NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Active Safety Surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense Population Following Emergency Use Authorization
Pfizer Protocol number	C4591011
DoD Protocol Number	WRNMMC-2022-0389
Protocol version identifier	Version 3.0
Date	09 August 2022
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	COVID-19 mRNA 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 SARS-CoV-2
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)
Marketing Authorization Holder(s) (MAH)	BioNTech Manufacturing GmbH
Joint PASS	No
Research question and objectives	Research question: What are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]), overall and in sub-cohorts of interest, among individuals in the United States Department of Defense (DoD) Military Health System (MHS) (ie, DoD Uniformed members of the Departments of the Army, Navy, and Air Force, including the active and reserve components of each Military Department and the Coast Guard, as well as beneficiaries) vaccinated with the Pfizer-BioNTech

	COVID-19 Vaccine as compared to expected rates of those events?
	
	Primary study objectives:
	
	• To assess whether individuals identified in the DoD MHS experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 Vaccine, specifically in the following groups:
	
	  • Individuals receiving at least one dose
	
	  • Individuals receiving the primary series (ie, two doses for the general population and three doses for immunocompromised individuals)
	
	  • Individuals receiving approved booster dose(s) of the Pfizer-BioNTech COVID-19 Vaccine (ie, a single booster dose or additional booster doses) after the primary series.
	
	• To assess whether sub-cohorts of interest (ie, pregnant women, immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 Vaccine, and individuals with prior SARS-CoV-2 infection) identified in the DoD MHS experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 Vaccine.
	
	Secondary study objective:
	
	• To characterize utilization patterns of the Pfizer-BioNTech COVID-19 Vaccine among the individuals identified within the DoD MHS,

	including estimating the proportion of individuals receiving at least one dose of the vaccine, 2-dose vaccine completion rate, 3-dose vaccine completion rate among the immunocompromised, booster dose(s) completion rate, distribution of time gaps between the doses for the primary series, distribution of time gaps between the completion of the primary series and booster dose(s), demographics and health histories of recipients, overall and among the sub-cohorts of interest.
Country of study	United States
Authors	Renu Garg, PhD, MPH Safety Surveillance Research Scientist Pfizer, Inc. New York, NY Mei Sheng Duh, ScD, MPH Managing Principal and Chief Epidemiologist Analysis Group, Inc. Boston, MA

Marketing Authorization Holder(s)

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

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AEM	Adverse event monitoring
AESI	Adverse events of special interest
AI	Associate Investigator
AMI	Acute myocardial infarction
BEST	Biologics Effectiveness and Safety
BLA	Biologics License Application
BMI	Body mass index
CAD	Coronary artery disease
CBER	Center for Biologics Evaluation and Research
CCI	Charlson comorbidity index
CDC	Centers for Disease Control and Prevention
ChAdOx1	Chimpanzee adenovirus Oxford 1
CI	Confidence interval
CMA	Conditional Marketing Authorization
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPT	Current Procedural Terminology
CRA	Clinical Research Associate
CRFs	Case report forms
CVX	Vaccine administered code set
DHA	Defense Health Agency
DIC	Disseminated intravascular coagulation
DoD	Department of Defense
DSA	Data Sharing Agreement
DUA	Data Use Agreement
DVT	Deep vein thrombosis
ED	Emergency department
EMA	European Medicines Agency
EMR	Electronic medical records
EU	European Union
EUA	Emergency Use Authorization
EU PAS	European Union Post-Authorization Safety
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HA	Hemagglutinin
HBV	Hepatitis B virus
HCPCS	Healthcare Common Procedure Coding System

Abbreviation	Definition
HCV	Hepatitis C virus
HepA-HepB	Hepatitis A and hepatitis B vaccine
Hib	Hemophilus influenza b vaccine
HJF	Henry M. Jackson Foundation
HPV	Human papillomavirus
HR	Hazard ratio
HZV	Zoster (shingles) vaccine
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-9-PCS	International Classification of Diseases, Ninth Revision, Procedure Coding System
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System
IDN	Integrated delivery network
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IHD	Immunization Healthcare Division
IIV	Influenza virus vaccine
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IRB	Institutional Review Board
IRR	Incidence rate ratio
ITP	Immune thrombocytopenia
KD	Kawasaki disease
LAIV	Influenza virus vaccine, live
LDS	Limited Data Sets
LLR	Log-likelihood ratio
LNP	Lipid nanoparticle
LOINC	Logical Observation Identifiers Names and Codes
MaxSPRT	Maximized sequential probability ratio test
MDCK	Madin-Darby Canine Kidney
MenACWY	Meningococcal conjugate
MenB	Serogroup B meningococcal
MDR	MHS Data Repository
MHS	Military Health System
MIS-A	Multisystem inflammatory syndrome in adults
MIS-C	Multisystem inflammatory syndrome in children
mRNA	Messenger ribonucleic acid
MVX	Manufacturers of Vaccines
NDC	National Drug Code

Abbreviation	Definition
NI	Non-interventional
NIS	Non-interventional study
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds ratio
PASS	Post-Authorization Safety Study
PDTS	Pharmacy data transaction system
PFR	Pfizer
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
Pr	Probability
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
PS	Propensity score
RCA	Rapid cycle analysis
RIV4	Recombinant influenza vaccine, quadrivalent
RR	Relative risk
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	SAS Institute
SC	Study Coordinator
SCCS	Self-controlled case series
SD	Standard deviation
SPEAC	Safety Platform for Emergency vACcines
STEMI	ST-elevation myocardial infarction
Td	Diphtheria and tetanus
TDap	Diphtheria, tetanus and (acellular) pertussis
TM	Transverse myelitis
TRICARE	US Department of Defense purchased care
TTS	Thrombosis with thrombocytopenia syndrome
UK	United Kingdom
US	United States
VAED	Vaccine-associated enhanced disease
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
VTE	Venous thromboembolism
WHO	World Health Organization
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

3.1. Department of Defense (DoD) Research Staff

Research Role	Name, degree(s)	Job Title	Affiliation	Address
DoD Principal Investigator	Limone C. Collins, Jr., MD	Chief, Vaccine Safety & Evaluation Section	Defense Health Agency (DHA), Immunization Healthcare Division	4954 North Palmer Road, Building 19, 4th Floor, Bethesda, MD 20889-5630571-499-9467 limone.c.collins.civ@mail.mil
DoD Associate Investigator	Christina E. Spooner, MS	Team Lead, Clinical Investigations, Vaccine Safety and Evaluation Section	Defense Health Agency, Immunization Healthcare Division	858-361-4706 christina.e.spooner.civ@mail.mil
DoD Associate Investigator	Srihari Seshadri, MBBS, PhD, MPH	Team Lead, Regulatory Investigations Office, Vaccine Safety and Evaluation Section	Defense Health Agency, Immunization Healthcare Division	7700 Arlington Blvd Falls Church, VA 22042 703-681-5709 srihari.seshadri.civ@mail.mil
DoD Consultant	CAPT Rachel Lee, MC, USN	Service Chief, Allergy, Immunology and Immunizations	Walter Reed National Military Medical Center	8901 Wisconsin Ave Bethesda, MD 20889 (301) 400-2369 Rachel.u.lee.mil@mail.mil
DoD Study Coordinator	Traci J. Vactor, BS	Health System Specialist, Vaccine Safety and Evaluation Section	Defense Health Agency, Immunization Healthcare Division	7700 Arlington Blvd Falls Church, VA 22042 703-681-5705 traci.j.vactor.civ@mail.mil
Clinical Research Associate	To be announced	To be announced	Henry M. Jackson Foundation	To be announced

3.2. Pfizer Principal Investigator of the Protocol

Research Role	Name, degree(s)	Job Title	Affiliation	Address
Principal Investigator	Renu Garg, PhD, MPH	Safety Surveillance Research Scientist	Pfizer, Inc.	235 East 42nd Street, New York, NY 10017

3.3. Analysis Group Research Staff

Research Role	Name, degree(s)	Job Title	Affiliation	Address
Principal Investigator	Mei Sheng Duh, ScD, MPH	Managing Principal and Chief Epidemiologist Visiting Scientist, Department of Biostatistics	Analysis Group, Inc. Harvard T. H. Chan School of Public Health	111 Huntington Ave 14th Floor Boston, MA 02199 677 Huntington Ave Boston, MA 02115
Principal Investigator	Maral DerSarkissian, PhD	Vice President and Senior Epidemiologist Adjunct Assistant Professor	Analysis Group, Inc. Fielding School of Public Health, University of California, Los Angeles	333 South Hope Street 27th Floor Los Angeles, CA 90071 650 Charles E Young Drive South Los Angeles, CA 90095
Associate Investigator	Priyanka Bobbili, ScD, MS	Manager	Analysis Group, Inc.	111 Huntington Ave 14th Floor Boston, MA 02199 677 Huntington Ave Boston, MA 02115

3.4. Roles and Responsibilities

3.4.1. DoD

Principal Investigator (PI): The PI is responsible for overseeing the conduct of the study in a manner that is consistent with Federal regulations, the IRB-approved protocol, and DoD policies and procedures, as applicable. The PI will provide guidance on study design and methods, receive data from DoD's MHS Data Repository (MDR), coordinate and communicate, as needed, with the IRB and key personnel, and conduct chart reviews as needed.

Associate Investigator (AI): The AI(s) are responsible for administrative activities related to study objectives, and for coordinating with the PI on study issues as they arise. The AI(s) will conduct chart reviews (as needed), oversee statistical analysis, and will assist with drafting any presentations, reports, or manuscripts.

Study Coordinator (SC): The study coordinator is responsible for utilizing information data systems to manage research data with the highest possible degree of integrity. The coordinator will receive, manage and de-identify data per DHA policies and the study protocol, and provide data for review and analysis using methods and measures to ensure secure data management. The study coordinator works with the clinical research associate, project manager and other study personnel to ensure that security measures and methods are practiced from data collection to data analysis.
Clinical Research Associate: The CRA is responsible for de-identifying data for reports and completing the data abstraction form. This individual works on-site at DHA Immunization Healthcare Division (IHD).

3.4.2. Henry M. Jackson Foundation (HJF)

HJF will provide one full-time data manager who will work on-site at DHA IHD and serve as the liaison between DoD, Pfizer, and Analysis Group. This individual is responsible for performing project management and data management research activities for study execution/implementation. Specific responsibilities include, but are not limited to, the following: provide de-identified MHS data for research activities; coordinate the medical record review, abstract chart data, complete case report forms, and manage data collection; participate in the development of the statistical analysis plan (SAP), tables of results, figures, study reports, and presentations; and assist DoD and Analysis Group with data issues as needed.

3.4.3. Analysis Group

PIs: The PIs will design the study methodology and lead development of the study protocol, SAP, study reports, and provide general scientific oversight of the project. They will ensure the study is conducted consistently with the IRB-approved protocol and DoD policies and procedures, as applicable, review all study materials, and oversee analyses.

AI: The AI will assist in drafting the study protocol, SAP, and study reports, and will coordinate with the PIs on study issues as they arise. The AI will conduct and oversee statistical analysis and will assist with drafting any presentations, reports, or manuscripts.

3.4.4. Pfizer

PI: The PI will lead the development of the study protocol and SAP, and will oversee the study implementation, data analysis, and study reports. The PI will also ensure compliance with all regulatory requirements.

4. ABSTRACT

Title: Active Safety Surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense Population Following Emergency Use Authorization

Protocol Version: 3.0; Date of Protocol: 09 August 2022

Authors: Renu Garg, PhD, MPH, Pfizer, Inc.; Mei Sheng Duh, ScD, MPH, Analysis Group, Inc.

Rationale and background:

In March 2020, the World Health Organization (WHO) declared a global pandemic for the coronavirus disease 2019 (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified by public health officials in China in December 2019.[1] The COVID-19 pandemic presents an unprecedented public health crisis. As of 23 June 2022, over 86.6 million COVID-19 cases and 1 million deaths have been reported in the United States (US) alone.[2]

Pfizer and BioNTech have partnered to develop a novel messenger RiboNucleic Acid (mRNA) vaccine against SARS-CoV-2 for the prevention of COVID-19 (Candidate BNT162b2). To this end, Pfizer is conducting a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study among healthy individuals (NCT04368728). Safety and efficacy data were first available for individuals 16 years of age and older and demonstrated 95% efficacy of the vaccine in the prevention of COVID-19 after two doses.[3,4] The Food and Drug Administration (FDA) initially granted Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 Vaccine in individuals 16 years of age and older on 11 December 2020, and then approved the vaccine for this population on 23 August 2021.[5] FDA expanded the EUA on 10 May 2021 to include children 12-15 years of age, and on 29 October 2021 to include lower-dose vaccine administration for children 5-11 years of age. The EUA was further amended on 12 August 2021 to include the administration of a third primary series dose in certain immunocompromised individuals 12 years of age and older received at least 28 days following the primary series of two doses. On 22 September 2021 the EUA was amended to allow for use of a single booster dose at least 6 months after completion of the primary series in certain populations, which on 19 November 2021 was expanded to all individuals 18 years of age or older,[6] and on 09 December 2021 was further expanded to all individuals above 16 years of age.[5,7,8,9,10] On 02 January 2022 the EUA was further amended to expand the booster dose to individuals 12 to 15 years of age, to shorten the time between completion of the primary series and booster dose to at least 5 months, and to allow for a third primary series dose for immunocompromised children aged 5 to 11 years of age.[12] On 29 March 2022, the FDA authorized a second booster dose of the vaccine for older people and certain immunocompromised individuals. Specifically, individuals 50 years of age and older and individuals 12 years of age and older with certain kinds of immunocompromising conditions who received the first booster more than 4 months prior are eligible for a second booster.[5]

This post-authorization active surveillance study of the vaccine and safety events of interest is being proposed in the Department of Defense (DoD) population. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the European Medicines Agency (EMA).

Research question and objectives:

Research question: What are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]), overall and in sub-cohorts of interest, among individuals in the United States DoD Military Health System (MHS) (ie, DoD Uniformed members of the Departments of the Army, Navy, and Air Force, including the active and reserve components of each Military Department and the Coast Guard, as well as beneficiaries) vaccinated with the Pfizer-BioNTech COVID-19 Vaccine as compared to expected rates of those events?

Primary study objectives:

- To assess whether individuals identified in the DoD MHS experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 Vaccine, specifically in the following groups:
    - Individuals receiving at least one dose
    - Individuals receiving the primary series (ie, two doses for the general population and three doses for immunocompromised individuals)
    - Individuals receiving approved booster dose(s) of the Pfizer-BioNTech COVID-19 Vaccine (ie, a single booster dose or additional booster doses) after the primary series
- To assess whether sub-cohorts of interest (ie, pregnant women, immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 Vaccine, and individuals with prior SARS-CoV-2 infection) identified in the DoD MHS experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 Vaccine.

Secondary study objective:

- To characterize utilization patterns of the Pfizer-BioNTech COVID-19 Vaccine among the individuals identified within the DoD MHS, including estimating the proportion of individuals receiving at least one dose of the vaccine, 2-dose vaccine completion rate, 3-dose vaccine completion rate among the immunocompromised, booster dose(s) completion rate, distribution of time gaps between doses for the primary series, distribution of time gaps between completion of the primary series and booster dose(s), demographics and health histories of recipients, overall and among the sub-cohorts of interest.

Study design: This post-EUA active safety surveillance study will employ a retrospective, longitudinal, observational cohort study design. The observed safety event of interest rates in the cohort of individuals who received the Pfizer-BioNTech Vaccine between 11 December 2020 and 30 June 2023 will be compared to expected rates derived in the following control groups:

- Active comparator cohort: recipients of influenza vaccine in the DoD MHS during 2016/2017 through 2018/2019 influenza seasons.
- General population comparator cohort: a random sample of contemporary unvaccinated controls in the DoD MHS.
- Self-controls: cases who experience safety events of interest following vaccination using the self-controlled case series (SCCS) design to compare the risk interval following vaccination to post-vaccination non-risk intervals in the same individual.

Population: The study population will be DoD Uniformed members of the Departments of the Army, Navy, and Air Force (including the active and reserve components of each Military Department and the Coast Guard) and beneficiaries (ie, family members and retirees) in the DoD MHS. Individuals will be required to have continuous enrollment for at least 6 months prior to vaccination date or index date for unvaccinated controls (ie, baseline period). The length of this period may be revised such that a 1-year continuous enrollment period may be considered in the case that attrition of the study population is less than 15% when applying a 1-year continuous enrollment, or baseline, period. Sensitivity analyses will also be conducted where a 2-year continuous enrollment period is required for all individuals. Individuals who receive at least one dose of COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech as part of their initial primary dose series will be excluded. Individuals who receive a booster dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the primary series of Pfizer-BioNTech vaccine doses (ie, a heterologous booster) will be analyzed as a separate subgroup, but will be excluded from the main overall analysis.

Variables:

- *Exposure*: Record of at least one dose of the Pfizer-BioNTech COVID-19 Vaccine in the period from 11 December 2020 to 30 June 2023 based on Current Procedural Terminology (CPT) codes, National Drug Codes (NDCs), Manufacturers of Vaccines (MVX) and vaccine administered (CVX) codes, and immunization records.
- *Influenza vaccine comparator*: Record of at least one dose of seasonal influenza vaccine during prior influenza seasons 2016/2017–2018/2019 based on CPT codes, NDCs, CVX codes, and immunization records.
- *Contemporary unvaccinated comparator*: No record of any COVID-19 vaccine on or after 11 December 2020.
- *Outcomes*: Safety events of interest for active surveillance based on the Center for Biologics Evaluation and Research (CBER) FDA Biologics Effectiveness and Safety (BEST) protocol and Klein et al. (2021).[13,14] Pregnancy safety outcomes (ie, spontaneous abortion, stillbirth, preterm birth, major congenital malformations, and small size for gestational age) will also be assessed.

- *Key Covariates*: Baseline demographic (ie, age, sex, geographic region) and clinical characteristics (eg, history of comorbidities, lifestyle health factors, immunizations).[15]
- *Subgroups*: Pregnant women, immunocompromised individuals, children, elderly, individuals with specific comorbidities, individuals with prior SARS-CoV-2 infection, and different groups based on vaccination status (eg, those receiving only one dose of Pfizer-BioNTech COVID-19 Vaccine) will be identified.

Data source: The DoD MHS is a single payer system that provides medical coverage and pharmacy benefits for active duty and retired military members, and their families (beneficiaries). There are 9.6 million enrollees included in the MHS, of whom 14.6% are active duty, 16.7% are active duty family members, 2.4% are national guard and reserve members, 8.6% are family members of national guard and reserve members, and 57.4% are family members and retirees.[16,17] The DoD prioritized vaccine distribution to healthcare workers and emergency services personnel, personnel performing activities associated with critical national capabilities, deploying individuals, other critical and essential support, individuals at the highest risk for developing severe illness from COVID-19, and adults age 75 and older.[18]

Study size: The sample size achieved will depend on the number of recipients of Pfizer-BioNTech COVID-19 Vaccine identified within the DoD MHS during the study period of 11 December 2020 to 30 June 2023.

Data analysis: The cohort design will compare the incidence of the safety event of interest between a COVID-19 vaccine recipient cohort and the respective comparator cohorts as follows:

- Multivariate adjustment using Poisson regression will be conducted for the selected safety events of interest, comparing incidence rates of safety events in individuals receiving COVID-19 vaccine to active comparators.
- Risk of safety events among COVID-19 vaccinated individuals and contemporary unvaccinated controls will be compared using inverse probability of treatment weighting (IPTW) to ensure baseline comparability of the cohorts.
- SCCS design with a post-vaccination control time period will be conducted for the selected safety events of interest. The incidence of safety events occurring in the risk interval following vaccination will be compared with the incidence of safety events occurring during all other times post-vaccination in the same individual (eg, up to 183 days after the last dose of vaccination).
- Case validation/adjudication through medical records review may be conducted if a statistically significant finding of association with a relative risk (RR) greater than 3.0 between the Pfizer-BioNTech COVID-19 Vaccine and a safety event is found in one of the study designs listed above.

CDC recently investigated myocarditis/pericarditis following mRNA COVID-19 vaccinations.[19] To provide additional context to the investigation conducted by CDC, separate safety analyses will be prioritized and performed to assess the risk of myocarditis/pericarditis following Pfizer-BioNTech COVID-19 vaccination.

Baseline demographics and clinical characteristics for individuals receiving Pfizer-BioNTech COVID-19 Vaccine, individuals who received seasonal influenza vaccination, and contemporary unvaccinated controls will be summarized using descriptive statistics. Descriptive statistics will also be used to summarize vaccine utilization patterns. A multivariate Poisson regression analysis will be conducted to compare the incidence rates of the safety events of interest. Inverse probability treatment weighting (IPTW) will be used to ensure comparability between contemporary unvaccinated controls and the cohort receiving Pfizer-BioNTech COVID-19 Vaccine.

Various subgroup analyses will also be conducted, examining different age groups, immunocompromised individuals, pregnancy, individuals with specific comorbidities patients, those who only received one dose of the Pfizer-BioNTech COVID-19 Vaccine, those receiving the primary series (ie, two doses for the general population; three doses for immunocompromised individuals), those receiving booster dose(s) (ie, a single booster dose or additional booster doses after the primary series), and those with prior SARS-CoV-2 infection based on medical history or pre-vaccination serology.

Separate subgroup analyses among pregnant women will assess pregnancy safety outcomes (ie, spontaneous abortion, stillbirth, preterm birth, major congenital malformations, and small size for gestational age). In addition, separate, stratified analyses (eg, age, different risk intervals) will assess the risk of myocarditis/pericarditis following Pfizer-BioNTech COVID-19 vaccination.

