for primary series analysis of the general population, immunocompromised individuals, and individuals with a history of COVID-19

Cohort	Inclusion criteria	Index date	Exclusion criteria
Dose 1 exposed	Record of a first dose in the primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine	Date of first dose	Record of any COVID-19 vaccine before the index date
Dose 2 exposed	Record of a second dose in the primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine	Date of second dose	Record of COVID-19 vaccine other than Pfizer-BioNTech original monovalent COVID-19 Vaccine before the index date
Dose 3 exposed[a]	For individuals aged 6 months through 4 years: record of a third dose in the primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine For individuals aged 5 years or older: record of a third dose in the primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine within 2 months after the second dose	Date of third dose	Record of COVID-19 vaccine other than Pfizer-BioNTech original monovalent 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, age, sex, 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 first dose in corresponding exposed individuals (e.g., within the same calendar month)	Record of any COVID-19 vaccine before the index date

Table 1. Cohort definitions for primary series analysis of the general population, immunocompromised individuals, and individuals with a history of COVID-19

Cohort	Inclusion criteria	Index date	Exclusion criteria
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, age, sex, 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 second dose in corresponding exposed individuals (e.g., within the same calendar month)	Record of any COVID-19 vaccine before the index date
Dose 3 unexposed[a]	No record of any COVID-19 vaccine as of the index date (i.e., cohort entry) and matched individually to individuals in the dose 3 exposed cohort on time–specific propensity score, age, sex, 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 third dose in corresponding exposed individuals (e.g., within the same calendar month)	Record of any COVID-19 vaccine before the index date

COVID-19 = coronavirus disease 2019.
a. Dose 3 of the primary series will be assessed for individuals aged 6 months through 4 years and for individuals aged 5 years and older whose third dose is received within 2 months of the first dose.

Individuals in the dose 1 cohort, dose 2 cohort, and dose 3 cohort (applicable only to individuals aged 6 months through 4 years and individuals aged 5 years and older whose third dose is received within 2 months of the first dose) will be matched to unexposed individuals (in a ratio of at least 1:1) on age, sex, state (if feasible, or broader geographic region if not feasible), and calendar time–specific propensity score, as described in Section 8.7.2.3.1. Individuals who receive 2 doses of the vaccine can contribute person-time to both the dose 1 exposed and dose 2 exposed cohorts, and individuals who receive 3 doses of the vaccine can contribute person-time to the dose 1, dose 2, and dose 3 exposed cohorts.

Individuals in the dose 1 unexposed, dose 2 unexposed, and dose 3 unexposed cohorts may also contribute person-time to the exposed cohorts if they subsequently receive Pfizer-BioNTech original monovalent COVID-19 Vaccine. Conversely, individuals in the dose 1, dose 2, and dose 3 exposed cohorts may be eligible for the unexposed cohorts before they receive their first dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine. However, an individual may contribute only once to the dose 1 unexposed cohort, once to the dose 2 unexposed cohort, and once to the dose 3 unexposed cohort.

As appropriate, data from the dose 1, dose 2, and dose 3 cohorts and their matched unexposed comparators will be pooled to obtain RR estimates corresponding to receipt of at least 1 dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine.

8.2.2.2. Analysis of a third dose received more than 2 months after the second dose in individuals aged 5 years and older

To be eligible for safety analyses of third doses (as an additional dose in a primary series or as a booster dose), individuals must be aged 5 years or older and must have previously received 2 doses of the Pfizer-BioNTech original monovalent COVID-19 Vaccine. Individuals who have received a COVID-19 vaccine other than the Pfizer-BioNTech Vaccine for the first or second dose will be excluded.

Cohort definitions for third dose analyses of the general population, immunocompromised individuals, and individuals with a history of COVID-19 are described in Table 2. To be eligible, individuals older than 1 year of age must be enrolled for at least 12 months before the index date or from the earliest date that they were eligible to receive the vaccine until the index date—whichever period is longer. Depending on whether data on vaccine dose number are recorded in the data sources, additional enrollment may be required from the beginning of authorization of the Pfizer-BioNTech original monovalent COVID-19 Vaccine (i.e., 11 December 2020) to enable dose number identification. The feasibility of determining dose number based on vaccine codes will be confirmed during the monitoring phase of the study, and all eligibility criteria will be fully documented in the SAP.

Table 2. Cohort definitions for third dose analyses of the general population, immunocompromised individuals, and individuals with a history of COVID-19

Cohort	Inclusion criteria	Index date	Exclusion criteria
Dose 3 exposed	Receipt of 3 doses of Pfizer-BioNTech original monovalent COVID-19 Vaccine, with the third dose received more than 2 months after the second dose The third dose may be either an additional dose in a primary series or a booster dose.	Date of third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine	• Record of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent COVID-19 Vaccine before the index date

Table 2. Cohort definitions for third dose analyses of the general population, immunocompromised individuals, and individuals with a history of COVID-19

Cohort	Inclusion criteria	Index date	Exclusion criteria
Dose 3 unexposed	• As of the index date, receipt of 2 doses in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine, with no receipt of a third dose of any COVID-19 vaccine • Individually matched to individuals in the dose 3 exposed cohort (in at least a ratio of 1:1) on time–specific propensity score (which is described in Section 8.7.2.3.1), age, sex, state of residence (if feasible, or broader geographic region if not feasible), calendar time, and time since receipt of dose 2	Randomly selected date in a period within close temporal proximity to the date of receipt of dose 3 in corresponding exposed individuals (e.g., within the same calendar month)	• Record of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent COVID-19 Vaccine before the index date

COVID-19 = coronavirus disease 2019.

Individuals who receive 3 doses of the Pfizer-BioNTech original monovalent COVID-19 Vaccine can contribute non-overlapping person-time to both the dose 3 exposed and dose 3 unexposed cohorts. Individuals in the dose 3 unexposed cohort may also contribute person-time to the dose 3 exposed cohort if they subsequently receive a third dose of the Pfizer-BioNTech original monovalent COVID-19 Vaccine more than 2 months after the second dose. Conversely, individuals in the dose 3 cohort may be eligible for inclusion in the dose 3 unexposed cohort before they receive a third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine.

8.2.3. Safety analysis in 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 4 in Section 8.2.3.1, Table 5 in Section 8.2.3.2, and Table 6 in Section 8.2.3.3) 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 pregnancy start and end dates.

In pregnant women, safety events assessed in the general population (see Table 8 in Section 8.3.2.1 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 3. Only Pfizer-BioNTech original monovalent 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 original monovalent 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 3. 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	All eligible pregnancies	4 weeks before estimated pregnancy start to end of pregnancy
Preterm birth	All eligible pregnancies	4 weeks before estimated pregnancy start to end of pregnancy or 36-6/7 weeks of gestation, whichever is earlier
Major congenital malformations	Singleton 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	Singleton 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 8 in Section 8.3.2.1.

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 8.4) 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.

8.2.3.1. Primary series analyses of general safety events, spontaneous abortion, stillbirth, and preterm birth in pregnant women

Cohort definitions for primary series analyses of general safety events, spontaneous abortion, stillbirth, and preterm birth are presented in Table 4. The primary series analysis will include dose 1, dose 2, and dose 3 if a third dose is received within 2 months of the second dose. Similar to the analytic approach in the general population, separate cohorts will be formed for each dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine to assess these

events. In addition to meeting criteria described in Table 2, individuals must also meet criteria in Table 4 to be included in the exposed/unexposed cohorts.

