NON-INTERVENTIONAL (NI) STUDY CONCEPT PROTOCOL

Title	Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
Protocol number	C4591012
Protocol version identifier	Version 2.0
Date of last version of protocol	27 January 2021
EU Post Authorization Study (PAS) register number	EUPAS39779
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
Research question and objectives	Research question: what are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]) among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine within the US Veterans Health Administration (VHA) system overall and in sub-cohorts of interest, as compared to expected rates of those events? *Primary study objectives:* • To assess whether individuals in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine; • To assess whether sub-cohorts of interest (i.e., immunocompromised,

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	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) in the VHA system 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 individuals within the VHA, including estimating the proportion of individuals receiving vaccine, 2-dose vaccine completion rate, and distribution of time gaps between the first and second dose, demographics and health histories of recipients, overall and among the sub-cohorts of interest.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ACOS	Associate Chief of Staff
AE	Adverse event
AEM	Adverse event monitoring
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
AMI	Acute myocardial infarction
BMI	Body mass index
CAD	Coronary artery disease
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CCI	Charlson comorbidity index
CDC	Centers for Disease Control and Prevention
CDW	Corporate Data Warehouse
CEP	Clinical Epidemiology Program
CMA	Conditional Marketing Authorization
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CPT	Current Procedural Terminology
CRADA	Cooperative Research and Data Agreement
CRFs	Case report forms
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
Tdap	Diphtheria, tetanus and (acellular) pertussis
Td	Diphtheria and tetanus
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
H_0	Null hypothesis
H_a	Alternative hypothesis
HBV	Hepatitis B virus
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C virus

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Abbreviation	Definition
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IRB	Institutional Review Board
KD	Kawasaki disease
LLR	Log-likelihood ratio
MaxSPRT	Maximized sequential probability ratio test
MenACWY	Meningococcal conjugate
MenB	Serogroup B meningococcal
MIS-A	Multisystem inflammatory syndrome in adults
mRNA	Messenger RiboNucleic Acid
MS	Multiple sclerosis
NDC	National Drug Codes
NIS	Non-interventional study
NNERC VAMC	Northern New England Research Consortium VA Medical Centers
NSAID	Non-steroidal anti-inflammatory drug
ON	Optic neuritis
PASS	Post-Authorization Safety Study
PE	Pulmonary embolism
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
PS	Propensity score
R&D	Research and Development
RCA	Rapid cycle analysis
RR	Relative risk
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	SAS Institute
SCCS	Self-controlled case series
SCRI	Self-controlled risk interval
SD	Standard deviation
SJS	Stevens-Johnson syndrome
SPEAC	Safety Platform for Emergency vACcines
SRSS	Subcommittee on Research Safety and Security
TEN	Toxic epidermal necrolysis
TM	Transverse myelitis

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Abbreviation	Definition
TTS	Thrombosis with thrombocytopenia syndrome
UK	United Kingdom
US	United States
VA	Department of Veterans Affairs
VAIRRS	VA Innovation and Research Review System
VAERS	Vaccine Adverse Event Reporting System
VHA	Veterans Health Administration
VINCI	VA Informatics and Computing Infrastructure
VINNE	Veteran's IRB of Northern New England
VISN	Veterans Integrated Service Networks
VSD	Vaccine Safety Datalink
VTE	Venous thromboembolism
WHO	World Health Organization
WOC	Without compensation
YRR	Your Reporting Responsibilities

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3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Protocol Version: 2.0; Date of Protocol: 31 Aug 2021

Authors: Yinong Young Xu, ScD, MA, MS, Veterans Affairs Medical Center; Cynthia de Luise, 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 January 7, 2021, over 21.4 million COVID-19 cases and 364,000 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). 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). The Food and Drug Administration (FDA) reviewed the available safety data 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] Therefore on December 11, 2020, the Pfizer-BioNTech COVID-19 vaccine was granted an Emergency Use Authorization (EUA) by the FDA to prevent COVID-19 in individuals 16 years of age and older.[5]

With respect to geographic regions other than the US, on December 2, 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.[6] On December 21, 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.[7]

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

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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 (e.g., immunocompromised individuals, elderly, and those with specific comorbidities).[4] Pfizer in collaboration with the US Veterans Health Administration (VHA) and Analysis Group herein propose post-EUA active safety surveillance of safety events of interest based primarily on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project and from the preliminary list of safety events of interest presented at the September 22, 2020, meeting of Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) on the enhanced safety monitoring of COVID-19 vaccines.[8,9] This safety surveillance study will identify and evaluate rapid, near real-time potential safety signals associated with the Pfizer-BioNTech COVID-19 vaccine in the large-scale VHA electronic medical record (EMR) database. The observed safety event of interest rates will be compared to expected rates derived from self-controls and active comparators receiving seasonal influenza vaccination. Part of the methodologies used in this study are constructed based on approaches previously used by the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program for the H1N1 vaccine.[10] This non-interventional study is designated as a Post-Authorization Safety Study (PASS) commitment to the US FDA and is a Category 3 commitment in the EU Risk Management Plan.

Research question and objectives:

Research question: what are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]) among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine within the US VHA system overall and in sub-cohorts of interest, as compared to expected rates of those events?

Primary study objectives:

- To assess whether individuals in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine;
- To assess whether sub-cohorts of interest (i.e., 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) in the VHA system 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 individuals within the VHA, including estimating the proportion of individuals receiving vaccine, 2-dose vaccine completion rate, and distribution of time gaps between the first and second dose, demographics and health histories of recipients, overall and among the sub-cohorts of interest.

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Study design: This post-EUA active safety surveillance program will employ a rapid-cycle, longitudinal, observational cohort study design to provide early real-world safety information.

- The self-controlled risk interval (SCRI) design will be used to sequentially monitor occurrence of safety events of interest while controlling for time-invariant confounders. The SCRI design uses data from cases (i.e., individuals who experience safety events of interest following vaccination) to compare the risk interval following vaccination to post-vaccination non-risk intervals ("post-vaccination control interval") in the same individual.

- An active comparator design will be used to sequentially monitor occurrence of safety events of interest with Pfizer-BioNTech COVID-19 vaccinations as compared to recipients of influenza vaccine in the VHA during 2014/2015 through 2018/2019 flu seasons. Data in peri-COVID time periods from January 2020 to present are excluded because of pandemic-associated under-utilization of health resources and under-reporting of medical events.

There will be additional study designs conducted during the signal evaluation phase if a signal is detected from the above analyses. These include self-controlled case series (SCCS) and comparison to unvaccinated contemporary controls. Additionally, signal evaluation analyses may also be conducted based on signals detected in external sources or based on regulatory request.

Population: The exposed population will be kept as broad as possible in order to capture safety events of interest that occur among all individuals receiving the Pfizer-BioNTech COVID-19 vaccine in the period from December 11, 2020 to present. Individuals will be included if they have a record of at least one dose of Pfizer-BioNTech COVID-19 vaccine. Individuals who receive at least one dose of COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech will be identified and summarized, but they will be excluded from further analysis. All individuals will be required to be enrolled in and not disenrolled from VHA benefits during the 1 year prior to vaccination date (i.e., baseline period). Depending on the attrition rate, the length of the baseline period may be modified to 6 months.

The influenza vaccine comparator cohort will be identified based on a record of at least one dose of seasonal influenza vaccine during prior flu seasons, from 2014/2015 through 2018/2019.

Variables:

- Exposures: Administration of Pfizer-BioNTech COVID-19 vaccine post-EUA approval will be identified based on the following (see Appendix Table 3 for additional details):

    - Current Procedural Terminology (CPT) and associated vaccine administration Healthcare Common Procedure Coding System (HCPCS) codes; OR

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- 10 and 11-digit National Drug Codes (NDCs); OR
- Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (i.e., Pfizer), lot number, injection site, and date(s) of immunization;[11]

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

- Administration of the seasonal influenza vaccine during 2014/2015 through 2018/2019 flu seasons will be identified based on the following (see Appendix Table 3 for additional details):
  - CPT codes and associated vaccine administration HCPCS codes; OR
  - 10 and 11-digit NDCs; OR
  - Immunization records that contain data on vaccine code descriptor, vaccine manufacturer, lot number, injection site, and date(s) of immunization.

- Outcomes: Safety events of interest for active surveillance (see Appendix Table 2) are based on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration's SPEAC Project, the FDA and the CDC's ACIP enhanced safety monitoring recommendations.

  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. The risk and control intervals for each safety event of interest are based on biological plausibility and precedents in the literature (see Table 1). Outpatient, emergency department (ED), and/or inpatient settings will be used to identify safety events of interest depending on the type of event. The specific encounter setting to be considered for each safety event of interest is summarized in Table 1 and can be assigned to 1) the risk interval following vaccination Pfizer-BioNTech COVID-19 vaccination, 2) the post-vaccination self-control interval, or 3) risk interval for the active comparators of receiving seasonal influenza vaccine. 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 (i.e., 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 captured; this means that if a safety event of interest is identified but diagnosis codes corresponding to the safety event of interest are also observed during the clean window, it will not be counted. The duration of the pre-specified clean window will differ by safety event of interest (see Appendix Table 2) in order to rule out pre-existing events.

- Key Covariates: Baseline demographic (i.e., age, sex, race/ethnicity, service region) and clinical characteristics (i.e., smoking, body mass index [BMI], history of

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anaphylaxis/allergic reactions, previous anaphylaxis to vaccine component, history of hospitalizations, frailty index, Charlson Comorbidity Index [CCI], selected comorbidities, and concurrent immunizations)[12] will be assessed based on available data (i.e., during 1-year baseline) prior to the date of vaccination with Pfizer-BioNTech COVID-19 vaccine and date of seasonal influenza vaccination for active comparators.