Milestones:

- Registration in the EU PAS register: To be registered before the start of data collection.
- DoD Institutional Review Board (IRB) approval (estimated): August 2022.
- Start of data collection: 31 January 2023.
- Interim report: 30 September 2023.
- End of data collection: 31 July 2024.
- Final study report: 31 January 2025.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	29 October 2021	3, 4, 8, 9.6, 9.6.2.1, 10.1	Applied administrative changes: • Added DoD as a responsible party and explanation of roles and responsibilities • Shortened Abstract • Indicated study population as "DoD Uniformed members of the Departments of the Army, Navy, and Air Force as well as beneficiaries" • Added information on data sharing agreement requirement • Added record retention section for DoD • Added sections for administrative, physical, and technical safeguards	To adhere to DoD specifications for the DHA IRB application
		4, 7	Changed designation of PASS from US FDA commitment/EMA Category 3 commitment to voluntary study	As per Information Request from CBER received on 13 August 2021
		4, 6	Updated estimated date of DoD IRB approval	Date was updated based on current available information
		4, 6	Updated definition of end of data collection	To clarify definition of end of data collection
		4, 9.1, 9.1.2, 9.3.1	Changed time period for identification of active comparator, ie, individuals with influenza vaccine, from seasons 2014/2015–2018/2019 to seasons 2016/2017–2018/2019	To restrict to time periods during which ICD-10-CM codes are available for baseline and follow-up covariates by shortening the exposure period for the influenza vaccine comparator so that the earliest start date for the baseline period is 01 October 2015, ie, the date that the ICD-10-CM codes were implemented for medical visits; also expect that 3 seasons will yield a large number of controls for the active comparator cohort
		9.1, 9.1.4	Added section on Medical Records Review under Study Design	To emphasize that medical records review is a separate study component of the study design only for cases identified as having a safety event of interest
		9.2.2, 9.7.3	Removed reporting of counts of individuals who received a COVID-19	As requested by DoD

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			vaccine from a different manufacturer in addition to the Pfizer-BioNTech COVID-19 Vaccine	
		9.3.3	Changed following baseline characteristics: • DoD service area from state level in US to global geographic region • Removed HIV	Clarification from DoD on data availability/privacy issues
		9.5, 9.6	Updated frequency of data cuts to indicate that data will be obtained at 3 different time points instead of monthly data extractions	To facilitate feasibility of study
		4, 9.7.5	Added a prioritized safety and risk factor analysis for myocarditis/pericarditis	To include a separate analysis focused on myocarditis and pericarditis based on emerging evidence regarding this event in association with mRNA COVID-19 vaccines; analysis also requested in CBER Information Request received on 30 June 2021
		Annex 3: Tables A-1 and A-2	Removed ICD-9-CM codes from definitions	As requested by DoD
2	09 August 2022	2	Updated the list of abbreviations.	To align with the new list of safety events and methodology.
		3	Updated responsible parties.	To describe new staff, roles, and responsibilities.
		4, 7	Updated background with more recent COVID-19 statistics, as well as expansion of EUA to individuals aged 5 years and older and use of a booster dose.	To report updated data on COVID-19 cases as well as most up-to-date information on EUA.
		4, 6	Updated study milestone dates and reduced to a single interim report.	Dates were updated based on current available information. Removed additional interim reports, as data extraction for additional interim reports would be very close to data extraction for the Final Report, reflecting a short period of additional data.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		4, 8	Updated the primary objectives to include individuals receiving at least one dose, individuals receiving the primary series, and individuals receiving approved booster dose(s) of the Pfizer - BioNTech COVID-19 Vaccine after the primary series. Updated secondary study objectives to include additional approved dose(s) vaccine completion rate and distribution of time gaps between the completion of the primary series and booster dose(s).	To address the potential for additional currently approved doses (ie, an additional primary series dose or a single booster dose) of Pfizer-BioNTech COVID-19 Vaccine according to current CDC guidance, and to allow for analysis of additional dose(s) if approved.
		4, 9.1, 9.2.3, 9.7	Updated the study design and data analysis description to align with the cohort study design and removed framework for signal detection, signal evaluation, and signal verification. • Added SCCS Design for Comparison with Post-Vaccination Control Time Period • Updated the description of medical records review • Removed self-controlled risk interval design • Removed seasonality-adjusted cases-centered analysis • Removed end-of-season analysis	Rapid-cycle signal detection will no longer be conducted to facilitate feasibility of study, and signal evaluation methods are adapted to align with a cohort study design.
		9.1, 9.1.1, 9.2, 9.2.1, 9.5	Specification of start and end of study period.	Clarity on data collection period.
		4, 9.3.2, 9.7.5, 9.9	Included description of pregnancy safety outcomes and analyses.	To further describe the planned analyses in the subgroup of pregnant patients.
		4, 9.1.3	Included example of the period over which incidence of safety events will be studied.	To elaborate on the SCCS method.
		4, 9.2.1, 9.3.3, 9.9	Updated the baseline period and requirement of continuous enrollment from 1 year to 6 months.	To prevent high attrition in this group, which may include a large number of recruits to the different Military Departments.
		4, 9.2.2, 9.2.3, 9.7.2	Specified that individuals who receive a booster dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the	To ensure all individuals who receive the Pfizer-BioNTech

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			primary series of Pfizer-BioNTech vaccine doses will be analyzed as a separate subgroup.	COVID-19 Vaccine are captured in the study.
		4, 9.2.3, Annex 3	Updated age subgroups.	To incorporate age groups consistent with the EMA's preferences.
		4, 9.3.1	Removed subgroup cohorts A-D	To align with a cohort study design.
		4, 9.3.2, Annex 3	Updated the list of outcomes to focus on 23 outcomes of interest	To focus on 23 outcomes of interest, identified from the CBER FDA BEST protocol and Klein (2021).[13,14]
		4, 9.1.1	Revised description of active comparator design to indicate that multivariate Poisson regression analyses will be performed.	To align with methods relevant for the cohort study design.
		4, 9.1.2	Updated description of contemporary unvaccinated control design	Updated language to clarify that IPTW will be used to ensure comparability of cohorts, in line with the FDA BEST protocol.[13] Elaborated on period effects that could impact the appropriateness of the active comparator design.
		4, 9.1.4, 9.7.3.4	Indicated that medical records review will occur following statistically significant finding of RR >3.0 from either active comparator, contemporary unvaccinated, or SCCS designs.	To further clarify under what scenarios medical records review will be conducted.
		9.1.4	Updated information on data that will be provided to identify the relevant patient record for the medical records review.	To reflect information that will be required by DoD.
		9.1.4, 9.6.1, 9.7.3	Updated language regarding case validation/adjudication via medical records review.	To align with the use of a cohort study design as rapid-cycle signal analysis will no longer be conducted.
		4, 9.2.3	Included individuals receiving additional approved doses of the Pfizer-BioNTech COVID-19 Vaccine as a subgroup of interest.	To address analyses for additional currently approved doses (ie, a single booster dose) of Pfizer-BioNTech COVID-19 Vaccine according to current CDC guidance, and

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
				to allow for analysis of additional dose(s) if approved.
		9.3.1	Updated exposure of interest to describe identification of first, second, and third doses of the Pfizer-BioNTech COVID-19 Vaccine, and include HCPCS, NDC, CVX and MVX codes.	To address the potential for additional currently approved doses (ie, an additional primary series dose or a single booster dose) of Pfizer-BioNTech COVID-19 Vaccine according to current CDC guidance, and to allow for analysis of additional dose(s) if approved.
		9.3.1, Annex 3	Updated codes to identify Pfizer-BioNTech COVID-19 Vaccine.	To incorporate newly available Biologics License Application (BLA)-licensed NDC.
		9.3.2, Annex 3	Included multisystem inflammatory syndrome in children (MIS-C) in addition to multisystem inflammatory syndrome in adults (MIS-A).	To account for the potential of MIS-C observed in individuals <21 years of age who receive the Pfizer-BioNTech COVID-19 Vaccine.
		9.3.2	Updated the clean window for outcome algorithms to 6 months for all outcomes except anaphylaxis.	To prevent high attrition in this group, which may include a large number of recruits to the different Military Departments.
		9.3.2	Updated to use a post-vaccination control time period only (for self-controlled designs) rather than using both pre- and post-vaccination control periods.	To address CBER request to remove the pre-vaccination control interval as its comparison to the risk interval may introduce bias and reduce the probability of subsequent vaccination.
		9.4	Presented updated statistics in DoD database.	To update information on DoD enrollment.
		9.5	Updated the power calculations based on the cohort study methodology.	Used Poisson regression to align with a cohort study design.
		9.6.1	Revised description of case report form (CRF).	To reflect the process and responsibilities of the various parties in creation of the CRF.
		9.7.2	Updated vaccine utilization patterns to include additional approved dose(s).	To address the potential for a third dose (additional or booster dose) of Pfizer-

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
				BioNTech COVID-19 Vaccine according to current CDC guidance.
		9.7.3.2	Updated description of the comparison with contemporary unvaccinated controls to account for the potential for 3 Pfizer-BioNTech COVID-19 Vaccine doses.	To address the potential for additional currently approved doses (ie, an additional primary series dose or a single booster dose) of Pfizer-BioNTech COVID-19 Vaccine according to current CDC guidance, and to allow for analysis of future approved doses.
		9.7.3.4	Defined the trigger for adjudication by medical records review to be a RR greater than 3.0 for any analyses of the association of Pfizer-BioNTech COVID-19 Vaccine and safety events.	To clarify when medical records review will be performed.
		4, 9.7.4	Updated section on myocarditis/pericarditis safety analysis and risk factor analysis	To include a separate analysis focused on myocarditis/pericarditis based on emerging evidence regarding this event in association with mRNA COVID-19 vaccines.
		9.7.5.1	Added section to outline pregnancy outcome analyses.	To include analysis of outcomes among pregnant women.
		9.8	Updated method through which de-identified data will be accessed.	To align with DoD processes.
		9.9	Updated the strengths/limitations to adapt to the new methodology	To align with a cohort study design and pregnancy subgroup analyses.
		11	Included exception for reporting of adverse events in pregnant women	To address the addition of analyses among pregnant women.
		Annex 3	Tables have been re-ordered	To account for new reference orders within the body of the protocol.
		Annex 3; Table A-1	Included CVX codes for COVID-19 and influenza vaccines.	For identification of vaccines in the DoD MHS data.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Annex 3; Table A-2 and Table A-3	Added ICD-9-CM and ICD-9-PCS codes to definitions	To account for the possibility of ICD-9 codes in the DoD database
			Minor changes to text throughout document	Clarity

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	To be registered before the start of data collection
DoD IRB approval (estimated)	August 2022
Start of data collection (estimated)	31 January 2023[1]
Interim report	30 September 2023
End of data collection (estimated)	31 July 2024[2]
Final study report	31 January 2025

Abbreviations: DoD, Department of Defense; IRB, Institutional Review Board.
Notes:
[1] Start of data collection is the planned date for starting data extraction for the purposes of the primary analysis (eg, simple counts to inform sample size calculation are not relevant). The initial data analysis will include the Pfizer-BioNTech COVID-19 Vaccine exposure since 11 December 2020, the EUA approval date by the US FDA.
[2] End of data collection is the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

7. RATIONALE AND BACKGROUND

In March 2020, the World Health Organization (WHO) declared a global pandemic for the coronavirus disease 2019 (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified by public health officials in China in December 2019.[1] The COVID-19 pandemic presents an unprecedented public health crisis. As of 23 June 2022, over 86.6 million COVID-19 cases and 1 million deaths have been reported in the United States (US) alone.[2] To date, the incidence of COVID-19 has continued to rise, largely affecting the elderly and middle-aged individuals, with worsening clinical sequelae linked to increasing age and comorbid conditions (eg, cardiovascular disease, active cancer, obesity, diabetes and chronic lung disease).[20,21] SARS-CoV-2 is a well-adapted highly infectious human pathogen with a case fatality rate that ranges between 0.5% and 20%, based on the individual's age, gender, race, and comorbidites.[22]

Pfizer and BioNTech have partnered to develop a novel messenger RiboNucleic Acid (mRNA) vaccine against SARS-CoV-2 for the prevention of COVID-19 (Candidate BNT162b2). To this end, Pfizer is conducting a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study among healthy individuals (NCT04368728). In their Phase 1 trial evaluating safety and immunogenicity of two mRNA vaccine candidates (ie, BNT162b1, BNT162b2) at various dose levels, candidate BNT162b2 was selected for advancement to a pivotal Phase 2/3 safety and efficacy evaluation due to its milder systemic reactogenicity profile, especially in older adults.[23] The study was initiated in July 2020 with a target enrollment of 43,998 individuals.[24]

The US Food and Drug Administration (FDA) announced that regulatory emergency use authorization (EUA) as well as full approval of any COVID-19 vaccine will require demonstrating prevention of the disease or decrease in its severity in at least 50% of the individuals who receive it. In addition, data from Phase 3 studies are required to include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to assess the vaccine's benefit-risk profile, especially adverse events and cases of severe COVID-19 in vaccinated study patients.[25,26] The FDA reviewed the first available safety and efficacy data of the Phase 1/2/3 trial from 37,586 participants 16 years of age and older and did not identify any specific safety concerns. In addition, the analysis of available efficacy data from 36,523 participants 12 years of age and older without evidence of prior SARS-CoV-2 infection at least 7 days after receiving the second dose demonstrated 95% efficacy of the vaccine in the prevention of COVID-19 (as confirmed by 8 vs. 162 COVID-19 cases in the vaccine and placebo groups, respectively).[3,4]

Based on these safety and efficacy data, as well as a review of manufacturing information regarding product quality and consistency, the FDA determined that the known and potential benefits of the vaccine outweighed the known and potential risks for the prevention of COVID-19 in individuals 16 years of age and older.[4] FDA initially granted EUA for the Pfizer-BioNTech COVID-19 Vaccine in individuals 16 years of age and older on 11 December 2020, and then approved the vaccine for this population on 23 August 2021.[5] FDA expanded the EUA on 10 May 2021 to include children 12-15 years of age, and on 29 October 2021 to include lower-dose vaccine administration for children 5-11 years of age. The EUA was further amended on 12 August 2021 to include the administration of a third

primary series dose in certain immunocompromised individuals 12 years of age and older received at least 28 days following the primary series of two doses. On 22 September 2021 the EUA was amended to allow for use of a single booster dose at least 6 months after completion of the primary series in certain populations, which on 19 November 2021 was expanded to all individuals 18 years of age or older,[6] and on 09 December 2021 was further expanded to all individuals above 16 years of age.[5,7,8,9,10] On 02 January 2022 the EUA was further amended to expand the booster dose to individuals 12 to 15 years of age, to shorten the time between completion of the primary series and booster dose to at least 5 months, and to allow for a third primary series dose for immunocompromised children aged 5 to 11 years of age.[12] On 29 March 2022, the FDA expanded the EUA for a second booster dose of the vaccine for individuals 50 years of age and older and individuals 12 years of age and older with certain kinds of immunocompromising conditions who received the first booster more than 4 months previously.[5]

With respect to geographic regions other than the US, on 02 December 2020, the United Kingdom (UK) was the first country in the world to grant temporary authorization for emergency use of the Pfizer-BioNTech COVID-19 Vaccine.[27] On 21 December 2020, the European Medicines Agency (EMA) granted the Pfizer-BioNTech COVID-19 Vaccine a conditional marketing authorization (CMA) for use among individuals 16 years of age and older throughout all of the European Union's (EU) 27 member states.[28]

As required by the EUA, post-authorization observational studies using real-world data are needed in order to assess the association between Pfizer-BioNTech COVID-19 Vaccine and pre-determined safety events of interest (including deaths, hospitalizations, and severe COVID-19) among individuals administered the vaccine in both the population at large and in populations of interest (eg, pregnant women, immunocompromised individuals, elderly, and those with specific comorbidities).[4] Post-authorization safety evaluations are important for identifying rare, serious safety events of interest in larger populations that may not have been detected during clinical trials (either due to sample size or selected study populations) and for ensuring a favorable benefit-risk ratio post-trial.

This post-EUA active safety surveillance study is being proposed in the Department of Defense (DoD) population to monitor safety events of interest following administration of the Pfizer-BioNTech COVID-19 Vaccine. As part of phased allocation of COVID-19 vaccinations, all healthcare providers, emergency services, and public safety personnel within the DoD population will qualify to receive the COVID-19 vaccine.[29] This safety surveillance study will identify and evaluate potential safety events associated with the Pfizer-BioNTech COVID-19 Vaccine in the large-scale DoD Military Health System (MHS) healthcare database, which includes clinical data from both electronic medical records (EMR) and administrative claims. The observed rates of safety events of interest will be compared to rates derived from self-controls, active comparators, and contemporary unvaccinated controls. Part of the methodologies used in this study are constructed based on approaches outlined in the CBER FDA BEST inferential protocol.[13]

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

Research question: What are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]), overall and in sub-cohorts of interest, among individuals in the US DoD MHS (ie, DoD Uniformed members of the Departments of the Army, Navy, and Air Force, including the active and reserve components of each Military Department and the Coast Guard, as well as beneficiaries) vaccinated with the Pfizer-BioNTech COVID-19 Vaccine as compared to expected rates of those events?

Primary study objectives:

- To assess whether individuals identified in the DoD MHS experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 Vaccine, specifically in the following groups:
    - Individuals receiving at least one dose
    - Individuals receiving the primary series (ie, two doses for the general population and three doses for immunocompromised individuals)
    - Individuals receiving approved booster dose(s) of the Pfizer-BioNTech COVID-19 Vaccine (ie, a single booster dose or additional booster doses) after the primary series
- To assess whether sub-cohorts of interest (ie, pregnant women, immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 Vaccine, and individuals with prior SARS-CoV-2 infection) identified in the DoD MHS experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 Vaccine.

Secondary study objective:

- To characterize utilization patterns of the Pfizer-BioNTech COVID-19 Vaccine among the individuals identified within the DoD MHS, including estimating the proportion of individuals receiving at least one dose of the vaccine, 2-dose vaccine completion rate, 3-dose vaccine completion rate among the immunocompromised, booster dose(s) completion rate, distribution of time gaps between doses for the primary series, distribution of time gaps between the completion of the primary series and booster dose(s), demographics and health histories of recipients, overall and among the sub-cohorts of interest.

9. RESEARCH METHODS

9.1. Study Design

This post-EUA active safety surveillance study will be conducted among DoD Uniformed members of the Departments of the Army, Navy, and Air Force (including the active and reserve components of each Military Department and the Coast Guard) and beneficiaries (ie,

family members and retirees) in the DoD MHS during the study period of 11 December 2020 to 30 June 2023. The study will employ a retrospective, longitudinal, observational cohort study design including the following:

- Safety events of interest associated with Pfizer-BioNTech COVID-19 vaccinations will be compared to two comparator populations:

  (a) Active comparator cohort: recipients of influenza vaccine in the DoD MHS during 2016/2017 through 2018/2019 influenza seasons.[30]

  (b) General population comparator cohort: a random sample of contemporary unvaccinated matched controls in the DoD MHS who will be identified during the same time period as individuals receiving Pfizer-BioNTech COVID-19 Vaccine to reflect the background rate of current safety events of interest. This analysis will be conducted in order to evaluate risk as compared to a comparable general population of individuals who do not receive any COVID-19 vaccine in the DoD MHS and provide context for interpretation of excess risk identified.

- A SCCS design will also be used (ie, cases who experience safety events of interest following vaccination) to compare the risk interval following vaccination to post-vaccination non-risk intervals in the same individual (eg, up to 183 days after the last dose of vaccination).

- A medical records review will be conducted as a separate study component (see Section 9.7.3.4 "Case Validation/Adjudication via Medical Records Review" for further details) to validate/adjudicate cases, ie, individuals who experienced specific safety events of interest, as necessary. Adjudication will be implemented for safety events of interest where a statistically significant finding of association with RR greater than 3.0 between the Pfizer-BioNTech COVID-19 Vaccine and a safety event is found in either the active comparator design, contemporary unvaccinated control design, or SCCS design.

9.1.1. Active Comparator Design

In the active comparator design, the frequency of safety events of interest among individuals who received Pfizer-BioNTech COVID-19 Vaccine between 11 December 2020 and 30 June 2023 will be compared with the event frequency among individuals who received the seasonal influenza vaccination in three prior seasons, between 2016/2017 through 2018/2019. Data in peri-COVID time periods from January 2020 to present are excluded because of pandemic-associated underutilization of health resources and underreporting of medical events.[31]

The same risk interval length (eg, 42 days) will be used to evaluate safety events of interest following vaccination with the Pfizer-BioNTech COVID-19 Vaccine and to assess safety events of interest occurring after vaccination for seasonal influenza in prior seasons. Multivariate Poisson regression analyses will be conducted to adjust for relevant baseline

and/or clinical characteristics (eg, age, sex, race, CCI and/or specific comorbidities of interest, state, etc.).

9.1.2. Contemporary Unvaccinated Control Design

To address period effects that could impact the appropriateness of using the active comparator cohort (ie, potential trends in the occurrence of safety events of interest), multivariate adjusted analyses will also be performed comparing individuals who received the Pfizer-BioNTech COVID-19 Vaccine to individuals who were not vaccinated at that point in time. The unvaccinated controls will be assigned an index date matched to a corresponding Pfizer-BioNTech COVID-19 vaccinee's vaccination date; these individuals can later receive the Pfizer-BioNTech COVID-19 Vaccine and enter the vaccination group if all inclusion and exclusion criteria are met. To address possible selection bias due to health seeking behaviors, the unvaccinated controls will be randomly selected from a population of patients who have regular use of medical care, defined as at least one outpatient (excluding ED, as ED visits may not be considered regular) or inpatient encounters in the 6 months (or two encounters within 1 year, if a 1-year baseline period is used) prior to vaccination. The encounters must be separated by > 30 days (for inpatient, by admission date), and if a 1-year baseline is used, at least one must be within six months prior to index date. This approach is consistent with the CBER Surveillance Program, Draft Master Protocol Assessment of Risk of Safety Outcomes Following COVID-19 Vaccination.[13]

The index date for the contemporary unvaccinated controls will be selected based on the distribution of index dates in the vaccinated cohort. If vaccination is associated with a regular healthcare encounter (ie, an evaluation and management code or similar), the contemporary unvaccinated control will be required to have an encounter within 30 days of the assigned index date, and the date of encounter will be set as the index date to ensure comparability of covariate measurement.

9.1.3. SCCS Design for Comparison with Post-Vaccination Control Time Period

The SCCS design with post-vaccination control time period will include cases (ie, individuals vaccinated with the Pfizer-BioNTech COVID-19 Vaccine who experience safety events of interest following vaccination) to compare the incidence of safety events occurring in the risk interval following vaccination with the incidence of safety events occurring during all other times post-vaccination in the same individual (eg, until the earliest of 183 days after the last dose of vaccination, disenrollment, death, end of data availability).

9.1.4. Medical Records Review

In a second phase of the study (see 9.7.3.4 Case Validation/Adjudication via Medical Records Review for further details), cases (ie, individuals who experienced specific safety events of interest) will be validated/adjudicated as necessary. Adjudication will be implemented for safety events of interest where a statistically significant association with RR greater than 3.0 between the Pfizer-BioNTech COVID-19 Vaccine and a safety event is found, in either the active comparator design, contemporary unvaccinated control design, or SCCS design. Analysis Group and the HJF data manager will provide the DoD PI and the MHS Data Repository (MDR) Analytics and Evaluation Team with a line listing of cases for

medical records data abstraction. The listing will contain an identifier (eg, DoDID) and other relevant information that is sufficient to identify the correct electronic health record for each patient. Name and social security number will only be used to access the paper/electronic health records and will not be included on the case abstraction form (detailed in section 9.4.2 "Case Report Forms"). The listing will also include gender, age at vaccination with the COVID-19, race/ethnicity, branch of service, category of beneficiary, relative date of vaccination, site of immunization, the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code of the safety events of interest, the ICD-10-CM code description, the relative date of diagnosis, days lapse, pregnancy, concurrent vaccines, and type of record (inpatient or outpatient).

9.2. Setting

The exposed population will be kept as broad as possible in order to capture safety events of interest that occur among all individuals receiving Pfizer-BioNTech COVID-19 Vaccine between 11 December 2020 and 30 June 2023.

9.2.1. Inclusion Criteria

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

- Record of at least one dose of Pfizer-BioNTech COVID-19 Vaccine in the period of 11 December 2020 to 30 June 2023; or
- Record of at least one dose of seasonal influenza vaccine during prior influenza seasons, from 2016/2017 to 2018/2019 (applies to active comparators only); or
- No record of any COVID-19 vaccine (applies to the contemporary unvaccinated controls only); and
- At least 6 months of continuous enrollment, ie, the baseline period, prior to date of Pfizer-BioNTech COVID-19 vaccination, seasonal influenza vaccination, or matched index date for unvaccinated controls.
    - A 1-year continuous enrollment period will be considered in the case that the attrition is less than 15% when applying a 1-year baseline.
    - Sensitivity analyses will also be conducted where a 2-year continuous enrollment period is required for all individuals.