Table 4. Cohort definitions for primary series analyses of general safety events, spontaneous abortion, stillbirth, and preterm birth in pregnant women[a]

Cohort	Inclusion criteria	Index date	Exclusion criteria
Dose 1 exposed	Record of a first dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine during the exposure window[b]	Date of first dose	Record of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent 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 original monovalent 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, if the first dose is administered before the exposure window, the pregnancy will NOT be eligible for dose 1 exposed cohort analysis but will be eligible for dose 2 exposed cohort analysis	Date of second dose	Record of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent 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)

Table 4. Cohort definitions for primary series analyses of general safety events, spontaneous abortion, stillbirth, and preterm birth in pregnant women[a]

Cohort	Inclusion criteria	Index date	Exclusion criteria
Dose 3 exposed	• Record of a third dose (either as an additional dose in a primary series or as a booster dose) of Pfizer-BioNTech original monovalent COVID-19 Vaccine during the exposure window • For analyses of general safety events, the first and second dose are not required to have been administered during the exposure window • For analyses of spontaneous abortion, stillbirth, and preterm birth, the first and/or second doses may be administered before the exposure window but only the third dose will be eligible for the dose 3 cohort	Date of third dose	Record of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent 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, stillbirth, and preterm birth) • Individually matched to women in dose 1 cohort on maternal age and pregnancy start date and US state (if feasible)	Equivalent of the gestational age (in days) at the time of the of the dose 1 exposed individual's index date[c]	Record of any COVID-19 vaccine as of the index date (or during the exposure window before the index date in analyses of spontaneous abortion, stillbirth, and preterm birth)
Dose 2 unexposed	Same criteria as the dose 1 unexposed cohort, but matched individually to women in the dose 2 exposed cohort	Equivalent of the gestational age (in days) at the time of the dose 2 exposed individual's index date[c]	Same criteria as those for the dose 1 unexposed cohort

Table 4. Cohort definitions for primary series analyses of general safety events, spontaneous abortion, stillbirth, and preterm birth in pregnant women[a]

Cohort	Inclusion criteria	Index date	Exclusion criteria
Dose 3 unexposed	Same criteria as those for the dose 1 unexposed cohort, but matched individually to women in the dose 3 exposed cohort	Equivalent of the gestational age (in days) at the time of the dose 3 exposed individual's index date[c]	Same criteria as those for the dose 1 unexposed cohort

COVID-19 = coronavirus disease 2019; FU = follow-up.
a. Safety events of interest listed in Table 8 in Section 8.3.2.1.
b. Pregnant women who have received their first dose of the Pfizer-BioNTech original monovalent COVID-19 Vaccine before the exposure window and their second dose of Pfizer-BioNTech original monovalent 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 the analysis). Similar rules will apply for pregnant women who have received their second dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine before the exposure window and their third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine during the exposure window. Further details will be described in the SAP.
c. Following exposed and unexposed women for the same duration will ensure that women have equal opportunity to be exposed during pregnancy. Furthermore, starting FU at the same gestational age for 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, dose 2 unexposed, and dose 3 unexposed cohorts may contribute to the dose 1, dose 2, and/or dose 3 exposed cohorts if they subsequently receive the Pfizer-BioNTech original monovalent COVID-19 Vaccine during the exposure window. Conversely, pregnant women in the dose 1, dose 2, or dose 3 cohorts may be eligible to contribute to the dose 1 unexposed, dose 2 unexposed, or dose 3 unexposed cohorts before they receive their first dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine. However, an individual woman may contribute only once to the dose 1 unexposed cohort, once to the dose 2 unexposed cohort, and once to the dose 3 unexposed cohort.

8.2.3.2. Analysis of general safety events, spontaneous abortion, stillbirth, and preterm birth in pregnant women following a third dose (either as an additional dose in a primary series or as a booster dose) received more than 2 months after the second dose

Eligibility criteria for third dose analyses of general safety events, spontaneous abortion, stillbirth, and preterm birth in pregnant women are described in Table 5. To be eligible, women must have received 2 doses of the Pfizer-BioNTech original monovalent COVID-19 Vaccine. They must be pregnant for at least 1 day after dose 2 and be continuously enrolled in their health plan from 12 months before the index date (as defined in Table 5) until the end of pregnancy. Depending on whether data on vaccine dose number are recorded in the data sources, additional enrollment may be required from the beginning of authorization of the Pfizer-BioNTech original monovalent COVID-19 Vaccine (i.e., 11 December 2020) to enable dose number identification. The feasibility of determining dose number based on vaccine codes will be confirmed during the monitoring phase of the study, and all eligibility criteria will be fully documented in the SAP.

The same exposure windows and eligible populations will be used as for the analysis of the doses in the primary series (as defined in Table 3). Only third doses of Pfizer-BioNTech original monovalent COVID-19 Vaccine (received as an additional dose in a primary series or as a booster dose) administered during the exposure windows and more than 2 months after the second dose will be considered for inclusion in the dose 3 exposed cohort. Women who receive a third dose after their pregnancy ends will not contribute person-time to the dose 3 exposed cohort but may contribute unexposed person-time to the dose 3 unexposed cohort.

Table 5. Cohort definitions for third dose analyses of general safety events[a], spontaneous abortion, stillbirth, and preterm birth in pregnant women

Cohort	Inclusion criteria	Index date	Exclusion criteria
General safety events			
Dose 3 exposed	• Receipt of a third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine (either as an additional dose in a primary series or as a booster dose) during the exposure window, more than 2 months after the second dose • Note that the first 2 doses are not required to have been received during the exposure window	• Date of third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine	• Receipt of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent COVID-19 Vaccine before the index date
Dose 3 unexposed	• As of the index date, receipt of 2 doses of Pfizer-BioNTech original monovalent COVID-19 Vaccine with no receipt of a third dose of any COVID-19 vaccine • Individually matched to women in the third dose–exposed cohort on maternal age, US state (if feasible, otherwise, geographic region), and pregnancy start date	• Equivalent to the gestational age (in days) at the time of the dose 3 exposed individual's index date	• Receipt of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent COVID-19 Vaccine before the index date • Receipt of a third dose of Pfizer-BioNTech monovalent COVID-19 Vaccine on or before the index date
Pregnancy outcomes			
Dose 3 exposed	• Receipt of a third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine (either as an additional dose in a primary series or as a booster dose) during the exposure window more than 2 months after the second dose. • Note that the first 2 doses are required to have been received during the exposure window.	• Date of third dose	• Receipt of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent COVID-19 Vaccine before the index date

Table 5. Cohort definitions for third dose analyses of general safety events[a], spontaneous abortion, stillbirth, and preterm birth in pregnant women

Cohort	Inclusion criteria	Index date	Exclusion criteria
Dose 3 unexposed	• No receipt of a third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine (either as an additional dose in a primary series or as a booster dose) during the exposure window, as of more than 2 months after the second dose • Note that the first 2 doses are required to have been received during the exposure window • Individually matched to women in the third dose–exposed cohort on maternal age, estimated pregnancy start, US state (if feasible; otherwise, geographic region), and time since second dose	• Equivalent to the gestational age (in days) at the time of the dose 3 exposed individual's index date	• Receipt of any COVID-19 vaccine other than Pfizer-BioNTech original monovalent COVID-19 Vaccine before the index date • Receipt of a third dose of COVID-19 vaccine during the exposure window, on or before the index date

COVID-19 = coronavirus disease 2019.
a. Safety events of interest listed in Table 8 in Section 8.3.2.1.
Note: Individuals who receive 3 doses of the vaccine can contribute person-time to both the dose 3 exposed and dose 3 unexposed cohorts. Individuals in the dose 3 unexposed cohort may contribute person-time to the dose 3 exposed cohort if they subsequently receive a third dose of the Pfizer-BioNTech original monovalent COVID-19 Vaccine. Conversely, individuals in the dose 3 exposed cohort may be eligible for the dose 3 unexposed cohort before they receive a third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine.