- Subgroups: Immunocompromised individuals (i.e., individuals diagnosed with symptomatic human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), hematologic malignancy, or other immune conditions; individuals diagnosed with solid malignancy, organ transplant, or rheumatologic/inflammatory conditions, all of whom were administered chemotherapy or immune modulators; individuals diagnosed with rheumatologic/inflammatory conditions and administered systemic corticosteroids; individuals who were administered chemotherapy, immune modulators, or systematic steroids for at least 14 days),[13] elderly, individuals with specific comorbidities,[12] those receiving only one dose of Pfizer-BioNTech COVID-19 vaccine, those with prior SARS-CoV-2 infection, those with regular use of VHA medical care, and VA priority group 1 veterans will be identified. Analyses will also be performed among individuals enrolled in the VHA with dual coverage who are also identified in linked Centers for Medicare & Medicaid Services (CMS) Medicare administrative claims data.

Data source: The VHA is the largest integrated health care system in the US, providing both inpatient and outpatient clinical care to over 9 million Veterans enrolled at more than 170 medical centers and 1,074 community-based outpatient clinics.[14] This study will use data from VHA's Corporate Data Warehouse (CDW), which is an integrated EMR system with a centralized data warehouse that is updated on a daily basis. The CDW does not include information on any care received outside of a VHA facility. The VA offers eligible Veterans long-term care services ranging from nursing homes and assisted-living centers to caregiver support in the Veterans' own homes.[15] In a subgroup analysis of individuals with both VHA and Medicare coverage, CDW data will be supplemented and linked with Medicare administrative claims data at the patient level to ensure a more comprehensive evaluation of the care an individual receives.

Study size: The sample size achieved will depend on the number of recipients of Pfizer-BioNTech COVID-19 vaccine within the VHA database, which will increase over time with subsequent analyses. As of January 21, 2021, 112,201 doses of Pfizer-BioNTech COVID-19 vaccine have been administered within the VHA (based on CPT code 91300) to a total of 107,458 patients.

Data analysis: A stepwise approach, illustrated in the diagram, will be performed for signal detection, evaluation, and verification.

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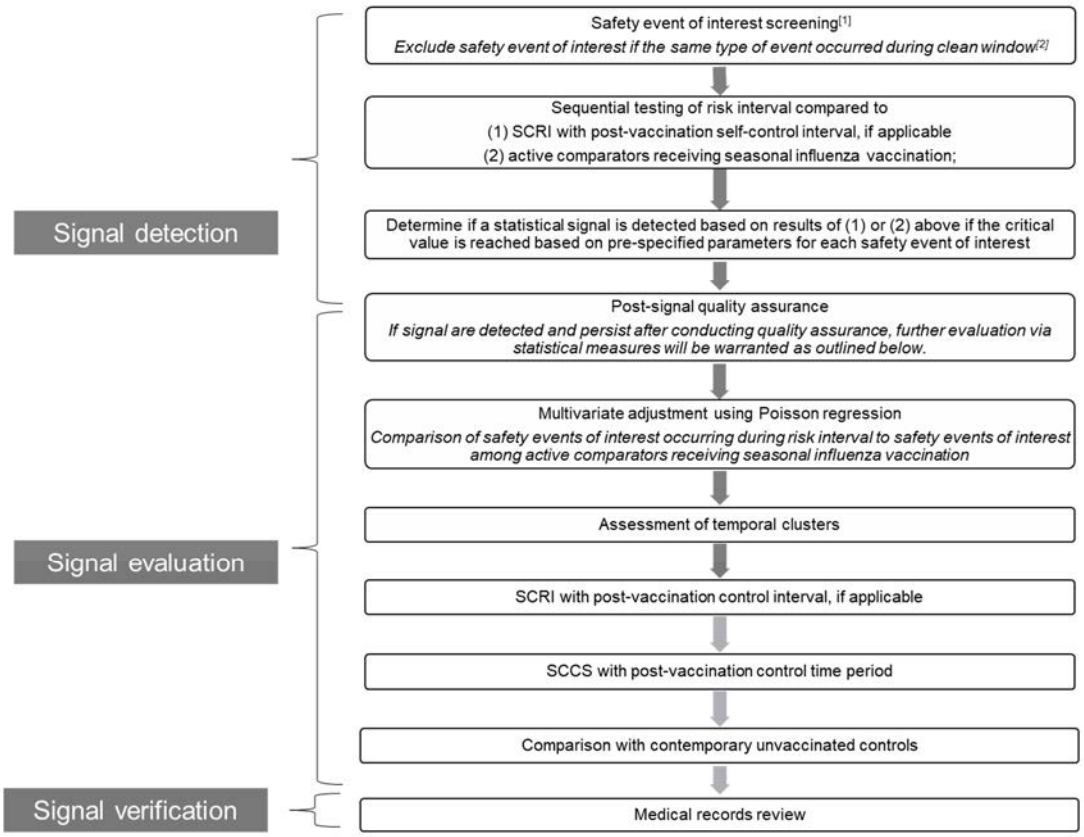

Notes:
[1] List of safety events of interest and corresponding definitions may be refined as the study progresses based on additional available information.
[2] The risk and control intervals selected for the SCRI analysis for each safety event of interest are based on biological plausibility and precedents in the literature. Only the individual's first instance during the specified clean window (i.e., the interval used to define incident outcomes) will be included. Note that only the first inpatient or outpatient occurrence of a safety event of interest following the clean window will be used to identify incident events (e.g., if an inpatient safety event of interest occurs in the clean window, a repeat occurrence will not be counted in the risk interval). However, event worsening will be counted as a safety event of interest. For example, 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 as a safety event of interest.

1) Signal detection: The goal is to provide rapid-cycle, near real-time safety surveillance. In the signal detection phase, the SCRI analysis will include post-vaccination control intervals for certain safety events of interest that require a COVID-19 diagnosis (i.e., severe COVID-19, multisystem inflammatory syndrome in adults [MIS-A]). To account for multiple testing and bi-weekly review of the data, the maximized sequential probability ratio test (MaxSPRT) using a binomial probability model will be applied. For comparison with individuals who received seasonal influenza vaccination, the Poisson-based MaxSPRT will be applied for all other safety events of interest.

Sequential analyses for each safety event of interest will commence once at least 3 events occur. This approach is consistent with the FDA's COVID-19 Vaccine Safety Surveillance Project to avoid spurious signals from a few early events.[16] Signals will be detected if the critical values are reached via the SCRI or active comparator analysis. Critical values will be

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determined for each safety event of interest based on historical incidence rate, expected upper limit of the number of events under the null hypothesis, and pre-specified significance level and power.

2) Signal evaluation: If signals are detected for safety events of interest based on the analysis described above, further evaluation will be conducted to refine and confirm such detections. This will include comprehensive quality assurance (for example, check for possible duplications of claims or medical records, checking for unusual clustering in claim or medical record accrual by service date for potential coding issues, check for geographical distribution of cases that may be related to lot numbers or diagnostic practice) and multivariate adjustment using Poisson regression to account for baseline differences between Pfizer-BioNTech COVID-19 vaccinated and active comparator cohorts. SCRI analyses using the post-vaccination control intervals and SCCS using post-vaccination control time periods will be conducted as an additional inferential analysis once enough post-vaccination time has accumulated. To address potential period effects, a comparison to contemporary unvaccinated controls will also be performed, with adjustment using inverse probability of treatment weighting (IPTW). The assessment of temporal clustering will also be conducted. Incidence rates will also be calculated and Kaplan-Meier methods will be used to analyze time to safety event of interest. Signal evaluation analyses will be conducted every six months.

3) Signal verification: diagnostic validation of the detected safety events of interest via adjudication of medical records by VHA clinicians for outcome verification will be conducted in a representative sample of cases. For rare events, potentially all cases may be adjudicated.

End-of-season analyses (over the course of the 30-month period) and an end-of-surveillance analysis (i.e., at 30 months) will be conducted. Various subgroup analyses will also be conducted, examining different age groups, immunocompromised individuals,[13] individuals with specific comorbidities,[12] those who only received one dose of the Pfizer-BioNTech COVID-19 vaccine, those with prior SARS-CoV-2 infection based on medical history or pre-vaccination serology, those receiving care regularly at VA facilities, those with VA Priority group 1 status, which determines these individuals are of highest priority for VHA care and likely receive all of their care within the VHA system, and lastly, those with additional Medicare coverage whose Medicare data can be linked to the CDW.

Notably, CDC recently investigated myocarditis/pericarditis following mRNA COVID-19 vaccinations.[17] 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. These analyses will be conducted to align with the rapid-cycle analysis performed by the Vaccine Safety Datalink (VSD).[18] 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 (e.g., 12-39 years, 40-49 years, 50-64 years, 65+ years), gender, and race/ethnicity, respectively. Incidence rate ratios will be summarized to compare the rate of myocarditis/pericarditis events between vaccinated individuals whose event occurs

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in a pre-specified risk interval versus vaccinated individuals whose event occurs in a comparison interval on the same calendar day. Myocarditis/pericarditis events will also be adjudicated via chart review and validated using the Brighton Collaboration's case definitions.[19] Risk factor analysis may also be conducted among confirmed cases. Lastly, additional data surrounding risk factors, clinical course, and sequelae of identified myocarditis/pericarditis event up to 365 days following the event will be collected and summarized.