9.2.2. Exclusion criteria

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

- Individuals who receive at least one dose of COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech as part of their initial primary dose series will be excluded.

9.2.3. Subgroups

Safety surveillance may be conducted for subgroups of interest, including, but not limited to:

- Pregnant women;
- Immunocompromised individuals;
- Different age groups defined by age on the index date, eg, 0 to <6 months (if feasible), 6 months to <1 year (if feasible), 1 to <5 years, 5 to <12 years, 12 to <18 years, 18 to <25 years, 25 to <30 years, 30 to <40 years, 40 to <50 years, 50 to <65 years, ≥65 years;
- Individuals with specific comorbidities;
- Individuals with prior SARS-CoV-2 infection based on medical history or pre-vaccination serology;
- Individuals who received only one dose of Pfizer-BioNTech COVID-19 Vaccine;
- Individuals receiving the primary series (ie, two doses for the general population and three doses for those who are immunocompromised);
- Individuals receiving approved booster dose(s) of the Pfizer-BioNTech COVID-19 Vaccine (ie, a single booster dose or additional booster doses) after the primary series;
- Individuals who receive a booster dose of a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech following completion of the primary series of Pfizer-BioNTech Vaccine doses (ie, a heterologous booster) will be excluded from main overall analyses, but will be analyzed as a separate subgroup. Safety events identified will not necessarily be attributed to the Pfizer-BioNTech vaccine since these occur following vaccination with a booster from a different manufacturer.

Additional subgroups of interest will be assessed as additional information becomes available from ongoing clinical trials, Vaccine Adverse Event Reporting System (VAERS), and other sources that will inform the Pfizer-BioNTech COVID-19 Vaccine safety profile.

9.3. Variables

9.3.1. Exposure of Interest

Administration of Pfizer-BioNTech COVID-19 Vaccine post-EUA approval will be identified based on the following (see Annex 3 Table A-1 for additional details):

- Current Procedural Terminology (CPT) code 91300, 91305, and associated vaccine administration Healthcare Common Procedure Coding System (HCPCS) codes: 0001A, 0002A, 0003A, 0004A, 0051A, 005A, 0053A, 0054A;[32,33] OR

- 10 and 11-digit National Drug Codes (NDCs) 59267-1000-1, 59267-1000-01, 59627-1000-2, 59627-1000-02, 59627-1000-3, 59627-1000-03, 59627-1025-1, 59627-1025-01;
    - Biologics License Application (BLA)-licensed NDC codes[a] 0069-1000-01, 0069-1000-02, 00069-1000-03, 0069-2025-01, 0069-2025-10, 0069-2025-25; OR

- Vaccine administered (CVX) codes 208, 217, 218, 219 and Manufacturers of Vaccines (MVX) code PFR; OR

- Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (ie, Pfizer), lot number, injection site, and date(s) of immunization.[34]

Relevant codes will be reviewed and amended if new codes are added.

Although certain codes for the Pfizer-BioNTech COVID-19 Vaccine may specify primary series or booster dose, this is not specified for all codes considered, and therefore the relative date and order of vaccines received is used to determine the specific dose (first, second, third, and booster dose). Individuals' first record of Pfizer-BioNTech COVID-19 vaccination will be categorized as the first dose. Among individuals with only two Pfizer-BioNTech COVID-19 vaccination records, the second vaccination record will be categorized as the second dose. Among individuals with more than two records of Pfizer-BioNTech COVID-19 vaccination, the vaccination date closest to 21 days after the first vaccination dose will be categorized as the second dose. Among individuals with only one Pfizer-BioNTech COVID-19 vaccination record after their second dose, that vaccination record will be categorized as the third dose if the dose was given closer to 28 days after the second dose (among immunocompromised individuals only) and as the booster dose if the dose was given closer to 180 days after the second dose. Among individuals with two or more records of Pfizer-BioNTech COVID-19 vaccination after their second dose, the vaccination date closest to 28 days after the second vaccination dose will be categorized as the third dose (among immunocompromised individuals only), and the vaccination date closest to 180 days after the second vaccination dose will be categorized as the booster dose.

Person-time at-risk will be analyzed separately for exposure to the first dose only, overlapping exposure to first and second doses, exposure to second dose only, overlapping exposure to second and third/booster doses, and exposure to third/booster dose only.

Administration of the seasonal influenza vaccine during 2016/2017 through 2018/2019 influenza seasons will be identified based on the following:

- CPT codes (Annex 3 Table A-1); OR

[a] BLA-licensed NDC for the Pfizer-BioNTech COVID-19 Vaccine are not currently being produced while EUA product is available, however they are included here for when they become active.

- 10 and 11-digit NDCs (Annex 3 Table A-1); OR
- CVX codes (Annex 3 Table A-1); OR
- Immunization records that contain data on vaccine code descriptor, vaccine manufacturer, lot number, injection site, and date(s) of immunization.

9.3.2. Outcomes

9.3.2.1. Safety Events of Interest

The safety events of interest for active surveillance were identified based on the list of adverse events of special interest from the CBER FDA BEST protocol and Klein et al. (2021).[13,14] The safety events of interest are outlined in Table 1. Endpoints of special interest, as noted by CDC's Advisory Committee on Immunization Practices (ACIP), are denoted in the footnote.[35] The list of safety events of interest may be revised over the course of the study, and if unanticipated potential safety events of interest are identified during the course of surveillance, they will be added to the list and included in the analyses. See Annex 3 Table A-2 for the operational definitions of the outcome variables based on ICD-9-CM diagnosis codes, ICD-10-CM diagnosis codes and Logical Observation Identifiers Names and Codes (LOINC) laboratory codes, which may be refined as the study progresses based on additional available information and the published literature (eg, frequency of ICD-10 codes). Outpatient (including emergency department) and/or inpatient settings will be used to identify safety events of interest, depending on the type of event. The specific encounter setting considered for each safety event of interest is summarized in Table 1. Any record of death will be captured, regardless of whether the individual died in a healthcare or non-healthcare setting.

Table 1. Safety events of interest, including outcome algorithms and risk intervals

Safety Event of Interest[a]	Setting (Inpatient [IP], Outpatient [OP])	Clean Window[g]	Risk Interval (Days)
Bell's palsy[30,36]	IP or OP[37]	6 months	1-42
Convulsion/seizures[b,30]	IP or OP[30]	6 months	1-90
Encephalitis/ encephalomyelitis[30]	IP only[37]	6 months	1-42
GBS[b,30,36]	IP, primary position only[37]	6 months	1-42
TM[c]	IP only[37]	6 months	1-42
Anaphylaxis[30,36]	IP or OP[37]	1 month	0-1
ITP[b]	IP or OP[37]	6 months	1-42
KD[b,38]	IP only[38]	6 months	1-28
MIS-A/MIS-C[b,d]	IP or OP[37]	6 months	1-42
AMI[b,e]	IP only[37]	6 months	1-28

Table 1. Safety events of interest, including outcome algorithms and risk intervals

Safety Event of Interest[a]	Setting (Inpatient [IP], Outpatient [OP])	Clean Window[g]	Risk Interval (Days)
Myocarditis[b,30,36]	IP or OP[37]	6 months	1-42
Pericarditis[b,30,36]	IP or OP[37]	6 months	1-42
Acute respiratory distress syndrome	IP or OP[37]	6 months	1-42
Cerebral venous sinus thrombosis	IP or OP[37]	6 months	1-28
DVT[f]	IP or OP[37]	6 months	1-28
DIC[b,f]	IP only[37]	6 months	1-28
Hemorrhagic stroke[b,30]	IP only[37]	6 months	1-28
Non-hemorrhagic stroke[b,30]	IP only[37]	6 months	1-28
Pulmonary embolism[e]	IP or OP[37]	6 months	1-28
Thrombosis with thrombocytopenia syndrome[b,39]	IP or OP[37]	6 months	1-42
Appendicitis[40]	IP only[37]	6 months	1-42
Death[b]	IP or OP[37]	6 months	0-42
Narcolepsy[b,c]	IP or OP[37]	6 months	1-42

Abbreviations: AMI, acute myocardial infarction; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; GBS, Guillain-Barré syndrome; ITP, immune thrombocytopenia; KD, Kawasaki disease; MIS-A, multisystem inflammatory syndrome in adults; MIS-C, multisystem inflammatory syndrome in children; TM, transverse myelitis.

a. Safety events of interest are based on the CBER FDA BEST protocol and Klein et al. (2021).[13,14]
b. Endpoints of special interest, as noted by CDC's Advisory Committee on Immunization Practices (ACIP).
c. Published risk intervals for demyelinating diseases and cranial disorders were applied to TM and narcolepsy.
d. As severe COVID-19 ranges from severe pneumonia, acute respiratory distress syndrome, and multisystem organ failure/MIS-A, a 1-42 day risk interval was applied in order to capture the 14-day incubation period of the disease and 4-5 day period from exposure to symptom onset. MIS-A and MIS-C cannot be analyzed in the active comparator design as historical controls would not meet the criteria of having a COVID-19 diagnosis.
e. Published risk intervals for myocarditis and pericarditis were applied to AMI.
f. Similar risk intervals were applied to all cardiovascular and hematological disorders characterized by damage to the blood vessels and/or arteries and clotting (ie, DVT, pulmonary embolism, DIC).
g. A 1-year clean window may be considered in the case that sample size attrition is less than 15% when applying this condition. Sensitivity analyses will be conducted with a 2-year clean window required for all individuals.

The risk intervals selected for the analysis for each safety event of interest are based on biological plausibility and precedents in the published literature. A safety event of interest will be counted if it can be assigned to 1) the risk interval following Pfizer-BioNTech COVID-19 vaccination, 2) the post-vaccination control interval (SCCS design), 3) the risk interval for the active comparators receiving seasonal influenza vaccine, and 4) risk interval for the contemporary unvaccinated controls. Events outside the intervals will not be counted.

Only the individual's first instance of a safety event of interest following a specified clean window (ie, the occurrence-free baseline period used to define incident outcomes during which individuals enter the study cohort only if the safety event of interest did not occur during this period) will be included; this means that if a safety event of interest is identified but diagnosis codes (or laboratory values in the case of select safety events of interest) corresponding to the safety event of interest are also observed during the clean window, it will not be counted. This approach is consistent with the FDA's COVID-19 Vaccine Safety Surveillance Project.[37] The pre-specified clean window of 6 months (or 1 year, if sample size allows) will be applied to all safety events of interest except for anaphylaxis (for which a 1-month clean window will be applied), in order to rule out pre-existing events. By way of example, safety events of interest for SCCS can be considered in the following ways:

- If a safety event of interest occurs in the individual's risk interval and there are no other diagnosis codes for the same safety event of interest in the clean window, the safety event of interest should be assigned to the risk interval.
    - If an outpatient safety event of interest occurs in the clean window and an inpatient occurrence for the same type of safety event of interest occurs in the risk interval, the inpatient occurrence will be counted in order to capture event exacerbation.
    - If a safety event of interest occurs in the risk interval and another diagnosis code for the same safety event of interest is identified during the post-vaccination control interval, then the safety event of interest will only be assigned to the risk interval.
    - If a safety event of interest occurs in the post-vaccination control interval and there are no other diagnoses for the same safety event of interest in the risk interval and clean window, then the safety event of interest will be assigned to the post-vaccination control interval.

The risk intervals for outcome evaluation for the active comparators (ie, individuals who received seasonal influenza vaccination) and contemporary unvaccinated controls (ie, individuals who did not receive the Pfizer-BioNTech COVID-19 Vaccine) will be the same as for the individuals who received Pfizer-BioNTech COVID-19 Vaccine.

However, it is possible that some safety events of interest do not have a precise time interval from which to evaluate risk, for example if biological plausibility is unknown or the diagnostic time window is more delayed than anticipated. In these cases, misspecification of the risk interval could result in misclassification and introduce bias, often toward the null. For instance, the assumption of a longer risk interval than is true may result in "washing out" detection of the safety event, and an erroneously short risk interval may similarly result in underestimation of effect when using post-vaccination time intervals for self-control. To address this, sensitivity analyses may be conducted with varying risk intervals (longer as well as shorter) in order to increase the likelihood that the safety risk is detected accurately.

9.3.2.2. Pregnancy outcomes

Pregnancy outcomes are listed separately in Table 2 below and will be assessed among pregnant women only. The eligible populations and exposure windows for analyses in pregnant women differ by safety event as described in the table. Only Pfizer-BioNTech COVID-19 Vaccine doses administered during the exposure windows will be considered for inclusion in the exposed cohorts. Additional details on pregnancy analyses are provided in Section 9.7.5.1.

Table 2. Pregnancy safety outcomes of interest, including eligible populations and exposure windows

Event	Definition	Eligible population	Exposure window
Spontaneous abortion	Spontaneous pregnancy loss before 20 completed weeks gestation	All eligible pregnancies	4 weeks before estimated pregnancy start to end of pregnancy or 19-6/7 weeks of gestation, whichever is earlier
Stillbirth	Fetal deaths at or after 20 completed weeks gestation	Pregnancies with gestational age ≥ 20 weeks	4 weeks before estimated pregnancy start to end of pregnancy
Preterm birth	Live birth before 37 completed weeks gestation	Live deliveries	4 weeks before estimated pregnancy start to end of pregnancy or 36-6/7 weeks of gestation, whichever is earlier
Major congenital malformations	Identified in live-born infants using code lists from the National Birth Defects Prevention Network,[41] 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.[42]	Live deliveries for which linkage to infant data is available	4 weeks before estimated pregnancy start to 13-6/7 weeks of gestation (end of first trimester)

Table 2. Pregnancy safety outcomes of interest, including eligible populations and exposure windows

Event	Definition	Eligible population	Exposure window
Small size for gestational age	Less than 10th percentile of weight for gestational age, based on diagnosis codes for small size for gestational age or combinations of diagnosis codes for birthweight (in categories) and gestational age (in categories)	Live deliveries for which linkage to infant data is available	4 weeks before estimated pregnancy start to end of pregnancy

9.3.3. Baseline Characteristics

The following data elements regarding baseline demographic and clinical characteristics will be assessed based on a 6 month baseline period (or 1 year, if sample size allows) prior to the date of vaccination with Pfizer-BioNTech COVID-19 Vaccine, date of seasonal influenza vaccination for active comparators, and assigned index date for contemporary unvaccinated controls. All diagnoses, procedures, and medications will be identified by the ICD-9-CM diagnosis codes, ICD-9-PCS (procedure coding system) codes, ICD-10-CM diagnosis codes, ICD-10-PCS codes, CPT codes, and LOINC laboratory results, or HCPCS procedure codes, and generic drug names, as appropriate (Annex 3 Table A-3). The following demographic and clinical characteristics will be assessed:

Demographics:

- Age
- Sex
- Geographic region of DoD service area in the US, ie, South, Midwest, West, Northeast, other (eg, Puerto Rico), and unknown
- Sponsor service (eg, Air Force, Army, Coast Guard, Marine Corps, Navy)
- Category of beneficiary (eg, active duty, retiree, active guard/reserve, dependent)

Clinical characteristics:

- Smoking status
- Body mass index (BMI)
- History of anaphylaxis/allergic reactions
- Previous anaphylaxis of vaccine component
- History of hospitalizations
- Pregnancy
- Charlson comorbidity index (CCI)
- Selected comorbidities
    - Autoimmune disease
    - Asthma
    - Bleeding diathesis or condition associated with prolonged bleeding
    - Cancer
    - Cardiovascular conditions
    - Chronic kidney disease/dialysis
    - Chronic obstructive pulmonary disease (COPD)/interstitial lung disease
    - Diabetes mellitus
    - Down syndrome
    - Sickle cell disease
    - Hepatitis B virus (HBV)
    - Hepatitis C virus (HCV)
    - Hyperlipidemia
    - Hypertension
    - Liver disease

  - Neurological disease
  - Other immune deficiencies
  - Solid organ transplant
  - Venous thromboembolism (VTE)
- Concurrent immunizations
  - Seasonal influenza vaccine
  - Tetanus diphtheria and pertussis (Tdap or Td)
  - Chickenpox (varicella)
  - Shingles (herpes zoster recombinant and/or live)
  - Human papillomavirus (HPV)
  - Pneumococcal conjugate
  - Pneumococcal polysaccharide
  - Hepatitis A
  - Hepatitis B
  - Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB)
  - Haemophilus influenza type b

9.4. Data Source

This study will be conducted in the DoD MHS database. The MHS is a single payer system that provides medical coverage and pharmacy benefits for active duty and retired military members, and their families (beneficiaries). Veterans who receive medical coverage through the Veterans Health Administration are not included. There are 9.6 million enrollees included in the MHS, of whom 1.4 million (14.6%) are active duty, 1.6 million (16.7%) are active duty family members, 230,000 (2.4%) are national guard and reserve members, 830,000 (8.6%) are family members of national guard and reserve members, and 5.5 (57.4%) million are family members and retirees.[16,17] The DoD also includes 64 hospitals, hundreds of clinics, 25,000 uniformed physicians, and 400,000 community network providers. The population within the MHS is demographically representative of the US overall, with slight over-representation of persons >65 years of age (20.1% in DoD MHS vs. 12.9% in the general US population).[43] The gender distribution is approximately 49% female and 51% male.

The DoD MHS provides care in two ways: direct and purchased care. Direct care is provided to beneficiaries within a global network of military hospitals and clinics. MHS uses an EMR that captures administrative and encounter information, as well as a detailed clinical record. Purchased care (through TRICARE, the DoD health insurance) is provided to beneficiaries by civilian providers who are paid via fee-for-service reimbursements or managed care contracts. MHS collects and verifies encounter and claims records for each service.[44]

All healthcare encounters, whether received through direct or purchased care, are archived, validated, and normalized within a central MDR. For those receiving direct care, all medical services are captured, as well as clinical details, diagnostic and laboratory test ordered, and test results. Information is collected at the point of care and available almost immediately. Direct care accounts for approximately 40% of care within the MHS, though this proportion may change over time.[45] The MHS purchased care data include records of physician services, hospital care (inpatient and outpatient), emergency room visits, home health, hospice, and

other services. Claims for laboratory and diagnostic testing are collected; however, unlike direct care, the results of these tests are not captured.

Prescription data from both direct and purchased care are captured within MHS's electronic medication ordering system called the Pharmacy Data Transaction System (PDTS). Dispensing details and physician-administered medication events are coded electronically and include the prescribed drug name and NDCs, dose, therapeutic class, quantity, refills, and fill location. Vaccination records include data on the vaccine code descriptor, vaccine manufacturer, lot number, injection site, and date(s) of immunization.

Each individual is assigned a unique identification number by the DoD Study Coordinator to allow for longitudinal follow-up to provide comprehensive information about the individual and his/her medical encounters. The MHS is an appropriate data source to evaluate the safety of the Pfizer-BioNTech COVID-19 Vaccine, as the vaccine was distributed through government facilities (including MHS facilities) as part of initial distribution, and analysis of DoD data will provide data on the safety of the vaccine. The DoD prioritized vaccine distribution to healthcare workers and emergency services personnel, personnel performing activities associated with critical national capabilities, deploying individuals, other critical and essential support, individuals at the highest risk for developing severe illness from COVID-19, and adults age 75 and older.[18] Specifically, as part of Phase 1a, all healthcare providers, emergency services, and public safety personnel within the DoD population will qualify for the vaccine.[29] Phase 1b.1 and 1b.2 will include those considered critical for national capabilities and individuals preparing to deploy outside of the US, respectively.[29]

9.5. Study Size

The sample size achieved will depend on the number of individuals administered the Pfizer-BioNTech COVID-19 Vaccine identified within the DoD MHS during the study period of 11 December 2020 to 30 June 2023, which will increase over time as the data will be obtained at 2 different time points to add newly vaccinated individuals and matched controls.

9.5.1. Power

Table 3 illustrates the estimated sample size required for the Poisson regression (comprising individuals receiving Pfizer-BioNTech COVID-19 Vaccine to influenza vaccine active comparators and contemporary unvaccinated controls) dependent on varying expected background rates of events in the population, and provides an overview of the sample size required to detect a threefold increase in the incidence rate ratio (IRR) with a power of 80% and an alpha level of 0.05.[46]

Power of ≥ 80% is typically desirable in drug safety research. Usually the FDA views a RR of >3 as meaningful, so this has been used for power calculations.[47] As an example, as shown in Table 3, the analyses would have sufficient power (80.0%) to detect an increased risk of safety events of interest associated with the Pfizer-BioNTech COVID-19 Vaccine by 3 fold with a baseline rate of 0.0001 events per person-year (or 10 events per 100,000 person-years) with a sample size of 1,567,268 (eg, 783,634 in the Pfizer-BioNTech COVID-19 vaccinated cohort, and 783,634 in the control cohort).

Table 3. Sample Size Calculations for the Poisson Regression[46]

Background Rate (Events per 100,000 Person-Years)	Incidence Rate Ratio	Sample size (N)
1	1.5	123,203,226
5	1.5	24,640,646
10	1.5	12,320,323
50	1.5	2,464,065
100	1.5	1,232,033
150	1.5	821,355
1	2.5	22,859,317
5	2.5	4,571,864
10	2.5	2,285,932
50	2.5	457,187
100	2.5	228,594
150	2.5	152,396
1	2.0	40,791,516
5	2.0	8,158,304
10	2.0	4,079,152
50	2.0	815,831
100	2.0	407,916
150	2.0	271,944
1	3.0	15,672,667
5	3.0	3,134,536
10	3.0	1,567,268
50	3.0	313,454
100	3.0	156,727
150	3.0	104,485

Notes:
The power calculations are based on assuming one sided α=0.05, a power of 80%, and a mean risk interval of 42 days. In Klein et al., background rates of safety events of interest ranged from 0.27 per 100,000 person-years (transverse myelitis) to 178 per 100,000 person-years (ischemic stroke).[14]

9.6. Data Management

Data for this study are stored and extracted from the DoD MDR database (previously described in Section 9.3.3) that contain information about demographics, vaccinations, procedures, diagnoses, and death. Data will be obtained at 2 different time points to add

newly vaccinated individuals and matched controls. The data will also be refreshed for individuals identified in the previous data extractions to identify receipt of additional doses of the Pfizer-BioNTech COVID-19 Vaccine.

Defense Health Agency (DHA)-managed data includes de-identified data, Personally Identifiable Information (PII), Protected Health Information (PHI), and/or Limited Data Sets (LDS). A Data Sharing Agreement (DSA) or Data Use Agreement (DUA) is required for work and/or research involving contractors (eg, non-government or non-military personnel) that will be handling certain types of data that are managed by the DHA. DSAs are administrative controls used by the DHA to document that the requested use of data managed by DHA is in compliance with Federal law and implementing DoD policies. A DSA is also required for government-only research.

9.6.1. Case Report Forms

For case validation/adjudication via the medical records review study component, which will be conducted as a separate second phase of the study, a CRF will be used to abstract data from paper and/or EMRs, as necessary, for cases identified in the safety analyses (see 9.7.3.4 for further details). CRFs will include the encrypted study ID and will not contain any identifiable information. The completed original CRFs 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 and DoD. The CRF will consist of two parts: (1) a chart review CRF that will be populated based on a direct extraction of relevant information from the DoD MDR and/or patient charts by the HJF data manager (and data abstractors as needed) for review by the adjudicators; (2) an adjudication page that will be completed by an adjudicator after reviewing data in the completed CRFs. HJF and DoD shall ensure that the CRFs are securely stored on DoD servers in an encrypted electronic and/or paper] form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

Data abstractors have ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs 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 CRFs must be signed by the responsible party abstracting medical records and/or adjudicating the endpoints to attest that the data contained on the forms are true and accurate based on their review of the data. Any corrections to entries made in the CRFs 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 CRFs must match those charts.