8.2.3.3. Analysis of small size for gestational age and major congenital malformations in pregnant women

Cohort definitions for analyses of small size for gestational age and major congenital malformations in pregnant women are presented in Table 6. For these analyses, separate cohorts of the following will be formed: (1) pregnant women exposed to at least a first, second, or third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine during the exposure window (as defined in Table 3) and (2) pregnant women not exposed to any COVID-19 vaccine during the exposure window (as defined in Table 3).

Table 6. Cohort definitions for analysis of small size for gestational age and major congenital malformations in pregnant women

Cohort	Inclusion criteria	Index date	Exclusion criteria
Exposed	Record of at least a first, second, or third dose (as an additional dose in a primary series or as a booster dose) of Pfizer-BioNTech original monovalent COVID-19 Vaccine during the exposure window (as defined in Table 3)	Estimated pregnancy start	Record of another brand of COVID-19 vaccine other than Pfizer-BioNTech original monovalent COVID-19 Vaccine during the exposure window No record of Pfizer-BioNTech original monovalent COVID-19 Vaccine during the exposure window
Unexposed	No record of any COVID-19 vaccine during the exposure window (as defined in Table 3), individually matched to women in the exposed cohort on maternal age and pregnancy start	Estimated pregnancy start	Record of any COVID-19 vaccine during the exposure window

COVID-19 = coronavirus disease 2019.

8.2.4. Follow-up

Events that can define the start and end of FU are provided in Table 7. Follow-up will end at the earliest of all possible events that define the end of FU.

Table 7. 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 8 in Section 8.3.2.1 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 8 in Section 8.3.2.1 for outcome-specific risk windows) • Receipt of any brand of 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 and brand of COVID-19 vaccine[c]

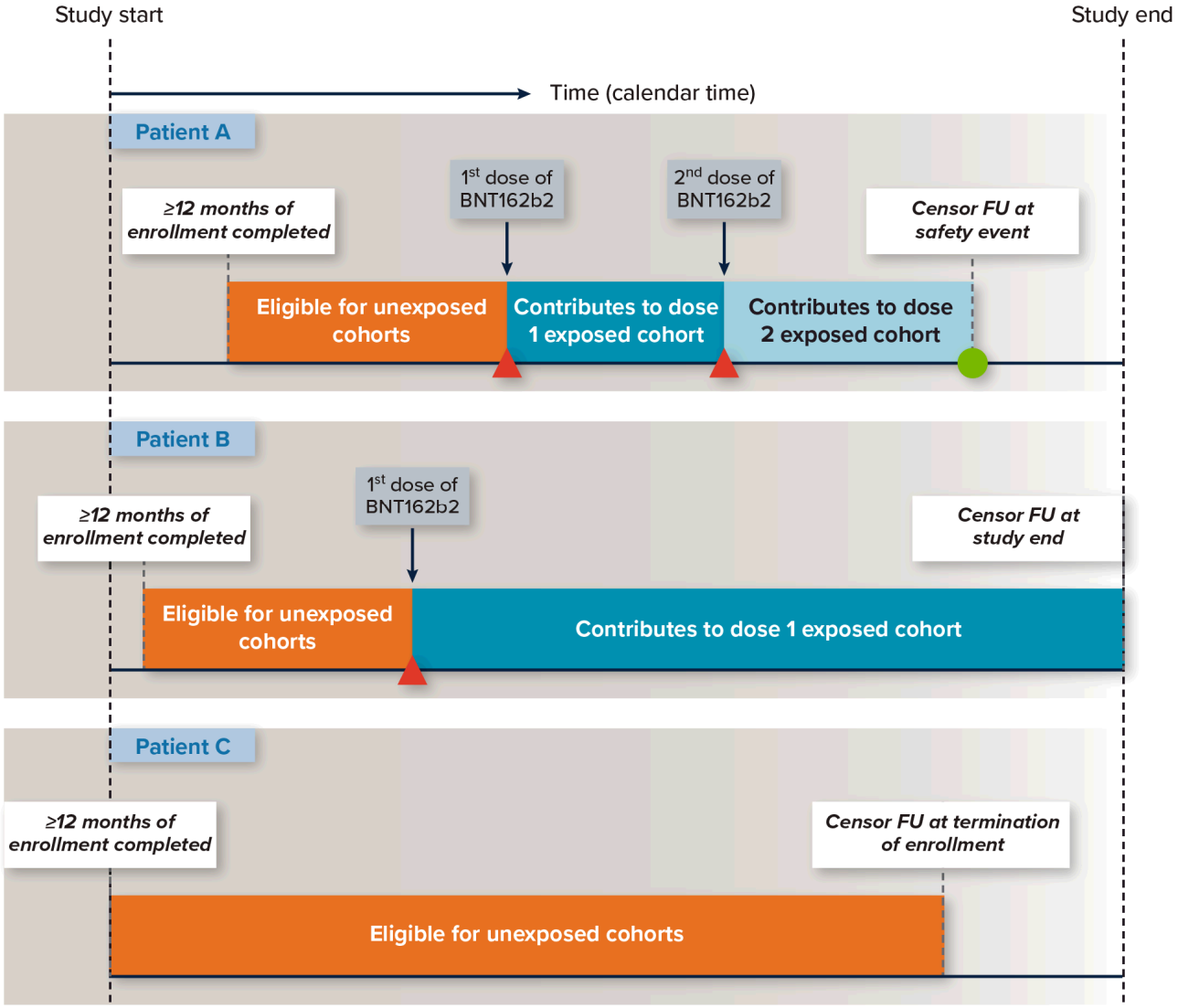
Table 7. Events defining the start and end of follow-up

Safety event of interest	Events defining the start of follow-up	Events defining the end of follow-up[a]
Stillbirth	• One day after the index date (if the index date is on or after estimated pregnancy start) or • Estimated pregnancy start	• End of pregnancy • Receipt of any brand of COVID-19 vaccine[c]
Preterm birth	• One day after the index date (if the index date is on or after estimated pregnancy start) or • Estimated pregnancy start	• End of pregnancy • 37 weeks of gestation • Receipt of any brand of 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)

COVID-19 = coronavirus disease 2019; FU = follow-up; SAP = statistical analysis plan.
a. For all analyses, the earliest of the listed events following the index date will mark the end of FU for each outcome. If FU ends due to the occurrence of a particular safety event of interest, FU will continue for all other safety events.
b. Safety events of interest are listed in Table 8 in Section 8.3.2.1.
c. For analyses of the primary series (doses 1, 2, and 3) only: If dose 2 is Pfizer-BioNTech original monovalent COVID-19 Vaccine, individuals will stop FU in the dose 1 cohort and may start FU 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 the FU for dose 1. Otherwise, the date of receipt of dose 2 will be included in the FU for dose 2. If dose 3 is Pfizer-BioNTech original monovalent COVID-19 Vaccine, individuals will stop FU in the dose 2 cohort and may start FU in the dose 3 cohort. (Note that dose 3 will only be included in primary series analyses in individuals aged 6 months through 4 years and in individuals aged 5 years and older whose third primary series dose is received within 2 months of the second dose.)
d. Major congenital malformations and small size for gestational age will be assessed in the infant.