Milestones:

- VHA CRADA execution: 8 January 2021;
- Determination of Institutional Review Board (IRB) exemption: 10 February 2021;
- Determination of Research Safety and Security exemption: 17 February 2021;
- Approval by Designated Member Review: 26 February 2021;
- Registration in the EU PAS register: 5 March 2021;
- Start of data collection: 11 May 2021;
- Interim reports: 30 June 2021; 31 December 2021; 30 June 2022, 31 December 2022;
- End of data collection: 30 June 2023;
- Final study report: 31 December 2023

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SUMMARY

Objective	Primary 1	Primary 2	Secondary
Aim	To assess whether individuals in the Veterans Health Administration (VHA) system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine.	To assess whether sub-cohorts of interest (i.e. immunocompromised, elderly, with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine.	To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA including estimating the proportion of individuals receiving vaccine, 2-dose vaccine completion rate, and distribution of time gaps between the first and second dose, demographics and health histories of recipients, overall and among the sub-cohorts of interest.
Study design	This post-EUA active safety surveillance program will employ a rapid-cycle, longitudinal, observational cohort study design to provide early real-world safety information. • The self-controlled risk interval (SCRI) design to sequentially monitor occurrence of safety events of interest while controlling for time-invariant confounders. This design allows inclusion of a post-vaccination control interval. • An active comparator design will be used to sequentially monitor occurrence of safety events of interest with Pfizer-BioNTech COVID-19 vaccinations as compared to recipients of influenza vaccine in the VHA during 2014/2015 through 2018/2019 flu seasons. Data in peri-COVID time periods from January 2020 to present are excluded because of pandemic-associated under-utilization of health resources and under-reporting of medical events. There will be additional study designs conducted during the signal evaluation phase if a signal is detected from the above analyses. These include self-controlled case series (SCCS) and comparison of vaccinated to unvaccinated contemporary controls. Additionally, signal evaluation analyses may also be conducted based on signals detected in external sources or based on regulatory request (e.g., myocarditis/pericarditis).		
Study population	The study will be kept as broad as possible in order to capture safety events of interest that occur among vaccinated individuals. Inclusion criteria: • Record of at least one dose of Pfizer-BioNTech COVID-19 vaccine in the period of December 11, 2020 to present, or • Record of at least one dose of seasonal influenza vaccine during prior flu seasons, from 2014/2015 through 2018/2019 (applies to active comparators only); and		

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Objective	Primary 1	Primary 2	Secondary
	• At least 1 year of enrollment in and no disenrollment from VHA benefits (i.e., the baseline period) prior to Pfizer-BioNTech COVID-19 or seasonal influenza vaccination date. Exclusion criteria: • Individuals who receive at least one dose of Pfizer-BioNTech COVID-19 vaccine in addition to a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech will be identified and summarized, but they will be excluded from further analysis. .		
Study Period	The study will be conducted for a period of 30 months, starting on December 11, 2020 onward, with data collection concluding on June 10, 2023.		
Exposure	Administration of Pfizer-BioNTech COVID-19 vaccine post-EUA approval will be identified based on records of the following (see Appendix Table 3 for additional details): • Current Procedural Terminology (CPT) and associated vaccine administration HCPCS codes; OR • 10 and 11-digit National Drug Codes (NDCs); OR • Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (i.e., Pfizer), lot number, injection site, and date(s) of immunization; Administration of the seasonal influenza vaccine during 2014/2015 through 2018/2019 flu seasons will be identified based on records of the following (see Appendix Table 3 for additional details): • CPT codes and associated vaccine administration HCPCS codes; OR • 10 and 11-digit NDCs; OR • Immunization records that contain data on vaccine code descriptor, vaccine manufacturer, lot number, injection site, and date(s) of immunization.		
Safety Events of Interest	Safety events of interest for active surveillance were identified based on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project, the FDA and the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) enhanced safety monitoring recommendations. The list of safety events 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. The risk and control intervals for each safety event of interest are based on biological plausibility and precedents in the literature. Outpatient, emergency department, and/or inpatient settings will be used to identify safety events of interest depending on the type of event. Safety events of interest can be assigned to 1) the risk interval following vaccination Pfizer-BioNTech COVID-19 vaccination, 2) the post-vaccination self-control interval, or 3) risk interval for the active comparators of receiving seasonal influenza vaccine. 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 (i.e., 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;		

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Objective	Primary 1	Primary 2	Secondary
	this means that if a safety event is identified but diagnosis codes corresponding to the safety event are also observed during the clean window, it will not be counted. The duration of the pre-specified clean window will differ by type of safety event of interest in order to rule out pre-existing events. **Neurologic:** • Aseptic meningitis • Bell's palsy • *Cerebrovascular non-hemorrhagic stroke* • Convulsions/seizures in individuals with controlled epilepsy • Encephalitis/encephalomyelitis • *Guillain-Barré Syndrome (GBS)* • *Generalized convulsion/seizures* • Multiple sclerosis (MS) • Optic neuritis (ON) • Other acute demyelinating diseases • Transverse myelitis (TM) **Immunologic:** • Anaphylaxis • Arthritis and arthralgia/joint pain • Autoimmune thyroiditis • Fibromyalgia • *Kawasaki disease (KD)* • *Multisystem inflammatory syndrome in adults (MIS-A)* • Vasculitides **Cardiac:** • *Acute myocardial infarction (AMI)* • Arrhythmia • Coronary artery disease (CAD) • Heart failure and cardiogenic shock • Microangiopathy		

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Objective	Primary 1	Primary 2	Secondary
	• *Myocarditis* • *Pericarditis* • Stress cardiomyopathy **Hematologic:** • *Cerebrovascular hemorrhagic stroke* • Chilblain-like lesions • *Disseminated intravascular coagulation (DIC)* • Deep vein thrombosis (DVT) • Hemolytic anemia • Hemorrhagic disease • Limb ischemia • Pulmonary embolism (PE) • Single organ cutaneous vasculitis • *Thrombocytopenia* • Thrombosis with thrombocytopenia syndrome (TTS) **Other:** • Acute kidney injury • Appendicitis • *Death* • Erythema multiforme • Liver injury • *Narcolepsy and cataplexy* • Non-anaphylactic allergic reactions • *Severe COVID-19 disease* • Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)		
Data source	The VHA Corporate Data Warehouse (CDW) database will be used and may be supplemented with Medicare administrative claims data from the Centers for Medicare & Medicaid Services (CMS).		

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Objective	Primary 1	Primary 2	Secondary
Data analysis	A stepwise approach will be performed for signal detection, evaluation, and verification. 1) Signal detection: The goal is to provide rapid-cycle, near real-time safety surveillance. SCRI analyses using the post-vaccination control intervals will be conducted for certain safety events of interest that require a COVID-19 diagnosis (i.e., severe COVID-19 illness, MIS-A). To account for multiple testing and bi-weekly review of the data, the maximized sequential probability ratio test (MaxSPRT) using a binomial probability model will be applied. For comparison with individuals who received seasonal influenza vaccination, the Poisson-based MaxSPRT will be applied for all other safety events of interest. Sequential analyses for each safety event of interest will commence once at least 3 events occur. This approach is consistent with the FDA's COVID-19 Vaccine Safety Surveillance Project to avoid spurious signals from a few early events. Signals will be detected if the critical values are reached via the SCRI or active comparator analysis. Critical values will be determined for each safety event of interest based on historical incidence rate, expected upper limit of the number of events under the null hypothesis, and pre-specified significance level and power. Incidence rates will also be calculated and Kaplan-Meier methods will be used to analyze time to safety event of interest. 2) Signal evaluation: If signals are detected for safety events of interest based on the analysis described above, further evaluation will be conducted to refine and confirm such detections. This will include comprehensive quality assurance (for example, check for possible duplications of claims or medical records, checking for unusual clustering in claim or medical record accrual by service date for potential coding issues, check for geographical distribution of cases that may be related to lot numbers or diagnostic practice) and multivariate adjustment using Poisson regression to account for baseline differences between Pfizer-BioNTech COVID-19 vaccinated and active comparator cohorts. SCRI analyses using the post-vaccination control intervals and the SCCS design with post-vaccination control time period will be conducted as an additional inferential analysis once enough post-vaccination time has accumulated. To address potential period effects, a comparison to contemporary unvaccinated controls will also be performed with adjustment using inverse probability of treatment weighting (IPTW). The assessment of temporal clustering will also be conducted. Signal evaluation analyses will be conducted very six months. 3) Signal verification: diagnostic validation of the detected safety events of interest via adjudication of medical records by VHA clinicians for outcome validation will be conducted in a representative sample of cases. For rare events, potentially all cases may be adjudicated. End-of-season analyses (over the course of the 30-month period) and an end-of-surveillance analysis (i.e., at 30 months) will be conducted. Various subgroup analyses will also be conducted, examining different age groups, immunocompromised individuals, individuals with specific comorbidities, those who only received one dose of the Pfizer-BioNTech COVID-19 vaccine, those with prior SARS-CoV-2 infection based on medical history or pre-		

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Objective	Primary 1	Primary 2	Secondary
	vaccination serology, those receiving care regularly at VA facilities, those with VA Priority group 1 status, which determines these individuals are of highest priority for VHA care and likely receive all of their care within the VHA system, and lastly, those with additional Medicare coverage whose Medicare data can be linked to the CDW. Notably, CDC recently investigated myocarditis/pericarditis following mRNA COVID-19 vaccinations. 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. These analyses will be conducted to align with the rapid-cycle analysis performed by the Vaccine Safety Datalink (VSD). 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 (e.g., 12-39 years, 40-49 years, 50-64 years, 65+ years), gender, and race/ethnicity, respectively. Incidence rate ratios will be summarized to compare the rate of myocarditis/pericarditis events between vaccinated individuals whose events occur in a pre-specified risk interval versus vaccinated individuals whose events occur in a comparison interval on the same calendar day. Myocarditis/pericarditis events will also be adjudicated via chart review and validated using the Brighton Collaboration's case definitions. Risk factor analysis may also be conducted among confirmed cases. Lastly, additional data surrounding the risk factors, clinical course, and sequelae of the identified myocarditis/pericarditis event up to 365 days following the event will be collected and summarized.		