9.6.2. Record Retention

9.6.2.1. DoD

To enable inspections and/or audits from Pfizer, representatives of the IRB, the FDA, and/or other regulatory agencies, the Immunization Healthcare Division must maintain records, including MDR reports, CRFs, clinical protocols, and any amendments. All records must be retained for a period of at least 10 years following completion of the study. Immunization Healthcare Division and Pfizer will agree upon any disposing of or the transferring of any records before the end of the retention period.

9.6.2.2. Analysis Group

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Analysis Group agrees to keep all study-related records, which includes study documents and deliverables such as the protocol, SAP, aggregated results tables, SAS programming files, and study report. The records should be retained by Analysis Group according to local regulations or as specified in the vendor contract, whichever is longer. Analysis Group must ensure that the records continue to be stored securely for so long as they are retained.

If Analysis Group 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 Analysis Group and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

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

9.7. Data Analysis

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

Data analyses will be conducted using SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC) or R Version 3.5.3 or its latest version (R Core Team, Vienna, Austria).

9.7.1. Baseline Characteristics

Baseline demographics and clinical characteristics for individuals receiving Pfizer-BioNTech COVID-19 Vaccine, individuals who received seasonal influenza vaccination, and contemporary unvaccinated controls will be summarized using descriptive statistics, consisting of the mean and standard deviation (SD) and median (interquartile range [IQR]) values for continuous variables and frequency distributions for categorical variables.

Standardized differences will be calculated between individuals who received the Pfizer-BioNTech COVID-19 Vaccine and with active comparators who received seasonal influenza vaccination. In addition, standardized differences will be calculated between contemporary unvaccinated controls and individuals receiving the Pfizer-BioNTech COVID-19 Vaccine. Standardized differences <10% will indicate that the characteristics between recipients of the Pfizer-BioNTech COVID-19 Vaccine and the respective comparator cohort are balanced.

9.7.2. Vaccine Utilization Patterns

Descriptive statistics will also be used to summarize vaccine utilization patterns, including proportion of individuals receiving at least one dose of vaccine, 2-dose vaccine completion rate, 3-dose vaccine completion rate among the immunocompromised, booster dose(s) vaccine completion rate, distribution of time gaps between doses for the primary series, distribution of time gaps between completion of the primary series and booster dose(s), and care setting where immunization was received (eg, outpatient clinic, pharmacy, inpatient ward). Frequencies of individuals who completed the primary series of two Pfizer-BioNTech vaccine doses followed by a dose of a COVID-19 vaccine from a different manufacturer (ie, a heterologous booster) will be summarized.

9.7.3. Safety Analyses

Several analyses corresponding to the designs discussed previously will be conducted to detect safety events associated with Pfizer-BioNTech COVID-19 Vaccine. Analyses will be conducted among all individuals receiving the vaccine, along with sub-cohorts receiving only one dose, the full primary series, or additional booster doses.

The observed safety event of interest rates will be compared to rates observed in the following control groups:

- Active comparator: recipients of seasonal influenza vaccine in the DoD MHS during 2016/2017 through 2018/2019 influenza seasons.
- General population comparator: a random sample of contemporary unvaccinated controls in the DoD MHS.
- Self-controls: cases who experience safety events of interest following vaccination using the SCCS design to compare the risk interval following vaccination to post-vaccination non-risk intervals in the same individual.

9.7.3.1. Multivariate Adjustment using Poisson Regression

A multivariate Poisson regression analysis will be conducted for the selected safety events of interest to compare the incidence rates of the safety events of interest occurring within the risk intervals for individuals receiving Pfizer-BioNTech COVID-19 Vaccine vs. active comparators receiving seasonal influenza vaccine in 2016/2017 and 2018/2019. The predictor would be whether the individual had received the Pfizer-BioNTech COVID-19 Vaccine or had received the influenza vaccine during historical seasons. Analyses will be adjusted for relevant baseline and/or clinical characteristics (eg, age, sex, race, CCI and/or specific comorbidities of interest, state, etc.).[30]

Safety analyses for the two safety events (ie, MIS-A/MIS-C) that require COVID-19 diagnosis cannot be performed using a comparison to historical influenza vaccines as historical controls would not meet the criteria of having a COVID-19 diagnosis. Therefore, these safety events will only be included in analyses using comparison with contemporary unvaccinated controls and SCCS design.

9.7.3.2. Comparison with Contemporary Unvaccinated Controls

Inverse probability treatment weighting (IPTW) will be used to ensure baseline comparability between the Pfizer-BioNTech COVID-19 vaccinated cohort and contemporary unvaccinated controls. The IPTW approach uses weights to create a "pseudo-population" in which the distribution of covariates is, on average, the same in each cohort.[48] IPTW is defined as the inverse of the individual's probability of receiving the first dose of Pfizer-BioNTech COVID-19 Vaccine, conditional on their demographic and clinical characteristics as of the index date. This approach assumes that an individual's probability of receiving Pfizer-BioNTech COVID-19 vaccination is constant for the first and second doses of the vaccine, and third dose if applicable, as the weight will be applied for all doses.[49] Initial IPTW will be calculated as 1 / propensity score (PS) for individuals who received the Pfizer-BioNTech COVID-19 Vaccine and 1/ (1-PS) for individuals with no record of COVID-19 vaccination. To avoid extreme weights, each individual's weight will be stabilized by the marginal probability of being in their assigned cohort. Therefore, the stabilized weights will be calculated as the probability (Pr) of the individual's exposure divided by the denominator noted above: Pr (Pfizer-BioNTech COVID-19 Vaccine = 1) / PS for individuals who received the Pfizer-BioNTech COVID-19 Vaccine and 1 - Pr (Pfizer-BioNTech COVID-19 Vaccine = 1) / (1-PS) for the contemporary unvaccinated controls. The distribution of weights will be examined to check for extreme values, and truncation will be considered if necessary.

Weighted Cox regression with robust standard errors to account for within-subject correlation will be conducted to compare the risk of safety events of interest between cohorts. Hazard ratios and corresponding 95% CIs will be summarized.

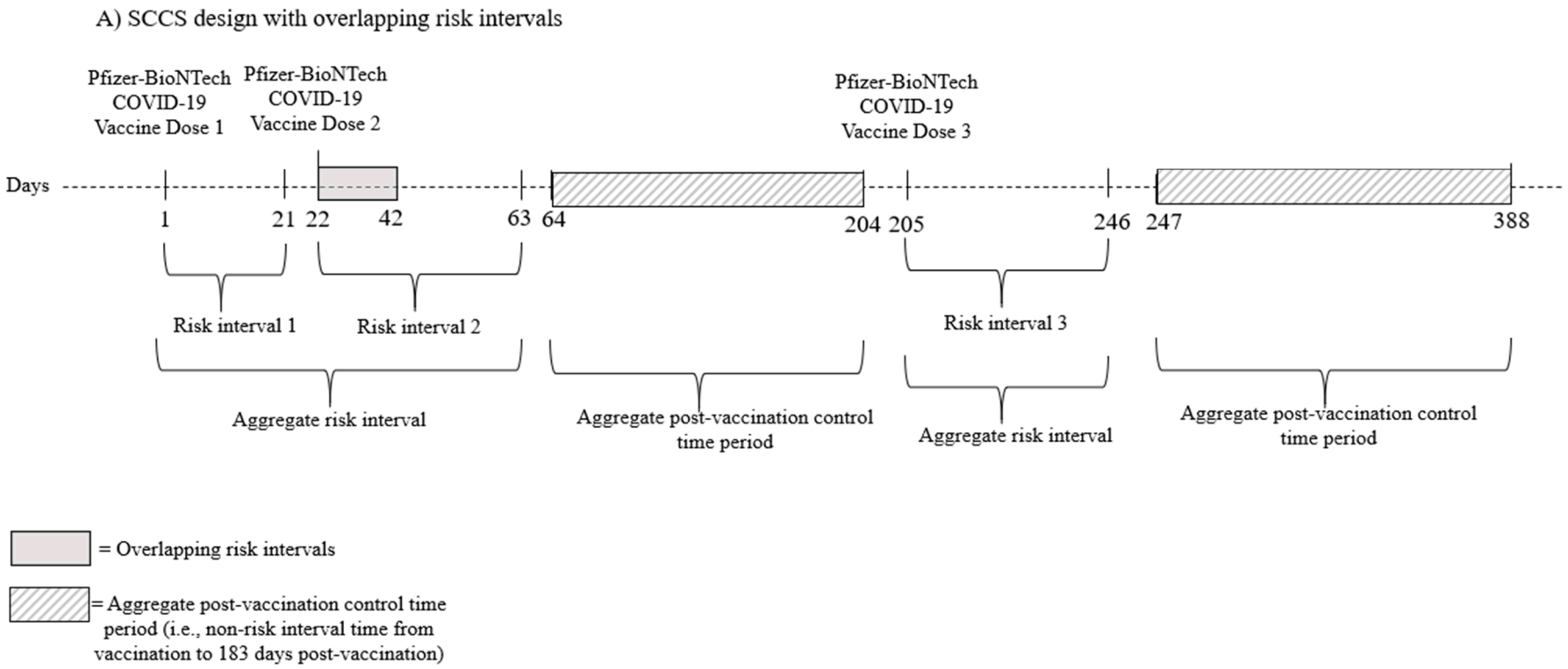
9.7.3.3. SCCS Design using Conditional Poisson Regression for Comparison with Post-Vaccination Control Time Period

The SCCS design with post-vaccination control time period will include cases (ie, individuals vaccinated with the Pfizer-BioNTech COVID-19 Vaccine who experience safety events of interest following vaccination) to compare the incidence of safety events occurring in the risk interval following vaccination with the incidence of safety events occurring during all other times post-vaccination in the same individual until the earliest of 183 days after the Pfizer-BioNTech COVID-19 vaccination, disenrollment, death, end of data availability. This analysis will be conducted for all safety events of interest.

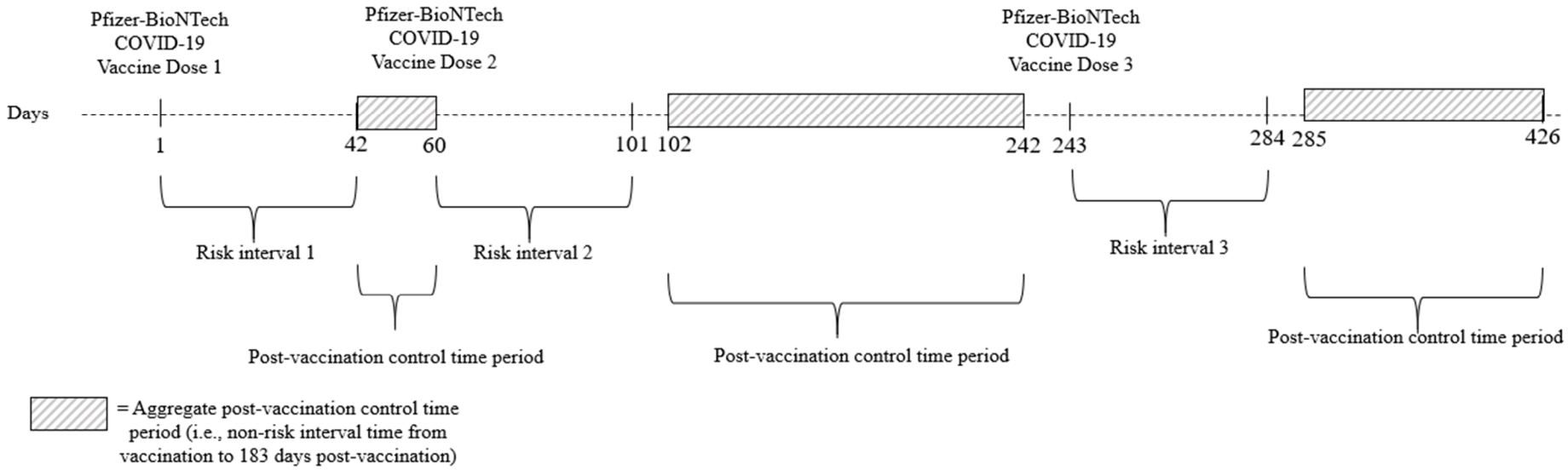
For individuals who receive two doses of the vaccine, the post-vaccination control time period may include time before and after Pfizer-BioNTech COVID-19 Vaccine dose 2 or solely include time after Pfizer-BioNTech COVID-19 Vaccine dose 2. Similarly, for individuals who receive three doses of the vaccine, the post-vaccination control time period

may include time before and after Pfizer-BioNTech COVID-19 Vaccine dose 2 and dose 3 or solely include time after Pfizer-BioNTech COVID-19 Vaccine dose 3. See Figure 1 below for an example of an individual who receives three doses of Pfizer-BioNTech COVID-19 Vaccine, where the safety event of interest has a 42-day risk interval window (eg, Bell's palsy; Table 1 in Section 9.3.2). Figure 1A demonstrates the SCCS design with the second dose received 21 days after the first (ie, the risk interval for dose 1 overlaps with the risk interval for dose 2), while Figure 1B demonstrates the SCCS design with the second dose received 60 days after the first (ie, with gaps between the end of dose 1 risk interval and dose 2). In both scenarios shown below (Figure 1A and Figure 1B), a third booster dose is received 183 days following dose 2, and the risk interval for dose 3 is shown. The post-vaccination control time period is displayed below as shading with gray lines. In the case where a third dose was received within the defined risk interval for dose 2, the aggregate post-vaccination control time period would be defined after the risk interval for dose 3.

Figure 1. Example of SCCS Design for Safety Event of Interest with a 42-day Risk Interval with Post-vaccination Control Intervals when Three Doses of Pfizer-BioNTech COVID-19 Vaccine are Administered



B) SCCS design with gap between risk intervals



A conditional Poisson regression model will be used to compare the rates of safety events of interest in the risk interval vs post-vaccination control time period. From this model we will report rate ratios and 95% CIs that will be interpretated as the rate ratio for the safety event of interest in the risk interval compared to the control interval.

9.7.3.4. Case Validation/Adjudication via Medical Records Review

If a statistically significant finding of association with RR greater than 3.0 between the Pfizer-BioNTech COVID-19 Vaccine and a safety event of interest is found in either the active comparator design, contemporary unvaccinated control design, or SCCS design, then case validation/adjudication through medical records review may be conducted.

Diagnostic validation of the detected safety events of interest (ie, cases) via adjudication of medical records by DoD MHS clinicians for outcome verification will be conducted in a representative sample of cases.

The total number of charts to be reviewed will depend on the number of safety events of interest detected, such that all cases may be reviewed where a small number of cases result in a safety event of interest being detected and a representative sub-sample may be reviewed where a larger number of cases results in a safety event of interest being detected.[50] An adjudication charter will be developed to govern medical records review and case validation/adjudication. Specifically, validation of detected safety events of interest will be performed through patient medical chart review in collaboration with an adjudication committee consisting of trained healthcare professionals.[51]

9.7.4. Prioritized Safety Analysis of Myocarditis/Pericarditis

Notably, CDC recently investigated the occurrence of myocarditis/pericarditis following mRNA COVID-19 vaccinations.[19] Therefore, separate safety analyses will be prioritized and performed to assess the risk of myocarditis/pericarditis following Pfizer-BioNTech COVID-19 vaccination, to provide additional context to the CDC investigation and address regulatory requests for further information on this safety event. The analytical approach is intended to align with the methodology used by the Vaccine Safety Datalink (VSD) and preliminary findings of myocarditis/pericarditis published by ACIP on June 23, 2021.[19,52] The VSD protocol defines myocarditis/pericarditis (ICD-10-CM codes B33.22, B33.23, I30, I40) events as the first event in 60 days identified through an ED or inpatient encounter, without a first diagnosis of COVID-19 (ie, COVID-19 diagnosis code or positive COVID-19 lab test) in the 30 days prior to or on the day of the event. This analysis will follow the outcome definition used in the VSD and uses three distinct risk intervals following vaccination (ie, 1-7 days, 1-21 days, and 1-42 days). This definition and the statistical approach differ from the analyses of other safety events of interest described in this protocol, but will facilitate comparison with the results presented by ACIP.[19,37]

This analysis will include all individuals who were vaccinated with the Pfizer-BioNTech COVID-19 Vaccine. The number of myocarditis/pericarditis events in the risk interval will be identified, and incidence rates per million doses will be summarized. Subgroup analyses

will also be performed, stratified by age (eg, 12-39 years, 40-49 years, 50-64 years, 65+ years), gender, and race/ethnicity, respectively.

In addition, vaccinated concurrent comparators will be selected among individuals who received the Pfizer-BioNTech COVID-19 Vaccine, and then events will be compared between vaccinees who are in their risk interval and vaccinees who are concurrently, on the same calendar date, in their comparison interval (ie, not in their risk interval). Poisson regression will then be used to calculate incidence rate ratios and 95% CIs to compare the rate of myocarditis/pericarditis events between those individuals who were in a risk interval versus those individuals who were in a comparison interval on the same calendar day. Data will be analyzed at the stratum level for each calendar day and will include strata for the independent variable of interest (ie, risk vs. comparison interval) and for adjustment variables (ie, age group, sex, race/ethnicity, and DoD service area). Thus, the number of myocarditis/pericarditis events in a risk or comparison interval on a calendar day will be modeled as a function of whether the stratum's vaccinees are in a risk versus comparison interval on that calendar day, controlling for age, sex, race/ethnicity, and DoD service area. The log of the number of individuals contributing data to each stratum on each calendar day will be included as an offset term in the Poisson model. Additionally, if it is suggested that calendar time may be associated with risk of post-vaccination myocarditis/pericarditis, to account for changes COVID-19 and other viruses circulating and other ecologic factors, analyses may also be stratified by calendar time, for example in 6 months increments.

In addition to analyzing codified data, case confirmation for myocarditis/pericarditis events identified in the codified data will be conducted based on medical chart review. Myocarditis/pericarditis cases will be confirmed and validated using the Brighton Collaboration's case definitions.[53] Risk factor analysis will also be conducted via logistic regression among confirmed cases of myocarditis/pericarditis to further evaluate variables associated with the event.

Additional data surrounding risk factors, clinical course, and sequelae of identified myocarditis/pericarditis events up to 365 days following the event will be collected and summarized. These will include an examination of other possible etiologies/risk factors (ie, prior COVID-19 infection, prior Coxsackie infection, other prior viral infections, other vaccines received, comorbid immunocompromising conditions and systemic immune-mediated diseases, demographics, and medication history); time between Pfizer-BioNTech COVID-19 doses and onset of myocarditis/pericarditis; echocardiogram information; lab troponin information; symptoms (eg, chest pain, shortness of breath, weakness or fatigue, arm or shoulder pain, heart palpitations cough, swelling in abdomen or legs, fever); treatments received for myocarditis/pericarditis (eg, non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, pericardectomy); healthcare resource utilization following the event, and long-term sequelae for up to one year following the event (for myocarditis: recovery, sudden cardiac death, heart failure cardiogenic shock, fulminant myocarditis, inflammatory cardiomyopathy, heart transplant, arrhythmia; for pericarditis: recovery, chronic pericarditis, restrictive pericarditis, recurrent pericarditis).

9.7.5. Subgroup Analysis

Separate analyses of baseline characteristics, vaccine utilization patterns and safety analyses in subgroups of interest may be conducted based on feasibility, sample size, and data available. These analyses will be performed for all subgroups listed in Section 9.2.3. In addition, specific subgroup analyses will be performed among pregnant women, as described in the following section. For each subgroup, a new set of IPTW will be generated, and analyses will be conducted as described above.

9.7.5.1. Pregnancy Analysis

A separate subgroup analysis among pregnant women will be conducted to:

- Estimate and compare the birth prevalence of pregnancy outcomes, ie, major congenital malformations and small size for gestational age, among pregnant women vaccinated with any dose of the Pfizer-BioNTech COVID-19 Vaccine with that among unvaccinated pregnant women
- Estimate and compare the risk of pregnancy outcomes, ie, spontaneous abortion, stillbirth, and preterm delivery, among pregnant women vaccinated with any dose of the Pfizer-BioNTech COVID-19 Vaccine with that among unvaccinated pregnant women
- Estimate and compare the birth prevalence of pregnancy outcomes, ie, major congenital malformations and small size for gestational age, among pregnant women vaccinated with a first or second dose (or third dose in immunocompromised) of the Pfizer-BioNTech COVID-19 Vaccine with that among unvaccinated pregnant women
- Estimate and compare the risk of pregnancy outcomes, ie, spontaneous abortion, stillbirth, and preterm delivery, among pregnant women vaccinated with a first or second dose (or third dose in immunocompromised) of the Pfizer-BioNTech COVID-19 Vaccine with that among unvaccinated pregnant women
- Estimate and compare the birth prevalence of pregnancy outcomes, ie, major congenital malformations and small size for gestational age, among pregnant women vaccinated with a booster dose of the Pfizer-BioNTech COVID-19 Vaccine with no receipt of a booster dose of any COVID-19 vaccine, among women who have previously received the primary series of the Pfizer-BioNTech COVID-19 Vaccine
- Estimate and compare the risk of pregnancy outcomes, ie, spontaneous abortion, stillbirth, and preterm delivery, among pregnant women vaccinated with a booster dose of Pfizer-BioNTech COVID-19 Vaccine with no receipt of a booster dose of any COVID-19 vaccine, among women who have previously received 2 doses of Pfizer-BioNTech COVID-19 Vaccine.

To be eligible for the pregnancy subgroup analysis, women must have a diagnosis code related to pregnancy (regardless of the timing of estimated pregnancy start relative to the study start date) and have a pregnancy outcome (eg, live birth, stillbirth, spontaneous abortion, ectopic pregnancy) recorded in the data source during the study period. Analysis of

major congenital malformations, preterm birth, and small size for gestational age will be limited to pregnancies ending in a live birth. Eligible populations (ie, denominators) for the analysis of each outcome are described further in Table 2 in Section 9.3.2.

In analyses of pregnant women, exposures to the Pfizer-BioNTech COVID-19 Vaccine occurring within 28 days (ie, 4 weeks) before the estimated pregnancy start or anytime during pregnancy will be considered will be included in the exposed cohort. Women with Pfizer-BioNTech COVID-19 Vaccine administrations within 28 days 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 and EMRs data and because this period may be of etiologic interest for some of these safety events. Exposure windows are defined in Table 2 in Section 9.3.2. For analyses of spontaneous abortion, stillbirth, and preterm birth, each dose of Pfizer-BioNTech COVID-19 Vaccine will contribute separate index dates, and the observation period will be censored at receipt of the following dose (eg, for analysis of the first dose, the index date will be the date of the first dose, and outcomes will be observed until receipt of the second dose). For each unvaccinated 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 analysis of small size for gestational age and congenital malformations, the index date in exposed and unexposed individuals is the estimated pregnancy start date.[54] Immortal time bias will be addressed by accounting for time-dependent variables within the model.