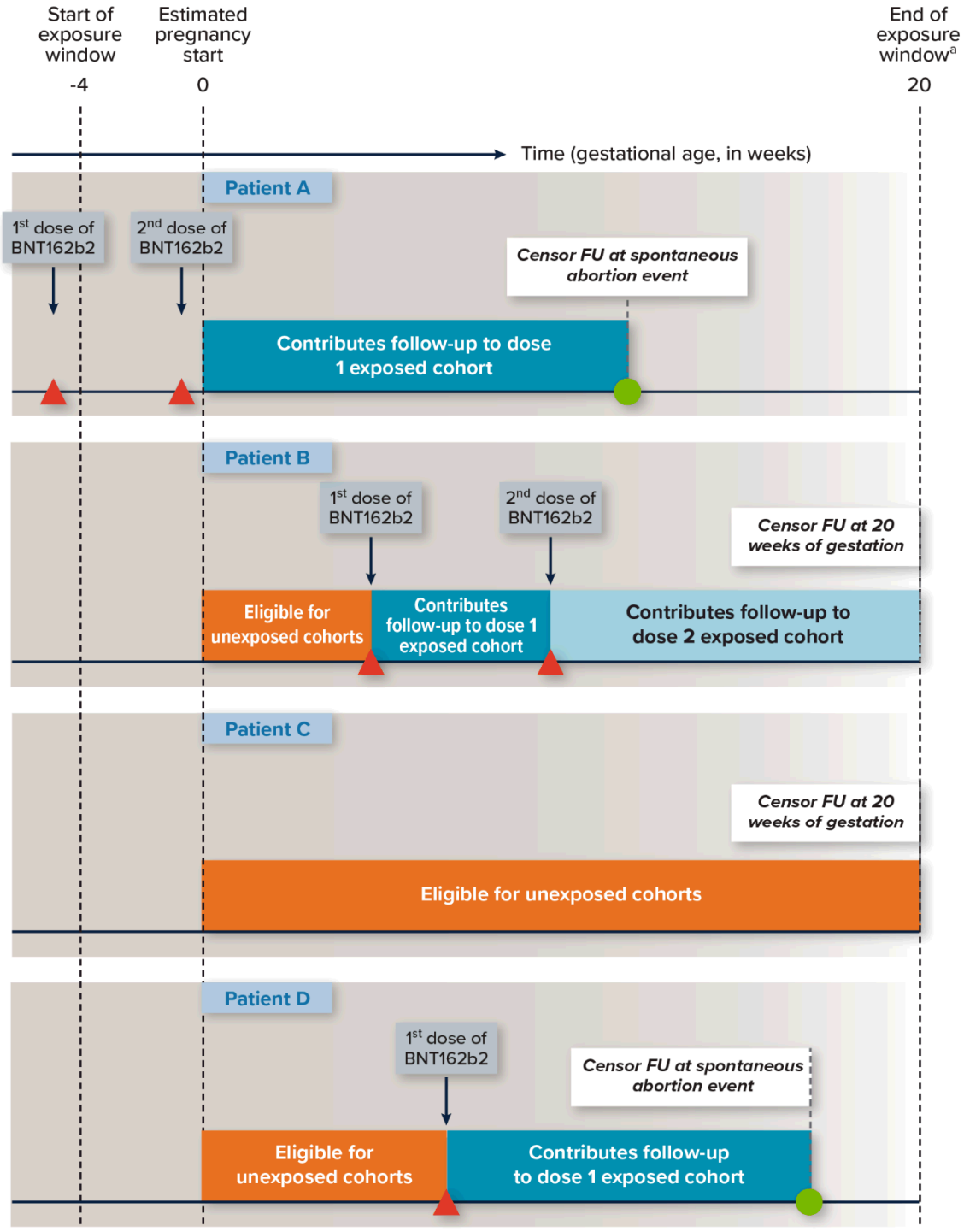
For illustrative purposes, Figure 1 depicts the timelines of hypothetical patients to show the concepts of eligibility for study cohorts and FU in primary series analyses of general safety events in the general population, immunocompromised individuals, or individuals with history of COVID-19. Figure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

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



BNT162b2 = Pfizer-BioNTech original monovalent COVID-19 Vaccine; COVID-19 = coronavirus disease 2019; FU = follow-up.
Note: If FU ends due to the occurrence of a particular safety event of interest, FU 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 a primary series analysis in pregnant women



BNT162b2 = Pfizer-BioNTech original monovalent COVID-19 Vaccine; COVID-19 = coronavirus disease 2019; FU = follow-up.
a. End of the exposure window is 20 weeks of gestation or pregnancy end, whichever is earlier.

8.3. Variables

8.3.1. Vaccine exposures

The primary exposure of interest is Pfizer-BioNTech original monovalent COVID-19 Vaccine. Receipt of Pfizer-BioNTech original monovalent 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 procedure codes or pharmacy dispensing codes, which will be specified in the SAP. Although vaccine administration codes distinguish between dose number (e.g., first, second, third, booster dose), it is anticipated that most vaccinations will be identified with codes that do not provide information on dose number. If feasible (to be determined during the monitoring phase of the study), dose number will be assigned based on vaccine administration codes. Otherwise, dose number will be assigned based on the ordinal number of the vaccinations (i.e., first, second, or third) recorded in the data sources, which would require that individuals be enrolled from the time of authorization of Pfizer-BioNTech original monovalent COVID-19 Vaccine. 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. COVID-19 vaccines available during the study period and codes will be documented in the SAP. 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.

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 may be designated as the primary study designs and/or linkage to immunization registries may be considered if feasible.

8.3.2. Outcomes

8.3.2.1. 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 8. Throughout the protocol, these safety events are referred to as "general safety events."

Safety events of interest include myocarditis/pericarditis and other 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 (Shimabukuro, 2021a), 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 original monovalent COVID-19 Vaccine evolves and feasibility of their assessment permits in the data sources.

Table 8. 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 original monovalent COVID-19 Vaccine)[a]
Cardiac	Myocarditis/pericarditis	1-21[b]
	Acute myocardial infarction	1-28
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
Hematologic	Deep vein thrombosis	1-28
	Disseminated intravascular coagulation	1-28
	Immune hemolytic anemia	1-42
	Immune thrombocytopenia	1-42

Table 8. 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 original monovalent COVID-19 Vaccine)[a]
	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

COVID-19 = coronavirus disease 2019.
a. Time interval following vaccination when individuals 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:

- Spontaneous abortion: spontaneous pregnancy loss before 20 completed weeks gestation, identified using diagnosis codes
- Stillbirth: fetal deaths at or after 20 completed weeks gestation, identified using diagnosis codes

- Preterm birth: live birth before 37 completed weeks gestation, identified using diagnosis codes

- 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, identified using diagnosis codes for small size for gestational age

8.3.2.2. 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 myocarditis/pericarditis will be validated for individuals aged 12 years and older. Algorithms for other outcomes that have signaled in other studies or surveillance systems may also be validated if the outcomes could be susceptible to substantial misclassification. 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 may be used to identify cases that will undergo clinician review. 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. Details of sensitivity analyses (quantitative bias analysis) to adjust for potential misclassification based on results from validation will be described in the SAP.

8.3.3. 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.