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5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	31 August 2021	6	Updated the Milestones section.	To add additional information that became available after the initial protocol was submitted to FDA regarding IRB review, EU PAS registration, and data collection dates.
1	31 August 2021	9.1.1	Added clarification on the self-controlled risk interval (SCRI) design, including a description of the measurements when there is a gap between risk intervals for the first and second dose and an illustration (new Figure 2B).	To respond to a request from Center for Biologics Evaluation and Research (CBER) to demonstrate how the period after the risk interval for dose 1 and prior dose 2 will be handled in the analysis if there is no overlap between the risk intervals for the two doses.
1	31 August 2021	9.1.1	Added that additional doses of the Pfizer-BioNTech COVID-19 vaccine may be included in the analysis.	To address the potential approval of additional doses. Details for this analysis will be further described in the statistical analysis plan.
1	31 August 2021	9.1.1, 9.3.3, 9.7.3, 9.7.5, 9.9	Removed SCRI design with pre-vaccination control interval and added SCRI design with post-vaccination control interval for 2 safety events of interest (severe COVID-19, multisystem inflammatory syndrome	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. Note additional and

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Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			in adults [MIS-A]) that could not be evaluated with the seasonal influenza vaccinated comparators. Revised Figures 1-5 to remove pre-vaccination control interval and provide examples for post-vaccination interval.	more robust analyses were added to signal evaluation phase (see new sections under 9.7.3.2.5 and 9.7.3.2.6). SCRI with post-vaccination control intervals was included in the signal detection phase to evaluate severe COVID-19 and MIS-A as they require COVID-19 diagnosis, which would not be observed in a seasonal influenza comparator.
1	31 August 2021	9.2.3, 9.4	Added clarification for the identification of subgroups who are immunocompromised s and individuals with specific comorbidities. Added one additional subgroup of interest (individuals with Medicare coverage for whom Veterans Health Administration [VHA] records can be linked to their Medicare claims).	To provide additional detail regarding how subgroups who are immunocompromised and individuals with specific comorbidities will be defined and operationalized. To respond to a query from CBER regarding the potential for incomplete data for healthcare encounters not received at VHA, an additional subgroup of individuals with linked Medicare data has been added.

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Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	31 August 2021	9.3.1	All measurement details concerning how Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine will be identified in the data to an Appendix Table 3 in Section 18. Appendix Table 3 includes all specific CPT/HCPCS/NDC codes previously listed in Section 9.3.1 as well as additional codes identified at the time of the data analysis.	To update the protocol with all relevant CPT/HCPCS/NDC codes, while maintaining concise language in the main text.
1	31 August 2021	9.3.1, 18	Added Appendix Table 4 in Section 18 regarding the LOINC codes used to identify COVID-19 RT-PCR Test among the study population and corresponding reference.	To provide additional details on how individuals with prior SARS-CoV-2 infection will be identified in the data.
1	31 August 2021	9.3.2, 18	Added frailty index as a baseline characteristic of interest.	To describe the identification of frailty in the Pfizer-BioNTech COVID-19 and seasonal influenza cohorts during the 1-year baseline period prior to vaccination as frailty may be a prognostic factor for safety events of interest.
1	31 August 2021	9.3.3, 18	Added four additional safety events of interest: thrombosis with thrombocytopenia syndrome, convulsions/seizures in individuals	To consider new safety events based on emerging research and align with codes from the FDA CBER COVID-19 Vaccine Safety

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Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			with controlled epilepsy, Steven-Johnson syndrome/Toxic epidermal necrolysis, and hemolytic anemia (increasing the number of safety events of interest from 42 to 46). Reclassified COVID-19-related safety events of interest to be measured independently of the patient's COVID-19 infection status; this change had no impact on the number of safety events of interest (reflected both in the revised text and revised Table 1). Added that the clean window may be extended (e.g., 2 years).	Surveillance: Active Monitoring Master Protocol.[20,21,22] The COVID-19-related safety events were reclassified to more closely align with the FDA CBER COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol. COVID-19-related safety events that were previously listed may not necessarily be related to COVID-19 infection (e.g., coronary artery disease), and therefore are defined independent of a COVID-19 diagnosis, with the exception of "severe COVID-19 disease" and "MIS-A" which requires a concurrent COVID-19 diagnosis. Extending the clean window will address the reduction in healthcare resource utilization during the pandemic to more accurately identify incident events.

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Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	31 August 2021	9.7.3.2	Clarified in the Signal Evaluation section that the signal evaluation analyses will be conducted every six months.	To provide additional detail on the timing of the signal evaluation analyses.
1	31 August 2021	9.1.3, 9.7.3.2.5	Added self-controlled case series (SCCS) design with full post-vaccination period as an additional analysis in the Signal Evaluation analysis. Added that Signal Evaluation analyses may also be conducted based on signals detected in external sources or based on regulatory request (e.g., myocarditis/pericarditis).	To further align with the CBER Master Protocol: Assessment of Risk of Safety Outcomes Following COVID-19 Vaccination (March 23, 2021).[23] SCCS analysis has increased power compared to SCRI design using post-vaccination control interval and has been added to complement the SCRI design. In addition, clarified that Signal Evaluation analyses may also be conducted based on signals detected in external sources or based on regulatory request even if such analyses were not first identified in the Signal Detection phase of this study.
1	31 August 2021	9.7.3.2.6	Added a comparison group of contemporary unvaccinated controls in the Signal Evaluation analysis.	To address the recommendation from CBER to include a contemporary control group of unvaccinated individuals due to potential period effects of an active

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Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
				comparator design that uses historical controls of influenza vaccinated individuals.
1	31 August 2021	9.7.8	Added new 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.[17]
1	31 August 2021	9.9	Added strengths and limitations associated with the addition of the SCCS design, contemporaneous unvaccinated controls, and subgroup analysis of individuals with linkage to Medicare claims data.	To further describe the rationale for these additional analyses.

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6. MILESTONES

Milestone	Planned date
VHA CRADA execution, Determination of IRB & Research Safety and Security exemptions, Approval by Designated Member Review[1-3]	January - February 2021
Registration in the EU PAS register	5 March 2021
Start of data collection	11 May 2021[4]
Interim reports	30 June 2021 31 December 2021 30 June 2022 31 December 2022
End of data collection	30 June 2023[5]
Final study report	31 December 2023

Abbreviations: ACOS, Associate Chief of Staff; COVID-19, Coronavirus disease 2019; CRADA, Cooperative Research and Data Agreement; IRB, Institutional Review Board; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; NNERC VAMC, Northern New England Research Consortium VA Medical Centers; R&D, Research and Development; SRSS, Subcommittee on Research Safety and Security; VA, Veterans Affairs; VAIRRS, VA Innovation and Research Review System; VINNE, Veteran's IRB of Northern New England; VHA, Veterans Health Administration; US, United States.

Notes:

[1] IRB exemption determination was granted in accordance with 38 CFR 16 by the Veteran's IRB of Northern New England (VINNE), White River Junction VA Medical Center, White River Junction, VT for the signal detection and signal evaluation phases. Prior to progressing to the signal verification phase for chart review, a second IRB review application will be submitted for an expedited or full review. The two-stage IRB application process is to expedite the initiation of the project.

[2] Research Safety and Security exemption determination was granted by the Subcommittee on Research Safety and Security (SRSS), VA Innovation and Research Review System (VAIRRS).

[3] Approved by Associate Chief of Staff for Research and Development (ACOS/R&D) and R&D Committee of the Northern New England Research Consortium VA Medical Centers (NNERC VAMC).

[4] Start of data collection is the date for starting data extraction for the purposes of the study analysis. The initial data analysis includes Pfizer-BioNTech COVID-19 vaccine exposures from December 11, 2020 (the EUA approval date by the US FDA) to March 12, 2021 (the data cutoff date).

[5] End of data collection is after the Pfizer-BioNTech COVID-19 vaccine exposure data reached 30 months post-EUA approval and the last day of the month that the study will be completed.

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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 January 7, 2021, over 21.4 million COVID-19 cases and 364,000 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 (e.g., cardiovascular disease, active cancer, obesity, diabetes and chronic lung disease).[24,25] 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.[26]

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 (i.e., 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.[27] The study was initiated in July 2020 with a target enrollment of 43,998 individuals.[28]

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 subjects.[29] The FDA reviewed the available safety 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] Therefore on December 11, 2020, the Pfizer-BioNTech COVID-19 vaccine was granted an EUA by the FDA to prevent COVID-19 in individuals 16 years of age and older.[5]

With respect to geographic regions other than the US, on December 2, 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.[6] On December 21, 2020, the European Medicines Agency (EMA) granted the Pfizer-BioNTech COVID-19 vaccine a

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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.[7]

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 (e.g., 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 ensure a favorable benefit-risk ratio post-trial. Pfizer in collaboration with the US Veterans Health Administration (VHA) of the Department of Veterans Affairs (VA) and Analysis Group herein propose post-EUA active safety surveillance of safety events of interest based primarily on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project and from the preliminary list of safety events of interest presented at the September 22, 2020, meeting of Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) on the enhanced safety monitoring of COVID-19 vaccines.[8,9] This safety surveillance study will identify and evaluate rapid, near real-time potential safety signals associated with the Pfizer-BioNTech COVID-19 vaccine in the large-scale VHA electronic medical record (EMR) database. The observed rates of safety event of interest will be compared to expected rates derived from self-controls and active comparators. Part of the methodologies used in this study are constructed based on approaches previously used by the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program for the H1N1 vaccine.[10] This non-interventional study is designated as a Post-Authorization Safety Study (PASS) commitment to the US FDA and is a Category 3 commitment in the EU Risk Management Plan.

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]) among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine within the US VHA system overall and in sub-cohorts of interest as compared to expected rates of those events?

Primary study objectives:

- To assess whether individuals in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine;

- To assess whether sub-cohorts of interest (i.e., immunocompromised, elderly, with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the VHA system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine.