For comparative analysis of pregnancy safety outcomes, potential demographic and clinical confounders and descriptive variables will be identified in relation to the index date (to be further described in the SAP). Vaccinated pregnant women will be matched to pregnant contemporary unvaccinated comparators (or in the case of third dose analyses, to the pregnant comparators who have not received a third dose of any COVID-19 vaccine) in a ratio of at least 1:1 on maternal age, state (if feasible, or broader geographic region if not feasible), and estimated pregnancy start in order to account for confounding by seasonality, maternal age, and differences in geographic distribution of COVID-19.[54] PS will then be estimated within the overall matched population and for the specific eligible population for each outcome. IPTW based on the PS will be used to adjust for confounding by other baseline covariates, as described in Section 9.7.3.2.

There are unique methodological challenges for observational studies of adverse fetal and newborn outcomes following vaccination during pregnancy, including temporal issues related to time-varying exposures, gestational age, and calendar time, confounding, and measurement of variables such as gestational age and outcomes.[55] To address immortal time bias, time-varying exposure variables may be included in regression models. Confounding will be accounted for by including potential confounding variables in PS models used to generate IPTW.[54,56,57,58] Algorithms established in the literature will be used to measure important confounders, including gestational age and pregnancy start. Doubly robust regression models will be employed that include IPTW and any remaining imbalanced covariates. For all outcomes, the relevant measure of relative risk and 95% CIs will be reported.

9.7.6. Incidence Rates and Time to Safety Event of Interest Analysis

Incidence rates (and corresponding 95% CIs) will be calculated for safety events of interest. Kaplan-Meier methods will be used to analyze time-to-event (ie, time to safety event of interest). If individuals do not experience the safety event of interest, they will be censored at the end of the risk interval. Median time to safety event of interest and corresponding CIs will be reported.

9.8. Quality Control

Analysis Group will access de-identified DoD data through a secure pre-specified process. Each data content area will be subject to high level variable name/type checks and to detailed trending comparisons. As an example, the diagnostic data is subject to the following checks:

- Referenced table exists
- Diagnosis type is correctly assigned by codes defining the diagnosis
- Percentages, rates, are as expected (check ranges and for missing)
- Both inpatient and outpatient diagnosis codes are captured. Referenced variables exist and are of appropriate length and type

Data retrieval will be coordinated by an experienced programmer/analyst. The analyst will write programming for retrieval of each data element from the electronic databases. Double programming will be performed for the first iteration of the analyses; results/datasets will be compared, and if any discrepancies are identified, both programmers will determine a resolution, bringing in a third programmer if needed. Subsequent iterations of analyses (ie, re-runs of the analyses) will be audited by a senior programmer. All tables will be reviewed by the project manager and the principal investigator to evaluate for internal consistency of counts and totals. All calculated variables will be checked against the component variables (cross tabs) to ensure accuracy. For example, categorical age would be compared with continuous age to confirm that each category of age contained only individuals of the expected age ranges within that category.

9.9. Strengths and Limitations of the Research Methods

To identify individuals who experienced safety events of interest associated with Pfizer-BioNTech COVID-19 Vaccine, the cohort study design offers some key advantages. Potential confounders can be accounted for in the statistical analysis to achieve balance between cohorts, using methods such as IPTW.[49] Additionally, the inclusion of a post-vaccination control time period and comparison to unvaccinated controls will account for increased detection bias from stimulated safety event of interest reporting due to heightened vigilance on COVID-19 vaccines.[59] Specifically, safety events of interest may be more likely to be reported or sought care for after vaccination with Pfizer-BioNTech COVID-19 Vaccine than before which may result in bias against the Pfizer-BioNTech COVID-19 Vaccine. To mitigate this bias, comparison against active comparators who received seasonal influenza vaccines will be performed, where a similar pattern of reporting after vaccination may be

expected. IPTW will also be implemented for contemporary unvaccinated controls in order to ensure that baseline characteristics between Pfizer-BioNTech COVID-19 vaccinees and contemporary unvaccinated controls are comparable.

The comparison of vaccinated to contemporary unvaccinated controls yields a more interpretable result than other planned analyses using SCCS and active comparators who receive seasonal influenza vaccination (ie, the increased risk of experiencing a specific safety event due to Pfizer-BioNTech COVID-19 vaccination). The potential for selection bias (ie, confounding by indication, healthy user bias) will be mitigated by comparing baseline demographic and clinical characteristics among the unvaccinated controls. Unvaccinated controls will be required to have similar healthcare-seeking behaviors as Pfizer-BioNTech COVID-19 vaccinees, including a minimum period (eg, 6 months) of enrollment in and no disenrollment from DoD benefits prior to their match date. However, it is noted that the mass vaccination campaign in the past year has provided various channels to receive vaccination, and therefore unvaccinated controls may be misclassified if they are vaccinated outside of the DoD MHS.

The DoD operates the largest cradle-to-grave healthcare database in the US. This data is both geographically and demographically representative of the US general population.[43] The DoD also provides comprehensive access to its covered beneficiaries, which allows prescriptions to be obtained at either no or low cost. In addition, as all DoD beneficiaries are eligible for healthcare coverage across locations of care, past studies have shown loss to follow-up to be minimized.[60] The DoD MHS database provides a range of additional benefits, including its comprehensive structure, large number of enrollees, and electronic accessibility, which will allow for analysis of the identified safety events of interest as well as pregnancy safety outcomes. The DoD MHS database also comprises of EMR data and allows for the possibility of chart review. Importantly, the DoD MHS database retains electronic immunization records that include manufacturer name and lot numbers, facilitating the identification of brand-specific vaccines, such as the Pfizer-BioNTech COVID-19 Vaccine. Moreover, the DoD data are updated frequently.

However, there are several limitations when relying on secondary data sources such as the DoD MHS database that should be noted. First, EMR data (such as laboratory and diagnostic test results) will not be available for all individuals in the DoD MHS (ie, purchased care only enrollees). As such, outcomes among these individuals will be identified via administrative claims data, which may be subject to the misspecification of billing codes or lack of documentation that may result in potential misclassification. For pregnancy outcomes specifically, while established algorithms will be used to define gestational age and pregnancy start, relying on such codes may also result in misclassification. Second, contemporary unvaccinated controls may be systematically different from individuals receiving Pfizer-BioNTech COVID-19 Vaccine. While IPTW will be performed to increase the comparability between cohorts, caution should be exercised when interpreting the results of real-world studies due to the potential bias from unmeasured or residual confounding. Third, patients who may have dual coverage through TRICARE or DoD and through Medicare may not be captured in the MHS healthcare database since their vaccinations may be covered through Medicare. For instance, for patients with Medicare Part B, TRICARE may serve as a second payer to Medicare. Therefore, if there is no cost share for a service

(such as vaccination) for a Medicare beneficiary provided outside of the DoD MHS, then there will be no evidence of that healthcare encounter within the MHS. This may particularly be an issue for misclassification of receipt of seasonal influenza vaccine and similarly, for the COVID-19 vaccine, since Medicare covers influenza vaccines at 100% without any further cost share, and there will be no TRICARE claim. As such, some patients who appear not to have received seasonal influenza vaccine may have indeed received the influenza vaccine. This limitation will be addressed by conducting stratified analyses within specific age groups that exclude Medicare beneficiaries.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

Patient personal data will be stored at the DHA Immunization Healthcare Division (IHD) in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The party(ies) performing medical record review 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, the party(ies) performing medical record review 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 regards to the processing of personal data, when study data are compiled for transfer to Pfizer, Analysis Group, and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. Identifiable data will not be transferred to Pfizer or other authorized parties, however, the single, patient-specific code will be used to help identify medical records for chart abstraction. High standards of confidentiality and protection of individuals' personal data consistent with the vendor contract and applicable privacy laws will be maintained.

The source documents for the medical records review study component will contain PHI collected on DoD Uniformed members of the Departments of the Army, Navy, and Air Force (including the active and reserve components of each Military Department and the Coast Guard) and beneficiaries. This information will be accessed and distributed within DoD only.

To ensure PHI remains confidential, the following safeguards will be implemented by DHA IHD:

10.1.1. Administrative Safeguards

- A security management policy will contain procedures to prevent, detect, contain, and correct security violations.
- A risk analysis will be performed to determine threats and vulnerabilities for security violations. Threats and control actions will be documented and reviewed periodically during the study to ensure compliance.
- The DoD Principal Investigator will be designated as having overall responsibility for the security of the PHI.
- A data back-up plan and recovery plan will be developed and implemented.
- Study personnel are not allowed to work on study materials off-site (ie, telecommuting).

10.1.2. Physical Safeguards

- The DHA IHD is located in access-controlled and secure areas. Personnel access is controlled by an access card and security guards. Visitors must be escorted at all times.
- The DoD study computers will only be accessible to those study personnel located at DHA IHD. Study personnel are not allowed to remove study computers from the DHA IHD work site.

10.1.3. Technical Safeguards

- The data stored on the DoD study computers and systems are CAC and/or password protected, and only those involved in the study are authorized access.
- Upon completion of the study, the data will be retained and/or disposed of as described in Section 9.
- Emergency access procedures will be set up so that both an Army-approved IT representative and a study project manager must be present to resolve any computer or software issues.

10.2. Patient Consent

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

10.3. Institutional Review board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and their relevant documents from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer. The study protocol will be reviewed by the US DoD IRB and affiliated privacy office.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology,[61] the FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting, Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data[62] and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).[63]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Structured Data Analysis

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

Human Review of Unstructured Data

This study protocol requires 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 adverse events (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 NIS adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the CRF 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 exposure during pregnancy in studies of pregnant women, data on the exposure to the Pfizer-BioNTech COVID-19 Vaccine during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

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

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, 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 (mm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

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

- *“Your Reporting Responsibilities (YRR) Training for Vendors.”*

These trainings must be completed by research staff members 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This protocol will be posted on publicly available registers following its finalization. The final study results will be made publicly available via the European Union Post Authorisation Safety (EU PAS) Register and may be submitted for publication in a peer reviewed medical journal.

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

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14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

17. 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: Active Safety Surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the United States Department of Defense Population Following Emergency Use Authorization

EU PAS Register® number: To be registered before the start of data collection **Study reference number (if applicable):** Not applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
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)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (ie population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1, 9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.1, 9.7

[b] 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.

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

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

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.2.3
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☐	☐	☒	
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.2.2

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)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.7.3.4
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
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?	☒	☐	☐	9.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
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)	☒	☐	☐	9.7.3.4
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)	☒	☐	☐	9.7.5.1, 9.9
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3.2.1, 9.7.5.1, 9.9

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.2.3

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)	☒	☐	☐	9.4

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.1.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☒	☐	☐	9.2.3
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.3.2
10.7	Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.2, 9.3.2

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2, 9.5

Comments:

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

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol:	Renu Garg
Date: dd/Month/year	08/August/2022
Signature:	Renu Garg

18. ANNEX 3. ADDITIONAL INFORMATION

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
COVID-19	CPT	91300	Pfizer: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNALNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted, for intramuscular use; Primary series, IC third dose, booster
		91305	Pfizer: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, tris-sucrose formulation, for intramuscular use; Primary series, IC third dose, booster
		91301	Moderna: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage, for intramuscular use.
		91302	AstraZeneca: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, chimpanzee adenovirus Oxford 1 (ChAdOx1) vector, preservative free, 5x1010 viral particles/0.5 mL dosage, for intramuscular use.
		91303	Janssen: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x1010 viral particles/0.5 mL dosage, for intramuscular use.
	HCPCS	0001A	Pfizer: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted; first dose
		0002A	Pfizer: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
			disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted; second dose
		0003A	Pfizer: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted; third dose
		0004A	Pfizer: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted; booster dose
		0051A	Pfizer: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, tris-sucrose formulation; first dose
		0052A	Pfizer: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, tris-sucrose formulation; second dose
		0053A	Pfizer: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, tris-sucrose formulation; third dose
		0054A	Pfizer: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, tris-sucrose formulation; booster dose

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
		0011A	Moderna: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage; first dose
		0012A	Moderna: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage; second dose
		0021A	AstraZeneca: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, chimpanzee adenovirus Oxford 1 (ChAdOx1) vector, preservative free, 5x1010 viral particles/0.5 mL dosage; first dose
		0022A	AstraZeneca: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, chimpanzee adenovirus Oxford 1 (ChAdOx1) vector, preservative free, 5x1010 viral particles/0.5 mL dosage; second dose
		0031A	Janssen: Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x1010 viral particles/0.5 mL dosage; single dose
	NDC	5926710001	Pfizer: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose; primary series, IC third dose, booster

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
		59267100001	Pfizer: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose; primary series, IC third dose, booster
		5926710002	Pfizer: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose; primary series, IC third dose, booster
		59267100002	Pfizer: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose; primary series, IC third dose, booster
		5926710003	Pfizer: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose; primary series, IC third dose, booster
		59267100003	Pfizer: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose; primary series, IC third dose, booster
		5926710251	Pfizer: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose, tris-sucrose formulation; primary series, IC third dose, booster
		59267102501	Pfizer: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose, tris-sucrose formulation; primary series, IC third dose, booster
		0069100001	Pfizer: COVID-19 vaccine for use in individuals 16 and older (COMIRNATY; FDA BLA License). 30 mcg/0.3 mL for adult 16+ (original formula)
		0069100002	Pfizer: COVID-19 vaccine for use in individuals 16 and older (COMIRNATY; FDA BLA License). 30 mcg/0.3 mL for adult 16+ (original formula)

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
		0069100003	Pfizer: COVID-19 vaccine for use in individuals 16 and older (COMIRNATY; FDA BLA License). 30 mcg/0.3 mL for adult 16+ (original formula)
		0069202510	Pfizer: Tris-sucrose formulation COVID-19 vaccine for use in individuals 16 and older (COMIRNATY; FDA BLA License). 30 mcg/0.3 mL for adult 16+ (EUA tris-sucrose formula).
		0069202525	Pfizer: Tris-sucrose formulation COVID-19 vaccine for use in individuals 16 and older (COMIRNATY; FDA BLA License). 30 mcg/0.3 mL for adult 16+ (EUA tris-sucrose formula).
		0069202501	Pfizer: Tris-sucrose formulation COVID-19 vaccine for use in individuals 16 and older (COMIRNATY; FDA BLA License). 30 mcg/0.3 mL for adult 16+ (EUA tris-sucrose formula).
		00310122210	AstraZeneca: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL
		00310122215	AstraZeneca: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL
		0310122210	AstraZeneca: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL
		0310122215	AstraZeneca: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL
		59676058005	Janssen: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL
		59676058015	Janssen: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL
		5967658005	Janssen: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
		5967658015	Janssen: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL
		80777027310	Moderna: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg (Primary series) or 50 mcg dose (Booster adult 18+)
		80777027399	Moderna:SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg (Primary series) or 50 mcg dose (Booster adult 18+)
		8077727310	Moderna: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg (Primary series) or 50 mcg dose (Booster adult 18+)
		8077727399	Moderna: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg (Primary series) or 50 mcg dose (Booster adult 18+)
		8077710099	Moderna: COVID-19 vaccine SPIKEVAX (COVID-19 Vaccine, mRNA; FDA BLA License) for use in individuals 18 and older, 0.5 mL dose (same as original EUA formula).
		8077710098	Moderna: COVID-19 vaccine SPIKEVAX (COVID-19 Vaccine, mRNA; FDA BLA License) for use in individuals 18 and older, 0.5 mL dose (same as original EUA formula).
	CVX	212	Janssen: SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL
		207	Moderna: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg/0.5mL dose or 50 mcg/0.25mL dose
		221	Moderna: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 50 mcg/0.5 mL dose

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
		208	Pfizer-BioNTech: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose
		217	Pfizer-BioNTech: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose, tris-sucrose formulation
		218	Pfizer-BioNTech: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 10 mcg/0.2 mL dose, tris-sucrose formulation
		219	Pfizer-BioNTech: SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 3 mcg/0.2 mL dose, tris-sucrose formulation
Seasonal Influenza	CPT	90470	H1N1 Immunization administration (intramuscular, intranasal), including counseling when performed
	CPT	90630	Vaccine for influenza for injection into skin, quadrivalent, preservative free
	CPT	90653	Vaccine for influenza for injection into muscle, inactivated, subunit, adjuvanted
	CPT	90654	Vaccine for influenza injection into skin, trivalent, preservative free
	CPT	90655	Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent, split virus, preservative free
	CPT	90656	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, preservative free
	CPT	90657	Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent (pediatric use)
	CPT	90658	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent
	CPT	90659	Influenza virus vaccine, whole virus, for intramuscular or jet injection use
	CPT	90660	Vaccine for influenza for nasal administration, trivalent

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	CPT	90661	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, cell culture-based, preservative and antibiotic free
	CPT	90662	Vaccine for influenza for injection into muscle, split virus, enhanced immunogenicity via increased antigen content
	CPT	90663	Influenza virus vaccine, pandemic formulation, H1N1
	CPT	90664	Vaccine for influenza for nasal administration, pandemic formulation
	CPT	90666	Vaccine for influenza for injection into muscle, pandemic formulation
	CPT	90667	Vaccine for influenza for injection into muscle, pandemic formulation
	CPT	90668	Vaccine for influenza for injection into muscle, pandemic formulation
	CPT	90672	Vaccine for influenza for nasal administration, tetravalent
	CPT	90673	Vaccine for influenza administered into muscle, preservative and antibiotic free, trivalent, recombinant DNA, hemagglutinin (HA) protein only
	CPT	90674	Vaccine for influenza for administration into muscle, 0.5 ml dosage, tetravalent, cell-culture based, preservative and antibiotic free
	CPT	90682	Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free
	CPT	90685	Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent, preservative free
	CPT	90686	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, preservative free
	CPT	90687	Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent (pediatric use)
	CPT	90688	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent
	CPT	90694	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, inactivated, adjuvanted, preservative free

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	CPT	90724	Immunization, active; influenza virus vaccine
	CPT	90756	Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free
	HCPCS	G0008	Administration of influenza virus vaccine
	HCPCS	G9141	Influenza a (H1N1) immunization administration (includes the physician counseling the patient/family)
	HCPCS	G9142	Influenza a (H1N1) vaccine, any route of administration
	HCPCS	Q2033	Influenza vaccine, recombinant hemagglutinin antigens, for intramuscular use (flublok)
	HCPCS	Q2034	Influenza virus vaccine, split virus, for intramuscular use (agriflu)
	HCPCS	Q2035	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (afluria)
	HCPCS	Q2036	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (flulaval)
	HCPCS	Q2037	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluvirin)
	HCPCS	Q2038	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluzone)
	HCPCS	Q2039	Influenza virus vaccine, not otherwise specified
	NDC	19515089101	FLULAVAL QUAD 2014 2015
	NDC	19515089111	FLULAVAL QUAD 2014 2015
	NDC	19515089302	FLULAVAL QUAD 2014 2015
	NDC	19515089307	FLULAVAL QUAD 2014 2015
	NDC	19515089441	FLULAVAL QUAD 2014 2015
	NDC	19515089452	FLULAVAL QUAD 2014 2015
	NDC	19515089801	FLULAVAL QUAD 2015 2016

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	19515089811	FLULAVAL QUAD 2015 2016
	NDC	19515090301	FLULAVAL QUAD 2016 2017
	NDC	19515090311	FLULAVAL QUAD 2016 2017
	NDC	19515090841	FLULAVAL QUAD 2016 2017
	NDC	19515090852	FLULAVAL QUAD 2016 2017
	NDC	19515089601	FLULAVAL QUAD 2017 2018
	NDC	19515089611	FLULAVAL QUAD 2017 2018
	NDC	19515091241	FLULAVAL QUAD 2017 2018
	NDC	19515091252	FLULAVAL QUAD 2017 2018
	NDC	33332001401	AFLURIA TRIVALENT 2014-2015
	NDC	33332001402	AFLURIA TRIVALENT 2014-2015
	NDC	33332011410	AFLURIA TRIVALENT 2014-2015
	NDC	33332011411	AFLURIA TRIVALENT 2014-2015
	NDC	33332011510	AFLURIA TRIVALENT 2015-2016
	NDC	33332011511	AFLURIA TRIVALENT 2015-2016
	NDC	33332001501	AFLURIA TRIVALENT 2015-2016
	NDC	33332001502	AFLURIA TRIVALENT 2015-2016
	NDC	33332031601	AFLURIA QUADRIVALENT 2016-2017
	NDC	33332031602	AFLURIA QUADRIVALENT 2016-2017
	NDC	33332011611	AFLURIA TRIVALENT 2016-2017
	NDC	33332011610	AFLURIA TRIVALENT 2016-2017
	NDC	33332001601	AFLURIA TRIVALENT 2016-2017
	NDC	33332001602	AFLURIA TRIVALENT 2016-2017
	NDC	33332031701	AFLURIA QUADRIVALENT 2017-2018
	NDC	33332031702	AFLURIA QUADRIVALENT 2017-2018

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	33332041710	AFLURIA QUADRIVALENT 2017-2018
	NDC	33332041711	AFLURIA QUADRIVALENT 2017-2018
	NDC	33332011710	AFLURIA TRIVALENT 2017-2018
	NDC	33332011711	AFLURIA TRIVALENT 2017-2018
	NDC	33332001701	AFLURIA TRIVALENT 2017-2018
	NDC	33332001702	AFLURIA TRIVALENT 2017-2018
	NDC	58160088141	FLUARIX 2014-2015
	NDC	58160088152	FLUARIX 2014-2015
	NDC	58160090141	FLUARIX QUAD 2014-2015
	NDC	58160090152	FLUARIX QUAD 2014-2015
	NDC	58160090341	FLUARIX QUAD 2015 2016
	NDC	58160090352	FLUARIX QUAD 2015 2016
	NDC	58160090541	FLUARIX QUAD 2016 2017
	NDC	58160090552	FLUARIX QUAD 2016 2017
	NDC	58160090741	FLUARIX QUAD 2017 2018
	NDC	58160090752	FLUARIX QUAD 2017 2018
	NDC	62577061301	FLUCELVAX 2014-2015
	NDC	62577061311	FLUCELVAX 2014-2015
	NDC	62577061401	FLUCELVAX 2015 2016
	NDC	62577061411	FLUCELVAX 2015 2016
	NDC	70461020001	FLUCELVAX QUADRIVALENT 2016 2017
	NDC	70461020011	FLUCELVAX QUADRIVALENT 2016 2017
	NDC	70461020101	FLUCELVAX QUADRIVALENT 2017 2018
	NDC	70461020111	FLUCELVAX QUADRIVALENT 2017 2018
	NDC	70461030110	FLUCELVAX QUADRIVALENT 2017 2018