8.3.3.1. 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 for each individual, 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 original monovalent COVID-19 Vaccine (categorized as appropriate, e.g., by year or month)
- Dose of vaccine received (e.g., 1, 2, 3)
- Comorbidities, identified in the 12 months before 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)
- Preeclampsia/eclampsia (captured only in subgroup analysis of pregnant women)
- Pregnancy status (on the index date), identified using an algorithm as described in Section 8.2.3

- 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 original monovalent 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 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 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 the index date, with proxies based on diagnosis and procedure codes (capture anticipated to be incomplete)
- Smoking, identified in the 12 months before the index date, with proxies based on diagnosis and procedure codes (capture anticipated to be incomplete)
- 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
- Gestational hypertension
- 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 original monovalent COVID-19 Vaccine) from 28 days before pregnancy up to and including the end of pregnancy, identified via pharmacy dispensing and procedure codes

8.3.3.2. 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 the 12 months 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 8.2.3.
- 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 COVID-19 (J12.82). If feasible, a positive laboratory test result for SARS-CoV-2 will be incorporated into the definition.

8.3.3.3. Subgroup analysis

Subgroup analysis will be conducted in the following age categories, as appropriate for safety events of interest: 0-4, 5-11, 12-17, 18-64, and 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 the following subgroups:

- Multisystem inflammatory syndrome in children: ages 0-4, 5-11, 12-17, and 18-20 years
- Convulsions: ages 0-4 years
- Kawasaki disease: ages 0-4 years
- Myocarditis/pericarditis: ages 0-4, 5-11, 12-17, 18-24, 25-29, 30-39, 40-49, 50-64, and 65 years and older

Additional subgroup analyses of myocarditis/pericarditis will be conducted by sex, age and age by sex together (in the above age categories), dose number, and calendar time. Additional subgroup analyses may be conducted for other specific safety events of interest that have signaled in other studies or vaccine safety surveillance systems. Additionally, analyses to identify risk factors for postvaccine outcomes will be conducted for myocarditis/pericarditis. These analyses will be described in the SAP.

8.4. Data sources

This study will use data from 5 data research partners, including data from 4 national insurers (CVS Health/Aetna, Carelon Research [formerly HealthCore/Anthem], Humana, and Optum) 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 focus on the research-eligible populations from each of the data research partners and will use the most recent data available within each partner's Sentinel Distributed Database 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. For safety analyses of birth outcomes (i.e., small size for gestational age and major congenital malformations) following maternal prenatal vaccination, maternal data in pregnant women will be linked with infant data to identify outcomes. 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, Carelon Research, 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 individuals 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 individuals have over 3 years of enrollment, and individuals 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 individual 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 an individual 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; 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.

8.4.1. 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 individuals' most recent available data).

Carelon Research (formerly HealthCore, Inc.) became a participant in the Sentinel System in 2008 and contributes both by submitting data to the Sentinel database and as a collaborator. As of 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 a median (quarter 1 [Q1], Q3) age of 40 (26-57) years.

8.4.2. 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 individuals, 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.

8.4.3. Humana

Humana Healthcare Research is a health economics and outcomes research subsidiary of Humana, which focuses on treatment effectiveness, drug safety, adherence, medical and pharmacy benefit design, disease management programs, and other healthcare services based on the Humana health plan member population. Humana Healthcare Research is an active collaborator and data 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.

8.4.4. Optum Research Database

The Optum Research Database is a proprietary research database that includes data drawn from a large US health plan affiliated with Optum and that contains eligibility data and medical claims for health plan members who are geographically diverse across the US. The Optum Research Database comprises approximately 3% to 4% of the US population, covering all ages, with 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.

8.5. Study size

The size of the exposed population will depend on the use of Pfizer-BioNTech original monovalent COVID-19 Vaccine, and the size of the comparator population will depend on the proportion of the source population that comprises unvaccinated individuals (or individuals not receiving a third dose) 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 for analysis of the primary series, Table 9 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 Table 9 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 myocarditis/pericarditis, with 5,000,000 exposed individuals and an estimated background rate of 10 per 100,000 person-years, we estimate a 92% probability that the upper bound of the observed RR would be below 2.5 assuming a 1:1 ratio between vaccinated and comparator person-time and that the true RR is 1.4.

Table 9. Study size calculations

Assumed true RR	Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021; Gubernot 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	Myocarditis/ pericarditis	1	500,000	0.04	0.06	0.07	0.09
			1,000,000	0.05	0.08	0.10	0.13
			2,500,000	0.07	0.13	0.19	0.26
			5,000,000	0.10	0.22	0.34	0.46
			10,000,000	0.16	0.38	0.59	0.75
			20,000,000	0.28	0.65	0.87	0.96
1.0	Myocarditis/ pericarditis	10	500,000	0.10	0.22	0.34	0.46
			1,000,000	0.16	0.38	0.59	0.75
			2,500,000	0.34	0.75	0.94	0.99
			5,000,000	0.59	0.96	1.00	1.00
			10,000,000	0.87	1.00	1.00	1.00
			20,000,000	0.99	1.00	1.00	1.00

Table 9. Study size calculations

Assumed true RR	Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021; Gubernot 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
1.0	Bell's palsy	25.2	500,000	0.34	0.75	0.94	0.99
			1,000,000	0.59	0.96	1.00	1.00
			2,500,000	0.93	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
1.0	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

Table 9. Study size calculations

Assumed true RR	Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021; Gubernot 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
1.2	Myocarditis/ pericarditis	1	500,000	0.03	0.05	0.06	0.07
			1,000,000	0.04	0.06	0.08	0.11
			2,500,000	0.05	0.09	0.15	0.21
			5,000,000	0.06	0.15	0.25	0.37
			10,000,000	0.08	0.25	0.45	0.63
			20,000,000	0.12	0.44	0.74	0.90
		10	500,000	0.06	0.15	0.25	0.37
			1,000,000	0.08	0.25	0.45	0.63
			2,500,000	0.14	0.53	0.83	0.95
			5,000,000	0.24	0.82	0.98	1.00
			10,000,000	0.42	0.98	1.00	1.00
			20,000,000	0.71	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

Table 9. Study size calculations

Assumed true RR	Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021; Gubernot 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
1.2	Bell's palsy	25.2	500,000	0.14	0.53	0.83	0.95
			1,000,000	0.24	0.82	0.98	1.00
			2,500,000	0.51	1.00	1.00	1.00
			5,000,000	0.80	1.00	1.00	1.00
			10,000,000	0.98	1.00	1.00	1.00
			20,000,000	1.00	1.00	1.00	1.00
1.2	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
			20,000,000	1.00	1.00	1.00	1.00
1.4	Myocarditis/ pericarditis	1	500,000	0.03	0.04	0.05	0.06
			1,000,000	0.03	0.05	0.07	0.09
			2,500,000	0.03	0.07	0.11	0.17
			5,000,000	0.03	0.10	0.18	0.29
			10,000,000	0.04	0.15	0.32	0.51
			20,000,000	0.04	0.26	0.57	0.80

Table 9. Study size calculations

Assumed true RR	Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021; Gubernot 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
1.4	Myocarditis/ pericarditis	10	500,000	0.03	0.10	0.18	0.29
			1,000,000	0.04	0.15	0.32	0.51
			2,500,000	0.05	0.31	0.66	0.88
			5,000,000	0.06	0.54	0.92	0.99
			10,000,000	0.08	0.83	1.00	1.00
			20,000,000	0.12	0.99	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
1.4	Bell's palsy	25.2	500,000	0.05	0.31	0.66	0.88
			1,000,000	0.06	0.55	0.92	0.99
			2,500,000	0.09	0.91	1.00	1.00
			5,000,000	0.14	1.00	1.00	1.00
			10,000,000	0.24	1.00	1.00	1.00
			20,000,000	0.43	1.00	1.00	1.00

Table 9. Study size calculations

Assumed true RR	Safety event of interest	Estimated background rate per 100,000 person-years (Black et al., 2021; Gubernot 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
1.4	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

RR = relative risk.
a. Estimates in this table assume a risk window duration of 21 days for myocarditis/pericarditis, 42 days for Guillain-Barré syndrome and Bell's palsy, and 28 days for myocardial infarction.