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Secondary study objectives:

- To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA including estimating the proportion of individuals receiving vaccine, 2-dose vaccine completion rate, and distribution of time gaps between the first and second dose, 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 program will employ a rapid-cycle, longitudinal, observational cohort study design to provide early real-world safety information. The self-controlled risk interval (SCRI) design will be used to sequentially monitor occurrence of safety events of interest while controlling for time-invariant confounders (such as sex, race, chronic illness, and state). In addition, safety events of interest associated with Pfizer-BioNTech COVID-19 vaccinations will be sequentially monitored and compared to recipients of influenza vaccine in the VHA between 2014/2015 to 2018/2019.[10,30]

9.1.1. Self-Controlled Risk Interval (SCRI) Design with Post-Vaccination Control Interval

The SCRI design uses data from cases (i.e., individuals who experience safety events of interest following vaccination) to compare the risk interval following vaccination to post-vaccination non-risk intervals ("post-vaccination control interval") in the same individual.[31] A length of 42 days has been used to define the risk interval in SCRI design studies for signal detection to ascertain the safety profile of the H1N1 vaccine.[10,30] The same length of risk interval is proposed here, subject to further modification based on clinical input, clinical trial data, biologic plausibility, and published literature. The day of vaccination will only be included in the risk period for those safety events of interest for which a same-day occurrence is biologically plausible (e.g., anaphylaxis).

A post-vaccination control interval will be used for certain safety events of interest for the following reasons: (1) a recent prior safety event of interest might preclude vaccination (i.e., anaphylaxis), (2) individuals might have an underlying condition that is also a contraindication for vaccination (i.e., seizure disorder), or (3) safety event of interest and vaccination may be seasonal in nature.[32] The time between the risk and control intervals will be determined based on the biological mechanism of action for each safety events of interest assessed, and may be subject to change based on further clinical input. Examples of the SCRI design with a post-vaccination control interval (in an individual who only receives the first dose of vaccine) is presented in Figure 1 below.

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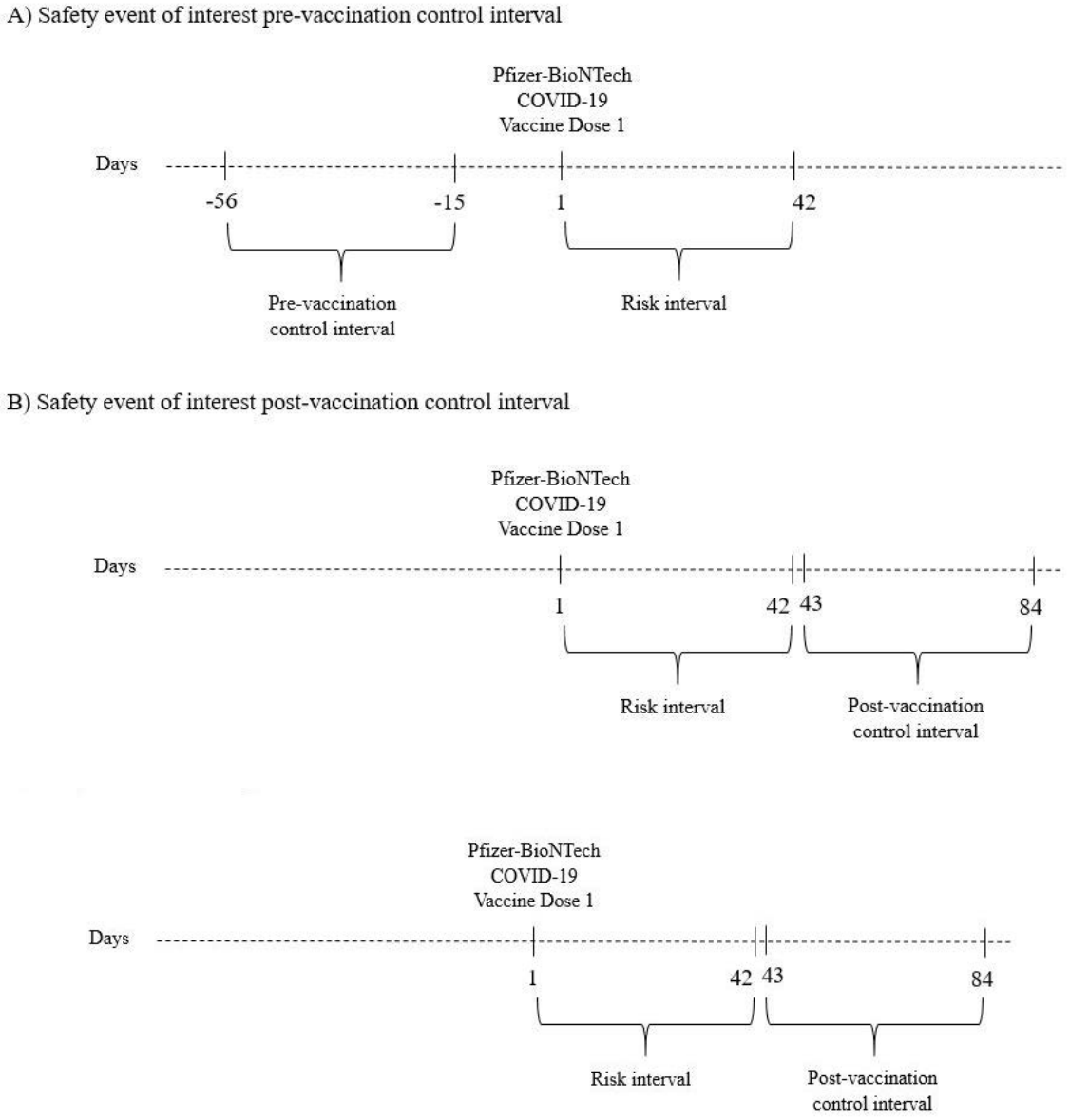
Figure 1. Example of SCRI Design for Assessment of a Safety Event of Interest with a 42-day Risk Interval in an Individual who Receives Only One Vaccine Dose, with Post-vaccination Control Intervals*



*The risk interval may include day 0, date of Pfizer-BioNTech COVID-19 vaccination, for some of the safety events of interest assessed (e.g., anaphylaxis). The length of the risk interval will vary across each safety event of interest and may be subject to change based on clinical input. Note that some individuals may not receive the complete course of vaccination, and thus may only receive the first dose of vaccine. This is represented in Figure 1 while Figure 2 represents an example where the complete course with 2 doses are received.

Two doses of the Pfizer-BioNTech COVID-19 vaccine are recommended 3 weeks apart. This study program will monitor safety events of interest that occur after dose 1 before dose 2 (i.e., during risk interval 1), after dose 2 (i.e., during risk interval 2), and aggregate for

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doses 1 and 2 (i.e., risk interval 1 + risk interval 2), respectively, for individuals receiving both doses. Additional doses of the Pfizer-BioNTech COVID-19 vaccine may be included in the analysis should they be approved, and those details will be described in the statistical analysis plan (SAP).

Given the risk intervals for specific safety events of interest range from 1 day to 90 days (please see Table 1 in Section 9.3.3), the time between the first and second dose may be longer or shorter than the recommended risk interval for a given safety event after the first dose. See Figure 2 below for SCRI design examples where a safety event with a 42 risk interval window (e.g., Bell's palsy; Table 1 in Section 9.3.3) is assessed in hypothetical individuals who receive two doses of Pfizer-BioNTech COVID-19 vaccine: Figure 2A shows the SCRI design with the second dose received 21 days after the first (i.e., the risk interval for dose 1 overlaps with the risk interval for dose 2), while Figure 2B shows the SCRI design with the second dose received 60 days after the first (i.e., there is a gap between the end of the risk interval for dose 1 and dose 2 initiation). For the first scenario (Figure 2A), the risk interval for dose 1 will be censored at the time of dose 2; further, safety events of interest that occur during the overlapping period of risk interval 1 and risk interval 2 (shown in gray shading in Figure 2A) may be flagged for separate analyses to discern the additive effect of Pfizer-BioNTech COVID-19 vaccine dose 1 and dose 2. For the second scenario (Figure 2B), events will only be measured during the risk intervals, ignoring the gap between the end of the risk interval for dose 1 and dose 2 initiation.

For each analysis, control intervals corresponding to the risk intervals will be defined either at end of the risk interval for dose 1 (for individuals with only one dose observed) or after the risk interval for dose 2 (for individuals with two doses observed), regardless of whether of the analyses focus on safety events after dose 1, after dose 2, or aggregated for doses 1 and 2 (Figure 2A and Figure 2B).