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	70461030112	FLUCELVAX QUADRIVALENT 2017 2018
	NDC	70461031803	FLUCELVAX
	NDC	70461031804	FLUCELVAX
	NDC	70461041810	FLUCELVAX
	NDC	70461041811	FLUCELVAX
	NDC	66019030101	FLUMIST QUAD 2014 2015
	NDC	66019030110	FLUMIST QUAD 2014 2015
	NDC	66019030201	FLUMIST QUAD 2015 2016
	NDC	66019030210	FLUMIST QUAD 2015 2016
	NDC	66019030301	FLUMIST QUAD 2016 2017
	NDC	66019030310	FLUMIST QUAD 2016 2017
	NDC	66019030401	FLUMIST QUAD 2017 2018
	NDC	66019030410	FLUMIST QUAD 2017 2018
	NDC	66521000001	FLUAD 2015 2016
	NDC	66521000011	FLUAD 2015 2016
	NDC	70461000101	FLUAD 2016 2017
	NDC	70461000111	FLUAD 2016 2017
	NDC	70461000201	FLUAD 2017 2018
	NDC	70461000211	FLUAD 2017 2018
	NDC	42874001401	FLUBLOK 2014 2015
	NDC	42874001410	FLUBLOK 2014 2015
	NDC	42874001501	FLUBLOK 2015 2016
	NDC	42874001510	FLUBLOK 2015 2016
	NDC	42874001601	FLUBLOK 2016 2017
	NDC	42874001610	FLUBLOK 2016 2017

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	42874001701	FLUBLOK 2017 2018
	NDC	42874001710	FLUBLOK 2017 2018
	NDC	42874011701	FLUBLOK 2017 2018 (Quad)
	NDC	42874011710	FLUBLOK 2017 2018 (Quad)
	NDC	66521011702	FLUVIRIN 2014 2015
	NDC	66521011710	FLUVIRIN 2014 2015
	NDC	66521011711	FLUVIRIN 2014 2015
	NDC	66521011712	FLUVIRIN 2014 2015
	NDC	66521011802	FLUVIRIN 2015 2016
	NDC	66521011810	FLUVIRIN 2015 2016
	NDC	66521011811	FLUVIRIN 2015 2016
	NDC	66521011812	FLUVIRIN 2015 2016
	NDC	70461011902	FLUVIRIN 2016 2017
	NDC	70461011910	FLUVIRIN 2016 2017
	NDC	70461011911	FLUVIRIN 2016 2017
	NDC	70461011912	FLUVIRIN 2016 2017
	NDC	70461012002	FLUVIRIN 2017 2018
	NDC	70461012010	FLUVIRIN 2017 2018
	NDC	70461012011	FLUVIRIN 2017 2018
	NDC	70461012012	FLUVIRIN 2017 2018
	NDC	49281039415	FLUZONE 2014-2015
	NDC	49281039478	FLUZONE 2014-2015
	NDC	49281039565	FLUZONE 2014-2015
	NDC	49281039588	FLUZONE 2014-2015
	NDC	49281062115	FLUZONE 2014-2015

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	49281062178	FLUZONE 2014-2015
	NDC	49281001450	FLUZONE PEDIATRIC PF 2014 2015
	NDC	49281001488	FLUZONE QUAD PED 2014 2015
	NDC	49281041410	FLUZONE QUADRIVALENT 2014 2015
	NDC	49281041450	FLUZONE QUADRIVALENT 2014 2015
	NDC	49281041458	FLUZONE QUADRIVALENT 2014 2015
	NDC	49281041488	FLUZONE QUADRIVALENT 2014 2015
	NDC	49281051400	FLUZONE QUADRIVALENT 2014 2015
	NDC	49281051425	FLUZONE QUADRIVALENT 2014 2015
	NDC	49281070840	FLUZONE INTRADERMAL QUADRIVALENT 2014 15
	NDC	49281070848	FLUZONE INTRADERMAL QUADRIVALENT 2014 15
	NDC	49281070948	FLUZONE INTRADERMAL 2014 2015
	NDC	49281070955	FLUZONE INTRADERMAL 2014 2015
	NDC	49281041510	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281041550	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281041558	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281041588	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281051500	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281051525	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281062315	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281051500	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281051525	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281062378	FLUZONE QUADRIVALENT 2015 2016
	NDC	49281039615	FLUZONE SPLIT 2015 2016
	NDC	49281039678	FLUZONE SPLIT 2015 2016

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	49281039765	FLUZONE HIGH DOSE PF 2015 2016
	NDC	49281039788	FLUZONE HIGH DOSE PF 2015 2016
	NDC	49281039965	FLUZONE HIGH DOSE PF 2016 2017
	NDC	49281039988	FLUZONE HIGH DOSE PF 2016 2017
	NDC	49281040165	FLUZONE HIGH DOSE PF 2017 2018
	NDC	49281040188	FLUZONE HIGH DOSE PF 2017 2018
	NDC	49281040365	FLUZONE HIGH DOSE PF 2018 2019
	NDC	49281040388	FLUZONE HIGH DOSE PF 2018 2019
	NDC	49281041610	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281041650	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281041658	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281041688	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281051600	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281051625	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281062515	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281062578	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281062515	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281062578	FLUZONE QUADRIVALENT 2016 2017
	NDC	49281071040	FLUZONE INTRADERMAL QUADRIVALENT 2016 2017
	NDC	49281071048	FLUZONE INTRADERMAL QUADRIVALENT 2016 2017
	NDC	49281041710	FLUZONE QUADRIVALENT 2017 2018
	NDC	49281041750	FLUZONE QUADRIVALENT 2017 2018
	NDC	49281041758	FLUZONE QUADRIVALENT 2017 2018
	NDC	49281041788	FLUZONE QUADRIVALENT 2017 2018
	NDC	49281051700	FLUZONE QUADRIVALENT 2017 2018

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	49281051725	FLUZONE QUADRIVALENT 2017 2018
	NDC	49281062715	FLUZONE QUADRIVALENT 2017 2018
	NDC	49281062778	FLUZONE QUADRIVALENT 2017 2018
	NDC	49281071240	FLUZONE INTRADERMAL QUADRIVALENT 2017 2018
	NDC	49281071248	FLUZONE INTRADERMAL QUADRIVALENT 2017 2018
	NDC	33332051925	Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul
	NDC	33332062910	Influenza virus vaccine (IIV), pandemic formulation, split virus, for intramuscular use
	NDC	66521020010	Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul
	NDC	49281065090	Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul
	NDC	49281065070	Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul
	NDC	49281065050	Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul
	NDC	49281065025	Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul
	NDC	49281065010	Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul
	NDC	66521020002	Influenza virus vaccine (IIV), pandemic formulation, split virus, for intramuscular use
	NDC	49281064015	Influenza virus vaccine (IIV), pandemic formulation, split virus, for intramuscular use
	NDC	66019020010	Influenza virus vaccine, live (LAIV), pandemic formulation, for intranasal use

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	66019020001	Influenza virus vaccine, live (LAIV), pandemic formulation, for intranasal use
	NDC	76420048301	Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.5 mL dosage, for int
	NDC	76420048201	Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.5 mL dosage, for int
	NDC	58160080815	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
	NDC	58160080401	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
	NDC	58160080202	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
	NDC	33332051901	Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul
	NDC	19515081652	Flulaval Quadrivalent
	NDC	19515084511	FLULAVAL
	NDC	19515085052	FLULAVAL
	NDC	19515089711	Flulaval Quadrivalent
	NDC	19515090011	Flulaval Quadrivalent
	NDC	19515090152	Flulaval Quadrivalent
	NDC	19515090652	Flulaval Quadrivalent
	NDC	19515090952	Flulaval Quadrivalent
	NDC	33332001801	AFLURIA
	NDC	33332011810	AFLURIA
	NDC	33332021920	Afluria Quadrivalent
	NDC	33332022020	Afluria Quadrivalent
	NDC	33332031801	AFLURIA QUADRIVALENT
	NDC	33332031901	Afluria Quadrivalent
	NDC	33332032001	Afluria Quadrivalent

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	33332041610	AFLURIA QUADRIVALENT
	NDC	33332041810	AFLURIA QUADRIVALENT
	NDC	33332041910	Afluria Quadrivalent
	NDC	33332042010	Afluria Quadrivalent
	NDC	49281012065	FLUZONE High-Dose Quadrivalent Northern Hemisphere
	NDC	49281018125	FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE
	NDC	49281032050	FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE
	NDC	49281033615	FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE
	NDC	49281040565	FLUZONE High-Dose
	NDC	49281041810	FLUZONE QUADRIVALENT
	NDC	49281041850	FLUZONE QUADRIVALENT
	NDC	49281041910	FLUZONE QUADRIVALENT
	NDC	49281041950	FLUZONE QUADRIVALENT
	NDC	49281042010	FLUZONE QUADRIVALENT
	NDC	49281042050	FLUZONE QUADRIVALENT
	NDC	49281051825	FLUZONE QUADRIVALENT
	NDC	49281051925	FLUZONE QUADRIVALENT
	NDC	49281052025	FLUZONE QUADRIVALENT
	NDC	49281062915	FLUZONE QUADRIVALENT
	NDC	49281063115	FLUZONE QUADRIVALENT
	NDC	49281063315	FLUZONE QUADRIVALENT
	NDC	49281064015	INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE
	NDC	49281071810	Flublok Quadrivalent
	NDC	49281071910	Flublok Quadrivalent
	NDC	49281072010	Flublok Quadrivalent Northern Hemisphere

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Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	NDC	58160080815	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
	NDC	58160080815	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
	NDC	58160088352	FLUARIX
	NDC	58160088552	FLUARIX QUADRIVALENT
	NDC	58160089652	FLUARIX QUADRIVALENT
	NDC	58160089852	FLUARIX QUADRIVALENT
	NDC	63851061301	FLUCELVAX
	NDC	66019030510	FluMist Quadrivalent
	NDC	66019030610	FluMist Quadrivalent
	NDC	66019030710	FluMist Quadrivalent
	NDC	70461001803	FLUAD
	NDC	70461001903	FLUAD
	NDC	70461002003	FLUAD
	NDC	70461012003	FLUAD QUADRIVALENT
	NDC	70461031903	FLUCELVAX QUADRIVALENT
	NDC	70461032003	FLUCELVAX QUADRIVALENT
	NDC	70461041910	FLUCELVAX QUADRIVALENT
	NDC	70461042010	FLUCELVAX QUADRIVALENT
	CVX	15	Influenza, split (incl. purified surface antigen)
	CVX	16	Influenza, whole
	CVX	69	Parainfluenza-3
	CVX	88	Influenza, unspecified formulation
	CVX	111	Influenza, live, intranasal
	CVX	123	Influenza, H5N1-1203
	CVX	125	Novel Influenza-H1N1-09, nasal

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	CVX	126	Novel influenza-H1N1-09, preservative-free
	CVX	127	Novel influenza-H1N1-09
	CVX	128	Novel Influenza-H1N1-09, all formulations
	CVX	135	Influenza, high dose seasonal
	CVX	140	Influenza, seasonal, injectable, preservative free
	CVX	141	Influenza, seasonal, injectable
	CVX	144	Influenza, seasonal, intradermal, preservative free
	CVX	149	Influenza, live, intranasal, quadrivalent
	CVX	150	Influenza, injectable, quadrivalent, preservative free
	CVX	151	Influenza nasal, unspecified formulation
	CVX	153	Influenza, injectable, Madin-Darby Canine Kidney (MDCK), preservative free
	CVX	155	Influenza, recombinant, injectable, preservative free
	CVX	158	Influenza, injectable, quadrivalent
	CVX	160	Influenza A monovalent (H5N1), ADJUVANTED-2013
	CVX	161	Influenza, injectable,quadrivalent, preservative free, pediatric
	CVX	166	Influenza, intradermal, quadrivalent, preservative free
	CVX	168	Influenza, trivalent, adjuvanted
	CVX	171	Influenza, injectable, MDCK, preservative free, quadrivalent
	CVX	185	Influenza, recombinant, quadrivalent,injectable, preservative free
	CVX	186	Influenza, injectable, MDCK, quadrivalent, preservative
	CVX	194	Influenza, Southern Hemisphere
	CVX	197	Influenza, high-dose, quadrivalent
	CVX	200	Influenza, Southern Hemisphere, pediatric, preservative free
	CVX	201	Influenza, Southern Hemisphere, preservative free
	CVX	202	Influenza, Southern Hemisphere, quadrivalent, with preservative

Annex 3 Table A- 1. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC, CVX Codes

Vaccine	Code Type	Code[37]	Manufacturer/Descriptions
	CVX	205	Influenza vaccine, quadrivalent, adjuvanted

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
Neurologic		
Convulsions/seizures[33,34]	• 345.2, Petit mal status • 345.3, Grand mal status • 780.31, Febrile convulsions (simple), unspecified • 780.32, Complex febrile convulsions • 780.39, Other convulsions	• G40.401, Other generalized epilepsy and epileptic syndromes, not intractable, with status epilepticus • G40.409, Other generalized epilepsy and epileptic syndromes, not intractable, without status epilepticus • G40.411, Other generalized epilepsy and epileptic syndromes, intractable, with status epilepticus

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• G40.419, Other generalized epilepsy and epileptic syndromes, intractable, without status epilepticus • G40.501, Epileptic seizures related to external causes, not intractable, with status epilepticus • G40.509, Epileptic seizures related to external causes, not intractable, without status epilepticus • G40.802, Other epilepsy, not intractable, without status epilepticus • G40.804, Other epilepsy, intractable, without status epilepticus • G40.821, Epileptic spasms, not intractable, with status epilepticus • G40.822, Epileptic spasms, not intractable, without status epilepticus

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• G40.823, Epileptic spasms, intractable, with status epilepticus • G40.824, Epileptic spasms, intractable, without status epilepticus • G40.901, Epilepsy, unspecified, not intractable, with status epilepticus • G40.909, Epilepsy, unspecified, not intractable, without status epilepticus • R56.00, Simple febrile convulsions • R56.01, Complex febrile convulsions • R56.9, Unspecified convulsions
Guillain-Barré syndrome (GBS)[33,34]	• 357.0, Guillain-Barre syndrome	• G61.0, Guillain-Barre syndrome

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
Encephalitis/encephalomyelitis[33,34]	• 323.41, Other encephalitis and encephalomyelitis due to infection classified elsewhere • 323.51, Encephalitis and encephalomyelitis following immunization procedures • 323.52, Myelitis following immunization procedures • 323.62, Other postinfectious encephalitis and encephalomyelitis • 323.81, Other causes of encephalitis and encephalomyelitis • 323.9, Unspecified causes of encephalitis, myelitis, and encephalomyelitis	• G04.00, Acute disseminated encephalitis and encephalomyelitis, unspecified • G04.02, Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis • G04.81, Other encephalitis and encephalomyelitis • G04.89, Other myelitis • G04.90, Encephalitis and encephalomyelitis, unspecified • G05.3, Encephalitis and encephalomyelitis in diseases classified elsewhere

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
Transverse myelitis (TM)[33,34]	• 341.20, Acute (transverse) myelitis not elsewhere specified • 342.21 Acute (transverse) myelitis in conditions classified elsewhere	• G37.3, Acute transverse myelitis in demyelinating disease of central nervous system
Bell's palsy[33,34]	• 351.0, Bell's Palsy • 351.8, Other facial nerve disorders • 351.9, Facial nerve disorder, unspecified	• G51.0, Bell's palsy • G51.8, Other disorders of facial nerve • G51.9, Disorder of facial nerve, unspecified
Immunologic		
Anaphylaxis[33,34]	• 999.4, Anaphylactic shock due to serum not elsewhere specified • 995.0, Other anaphylactic reaction	• T78.2XXA, Anaphylactic shock, unspecified, initial encounter • T80.52XA, Anaphylactic reaction due to vaccination, initial encounter

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	**Operational Definition**	**Operational Definition**
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
Multisystem inflammatory syndrome in adults *(MIS-A)/ multisystem inflammatory syndrome in children (MIS-C)*[54]	N/A	≥1 diagnosis code for COVID-19 and ≥1 diagnosis code for other specified systemic involvement of connective tissue or multisystem inflammatory syndrome in the risk/control interval after the COVID-19 code • U07.1 COVID-19 • M35.8, Other specified systemic involvement of connective tissue • M35.81, Multisystem inflammatory syndrome • M35.89, Other specified systemic involvement of connective tissue

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	**Operational Definition**	**Operational Definition**
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		MIS-A will be defined in individuals ≥21 years of age, while MIS-C will be defined among individuals <21 years of age
Immune Thrombocytopenia (ITP)	N/A	• D.69.3, Immune thrombocytopenic purpura
Kawasaki disease (KD)	• 446.1, Acute febrile mucocutaneous lymph node syndrome [MCLS]	• M30.3, Mucocutaneous lymph node syndrome [Kawasaki]
Cardiac		
Myocarditis[33,34]	• 074.23, Coxsackie myocarditis • 422, Acute myocarditis in diseases classified elsewhere • 422.9, Acute myocarditis, unspecified	• B33.22, Viral myocarditis • I40.0, Infective myocarditis • I40.1, Isolated myocarditis • I40.8, Other acute myocarditis

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 422.91, Idiopathic myocarditis • 422.99, Other acute myocarditis • 429.0, Myocarditis, unspecified	• I40.9, Acute myocarditis, unspecified • I41, Myocarditis in diseases classified elsewhere • I51.4, Myocarditis, unspecified
Pericarditis[33,34]	• 074.21, Coxsackie pericarditis • 420.90, Acute pericarditis, unspecified • 420.91, Acute idiopathic pericarditis • 420.99, Other acute pericarditis • 420.0, Acute pericarditis in diseases classified elsewhere	• B33.23, Viral pericarditis • I30.0, Acute nonspecific idiopathic pericarditis • I30.1, Infective pericarditis • I30.8, Other forms of acute pericarditis • I30.9, Acute pericarditis, unspecified • I32, Pericarditis in diseases classified elsewhere

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
Acute myocardial infarction (AMI)[55]	• 410.01, Acute myocardial infarction of anterolateral wall, initial episode of care • 410.11, Acute myocardial infarction of other anterior wall, initial episode of care • 410.21, Acute myocardial infarction of inferolateral wall, initial episode of care • 410.31, Acute myocardial infarction of inferoposterior wall, initial episode of care • 410.41, Acute myocardial infarction of other inferior wall, initial episode of care • 410.51, Acute myocardial infarction of other lateral wall, initial episode of care	• I21, Acute myocardial infarction • I22.0, Subsequent ST elevation (STEMI) myocardial infarction of anterior wall • I22.1, Subsequent ST elevation (STEMI) myocardial infarction of inferior wall • I22.2, Subsequent non-ST elevation (NSTEMI) myocardial infarction • I22.8, Subsequent ST elevation (STEMI) myocardial infarction of other sites • I22.9, Subsequent ST elevation (STEMI) myocardial infarction of unspecified site

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	**Operational Definition**	**Operational Definition**
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 410.61, True posterior wall infarction, initial episode of care • 410.71, Subendocardial infarction, initial episode of care • 410.81, Acute myocardial infarction of other specified sites, initial episode of care • 410.91, Acute myocardial infarction of unspecified site, initial episode of care	
Hematologic		
Thrombosis with thrombocytopenia syndrome (TTS)	Diagnosis of both acute venous or arterial thromobsis AND new onset thrombocytopenia AND no history of receipt of heparin within 100 days.[56]	Diagnosis of both acute venous or arterial thromobsis AND new onset thrombocytopenia AND no history of receipt of heparin within 100 days.[56]

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	Acute venous or arterial thromobosis[54] • 411.81, Acute coronary occlusion without myocardial infarction • 429.89, Other ill-defined heart diseases • 433.91, Occlusion and stenosis of unspecified precerebral artery with cerebral infarction • 433.21, Occlusion and stenosis of vertebral artery with cerebral infarction • 433.01, Occlusion and stenosis of basilar artery with cerebral infarction • 433.11, Occlusion and stenosis of carotid artery with cerebral infarction • 433.81, Occlusion and stenosis of other specified precerebral artery with cerebral infarction	Acute venous or arterial thromobosis[54] • I24.0, Acute coronary thrombosis not resulting in myocardial infarction • I51.3, Intracardiac thrombosis, not elsewhere classified • I63.00, Cerebral infarction due to thrombosis of unspecified precerebral artery • I63.011, Cerebral infarction due to thrombosis of right vertebral artery • I63.012, Cerebral infarction due to thrombosis of left vertebral artery • I63.013, Cerebral infarction due to thrombosis of bilateral vertebral arteries

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 434.01, Cerebral thrombosis with cerebral infarction • 437.6, Nonpyogenic thrombosis of intracranial venous sinus • 444.09, Other arterial embolism and thrombosis of abdominal aorta • 444.1, Embolism and thrombosis of thoracic aorta • 444.21, Arterial embolism and thrombosis of upper extremity • 444.22, Arterial embolism and thrombosis of lower extremity • 444.81, Embolism and thrombosis of iliac artery • 444.89, Embolism and thrombosis of other specified artery	• I63.019, Cerebral infarction due to thrombosis of unspecified vertebral artery • I63.02, Cerebral infarction due to thrombosis of basilar artery • I63.031, Cerebral infarction due to thrombosis of right carotid artery • I63.032, Cerebral infarction due to thrombosis of left carotid artery • I63.033, Cerebral infarction due to thrombosis of bilateral carotid arteries • I63.039, Cerebral infarction due to thrombosis of unspecified carotid artery • I63.09, Cerebral infarction due to thrombosis of other precerebral artery

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 444.9, Embolism and thrombosis of unspecified artery • 452, Portal vein thrombosis • 453.87, Acute venous embolism and thrombosis of other thoracic veins • 453.2, Other venous embolism and thrombosis of inferior vena cava • 453.3, Other venous embolism and thrombosis of renal vein • 453.40, Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity • 453.41, Acute venous embolism and thrombosis of deep vessels of proximal lower extremity	• I63.30, Cerebral infarction due to thrombosis of unspecified cerebral artery • I63.311, Cerebral infarction due to thrombosis of right middle cerebral artery • I63.312, Cerebral infarction due to thrombosis of left middle cerebral artery • I63.313, Cerebral infarction due to thrombosis of bilateral middle cerebral arteries • I63.319, Cerebral infarction due to thrombosis of unspecified middle cerebral artery • I63.321, Cerebral infarction due to thrombosis of right anterior cerebral artery

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 453.42, Acute venous embolism and thrombosis of deep vessels of distal lower extremity • 453.83, Acute venous embolism and thrombosis of upper extremity, unspecified • 453.81, Acute venous embolism and thrombosis of superficial veins of upper extremity • 453.82, Acute venous embolism and thrombosis of deep veins of upper extremity • 453.84, Acute venous embolism and thrombosis of axillary veins • 453.85, Acute venous embolism and thrombosis of subclavian veins	• I63.322, Cerebral infarction due to thrombosis of left anterior cerebral artery • I63.323, Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries • I63.329, Cerebral infarction due to thrombosis of unspecified anterior cerebral artery • I63.331, Cerebral infarction due to thrombosis of right posterior cerebral artery • I63.332, Cerebral infarction due to thrombosis of left posterior cerebral artery • I63.333, Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
Thrombocytopenia[57]	• 453.86, Acute venous embolism and thrombosis of internal jugular veins • 453.6, Venous embolism and thrombosis of superficial vessels of lower extremity • 453.89, Acute venous embolism and thrombosis of other specified veins • 455.4, External thrombosed hemorrhoids • 455.7, Unspecified thrombosed hemorrhoids • 607.89, Other specified disorders of penis	• I63.339, Cerebral infarction due to thrombosis of unspecified posterior cerebral artery • I63.341, Cerebral infarction due to thrombosis of right cerebellar artery • I63.342, Cerebral infarction due to thrombosis of left cerebellar artery • I63.343, Cerebral infarction due to thrombosis of bilateral cerebellar arteries • I63.349, Cerebral infarction due to thrombosis of unspecified cerebellar artery • I63.39, Cerebral infarction due to thrombosis of other cerebral artery • I63.6, Cerebral infarction due to cerebral venous thrombosis, nonpyogenic