8.6. Data management

8.6.1. Data collection tools

As the analyses will be based on secondary data, the only data collection tool (DCT) that may be applicable will be data abstraction forms that will be developed for the purpose of validation of select outcomes 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 individual 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.

8.6.2. 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.

8.6.3. Data oversight

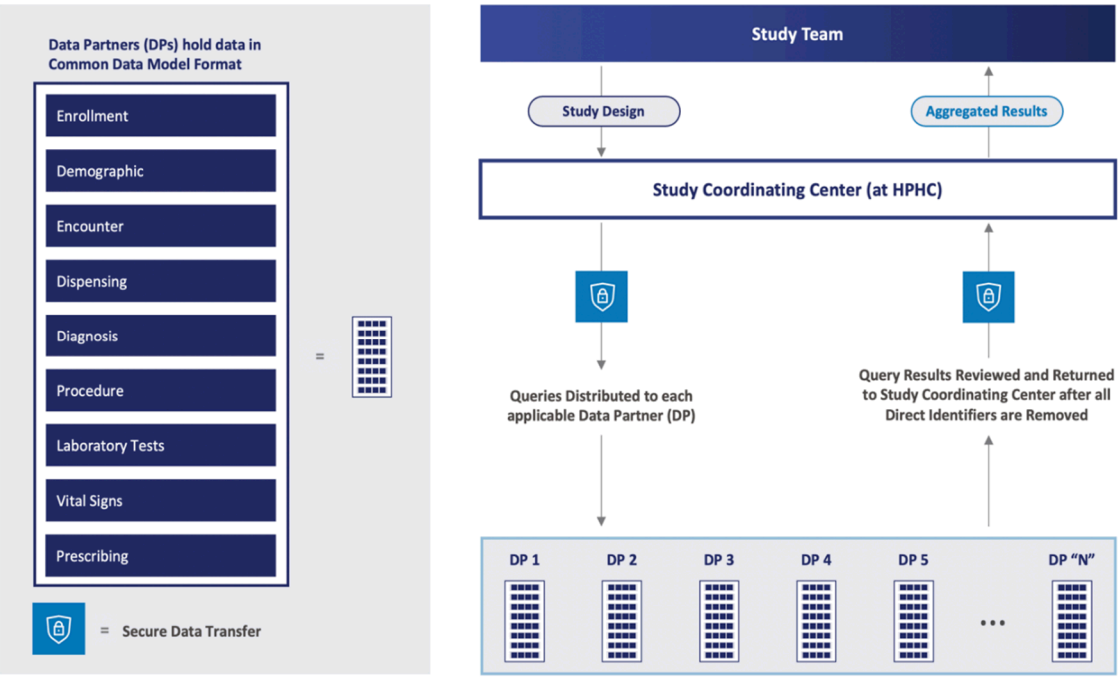
HPHCI, located in Boston, Massachusetts, will serve as the coordinating center for the proposed study. HPHCI staff or contractors will be responsible for writing and distributing SAS programs that can be used to evaluate the data included in databases at participating data research partners. The distributed 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 (National Institute of Standards and Technology (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



8.7. Data analysis

Analyses will initially be conducted separately within the data from each data source. Data source–specific results will be returned to the study coordinating center, which will aggregate results across the data sources for reporting. Pooled analysis of RR and prevalence 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.

8.7.1. Descriptive analysis

Descriptive analysis will report on utilization of Pfizer-BioNTech original monovalent 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, at least 2 doses, and at least 3 doses of Pfizer-BioNTech original monovalent COVID-19 Vaccine will be estimated within the overall study population, among individuals who are immunocompromised, among individuals with a history of COVID-19, and among pregnant women. If additional doses of Pfizer-BioNTech original monovalent COVID-19 Vaccine are authorized and available in the data sources, the proportion of individuals receiving additional doses (at least 4 doses, at least 5 doses, etc.) will also be described.

Among individuals who receive a second dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine, the proportion of individuals will be reported by type of second dose of COVID-19 vaccine, and time between the first and second doses will be described within the overall study population, among pregnant women, among immunocompromised individuals, among individuals with a history of COVID-19, and stratified by age (6 months through 4 years and ≥ 5 years). Among individuals who receive a third dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine, the proportion of individuals will be reported by type of third dose of COVID-19 vaccine, and time between the second and third doses will be described within the overall study population, among pregnant women, among immunocompromised individuals, among individuals with a history of COVID-19, and stratified by age (6 months through 4 years and ≥ 5 years).

Additionally, characteristics (i.e., demographics, comorbidities, and other potential covariates) of the matched and unmatched study 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.

The following descriptive analyses will be performed for specific safety events of interest:

- The number and proportion of individuals 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 FU in the exposed and unexposed cohorts contributing to analyses of vaccine-associated enhanced disease will be output.
- The proportion of myocarditis/pericarditis cases with subsequent serious cardiovascular conditions (up to 1 year after diagnosis, using all available data) will be estimated among individuals vaccinated with Pfizer-BioNTech original monovalent COVID-19 Vaccine and in individuals not vaccinated with a COVID-19 vaccine, using structured data from claims and electronic health records (where available, as not all research partners have electronic health records data available in the Sentinel Distributed Database). These analyses will be described in the SAP.

8.7.2. 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 FU care for events that have happened in the past from incident events occurring during FU. The washout periods for defining incident events will depend on the outcome and will be specified in the SAP.

8.7.2.1. 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).

8.7.2.2. Measures of association

For comparative analyses of general safety events, Cox models or Poisson regression will be used to estimate RRs and 95% CIs within the matched cohorts. For pregnancy outcomes, hazard ratios and 95% CIs will be estimated using Fine-Gray subdistribution proportional hazards models (using gestational age as the time scale) to account for competing risks of other end-of-pregnancy events (e.g., termination, stillbirth) (Fine JP and Gray RJ, 1999).

For comparative analysis of small size for gestational age and major congenital malformations, modified Poisson regression (Zou, 2004) will be used to estimate prevalence ratios and 95% CIs within the matched cohorts.

For the dose 1 comparative risk estimation for general safety events and pregnancy outcomes, 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 FU 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.

Similarly, for dose 2 comparative risk estimation for general safety events and pregnancy outcomes, when a third dose of vaccine is administered before the risk interval following dose 2 is complete, the risk interval will be truncated at the time of dose 3, and FU after dose 3 will be excluded from the dose 2 estimation. In this situation, for the dose 3 comparative risk estimation, the risk interval will start on the date of the third vaccine dose and will extend for the duration of the risk interval for dose 3.

For comparative analysis of outcomes identified separately in dose 1, dose 2, and dose 3 cohorts, comparative risks will be estimated separately by dose number. If comparative risk estimates are similar for dose 1, dose 2, and dose 3, then data from the dose 1 exposed/dose 1 unexposed cohorts, the dose 2 exposed/dose 2 unexposed cohorts, and the dose 3 exposed/dose 3 unexposed cohorts will be combined to obtain comparative risk estimates associated with at least 1 dose of the vaccine.