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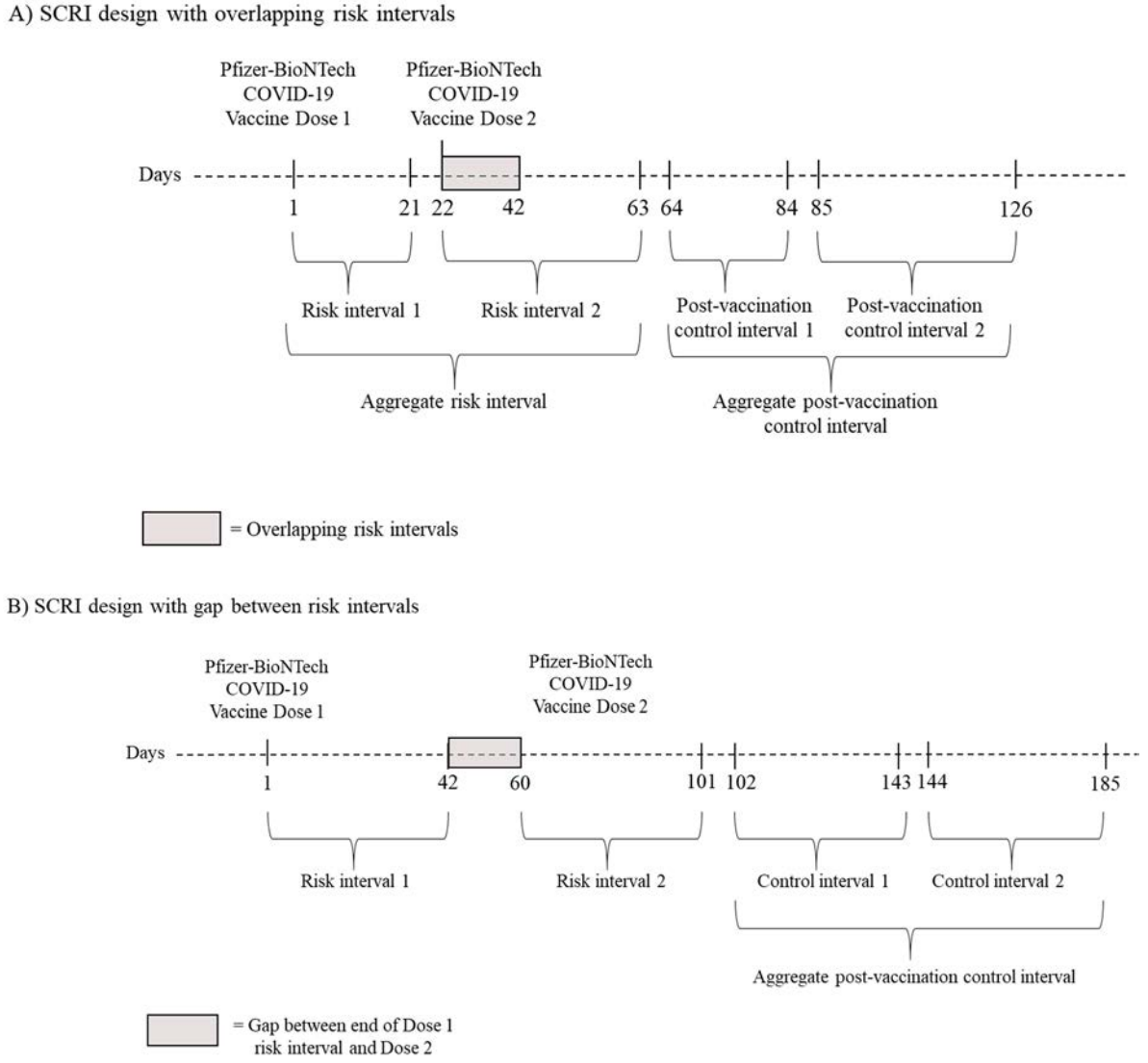
Figure 2. Example of SCRI Design for Assessment of a Safety Event of Interest with a 42-day Risk Interval in an Individual who Receives Two Vaccine Doses, with Post-vaccination Control Intervals



9.1.2. Active Comparator Design

In the active comparator design, the frequency of safety events of interest among individuals who received Pfizer-BioNTech COVID-19 vaccine from December 11, 2020 onward will be compared with the event frequency among recipients of the seasonal influenza vaccination in five prior seasons, between 2014/2015 through 2018/2019. Data in peri-COVID time periods from January 2020 to present are excluded because of pandemic-associated under-utilization of health resources and under-reporting of medical events. The same risk interval length (e.g., 42 days) will be used to evaluate safety events of interest following vaccination with Pfizer-BioNTech COVID-19 vaccine and to assess safety events of interest occurring after vaccination for seasonal influenza in prior seasons. The observed number of safety events of

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interest for Pfizer-BioNTech COVID-19 vaccine will be compared to the expected number calculated for the influenza vaccine in past seasons.[10]

9.1.3. Additional Study Designs in the Signal Evaluation Phase

There will be additional study designs conducted during the signal evaluation phase if a signal is detected from the above analyses in the signal detection phase. These include analyses using self-controlled case series (SCCS) and comparison of vaccinated unvaccinated contemporary controls. Additionally, signal evaluation analyses may also be conducted for signals detected in external sources or based regulatory request (e.g., myocarditis/pericarditis). These analyses are further detailed in Section 9.7.3.2.

9.1.4. Study Period

The study will be conducted for a period of 30 months, starting on December 11, 2020 onward, with data collection concluding on June 10, 2023.

9.2. Setting

The study population will be kept as broad as possible in order to capture safety events of interest that occur among all vaccinated individuals.

9.2.1. Inclusion Criteria

- Record of at least one dose of Pfizer-BioNTech COVID-19 vaccine in the period of December 11, 2020 to present, or
- Record of at least one dose of seasonal influenza vaccine during prior flu seasons, from 2014/2015 to 2018/2019 (applies to active comparators only); and
- At least 1 year of enrollment in and no disenrollment from VHA benefits (i.e., the baseline period) prior to Pfizer-BioNTech COVID-19 or seasonal influenza vaccination date.

9.2.2. Exclusion criteria

- Individuals who receive at least one dose of Pfizer-BioNTech COVID-19 vaccine in addition to a COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech will be identified and summarized, but they will be excluded from further analysis.

9.2.3. Subgroups

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

- Immunocompromised individuals, defined as individuals diagnosed with symptomatic human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), hematologic malignancy, or other immune conditions; individuals diagnosed with solid malignancy, organ transplant, or rheumatologic/inflammatory conditions, all of whom were administered chemotherapy or immune modulators; individuals diagnosed with rheumatologic/inflammatory conditions and administered

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systemic corticosteroids; or individuals who were administered chemotherapy, immune modulators, or systematic steroids for at least 14 days;[13]

- Different age groups, with a focus on the elderly (e.g., < 35, 35 - < 45, 45 - < 55, 55 - < 65, 65 - < 75, ≥ 75);

- Individuals with specific comorbidities identified as high risk for COVID-19 by the CDC (i.e., cancer, chronic kidney disease, chronic obstruction pulmonary disease [COPD], Down Syndrome, cardiovascular conditions [e.g., heart failure, coronary artery disease, or cardiomyopathies], immunocompromised state from solid organ transplant, obesity [body mass index (BMI) of 30 kg/m2 or higher but < 40 kg/m2], severe obesity [BMI of 40 kg/m2or higher], sickle cell disease, smoking, type 1 and 2 diabetes mellitus);[12]

- Individuals receiving only one dose of Pfizer-BioNTech COVID-19 vaccine;

- Individuals with prior SARS-CoV-2 infection based on medical history or pre-vaccination serology (Appendix Table 4);

- Individuals with regular use of VHA medical care, defined as at least two outpatient (excluding emergency department [ED], as ED visits may not be considered regular) or inpatient encounters in the one year prior to vaccination. The encounters must be separated by > 30 days (for inpatient, by admission date), and at least one must be within six months prior to the date of vaccination. This will ensure that individuals have ongoing health care encounters, particularly near the vaccination date, and regularly receive their healthcare from VHA facilities, rather than outside facilities that would not be captured in the VHA's Corporate Data Warehouse (CDW);

- Individuals who are in the VA priority group 1 Veteran. These individuals have either the highest levels of service connected disability (≥50% disabling), are considered unemployable, or have received the medal of honor.[33] Individuals categorized as priority group 1 are the highest priority for VHA care. This will ensure that the individual is more likely to receive all of their care from a VA facility.

- Individuals enrolled in the VHA with dual coverage who are also identified in the Centers for Medicare & Medicaid Services (CMS) Medicare administrative claims data, which will be linked to the CDW, in order to supplement CDW data for a more complete evaluation of healthcare encounters.

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.

Given that VA population has a median age of over 46 years for females and is comprised of approximately 90% males, the evaluation of the Pfizer-BioNTech COVID-19 vaccine safety

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during pregnancy, including fetal death and infant outcomes, may have poor feasibility and will therefore not be conducted.

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 Appendix Table 3 for additional details):

- Current Procedural Terminology (CPT) codes and associated vaccine administration HCPCS codes; OR
- 10 and 11-digit National Drug Codes (NDCs); OR
- Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (i.e., Pfizer), lot number, injection site, and date(s) of immunization.[11]

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

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

Administration of the seasonal influenza vaccine during 2014/2015 through 2018/2019 flu seasons will be identified based on the following (see Appendix Table 3 for additional details):

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

9.3.1.1. Pfizer-BioNTech COVID-19 Vaccine Groups of Interest

While the primary vaccination group of interest is all individuals receiving Pfizer-BioNTech COVID-19 vaccine (irrespective of receipt of seasonal influenza vaccination), additional subsets of the study population will be studied, similar to the PRISM safety surveillance program of H1N1 vaccine safety:[10]

Cohort A: Individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine who did not receive the influenza vaccine during the flu season in which COVID-19 vaccination occurred;

Cohort B: Individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine who received the seasonal influenza vaccine at least 42 days prior to COVID-19 vaccination during the same flu season in which COVID-19 vaccination occurred;

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Cohort C: Individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine who received the seasonal influenza vaccine within 42 days before or any time after COVID-19 vaccination during the same flu season in which COVID-19 vaccination occurred;

Cohort D: Individuals vaccinated with both Pfizer-BioNTech COVID-19 vaccine and the seasonal influenza vaccine on the same day.

The following sub-cohorts will be assessed for each of the Cohorts A-D:

- Individuals vaccinated with only 1 dose (i.e., incomplete course) of Pfizer-BioNTech COVID-19 vaccine;

- Individuals vaccinated with 2 doses (i.e., complete course) of Pfizer-BioNTech COVID-19 vaccine.