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**

	• 287.31, Immune thrombocytopenic purpura
	• 287.39, Other primary thrombocytopenia
	
	Heparin[54]
	• HCPCS
	  ○ J1642, Injection, heparin sodium, (heparin lock flush), per 10 units
	  ○ J1644, Injection, heparin sodium, per 1000 units
	  ○ E1520, Heparin infusion pump for hemodialysis
		• I67.6, Nonpyogenic thrombosis of intracranial venous system
		• I74.09, Other arterial embolism and thrombosis of abdominal aorta
		• I74.10, Embolism and thrombosis of unspecified parts of aorta
		• I74.11, Embolism and thrombosis of thoracic aorta
		• I74.19, Embolism and thrombosis of other parts of aorta
		• I74.2, Embolism and thrombosis of arteries of the upper extremities
		• I74.3, Embolism and thrombosis of arteries of the lower extremities
		• I74.4, Embolism and thrombosis of arteries of extremities, unspecified

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I74.5, Embolism and thrombosis of iliac artery • I74.8, Embolism and thrombosis of other arteries • I74.9, Embolism and thrombosis of unspecified artery • I81, Portal vein thrombosis • I82.210, Acute embolism and thrombosis of superior vena cava • I82.220, Acute embolism and thrombosis of inferior vena cava • I82.290, Acute embolism and thrombosis of other thoracic veins • I82.3, Embolism and thrombosis of renal vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.401, Acute embolism and thrombosis of unspecified deep veins of right lower extremity • I82.402, Acute embolism and thrombosis of unspecified deep veins of left lower extremity • I82.403, Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral • I82.409, Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity • I82.411, Acute embolism and thrombosis of right femoral vein • I82.412, Acute embolism and thrombosis of left femoral vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.413, Acute embolism and thrombosis of femoral vein, bilateral • I82.419, Acute embolism and thrombosis of unspecified femoral vein • I82.421, Acute embolism and thrombosis of right iliac vein • I82.422, Acute embolism and thrombosis of left iliac vein • I82.423, Acute embolism and thrombosis of iliac vein, bilateral • I82.429, Acute embolism and thrombosis of unspecified iliac vein • I82.431, Acute embolism and thrombosis of right popliteal vein • I82.432, Acute embolism and thrombosis of left popliteal vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.433, Acute embolism and thrombosis of popliteal vein, bilateral • I82.439, Acute embolism and thrombosis of unspecified popliteal vein • I82.441, Acute embolism and thrombosis of right tibial vein • I82.442, Acute embolism and thrombosis of left tibial vein • I82.443, Acute embolism and thrombosis of tibial vein, bilateral • I82.449, Acute embolism and thrombosis of unspecified tibial vein • I82.451, Acute embolism and thrombosis of right peroneal vein • I82.452, Acute embolism and thrombosis of left peroneal vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.453, Acute embolism and thrombosis of peroneal vein, bilateral • I82.459, Acute embolism and thrombosis of unspecified peroneal vein • I82.461, Acute embolism and thrombosis of right calf muscular vein • I82.462, Acute embolism and thrombosis of left calf muscular vein • I82.463, Acute embolism and thrombosis of calf muscular vein, bilateral • I82.469, Acute embolism and thrombosis of unspecified calf muscular vein • I82.491, Acute embolism and thrombosis of other specified deep vein of right lower extremity

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.492, Acute embolism and thrombosis of other specified deep vein of left lower extremity • I82.493, Acute embolism and thrombosis of other specified deep vein of lower extremity, bilateral • I82.499, Acute embolism and thrombosis of other specified deep vein of unspecified lower extremity • I82.4Y1, Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity • I82.4Y2, Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity • I82.4Y3, Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.4Y9, Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity • I82.4Z1, Acute embolism and thrombosis of unspecified deep veins of right distal lower extremity • I82.4Z2, Acute embolism and thrombosis of unspecified deep veins of left distal lower extremity • I82.4Z3, Acute embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral • I82.4Z9, Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity • I82.601, Acute embolism and thrombosis of unspecified veins of right upper extremity

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.602, Acute embolism and thrombosis of unspecified veins of left upper extremity • I82.603, Acute embolism and thrombosis of unspecified veins of upper extremity, bilateral • I82.609, Acute embolism and thrombosis of unspecified veins of unspecified upper extremity • I82.611, Acute embolism and thrombosis of superficial veins of right upper extremity • I82.612, Acute embolism and thrombosis of superficial veins of left upper extremity • I82.613, Acute embolism and thrombosis of superficial veins of upper extremity, bilateral

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.619, Acute embolism and thrombosis of superficial veins of unspecified upper extremity • I82.621, Acute embolism and thrombosis of deep veins of right upper extremity • I82.622, Acute embolism and thrombosis of deep veins of left upper extremity • I82.623, Acute embolism and thrombosis of deep veins of upper extremity, bilateral • I82.629, Acute embolism and thrombosis of deep veins of unspecified upper extremity • I82.A11, Acute embolism and thrombosis of right axillary vein • I82.A12, Acute embolism and thrombosis of left axillary vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.A13, Acute embolism and thrombosis of axillary vein, bilateral • I82.A19, Acute embolism and thrombosis of unspecified axillary vein • I82.B11, Acute embolism and thrombosis of right subclavian vein • I82.B12, Acute embolism and thrombosis of left subclavian vein • I82.B13, Acute embolism and thrombosis of subclavian vein, bilateral • I82.B19, Acute embolism and thrombosis of unspecified subclavian vein • I82.C11, Acute embolism and thrombosis of right internal jugular vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.C12, Acute embolism and thrombosis of left internal jugular vein • I82.C13, Acute embolism and thrombosis of internal jugular vein, bilateral • I82.C19, Acute embolism and thrombosis of unspecified internal jugular vein • I82.811, Embolism and thrombosis of superficial veins of right lower extremity • I82.812, Embolism and thrombosis of superficial veins of left lower extremity • I82.813, Embolism and thrombosis of superficial veins of lower extremities, bilateral

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.819, Embolism and thrombosis of superficial veins of unspecified lower extremity • I82.890, Acute embolism and thrombosis of other specified veins • I82.90, Acute embolism and thrombosis of unspecified vein • K64.5, Perianal venous thrombosis • N48.81, Thrombosis of superficial vein of penis Thrombocytopenia[57] • D69.3, Immune thrombocytopenic purpura

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**

		Heparin[54]
		• HCPCS
		  ○ J1642, Injection, heparin sodium, (heparin lock flush), per 10 units
		  ○ J1644, Injection, heparin sodium, per 1000 units
		  ○ E1520, Heparin infusion pump for hemodialysis

Disseminated intravascular coagulation (DIC)[55]	• 286.6, Defibrination syndrome	• D65, Disseminated intravascular coagulation [defibrination syndrome]
Deep vein thrombosis (DVT)[55]	• 453.2, Other venous embolism and thrombosis of inferior vena cava	• I82.401, Acute embolism and thrombosis of unspecified deep veins of right lower extremity

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 453.3, Other venous embolism and thrombosis of renal vein • 453.40, Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity • 453.41, Acute venous embolism and thrombosis of deep vessels of proximal lower extremity • 453.42, Acute venous embolism and thrombosis of deep vessels of distal lower extremity • 453.82, Acute venous embolism and thrombosis of deep veins of upper extremity	• I82.402, Acute embolism and thrombosis of unspecified deep veins of left lower extremity • I82.403, Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral • I82.409, Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity • I82.411, Acute embolism and thrombosis of right femoral vein • I82.412, Acute embolism and thrombosis of left femoral vein • I82.413, Acute embolism and thrombosis of femoral vein, bilateral • I82.419, Acute embolism and thrombosis of unspecified femoral vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.421, Acute embolism and thrombosis of right iliac vein • I82.422, Acute embolism and thrombosis of left iliac vein • I82.423, Acute embolism and thrombosis of iliac vein, bilateral • I82.429, Acute embolism and thrombosis of unspecified iliac vein • I82.431, Acute embolism and thrombosis of right popliteal vein • I82.432, Acute embolism and thrombosis of left popliteal vein • I82.433, Acute embolism and thrombosis of popliteal vein, bilateral • I82.439, Acute embolism and thrombosis of unspecified popliteal vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.441, Acute embolism and thrombosis of right tibial vein • I82.442, Acute embolism and thrombosis of left tibial vein • I82.443, Acute embolism and thrombosis of tibial vein, bilateral • I82.449, Acute embolism and thrombosis of unspecified tibial vein • I82.451, Acute embolism and thrombosis of right peroneal vein • I82.452, Acute embolism and thrombosis of left peroneal vein • I82.453, Acute embolism and thrombosis of peroneal vein, bilateral • I82.459, Acute embolism and thrombosis of unspecified peroneal vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.461, Acute embolism and thrombosis of right calf muscular vein • I82.462, Acute embolism and thrombosis of left calf muscular vein • I82.463, Acute embolism and thrombosis of calf muscular vein, bilateral • I82.469, Acute embolism and thrombosis of unspecified calf muscular vein • I82.491, Acute embolism and thrombosis of other specified deep vein of right lower extremity • I82.492, Acute embolism and thrombosis of other specified deep vein of left lower extremity • I82.493, Acute embolism and thrombosis of other specified deep vein of lower extremity, bilateral

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.499, Acute embolism and thrombosis of other specified deep vein of unspecified lower extremity • I82.4Y1, Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity • I82.4Y2, Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity • I82.4Y3, Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral • I82.4Y9, Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity • I82.4Z1, Acute embolism and thrombosis of unspecified deep veins of right distal lower extremity

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.4Z2, Acute embolism and thrombosis of unspecified deep veins of left distal lower extremity • I82.4Z3, Acute embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral • I82.4Z9, Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity • I82.601, Acute embolism and thrombosis of unspecified veins of right upper extremity • I82.602, Acute embolism and thrombosis of unspecified veins of left upper extremity • I82.603, Acute embolism and thrombosis of unspecified veins of upper extremity, bilateral

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I82.609, Acute embolism and thrombosis of unspecified veins of unspecified upper extremity • I82.621, Acute embolism and thrombosis of deep veins of right upper extremity • I82.622, Acute embolism and thrombosis of deep veins of left upper extremity • I82.623, Acute embolism and thrombosis of deep veins of upper extremity, bilateral • I82.629, Acute embolism and thrombosis of deep veins of unspecified upper extremity • I82.890, Acute embolism and thrombosis of other specified veins • I82.90, Acute embolism and thrombosis of unspecified vein

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
Pulmonary embolism[55]	• 415.13, Saddle embolus of pulmonary artery • 415.0, Acute cor pulmonale 415.19, Other pulmonary embolism and infarction	• I26.02, Saddle embolus of pulmonary artery with acute cor pulmonale • I26.09, Other pulmonary embolism with acute cor pulmonale • I26.92, Saddle embolus of pulmonary artery without acute cor pulmonale • I26.93, Single subsegmental pulmonary embolism without acute cor pulmonale • I26.94, Multiple subsegmental pulmonary emboli without acute cor pulmonale • I26.99, Other pulmonary embolism without acute cor pulmonale
Cerebral venous sinus thrombosis[12]	• 325, Phlebitis and thrombophlebitis of intracranial venous sinuses	• G08, Intracranial and intraspinal phlebitis and thrombophlebitis

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 434.01, Cerebral thrombosis with cerebral infarction • 437.6, Nonpyogenic thrombosis of intracranial venous sinus Exclude if incident case occurs any time during pregnancy or within 6 weeks after pregnancy ends: • 671.5x, Other phlebitis and thrombosis in pregnancy and the puerperium	• I63.6, Cerebral infarction due to cerebral venous thrombosis, nonpyogenic • I67.6, Nonpyogenic thrombosis of intracranial venous system Exclude if incident case occurs any time during pregnancy or within 6 weeks after pregnancy ends: • O22.5x Cerebral venous thrombosis in pregnancy • O87.3 Cerebral venous thrombosis in the puerperium
Hemorrhagic stroke[33,34]	• 431, Intracerebral hemorrhage • 432.1, Subdural hemorrhage • 432.9, Unspecified intracranial hemorrhage	• I60.9, Nontraumatic subarachnoid hemorrhage, unspecified • I61.0, Nontraumatic intracerebral hemorrhage in hemisphere, subcortical

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I61.1, Nontraumatic intracerebral hemorrhage in hemisphere, cortical • I61.2, Nontraumatic intracerebral hemorrhage in hemisphere, unspecified • I61.3, Nontraumatic intracerebral hemorrhage in brain stem • I61.4, Nontraumatic intracerebral hemorrhage in cerebellum • I61.5, Nontraumatic intracerebral hemorrhage, intraventricular • I61.6, Nontraumatic intracerebral hemorrhage, multiple localized • I61.8, Other nontraumatic intracerebral hemorrhage • I61.9, Nontraumatic intracerebral hemorrhage, unspecified

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• I62.1, Nontraumatic extradural hemorrhage • I62.00, Nontraumatic subdural hemorrhage, unspecified • I62.01, Nontraumatic acute subdural hemorrhage • I62.02, Nontraumatic subacute subdural hemorrhage • I62.9, Nontraumatic intracranial hemorrhage, unspecified
Non-hemorrhagic stroke[33,34]	• 433.91, Occlusion and stenosis of unspecified precerebral artery with cerebral infarction • 433.21, Occlusion and stenosis of vertebral artery with cerebral infarction	• I63, Cerebral infarction

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 433.01, Occlusion and stenosis of basilar artery with cerebral infarction • 433.11, Occlusion and stenosis of carotid artery with cerebral infarction • 433.31, Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction • 433.81, Occlusion and stenosis of other specified precerebral artery with cerebral infarction • 434.01, Cerebral thrombosis with cerebral infarction • 434.11, Cerebral embolism with cerebral infarction • 434.91, Cerebral artery occlusion, unspecified with cerebral infarction	

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
Acute respiratory distress syndrome[47]	518.82 Other pulmonary insufficiency, not elsewhere classified	• J80, Acute respiratory distress syndrome
Other		
Death	• Defined by the "deathcode" variable. 'Y' indicates the person is dead	• Defined by the "deathcode" variable. 'Y' indicates the person is dead
Narcolepsy[55]	• 347, Narcolepsy, without cataplexy • 347.01, Narcolepsy, with cataplexy • 347.1, Narcolepsy in conditions classified elsewhere, without cataplexy • 347.11, Narcolepsy in conditions classified elsewhere, with cataplexy	• G47.411, Narcolepsy with cataplexy • G47.419, Narcolepsy without cataplexy • G47.421, Narcolepsy in conditions classified elsewhere with cataplexy • G47.429, Narcolepsy in conditions classified elsewhere without cataplexy
Appendicitis[55]	• 540.9, Acute appendicitis without mention of peritonitis	• K35.20, Acute appendicitis with generalized peritonitis, without abscess

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	Operational Definition	Operational Definition
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
	• 541, Appendicitis, unqualified • 542, Other appendicitis	• K35.21, Acute appendicitis with generalized peritonitis, with abscess • K35.30, Acute appendicitis with localized peritonitis, without perforation or gangrene • K35.31, Acute appendicitis with localized peritonitis and gangrene, without perforation • K35.32, Acute appendicitis with perforation and localized peritonitis, without abscess • K35.33, Acute appendicitis with perforation and localized peritonitis, with abscess • K35.80, Unspecified acute appendicitis • K35.890, Other acute appendicitis without perforation or gangrene

Annex 3 Table A- 2. Operational Definitions of Safety Events of Interest

Variable	**Operational Definition**	**Operational Definition**
	Defined by the presence of any of the following ICD-9-CM codes (inclusive)*:	**Defined by the presence of any of the following ICD-10-CM codes (inclusive)*:**
		• K35.891, Other acute appendicitis without perforation, with gangrene • K36, Other appendicitis • K37, Unspecified appendicitis

* A Medicare General Equivalence Mappings (GEMs)-based crosswalk was used to map ICD-9-CM codes obtained in the literature to ICD-10-CM codes. For ICD-9-CM codes not found in the literature, backwards mapping was applied to ICD-10-CM codes identified in 2021 ICD-10-CM Centers for Medicare & Medicaid Services Coding Guidelines.

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
Demographic Characteristics		
Age	Continuous variable; Categorical variable: • 0 to <6 months (if feasible) • 6 months to <1 year (if feasible) • 1 to <5 years • 5 to <12 years • 12 to <18 years • 18 to <25 years • 25 to <30 years • 30 to <40 years • 40 to <50 years • 50 to <65 years • ≥65 years	Age as of the date prior to Pfizer-BioNTech COVID-19 vaccination (and/or date of seasonal influenza vaccination for active comparators, matched index date for contemporary unvaccinated controls)
Sex	Categorical variable: • Male • Female • Unknown	
Geographic Region	Geographic regions	State and/or country of residence
Sponsor service	Categorical variable: • Army • Air Force • Coast Guard	

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
	• Marine Corps • Navy • Other • Unknown	
Beneficiary category	Categorical variable: • Active Duty • Retirees • Active Guard/Reserve • Dependents of Active Duty • Dependents of Retiree • Dependent Survivor • Dependent of Active Guard/Reserve • Inactive Guard/Reserve • Family Member of Inactive Guard/Reserve • Other • Unknown	
Clinical Characteristics		
Smoking	Dichotomous variable	Defined by the "tobacco" variable. 'Y' indicates the person is a tobacco user ICD-9-CM codes: • 305.1, Tobacco use disorder • V15.82, History of tobacco use

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		ICD-10-CM codes: • F17.200, Nicotine dependence, unspecified, uncomplicated • Z7.20, Tobacco use • Z87.891, Personal history of nicotine dependence
Body mass index (BMI)	Continuous variable; Categorical variable: • Underweight (<18.5) • Normal weight (18.5-24.9) • Overweight (25-29.9) • Obese (≥30 - <40) • Severe obesity (≥40) • Unknown	Calculated from height and weight data (kg/m^2) ICD-9-CM codes: • V85.0, Body Mass Index less than 19, adult • V85.1, Body Mass Index between 19-24, adult • V85.2, Body mass index between 25-29, adult • V85.3, Body mass index between 30-39, adult • V85.4, Body mass index 40 and over, adult ICD-10-CM codes: • Z68.1, Body Mass Index 19.9 or less, adult • Z68.2, Body mass index 20-29, adult • Z68.3, Body mass index between 30-39, adult • Z68.4, Body mass index 40 and over, adult
History of anaphylaxis/allergic reactions	Dichotomous variable	ICD-9-CM code: • V13.81, Personal history of anaphylaxis • V14.0 - V14.6, V14.8, V14.9, Personal history of allergy to drugs, medications and biological substances, excluding serum and vaccine • V15.0x, Other allergy

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		• 525.66, Allergy to existing dental restorative material • 995.0, Other anaphylactic shock, not elsewhere classified • 995.1, Angioneurotic edema, not elsewhere classified • 995.21, Arthus phenomenon • 999.27, Other drug allergy • 995.3, Allergy, unspecified, not elsewhere classified • 995.6x, Anaphylactic shock due to food • 999.41, Anaphylactic reaction due to administration of blood and blood products • 999.49, Anaphylactic reaction due to other serum ICD-10-CM code: • Z87.892 Personal history of anaphylaxis • Z88.0 - Z88.6, Z88.8, Z88.9, Allergy status to drugs, medications and biological substances, excluding serum and vaccine • T78.00xx-T78.09xx, Anaphylactic reaction due to food, initial encounter, subsequent encounter and sequela • T78.2xxx, Anaphylactic shock, initial encounter, subsequent encounter and sequela • T78.3xxx, Angioneurotic edema, initial encounter, subsequent encounter and sequela • T78.41xx, Arthus phenomenon

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		• T80.51xx, Anaphylactic reaction due to administration of blood and blood products, initial encounter, subsequent encounter and sequela • T80.59xx, Anaphylactic reaction due to other serum, initial encounter, subsequent encounter and sequela • T88.6xxx, Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter, subsequent encounter and sequela
Previous anaphylaxis of vaccine component	Dichotomous variable	ICD-9-CM code: • 999.42, Anaphylactic reaction due to vaccination • V14.7, Personal history of allergy to serum or vaccine ICD-10-CM codes: • T80.52xx, Anaphylactic reaction due to vaccination, initial encounter, subsequent encounter and sequela • Z28.04, Immunization not carried out because of patient allergy to vaccine or component • Z88.7, Allergy status to serum and vaccine

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
History of hospitalizations	Dichotomous variable; Continuous variable	Defined by having any hospitalizations (dichotomous) and number of hospitalizations (continuous)
Pregnancy	Dichotomous variable	LOINC code: • 82810-3, Pregnancy status • 11449-6, Pregnancy status - Reported ICD-9-CM codes: • V22.x, Normal pregnancy • V23.x, V23.xx, Supervision of high-risk pregnancy ICD-10-CM codes: • Z33.1, Pregnant state, incidental • Z33.3, Pregnant state, gestational carrier • Z34, Supervision of normal pregnancy • O09.x, Supervision of high risk pregnancy
Charlson Comorbidity Index (CCI)	Continuous variable	ICD-9-CM codes: • 410.x, 412.x, Myocardial infarction • 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 - 425.9, 428.x, Congestive heart failure

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		• 093.0, 437.3, 440.x, 441.x, 443.1 - 443.9, 447.1, 557.1, 557.9, V43.4, Peripheral vascular disease • 362.34, 430.x - 438.x, Cerebrovascular disease • 290.x, 294.1, 331.2, Dementia • 416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8, Chronic pulmonary disease • 446.5, 710.0 - 710.4, 714.0 - 714.2, 714.8, 725.x, Rheumatic disease • 531.x - 534.x, Peptic ulcer disease • 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7, Mild liver disease • 250.0 - 250.3, 250.8, 250.9, Diabetes without chronic complication • 250.4 - 250.7, Diabetes with chronic complication • 334.1, 342.x, 343.x, 344.0 - 344.6, 344.9, Hemiplegia or paraplegia • 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0 - 583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x, Renal disease • 140.x - 172.x, 174.x - 195.8, 200.x - 208.x, 238.6, Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin • 456.0 - 456.2, 572.2- 572.8, Moderate or severe liver disease • 196.x - 199.x, Metastatic solid tumor

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		ICD-10-CM codes: • I21.x, I21.xx, I22.x, I25.2, Myocardial infarction • I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43, I43.x, I50.x, I50.xx, Congestive heart failure • I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9, Peripheral vascular disease • G45, G45.x, G46.x, H34.0, I60.x - I63.x, I60.xx - I63.xx, I60.xxx - I63.xxx, I65.x - I69.x, I65.xx - I69.xx, I65.xxx - I69.xxx, Cerebrovascular disease • F00.x - F03.x, F00.xx - F03.xx, F05, F05.1, G30.x, G31.1, Dementia • I27.8, I27.9, J40.x - J47.x, J40.xx - J47.xx, J40.xxx - J47.xxx, J60.x - J67.x, J68.4, J70.1, J70.3, Chronic pulmonary disease • M05, M05.x, M05.xx, M05.xxx, M06, M06.x, M06.xx, M06.xxx, M31.5, M32.x - M34.x, M32.xx - M34.xx, M35.1, M35.3, M36.0, Rheumatic disease • K25.x - K28.x, Peptic ulcer disease • B18.x, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73.x, K74.x, K74.xx, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4, Mild liver disease • E10.0, E10.1x, E10.6x, E10.6xx, E10.8, E10.9, E11.0x, E11.1x, E11.6x, E11.6xx, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0x,