Because each dose of vaccine within the same individual will be considered a separate observation when combined in analyses and because some individuals may contribute to both the exposed and unexposed cohorts, the correlation between dose 1, dose 2, and dose 3 will

be accounted for when estimating the variance, using appropriate statistical methods to be detailed in the SAP.

8.7.2.3. Methods for addressing confounding

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

Analysis of nonpregnant populations will use matching on age, sex, 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. Additionally, analysis of third doses received more than 2 months after the second dose will also match on time since receipt of the second dose.

8.7.2.3.1.1. Analysis of general safety events following primary series

Among the general population, immunocompromised individuals, and individuals with a history of COVID-19, the risk of general safety events will be compared among individuals who have received at least the first dose in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine versus those among individuals who have not received any COVID-19 vaccine during a concurrent time. In individuals aged 6 months through 4 years, these analyses will include doses 1, 2, and 3. Details for handling the timing between individual doses in this age group will be described in the SAP. In individuals aged 5 years and older, these analyses will include dose 1 and dose 2, as well as dose 3 if a third dose is received within 2 months of the second dose.

Estimation of propensity scores will be performed for the dose 1, 2, and 3 (if applicable) cohorts combined. However, matching of exposed to unexposed individuals will be done separately for the dose 1 exposed cohort, the dose 2 exposed cohort, and the dose 3 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—whether dose 1, dose 2, or dose 3—during the considered month would contribute vaccinated index dates during the time interval; if an individual received more than 1 dose during a calendar month, all eligible 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 all unexposed person-time within the time interval. In this context, "unexposed person-day" refers to a day in which the individual 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 8.3.3). The model will combine dose 1, dose 2, and dose 3 index dates, which assumes that the factors influencing an individual's likelihood of being vaccinated does not change between dose 1, dose 2, and dose 3.

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, for the dose 2 exposed cohort, and for the dose 3 exposed cohort and will be done by age and 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, once for the dose 2 unexposed cohort, and once for the dose 3 unexposed cohort. Individuals who match as an unvaccinated index date in one time interval will not be considered for the same unvaccinated cohort (i.e., dose 1 unexposed cohort, dose 2 unexposed cohort, or dose 3 unexposed cohort) in future time intervals. However, if an individual becomes vaccinated after being selected as an unexposed match, they may be eligible for the dose 1, dose 2, and/or dose 3 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.

8.7.2.3.1.2. Analysis of general safety events following third doses received more than 2 months after the second dose in individuals aged 5 years and older

In individuals aged 5 years and older who have received 2 doses in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine, the risk of general safety events will be compared in individuals who have received a third dose (either as an additional dose within a

primary series or as a booster dose) more than 2 months after the second dose, versus that among individuals who have not received a third dose of any COVID-19 Vaccine during a concurrent time period.

Estimation of propensity scores and matching will be performed for the dose 3 exposed cohort within narrow time periods to account for changing predictors of receipt of third doses of the vaccine over time and the seasonality of circulating infections. Matching will occur within each time period by age, sex, state (if feasible, or broader geographic region if not feasible), and time since dose 2 receipt. Propensity score estimation will be conducted following similar steps as for the primary series analysis (as described in Section 8.7.2.3.1.1). The matching and propensity score estimation process will be conducted first for the general population and then will be repeated separately for individuals who are immunocompromised and individuals with a history of COVID-19. Further details on the matching process and estimation of propensity scores will be described in the SAP.

8.7.2.3.2. Pregnant women

8.7.2.3.2.1. Analysis of general safety events, spontaneous abortion, stillbirth, and preterm birth following a primary series in pregnant women

The risk of general safety events, spontaneous abortion, stillbirth, and preterm birth will be compared among women who have received at least the first dose in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine versus those among pregnant women who have not received any COVID-19 vaccine during a concurrent time period. These analyses will include dose 1 and dose 2, as well as dose 3 if a third dose is received within 2 months of the second dose.

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).

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). The matching will be done separately for the dose 1 exposed cohort, for the dose 2 exposed cohort, and for the dose 3 exposed cohort.

An individual may be selected for each unexposed cohort (i.e., dose 1 unexposed, dose 2 unexposed cohort, or dose 3 unexposed cohort) only once. However, if an individual becomes vaccinated after being selected as an unexposed match, they may be eligible for the exposed cohort(s).

b. The propensity to be vaccinated will be estimated among all matched individuals. 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 8.3.3). The model will combine dose 1, dose 2, and dose 3 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.

8.7.2.3.2.2. Analysis of general safety events, spontaneous abortion, stillbirth, and preterm birth following third doses received more than 2 months after the second dose in pregnant women

In pregnant women who have received 2 doses in a primary series of Pfizer-BioNTech original monovalent COVID-19 Vaccine, the risk of general safety events, spontaneous abortion, stillbirth, and preterm birth will be compared among women who have received a third dose (either as an additional dose in a primary series or as a booster dose) more than 2 months after the second dose versus that among women who have not received a third dose of any COVID-19 vaccine. To minimize confounding by seasonality and maternal age, within the data from each data research partner, pregnant women in the dose 3 exposed cohort will be matched to women in the dose 3 unexposed cohort on estimated pregnancy start date (+/- 14 days), state (if feasible, or broader geographic region if not feasible), maternal age, and time since receipt of dose 2. Propensity score estimation will be conducted following a similar process as that for the primary series analysis of general safety events, spontaneous abortion, stillbirth, and preterm birth in pregnant women (as described in Section 8.7.2.3.2.1). As with the primary series analysis, propensity scores will be estimated within the matched population of dose 3 exposed and dose 3 unexposed individuals 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 conducted 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). Further details on the matching process and estimation of propensity scores will be described in the SAP.

8.7.2.3.2.3. Analysis of birth outcomes following receipt of at least 1 dose in pregnant women

Analysis of major congenital malformations and small size for gestational age will compare singleton birth prevalence in infants born to pregnant women who have received at least 1 dose of Pfizer-BioNTech original monovalent COVID-19 Vaccine during the outcome-specific exposure window to women with singleton pregnancies who have not received any COVID-19 vaccine during the outcome-specific exposure window.

To minimize confounding by seasonality and maternal age, within the data from each data research partner, pregnant women in the exposed cohort will be matched to women in the unexposed cohort on estimated pregnancy start date (+/- 14 days), state (if feasible, or broader geographic region if not feasible), and maternal age. Propensity score estimation will be conducted following a similar process as for the primary series analysis of general safety events, spontaneous abortion, stillbirth, and preterm birth (as described in Section 8.7.2.3.2.1). Details on the matching process and estimation of propensity scores will be described in the SAP.

8.7.3. Sensitivity analysis

8.7.3.1. 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. Additional sensitivity analyses will incorporate a cohort design with historical unexposed comparators for pregnancy and birth outcomes.

8.7.3.2. Self-controlled risk interval design

Sensitivity analyses incorporating a SCRI design will be implemented for outcomes with an acute onset and short risk intervals (i.e., risk intervals no longer than 42 days; specific outcomes to be indicated 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 that in a control interval within the same individual.

For the primary series analysis, the risk interval will combine person-time in the risk intervals after the first dose, after the second dose, and after the third dose (if applicable).

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); to avoid bias due to healthy vaccinee effects, pre-vaccination periods will not be used. 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.