9.3.2. Baseline Characteristics

The following data elements regarding baseline demographic and clinical characteristics will be assessed based on a 1-year baseline period prior to the date of vaccination with Pfizer-BioNTech COVID-19 vaccine and date of seasonal influenza vaccination for active comparators. Depending on the attrition rate, the length of the baseline period may be modified to 6 months. All diagnoses, procedures, and medications will be identified by the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes, ICD-10-PCS (procedure coding system) codes, CPT, or Healthcare Common Procedure Coding System (HCPCS) procedure codes, and generic drug names, as appropriate (Appendix Table 1). The following demographic and clinical characteristics will be assessed:

Demographics:

- Age
- Sex
- Race/ethnicity
- VHA service area

Clinical characteristics:

- Smoking status
- BMI
- History of anaphylaxis/allergic reactions
- Previous anaphylaxis of vaccine component
- History of hospitalizations
- Frailty index
- Charlson comorbidity index (CCI)
- Selected comorbidities
    - Autoimmune disease
    - Asthma

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  - Bleeding diathesis or condition associated with prolonged bleeding
  - Cancer
  - Cardiovascular conditions
  - Chronic kidney disease/dialysis
  - COPD/interstitial lung disease
  - Diabetes mellitus
  - Down syndrome
  - Sickle cell disease
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - HIV
  - 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

Specific covariates of interest for the prioritized analysis of myocarditis/pericarditis are described in Section 9.7.8.

9.3.3. Outcomes

The safety events of interest for active surveillance were identified based on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration's SPEAC Project, the FDA and CDC enhanced safety monitoring recommendations.[8,9] Endpoints of special interest in signal detection, as noted by the FDA and CDC's ACIP are denoted in italics. [9] 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 Appendix Table 2 for the operational definitions of the outcome variables based on ICD-10-CM diagnosis codes, which may be refined as the study progresses based on additional available information and the published literature (e.g., frequency of ICD-10-CM codes).

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Outpatient, ED, 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. The following safety events of interest will be assessed:

Neurologic:

- Aseptic meningitis
- Bell's palsy
- *Cerebrovascular non-hemorrhagic stroke*
- Convulsions/seizures in individuals with controlled epilepsy
- Encephalitis/encephalomyelitis
- *Guillain-Barré Syndrome (GBS)*
- *Generalized convulsion/seizures*
- Multiple sclerosis (MS)
- Optic neuritis (ON)
- Other acute demyelinating diseases
- Transverse myelitis (TM)

Immunologic:

- Anaphylaxis
- Arthritis and arthralgia/joint pain
- Autoimmune thyroiditis
- Fibromyalgia
- *Kawasaki disease (KD)*
- *Multisystem inflammatory syndrome in adults (MIS-A)*
- Vasculitides

Cardiac:

- *Acute myocardial infarction (AMI)*
- Arrhythmia
- Coronary artery disease (CAD)
- Heart failure and cardiogenic shock
- Microangiopathy
- *Myocarditis*
- *Pericarditis*
- Stress cardiomyopathy

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Hematologic:

- *Cerebrovascular hemorrhagic stroke*
- Chilblain-like lesions
- *Disseminated intravascular coagulation (DIC)*
- Deep vein thrombosis (DVT)
- Hemolytic anemia
- Hemorrhagic disease
- Limb ischemia
- Pulmonary embolus (PE)
- Single organ cutaneous vasculitis
- *Thrombocytopenia*
- Thrombosis with thrombocytopenia syndrome (TTS)

Other:

- Acute kidney injury
- Appendicitis
- *Death*
- Erythema multiforme
- Liver injury
- *Narcolepsy and cataplexy*
- Non-anaphylactic allergic reactions
- *Severe COVID-19 disease*
- Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)

The risk intervals selected for each safety event of interest are based on biological plausibility and precedents in the published literature (Table 1). A safety event of interest will only be counted if it can be assigned to 1) the risk interval following Pfizer-BioNTech COVID-19 vaccination (all designs), 2) the post-vaccination control interval (self-controlled designs), or 3) the risk interval for the active comparators receiving seasonal influenza vaccine (active comparator design). 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 (i.e., 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. The duration of the pre-specified window will differ by safety events of interest in order to rule out pre-existing events. This approach is consistent with the FDA's COVID-19 Vaccine Safety Surveillance Project.[16] Additionally, the length of the clean window may be extended (e.g., 2 years) given the reduction in healthcare resource utilization since the start of the pandemic. By way of example, a safety events of interest for the SCRI design can be considered in the following ways:

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- 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 (e.g., 1-year prior to vaccination date), the safety event of interest should be assigned to the risk interval.
    - However, 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 who received seasonal influenza vaccination 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 (and control) intervals 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" the signal, 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. Additionally, if further refinement and evaluation is necessary, temporal scan statistics may be used to empirically identify the at-risk time interval by evaluating clusters of safety events of interest. This will be further described in the SAP.

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Table 1. Outcome algorithms for SCRI analysis, with risk and control intervals

Safety Event of Interest	Setting (Inpatient [IP], Outpatient [OP], Emergency Department [ED])	Clean window	Risk interval (days)	Post-vaccination control interval (days)
Neurologic				
Aseptic meningitis	IP only[16]	6 months[16]	1-42[34]	43-84[34]
Bell's palsy[16]	IP or OP	6 months	1-42	43-84
Cerebrovascular non-hemorrhagic stroke[16]	IP only	1 year	1-28	29-56
Convulsions/seizures in individuals with controlled epilepsy[35]	IP or OP-ED	1 year	1-90	91-180
Encephalitis/encephalomyelitis[16]	IP only	6 months	1-42	43-84
Guillain-Barré Syndrome (GBS)[16]	IP, primary position on	1 year	1-42	43-84
Generalized convulsion/seizures[10]	IP or OP-ED	6 months	0-14	15-29
Multiple sclerosis (MS)[10,30]	IP or OP	1 year	1-42	43-84
Optic neuritis (ON)[10,30]	IP or OP	1 year	1-42	43-84
Other acute demyelinating diseases[10,30]	IP or OP	1 year	1-42	43-84
Transverse myelitis (TM)[16]	IP or OP-ED	1 year	1-42	43-84
Immunologic				
Anaphylaxis	IP or OP-ED[16]	1 month[16]	0-1[16]	7-8[10,30]
Arthritis and arthralgia/joint pain[a]	IP or OP	1 year	1-42	43-84
Autoimmune thyroiditis[a]	IP or OP	1 year	1-42	43-84
Fibromyalgia[a]	IP or OP	1 year	1-42	43-84
Kawasaki disease (KD)[36]	IP only	1 year	1-28	29-56
Multisystem inflammatory syndrome in adults (MIS-A)[16]	IP or OP-ED	1 year	1-42	43-84
Vasculitides[b]	IP only	1 year	1-28	29-56
Cardiac				
Acute myocardial infarction (AMI)[16]	IP only	1 year	1-28	29-56

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Table 1. Outcome algorithms for SCRI analysis, with risk and control intervals

Safety Event of Interest	Setting (Inpatient [IP], Outpatient [OP], Emergency Department [ED])	Clean window	Risk interval (days)	Post-vaccination control interval (days)
Arrhythmia[c]	IP only	1 year	1-42	43-84
Coronary artery disease (CAD)[c]	IP only	1 year	1-42	43-84
Heart failure and cardiogenic shock[c]	IP only	1 year	1-42	43-84
Microangiopathy[b]	IP only	1 year	1-28	29-56
Myocarditis[16]	IP or OP	1 year	1-42[d]	43-84
Pericarditis[16]	IP or OP	1 year	1-42[d]	43-84
Stress cardiomyopathy[c]	IP only	1 year	1-42	43-84
Hematologic				
Cerebrovascular hemorrhagic stroke[16]	IP only	1 year	1-28	29-56
Chillblain-like lesions[b]	IP or OP	1 year	1-28	29-56
Disseminated intravascular coagulation (DIC)[16]	IP or OP-ED	1 year	1-28	29-56
Deep vein thrombosis (DVT)[16]	IP or OP	1 year	1-28	29-56
Hemolytic anemia[e]	IP or OP	1 year	1-42	43-84
Hemorrhagic disease[b]	IP only	1 year	1-28	29-56
Limb ischemia[b]	IP only	1 year	1-28	29-56
Pulmonary embolus (PE)[16]	IP or OP	1 year	1-28	29-56
Single organ cutaneous vasculitis[b]	IP only	1 year	1-28	29-56
Thrombocytopenia[16]	IP or OP	1 year	1-42	43-84
Thrombosis with thrombocytopenia syndrome (TTS)[e]	IP or OP	1 year	1-42	43-84
Other				
Acute kidney injury[f]	IP only	6 months	1-42	43-84
Appendicitis[16]	IP or OP-ED	1 year	1-42	43-84
Death	IP or OP	1 year	0-42	43-85

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Table 1. Outcome algorithms for SCRI analysis, with risk and control intervals

Safety Event of Interest	Setting (Inpatient [IP], Outpatient [OP], Emergency Department [ED])	Clean window	Risk interval (days)	Post-vaccination control interval (days)
Erythema multiforme[g]	IP only	6 months	1-2	8-9
Liver injury[f]	IP or OP	1 year	1-42	43-84
Narcolepsy and cataplexy	IP or OP[16]	1 year[16]	1-42[16]	43-84
Non-anaphylactic allergic reactions[10,30]	IP or OP	6 months	1-2	8-9
Severe COVID-19 disease[h]	IP only	1 year	1-42	43-84
Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)[g]	IP only	6 months	1-2	8-9

Notes:

a. Published setting, clean window, and risk and control intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., arthritis and arthralgia/joint pain, fibromyalgia and autoimmune thyroiditis).

b. Published setting, clean window, and risk and control intervals for DVT, pulmonary embolus and DIC were applied to other cardiovascular and hematological disorders characterized by damage to the blood vessels and/or arteries and clotting (i.e., microangiopathy, limb ischemia, hemorrhagic disease, chilblain-like lesions, single organ cutaneous vasculitis and vasculitides). The published risk and control intervals for KD were applied to vasculitides given that KD is a type of medium and small-vessel vasculitis.

c. Published setting, clean window, and risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (i.e., heart failure and cardiogenic shock, stress cardiomyopathy, CAD, arrhythmia).

d. For the prioritized safety analysis of myocarditis/pericarditis, additional risk intervals (i.e., 1-7 days and 1-21 days) will be examined and are described in Section 9.7.8.

e. Published setting, clean window and risk and control intervals for thrombocytopenia were applied to hemolytic anemia and TTS.

f. Risk intervals of 42 days were applied for acute kidney injury and liver injury to be consistent with other similar safety events of interest.

g. Published setting, clean window, and risk and control intervals for non-anaphylactic allergic reactions were applied to hypersensitivity disorders (i.e., erythema multiforme and SJS/TEN).

h. 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.