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		E13.1x, E13.6x, E13.6xx, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9, Diabetes without chronic complication • E10.2x - E10.5x, E10.2xx - E10.5xx, E10.7, E11.2x - E11.5x, E11.2xx - E11.5xx, E11.7, E12.2 - E12.5, E12.7, E13.2 - E13.5x, E13.7, E14.2 - E14.5, E14.7, Diabetes with chronic complication • G04.1, G11.4, G80.1, G80.2, G81.x, G81.xx, G82.x, G82.xx, G83.0, G83.1-G83.3, G83.1x-G83.3x, G83.4, G83.9, Hemiplegia or paraplegia • I12.0, I13.1x, N03.2 - N03.7, N05.2 - N05.7, N18.x, N19, N25.0, Z49.0x - Z49.3x, Z94.0, Z99.2, Renal disease • C00-C75, C00.x-C75.x, C00.xx-C75.xx (excluding C44, C44.x and C44.xx), C7A., C7A.x, C7A.xx, C7B., C7B.x, C7B.xx, C76-C80, C76.x-C80.x, C76.xx-C80.xx, C81-C96, C81.x-C96.x, C81.xx-C96.xx, Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin • I85.0, I85.9, I86.4, I98.2, K70.4x, K71.1x, K72.1x, K72.9x, K76.5, K76.6, K76.7, Moderate or severe liver disease • C77.x - C80.x, C77.xx - C80.xx, Metastatic solid tumor
Comorbidities	Categorical variable: • Autoimmune disease	Autoimmune disease (immunocompromised state [weakened immune system] from solid organ transplant): ICD-9-CM codes:

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
	• Asthma • Bleeding diathesis or condition associated with prolonged bleeding • Cancer • Cardiovascular conditions (eg, heart failure, CAD, cardiomyopathies) • Chronic kidney disease/dialysis • COPD/interstitial lung disease • Diabetes mellitus (ie, Type 2 diabetes) • Down syndrome • Sickle cell disease • HBV • HCV • Hyperlipidemia • Hypertension • Liver disease • Neurological disease • Other immune deficiencies • Solid organ transplant • VTE	• 245.2, Chronic lymphocytic thyroiditis • 340, Multiple sclerosis • 357, Acute infective polyneuritis • 357.4, Polyneuropathy in other diseases classified elsewhere • 694.3, Impetigo herpetiformis • 696.1, Other psoriasis • 696, Psoriatic arthropathy • 695.4, Lupus erythematosus • 714, 714.x, 714.xx, Rheumatoid arthritis and other inflammatory polyarthropathies • 359.6, Symptomatic inflammatory myopathy in diseases classified elsewhere • 357.1, Polyneuropathy in collagen vascular disease • 714.89, Other specified inflammatory polyarthropathies • 714.9, Unspecified inflammatory polyarthropathy • 446.5, Giant cell arteritis • 710.2, Sicca syndrome ICD-10-CM codes: • D69.3, Immune thrombocytopenic purpura • E06.3, Autoimmune thyroiditis • G35, MS • G61.0 and G65.0, GBS and sequelae of GBS • L40.x, L40.5x, Psoriasis • L93.x, Lupus erythematosus

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		• M05.x, M05.xx, M05.xxx, Rheumatoid arthritis with rheumatoid factor • M06.x, M06.xx, M06.xxx, Other rheumatoid arthritis • M31.5, M31.6, Giant cell arteritis • M35.0x, Sicca (Sjogren's) syndrome • E10, E10.x, E10.xx, Type 1 diabetes mellitus • N05.9, Glomerulonephritis • D84.9, Immunodeficiency, unspecified Asthma: ICD-9-CM codes: • 493.xx, Asthma ICD-10-CM codes: • J45.2x - J45.3x, Mild intermittent asthma • J45.4x, Moderate persistent asthma • J45.5x, Severe persistent asthma • J45.9x, Other and unspecified asthma Bleeding diathesis or condition associated with prolonged bleeding: ICD-9-CM codes: • 286.x, Coagulation defects • 289.8x, Other specified diseases of blood and blood-forming organs • 287, 287.x, 287.xx, Purpura and other hemorrhagic conditions

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		ICD-10-CM codes: • D65, Disseminated intravascular coagulation • D66, Hereditary factor VIII deficiency • D67, Hereditary factor IX deficiency • D68, D68.x, D68.xx, Other coagulation defects • D69, D69.x, D69.xx, Purpura and other hemorrhagic conditions Cancer: ICD-9-CM codes: • 140.x -149.x, Malignant neoplasm of lip, oral cavity, and pharynx • 150.x -159.x, Malignant neoplasm of digestive organs and peritoneum • 160.x -165.x, Malignant neoplasm of respiratory and intrathoracic organs • 170.x -176.x, Malignant neoplasm of bone, connective tissue, skin, and breast • 179.x - 189.x, Malignant neoplasm of genitourinary organs • 190.x - 199.x, Malignant neoplasm of other unspecified sites • 200.xx - 208.xx, Malignant neoplasm of lymphatic and hematopoietic tissue • 209.0x - 209.3x, Malignant neuroendocrine tumors • 230.x - 234.x, Carcinoma in situ of digestive organs

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		ICD-10-CM codes: • C00-C75, C00.x-C75.x, C00.xx-C75.xx, C7A., C7A.x, C7A.xx, C7B., C7B.x, C7B.xx, Malignant neoplasms, stated or presumed to be primary (of specified sites), and certain specified histologies, except neuroendocrine, and of lymphoid, hematopoietic and related tissue • C76-C80, C76.x-C80.x, C76.xx-C80.xx, Malignant neoplasms of ill-defined, other secondary and unspecified sites • C81-C96, C81.x-C96.x, C81.xx-C96.xx, Malignant neoplasms of lymphoid, hematopoietic and related tissue Cardiovascular conditions (eg, heart failure, coronary artery disease [CAD], cardiomyopathies): ICD-9-CM codes: • 428.xx, Heart failure • 414.01, 429.2, 411.1, 413.9, 414.11, 414.12, 414.05, 414.02, 414.04, 414.03, 414.06, 414.07, 414.2, 411.81, 411.89, CAD • 425.xx, Cardiomyopathy ICD-10-CM codes: • 150.x, 150.xx, Heart failure • I24.0, I24.8, I24.9, I25.10, I25.110, I25.111, I25.118, I25.119, I25.41, I25.42, I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718,

Annex 3 Table A- 3. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, CAD • I42.x, Cardiomyopathy Chronic kidney disease/dialysis: ICD-9-CM codes: • 283.11, Hemolytic-uremic syndrome • 403, 403.x, 403.xx, Hypertensive chronic kidney disease • 404, 404.x, 404.xx, Hypertensive heart and chronic kidney disease • 440.1, Atherosclerosis of renal artery • 442.1, Aneurysm of renal artery • 572.4, Hepatorenal syndrome • 274.1, Gouty nephropathy, unspecified • 710, Systemic lupus erythematosus • 710.2, Sicca syndrome • 580, 580.x, 580.xx, Acute glomerulonephritis • 581.x, 581.xx, Nephrotic syndrome • 582, 582.x, 582.xx, Chronic glomerulonephritis • 583, 583.x, 583,xx, Nephritis and nephropathy, not specified as acute or chronic • 591, Hydronephrosis • 593.3, Stricture or kinking of ureter

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Variable	Description	Operational definition
		• 592, Calculus of kidney • 592.1, Calculus of ureter • 590.9, Infection of kidney, unspecified • 584.x, Acute kidney failure • 585.x, Chronic kidney disease • 588.x, 588.xx, Disorders resulting from impaired renal function • 587, Renal sclerosis, unspecified • 753.1x, Cystic kidney disease • 753.2, 753.2x, Obstructive defects of renal pelvis and ureter ICD-10-CM codes: • D59.3, Hemolytic-uremic syndrome • I12.x, Hypertensive chronic kidney disease • I13.x, I13.xx, Hypertensive heart and chronic kidney disease • I70.1, Atherosclerosis of renal artery • I72.2 Aneurysm of renal artery • K76.7, Hepatorenal syndrome • M10.30-M10.39, M10.30x-M10.37x, Gout due to renal impairment • M32.14, Glomerular disease in systemic lupus erythematosus • M32.15, Tubulo-interstitial nephropathy in systemic lupus erythematosus

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Variable	Description	Operational definition
		• M35.04, Sicca syndrome with tubulo-interstitial nephropathy • N00.x-N07.x, N08, Glomerular diseases • N13.1, N13.2, N13.3x, Obstructive and reflux uropathy • N14.x, Nephropathy • N15.x, Other renal tubulo-interstitial diseases • N16, Renal tubulo-interstitial disorders in diseases classified elsewhere • N17.x, N18.x, N19, Acute kidney failure and chronic kidney disease • N25.x, N26.x, N25.xx, Other disorders of kidney and ureter • Q61.02, Q61.11x, Q61.2-Q61.9, Cystic kidney disease • Q62.x, Q62.xx, Congenital obstructive defects of renal pelvis and congenital malformation of ureter COPD/interstitial lung disease: ICD-9-CM codes: • 491.9, Unspecified chronic bronchitis • 492.8, Other emphysema • 491.x, 491.xx, Chronic bronchitis • 493.2, Chronic obstructive asthma, unspecified • 496, Chronic airway obstruction, not elsewhere classified

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Variable	Description	Operational definition
		• 516, 516.x, 516.xx, Other alveolar and parietoalveolar pneumonopathy • 515, Postinflammatory pulmonary fibrosis • 518.x, 518.xx, Other diseases of lung • 714.81, Rheumatoid lung ICD-10-CM codes: • J41.x Simple and mucopurulent chronic bronchitis • J42, Unspecified chronic bronchitis • J43.x, Emphysema • J44.x, Other COPD • J80, J81.x, J82.xx, J84.xx, J84.xxx, Other respiratory diseases principally affecting the interstitium • M05.10, Rheumatoid lung disease with rheumatoid arthritis of unspecified site Diabetes mellitus: ICD-9-CM codes: • 250.xx, Diabetes mellitus ICD-10-CM codes: • E10.x, E10.xx, E10.xxx, Type 1 diabetes mellitus • E11.x, E11.xx, E11.xxx, Type 2 diabetes mellitus Down syndrome: ICD-9-CM codes: • 758.x, Down syndrome ICD-10-CM codes:

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Variable	Description	Operational definition
		• Q90.x, Down syndrome Sickle cell disease: ICD-9-CM codes: • 282.xx, Sickle-cell disease ICD-10-CM codes: • D57, D57.x, D57.xx, D57.xxx, Sickle-cell disorders HBV: ICD-9-CM codes: • 70.33, Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta • 70.32, Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta • 70.3, Viral hepatitis B without mention of hepatic coma, acute or unspecified, without mention of hepatitis delta • 70.2, Viral hepatitis B with hepatic coma, acute or unspecified, without mention of hepatitis delta ICD-10-CM codes: • B18.0, B18.1, Chronic viral hepatitis B • B19.1, B19.1x, Unspecified viral hepatitis B HCV: ICD-9-CM codes: • 70.7, Unspecified viral hepatitis C without hepatic coma

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Variable	Description	Operational definition
		• 70.71, Unspecified viral hepatitis C with hepatic coma • 70.54, Chronic hepatitis C without mention of hepatic coma ICD-10-CM codes: • B18.2, Chronic viral hepatitis C • B19.2x, Unspecified viral hepatitis C Hyperlipidemia ICD-9-CM codes: • 272.0x, Pure hypercholesterolemia • 272.1x, Pure hyperglyceridemia • 272.2x, Mixed hyperlipidemia • 272.4x, Hyperlipidemia, NOS ICD-10-CM codes: • E78.0-E78.5, E78.0x, E78.4x, Hyperlipidemia Hypertension: ICD-9-CM codes: • 401.1, Benign essential hypertension • 401.9, Essential hypertension, NOS • 405.1, Benign secondary hypertension • 405.9, Secondary hypertension, NOS • 997.91, Hypertension, NOS ICD-10-CM codes: • H35.03x, Hypertensive retinopathy

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Variable	Description	Operational definition
		• I10, I11.x-I16.x, I13.xx, Hypertensive diseases • I67.4, Hypertensive encephalopathy diseases Liver disease: ICD-9-CM codes: • 571, 571.x, Alcoholic fatty liver • 572, 572.x, Hepatic encephalopathy • 573.x, Other disorder of liver • 570, Acute and subacute necrosis of liver ICD-10-CM codes: • K70.x, K70.xx, Alcoholic fatty liver • K71.x, K71.xx, Toxic liver disease • K72.xx, Hepatic failure, not elsewhere classified • K73.x, Chronic hepatitis, not elsewhere specified • K74.x, K74.xx, Fibrosis and cirrhosis of liver • K75.x, K75.xx, Other inflammatory liver diseases • K76.x, K76.xx, Other diseases of liver • K77, Liver disorders in diseases classified elsewhere Neurological disease: ICD-9-CM codes: • 780.97, Altered mental status • 780.93, Memory loss • 781.8, Neurologic neglect syndrome • 797, Senility without mention of psychosis

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Variable	Description	Operational definition
		• V62.89, Other psychological or physical stress, not elsewhere classified • 799.5x, Signs and symptoms involving cognition • 780.99, Other general symptoms • 780.4, Dizziness and giddiness • 781.1, Disturbances of sensation of smell and taste • V41.5, Problems with smell and taste • 368.16, Psychophysical visual disturbances • 307.9, Other and unspecified special symptoms or syndromes, not elsewhere classified • 300.9, Unspecified nonpsychotic mental disorder • 308.9, Unspecified acute reaction to stress • 307.9, Other and unspecified special symptoms or syndromes, not elsewhere classified • V62.85, Homicidal ideation • V62.84, Suicidal ideation • 799.24, Emotional lability • 799.23, Impulsiveness • 799.29, Other signs and symptoms involving emotional state • V40.39, Other specified behavioral problem ICD-10-CM codes: • R41, R41.x, R41.xx, Other symptoms and signs involving cognitive functions and awareness • R42, Dizziness and giddiness • R43, R43.x, Disturbances of smell and taste

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Variable	Description	Operational definition
		• R44, R44.x, Other symptoms and signs involving general sensations and perceptions • R45, R45.x, R45. xx, Symptoms and signs involving emotional state • R46, R46.x, R46. xx, Symptoms and signs involving appearance and behavior Other immune deficiencies: ICD-9-CM codes: • 279.x, 279.xx, Deficiency of humoral immunity • 135, Sarcoidosis • 273.x, Disorders of plasma protein metabolism ICD-10-CM codes: • D80, D80.x, Immunodeficiency with predominantly antibody defects • D81, D81.x, D81.xx, Combined immunodeficiencies • D82, D82.x, Immunodeficiency associated with other major defects • D83, D83.x, Common variable immunodeficiency • D84, D84.x, D84.xx, Other immunodeficiencies • D86, D86.x, D86.xx, Sarcoidosis • D89, D89.x, D89.xx, Other disorders involving the immune mechanism, not elsewhere classified VTE: ICD-9-CM codes:

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Variable	Description	Operational definition
		• 415.1x, Pulmonary embolism and infarction • 451.x, 451.xx, Phlebitis and thrombophlebitis • 452, Portal vein thrombosis • 453.x, 453.xx, Other venous embolism and thrombosis ICD-10-CM codes: • I26, I26.x, I26.xx, Pulmonary embolism • I80, I80.x, I80.xx, I80.xxx, Phlebitis and thrombophlebitis • I81, Portal vein thrombosis • I82, I82.x, I82.xx, I82.xxx, Other venous embolism and thrombosis Solid organ transplant: CPT codes: • 32850-32856, Transplantation of lung • 33930-33945, Transplantation of heart • 44132, 44133, 47133, 47135, 47140-47147, Transplantation of liver • 44135-44137, 44715, 44720, 44721, Transplantation of intestine • 48160, 48550-48552, 48554, 48556, Transplantation of pancreas • 50300, 50320, 50323, 50325, 50327, 50328, 50329, 50340, 50340, 50360, 50365, 50370, 50380, Renal transplantation ICD-9-PCS codes:

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Variable	Description	Operational definition
		• 00.91 - 00.93, Transplant from donor or cadaver • 37.51, Heart transplantation • 33.51, Unilateral lung transplantation • 33.52, Bilateral lung transplantation • 46.97, Transplant of intestine • 50.59, Other transplant of intestine • 52.82, Homotransplant of pancreas • 55.69, Other kidney transplant ICD-10-PCS codes: • 02YA0Z0, 02YA0Z1, Transplantation of heart • 0BYC0Z0, 0BYC0Z1, 0BYD0Z0, 0BYD0Z1, 0BYF0Z0, 0BYF0Z1, 0BYG0Z0, 0BYG0Z1, 0BYH0Z0, 0BYH0Z1, 0BYJ0Z0, 0BYJ0Z1, 0BYK0Z0, 0BYK0Z1, 0BYL0Z0, 0BYL0Z1, 0BYM0Z0, 0BYM0Z1, Transplantation of lung • 0DY60Z0, 0DY60Z1, Transplantation of stomach • 0DY80Z0, 0DY80Z1, Transplantation of small intestine • 0DYE0Z0, 0DYE0Z1, Transplantation of large intestine • 0FY00Z0, 0FY00Z1, Transplantation of liver • 0FYG0Z0, 0FYG0Z1, Transplantation of pancreas • 0TY00Z0, 0TY00Z1, 0TY10Z0, 0TY10Z1, Transplantation of kidney
Concurrent immunizations	Categorical variable: • Seasonal influenza	Description of immunization, immunization ID, lot number, and manufacturer code will be available.

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Variable	Description	Operational definition
	• Tetanus diphtheria and pertussis (Tdap or Td) • Chickenpox (Varicella) • Shingles (Herpes Zoster recombinant and/or live) • Human papillomavirus (HPV) • Pneumococcal conjugate • Pneumococcal polysaccharide • Hepatitis A • Hepatitis B • Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB) • Haemophilus influenza type b	Seasonal influenza: • See Annex 3 Table A-3 Tetanus diphtheria and pertussis (Tdap or Td): • CPT codes: ○ 90714, Tetanus and diphtheria toxoids adsorbed (Td), preservative free, when administered to individuals 7 years or older, for intramuscular use ○ 90715, Tdap administered to individuals 7 years or older, for intramuscular use ○ 90718, Tetanus and diphtheria toxoids (Td) adsorbed when administered to individuals 7 years or older, for intramuscular use Chickenpox (Varicella) • CPT codes: ○ 90396, Varicella-zoster immune globulin, human, for intramuscular use ○ 90716, Varicella virus vaccine, live, for subcutaneous use Shingles (Herpes Zoster recombinant and/or live) • CPT codes: ○ 90396, Varicella-zoster immune globulin, human, for intramuscular use ○ 90736, Zoster (shingles) vaccine (HZV), live, for subcutaneous injection

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Variable	Description	Operational definition
		○ 90750, Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use Human papillomavirus (HPV) • CPT codes: ○ 90649, Human Papillomavirus vaccine, types 6, 11, 16, 18, quadrivalent (4vHPV), 3 dose schedule, for intramuscular use ○ 90650, Human Papillomavirus vaccine, types 16, 18, bivalent (2vHPV), 3 dose schedule, for intramuscular use ○ 90651, Human Papillomavirus vaccine types 6, 11, 16, 18, 31, 33, 45, 52, 58, nonavalent (9vHPV), 2 or 3 dose schedule, for intramuscular use Pneumococcal conjugate • CPT codes: ○ 90669, Pneumococcal conjugate vaccine, 7 valent, for intramuscular use ○ 90670, Pneumococcal conjugate vaccine, 13 valent (PCV13), for intramuscular use • HCPCS codes (used pneumococcal conjugate and polysaccharide): ○ G0009, Administration of pneumococcal vaccine ○ G8864, Code for Pneumococcal vaccine administered or previously received

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Variable	Description	Operational definition
		Pneumococcal polysaccharide: • CPT code: o 90732, Pneumococcal polysaccharide vaccine, 23-valent (PPSV23), adult or immunosuppressed patient dosage, when administered to individuals 2 years or older, for subcutaneous or intramuscular use Hepatitis A • CPT codes o 90632, Hepatitis A vaccine, adult dosage, for intramuscular use o 90633, Hepatitis A vaccine (HepA), pediatric/adolescent dosage-2 dose schedule, for intramuscular use o 90634, Hepatitis A vaccine (HepA), pediatric/adolescent dosage-3 dose schedule, for intramuscular use o 90730, Hepatitis A vaccine o 90636, Hepatitis A and hepatitis B vaccine (HepA-HepB), adult dosage, for intramuscular use Hepatitis B • CPT codes: o 90731, Hepatitis B vaccine o 90739, Hepatitis B vaccine (HepB), adult dosage, 2 dose schedule, for intramuscular use

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Variable	Description	Operational definition
		○ 90740, Hepatitis B vaccine (HepB), dialysis or immunosuppressed patient dosage, 3 dose schedule, for intramuscular use ○ 90743, Hepatitis B vaccine (HepB), adolescent, 2 dose schedule, for intramuscular use ○ 90744, Hepatitis B vaccine (HepB), pediatric/adolescent dosage, 3 dose schedule, for intramuscular use ○ 90745, Hepatitis B vaccine, adolescent/high risk infant dosage, for intramuscular use ○ 90746, Hepatitis B vaccine (HepB), adult dosage, 3 dose schedule, for intramuscular use ○ 90747, Hepatitis B vaccine (HepB), dialysis or immunosuppressed patient dosage, 4 dose schedule, for intramuscular use • HCPCS codes: ○ G0010, Administration of Hepatitis B vaccine Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB) • CPT codes: ○ 90619, Meningococcal conjugate vaccine, serogroups A, C, W, Y, quadrivalent, tetanus toxoid carrier (MenACWY-TT), for intramuscular use ○ 90620, Meningococcal recombinant protein and outer membrane vesicle vaccine, serogroup B (MenB-4C), 2 dose schedule, for intramuscular use

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Variable	Description	Operational definition
		○ 90621, Meningococcal recombinant lipoprotein vaccine, serogroup B (MenB-FHbp), 2 or 3 dose schedule, for intramuscular use ○ 90733, Meningococcal polysaccharide vaccine, serogroups A, C, Y, W-135, quadrivalent (MPSV4), for subcutaneous use ○ 90734, Meningococcal conjugate vaccine, serogroups A, C, W, Y, quadrivalent, diphtheria toxoid carrier (MenACWY-D) or CRM197 carrier (MenACWY-CRM), for intramuscular use Haemophilus influenza type b • CPT codes: ○ 90645, Hemophilus influenza b vaccine (Hib), HbOC conjugate (4 dose schedule), for intramuscular use ○ 90646, Hemophilus influenza b vaccine (Hib), PRP-D conjugate, for booster use only, intramuscular use ○ 90647, Haemophilus influenzae type b vaccine (Hib), PRP-OMP conjugate, 3 dose schedule, for intramuscular use ○ 90648, Haemophilus influenzae type b vaccine (Hib), PRP-T conjugate, 4 dose schedule, for intramuscular use ○ 90737, Hemophilus influenza B

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Variable	Description	Operational definition
		○ 90748, Hepatitis B and Haemophilus influenzae type b vaccine (Hib-HepB), for intramuscular use

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