8.7.3.3. Cohort design with historical unexposed comparators (pregnancy and birth outcomes)

If feasible, a cohort design with historical unexposed individuals as comparators will be used to assess pregnancy and birth outcomes. For the cohort design with historical unexposed comparators, the comparator cohorts will be identified and followed in a time period before the introduction of COVID-19 vaccines. Exposed and unexposed individuals will be matched on maternal age and estimated pregnancy start, using similar methods as for the cohort design with concurrent unexposed comparators in pregnant women.

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 pregnancy outcome 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.

8.7.3.4. Risk intervals

8.7.3.5. Outcome misclassification

Misclassification of outcome events may result in bias of the estimated effect measure estimates, particularly if the misclassification is differential between exposure groups. Quantitative bias analysis will be implemented to correct comparative risk estimates of myocarditis/pericarditis in individuals aged 12 years and older for differential outcome misclassification (i.e., positive predictive value and sensitivity) by exposure status. Details will be provided in the SAP.

8.7.3.6. Pfizer-BioNTech original monovalent COVID-19 Vaccine 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.

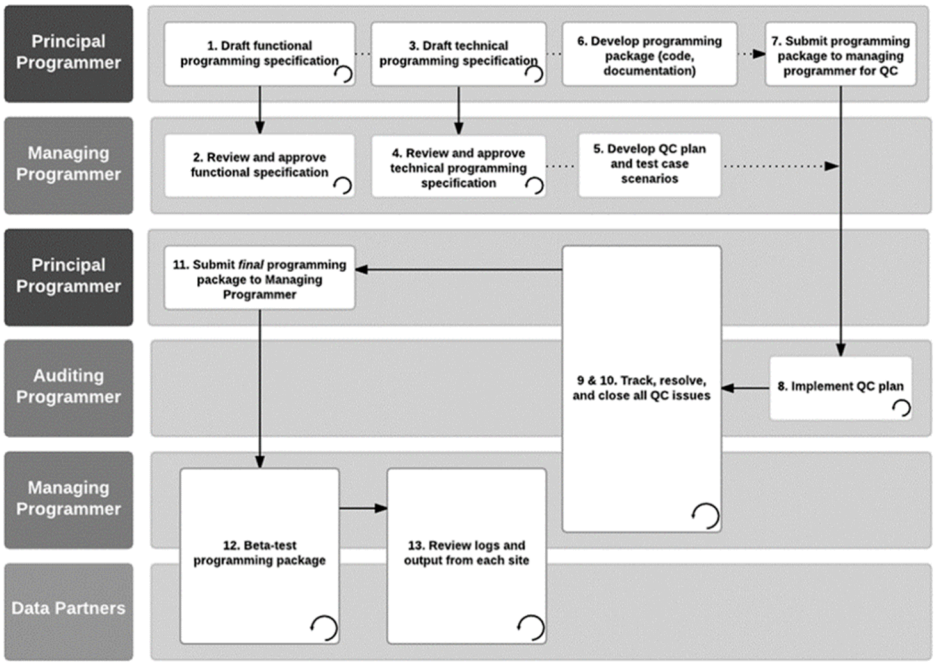
For other safety events of interest for which the risk intervals are not well characterized (to be defined in the SAP), descriptive analyses of the timing of events relative to vaccination will be conducted. If they are identified, temporal clusters will be used to define alternative risk intervals that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

8.8. 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, 2017; Sentinel Initiative, 2021). The data curation approach is consistent with guidance set forth by the US FDA in its current recommendations for data QA, Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, Section IV.E Best Practices – Data Sources: Quality Assurance (QA) and Quality Control (QC), published in May 2013 (FDA, 2013; Sentinel, 2017). This Guidance describes best practices that particularly apply to observational studies designed to assess the risk associated with a drug exposure using electronic healthcare data.

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



QC = quality control.

8.9. 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 an individual'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 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 and potential misclassification of unexposed status, 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. In primary series analyses, forming 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 for pregnancy and birth outcomes and the SCRI design will not be subject to this limitation. However, it is anticipated that even with separate matching of doses that FU 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 be used to study this outcome.

Finally, analyses of third doses of Pfizer-Bio-N-Tech COVID-19 Vaccine (either as an additional dose in a primary series or as a booster dose) may be limited by small numbers of third dose recipients. A large proportion of individuals may be excluded from these analyses if many individuals do not have available information on dose number, as enrollment from the beginning of the authorization of COVID-19 vaccines would be needed to enable dose number identification. The overall number of pregnant women included in the analysis of third doses may be low due to lower COVID-19 vaccine uptake in pregnant women and because pregnant women will be identified by their pregnancy outcomes, which means that

women will not be identified as pregnant and eligible to be included in the population of pregnant women until months after they give birth or their pregnancy otherwise ends.

8.10. Other aspects

Not applicable

9. 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.

9.1. 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—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 the protection of patients' 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. Patients' 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 individuals 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.

9.2. 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.

9.3. Institutional review board/Independent ethics committee

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/independent ethics committee (IECs). All correspondence with the IRB or IEC and applicable documentation will be retained as part of the study materials. Copies of IRB/IEC approvals must be forwarded to Pfizer.

9.4. 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 (ISPE, 2015) issued by the International Society for Pharmacoepidemiology and Good Epidemiological Practice guidelines issued by the International Epidemiological Association (IEA, 2007).

10. 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.

10.1. 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.

10.2. 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 original monovalent 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 AEs.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form and constitutes all clinical information known regarding these AEs. No FU 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 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 Your Reporting Responsibilities training materials.

11. 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 FU. After the end of the third year of FU, the final report will be produced, including the analysis and interpretation of each outcome including pregnancy safety outcomes. The final report will be posted to the EU PAS Register. A manuscript reporting on the results from the final analysis will also be submitted to a relevant peer-reviewed journal. Pfizer will notify the EMA 2 weeks after receiving the journal's notification of acceptance of the final manuscript for publication.

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2022). 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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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title: A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine in the United States

EU PAS Register® number: EUPAS43468
Study reference number (if applicable): Not applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	5
1.1.2 End of data collection[3]	☒	☐	☐	5
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	5
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (ie population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7, 8.2.1, 8.2.2, 8.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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

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

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1, 8.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7.2.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.7.2.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.1
	4.2.2 Age and sex	☒	☐	☐	8.2
	4.2.3 Country of origin	☒	☐	☐	8.4
	4.2.4 Disease/indication	☐	☐	☒	
	4.2.5 Duration of follow-up	☒	☐	☐	8.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.1, 8.3.1, 8.7.3
5.3	Is exposure categorised according to time windows?	☒	☐	☐	8.2.3
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.1, 8.2.2, 8.2.3

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3.2.2
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.3.3.1, 8.7.2.3
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.1, 8.3.1, 8.3.2.2, 8.7.3

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.3.3.2, 8.3.3.3

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.3.1
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.3.2
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.3.3
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3.1
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3.1
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.3.2
	9.3.3 Covariates and other characteristics?	☒	☐	☐	8.3.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.1
10.4 Are stratified analyses included?	☒	☐	☐	8.3.3.2, 8.3.3.3
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.7.2.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7.3

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	8.1, 8.3.1, 8.3.2.2, 8.7.3, 8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.7.3.2, 8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.1, 8.5, 8.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol:	Alison Kawai	
Date: dd/Month/year	30/Jun/2022	
Signature:	Alison Kawai	

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

Document Name:	C4591009_PROTOCOL AMENDMENT 3_V4_30JUN2023
Document Title:	C4591009_PROTOCOL AMENDMENT 3_V4_30JUN2023

Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	13-Jul-2023 13:59:43	Manager Approval
De Bernardi, Barbara	15-Jul-2023 21:35:44	EUQPPV Approval