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9.4. Data Source

The VHA is the largest integrated health care system in the US, providing both inpatient and outpatient clinical care to over 9 million Veterans enrolled at more than 170 medical centers and 1,074 community-based outpatient clinics.[14] VHA's health care delivery system is organized regionally around 18 Veterans Integrated Service Networks (VISNs) across the US. Each VISN is responsible for health care planning and resource allocation in a particular geographical region. For example, the VA New England Healthcare System (VISN 1) covers VHA facilities in Massachusetts, Connecticut, New Hampshire, Maine, and Rhode Island, while the VA Heart of Texas Health Care Network (VISN 17) oversees the facilities in Texas.

The VHA also maintains its own mortality data where 99% of enrollees' deaths are reported within one month of occurrence. As of January 7, 2021, the VHA has had over 174,000 confirmed COVID-19 cases.[37] Among active and convalescent cases, approximately 145,000 are Veterans and approximately 15,000 are employees (with an estimated 630 as Veteran employees).[33] While African American Veterans make up approximately 12% of the VHA,[38] the burden of COVID-19 cases are skewed, with African American Veterans comprising approximately 20% of all COVID-19 cases.[37] Approximately 7,099 COVID-19-infected VA patients have died, an estimated 2,738 in VHA hospitals.[37]

The objectives of this study will be addressed using data from VHA's CDW, which is an integrated EMR system with a centralized data warehouse that is updated on a daily basis. The CDW stores data in separate databases, one for each type of clinical information (e.g., inpatient medication, inpatient admission, outpatient medication, outpatient visit). Individual demographic information such as date of birth and gender are also available. Immunization records include information on manufacturer, lot number, injection site, and concurrent immunizations. The CDW does not include information on any care received outside of a VHA facility.

Each individual is assigned a unique identification number to allow for longitudinal follow-up as well as to cross-reference to the various separate databases. For example, in each inpatient admission record, there is information on the primary discharge diagnosis (and as many as 15 secondary diagnoses), date of admission, date of discharge, and length of stay. This record can then be linked to other information of that inpatient stay located in other files, including procedures that the patient underwent during the hospitalization, medical specialty of the provider, and prescriptions dispensed. Other files are similarly structured, and therefore may be linked together to provide comprehensive information about the patient and his/her medical encounters.

The VHA database is an appropriate data source to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine for the following reasons. First, as the vaccine will be distributed through government facilities (including VHA) as part of initial distribution, analysis of VHA data will provide early data on the safety of the vaccine. Veterans living in long-term care facilities and Veterans who are healthcare workers will be prioritized in the first wave of Pfizer-BioNTech COVID-19 vaccinations.[39] The VA offers eligible Veterans long-term care services ranging from nursing homes and assisted-living centers to caregiver

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support in the Veterans' own homes.[15] Secondly, and relatedly, VHA data are refreshed daily and would thus enable early and rapid data analysis. Third, the VHA population is on average older than the general US population.[40] Of these, about 30% (roughly 1,000,000 individuals) use VHA health services almost exclusively (i.e., those with a priority group of 1 or 4; Veterans assigned to Priority group 4 are either accepting VA assistance or housebound benefits, or have been determined to be "catastrophically disabled" by the VA.[33]), which lends itself to having complete, longitudinal healthcare data for such individuals who may be at higher risk of COVID-19 due to older age.[41,42] These priority groups include Veterans with the highest levels of service-connected disability and are therefore, the highest priority for VHA care.[33] Finally, the VHA population has, on average, more comorbid conditions than the general population, which also indicates that these individuals may be at higher risk of COVID-19.[43] While the VHA population is predominantly male (approximately 90%), and thus lacks generalizability to females, it will still provide a useful setting to examine real-world vaccine safety.

Since it is possible that individuals may not have all their health encounters within the VHA, (especially older veterans who are also covered by Medicare), additional subgroup analyses will be conducted in which the CDW data will be supplemented with data from CMS, linking Medicare administrative claims data at the patient level to ensure a more comprehensive evaluation of the care an individual receives. Medicare data will include eligibility files and claims for services received in the inpatient and outpatient setting, as well as skilled nursing facilities, hospice, and home health agencies, and will cover the US primarily among those aged 65 years or older.

9.5. Study Size

The sample size achieved will depend on the number of recipients of Pfizer-BioNTech COVID-19 vaccine within the VHA database during the study period, which will increase over time with subsequent analyses. The population size will increase with each bi-weekly analysis as the Pfizer-BioNTech COVID-19 vaccine becomes more readily available and a greater number of individuals are vaccinated. Specifically, the data will be refreshed on a biweekly basis and a continuous sequential test procedure will be used to reevaluate data according to this schedule. As of January 21, 2021, 112,201 doses of Pfizer-BioNTech COVID-19 vaccine have been administered within the VHA (based on CPT code 91300) to a total of 107,458 patients.

As a result of the ability to perform near-real-time analysis, the risk interval (and post-vaccination control interval, for applicable safety events of interest) may have only partially elapsed in some cases. To account for this, we will use methods adopted in previous studies,[10,44,45] whereby risk intervals will be scaled (or truncated) in order to ensure an equivalent length (or a fixed ratio) of time is assessed between the control and risk intervals.

9.5.1. Power

Power calculations for the rapid cycle analysis (RCA) approaches proposed for safety event of interest signal detection will be conducted according to the methods of Kulldorff et al.[46,47] Table 2 illustrates the estimated power for the RCA approach using the Poisson-based

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maximized sequential probability ratio test (MaxSPRT), and provides an overview of the power required to detect varying relative risk (RR) estimates with an alpha level of 0.01. T denotes the expected number of safety events of interest to occur during the risk interval of interest (Table 2 and Table 3). 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 here.[48] As an example, as shown in Table 2, the surveillance system 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 when the expected number of safety events of interest reaches 6 events.

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Table 2. Estimated Statistical Power for the Poisson-based MaxSPRT[46]

	True relative risk					
T	1.2	1.5	2	3	5	10
0.1	0.013	0.018	0.027	0.049	0.106	0.281
0.2	0.013	0.018	0.029	0.058	0.138	0.401
0.5	0.014	0.023	0.042	0.105	0.299	0.768
1	0.015	0.027	0.059	0.173	0.510	0.957
1.5	0.016	0.032	0.077	0.251	0.693	0.995
2	0.017	0.036	0.097	0.334	0.821	0.9994
2.5	0.018	0.041	0.118	0.415	0.900	0.9999452
3	0.019	0.045	0.139	0.489	0.945	0.9999949
4	0.020	0.053	0.180	0.616	0.984	1
5	0.021	0.061	0.222	0.718	0.996	1
6	0.023	0.070	0.267	0.800	0.9990	1
8	0.025	0.089	0.362	0.909	0.9999529	1
10	0.027	0.110	0.455	0.962	0.9999982	1
12	0.030	0.131	0.542	0.985	0.9999999	1
15	0.033	0.163	0.651	0.996	1	1
20	0.039	0.223	0.795	0.999722	1	1
25	0.045	0.287	0.888	0.99998301	1	1
30	0.051	0.354	0.943	0.99999913	1	1
40	0.064	0.482	0.986	1	1	1
50	0.078	0.597	0.997	1	1	1
60	0.094	0.698	0.99948292	1	1	1
80	0.128	0.843	0.99998632	1	1	1
100	0.164	0.925	0.99999971	1	1	1
120	0.205	0.967	0.99999999	1	1	1
150	0.268	0.991	1	1	1	1
200	0.381	0.9992	1	1	1	1
250	0.491	0.9999445	1	1	1	1
300	0.594	0.99999665	1	1	1	1
400	0.759	0.99999999	1	1	1	1
500	0.868	1	1	1	1	1
600	0.933	1	1	1	1	1
800	0.985	1	1	1	1	1
1,000	0.997	1	1	1	1	1

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9.6. Data Management

Data for this study will be stored and extracted from the VHA database (previously described in Section 9.4) that contain information about patient demographics, vaccinations, procedures, diagnoses, and death.

9.6.1. Case report forms (CRFs)/Electronic data record

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

A CRF is required and should be completed for each included patient in the signal verification phase that requires EMR and chart review (see Section 9.7.3.3). 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. The CRF will consist of two parts: (1) a database CRF that will be populated based on a direct extraction of data from the VA CDW for review by the adjudicators; (2) an adjudication page that will be completed by an adjudicator after reviewing data in the completed CRFs. Analysis Group shall ensure that the CRFs are securely stored on VHA 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.

Analysis Group has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the database 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 adjudication page must be signed by the adjudication committee members to attest that the data contained on the forms are true and accurate based on their review of the EMR 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

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 Institute (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.

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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. The SAP will also provide additional detail regarding the evaluation of a threshold of excess risk for each of the safety events of interest. Consistent with the approach of Kulldorff et al., this will be determined based on background incidences for each event (e.g., based on historical influenza vaccinated active comparator cohort data to be evaluated during the study), in addition to pre-specified significance level (e.g., alpha = 0.01 or 0.05) and power.[46] This information, in conjunction with a clinically meaningful RR (e.g., 2 or 3) and the expected upper limit of events under the null hypothesis will allow for the calculation of critical values of each safety event of interest using the MaxSPRT method. Greater power (e.g., 80%) is also a natural criterion to use when selecting the upper limit on the length of surveillance, and in turn, the expected number of events to occur, although there is ultimately a tradeoff between that power and the time allowed to identify the expected number of events to occur.

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). In addition, SaTScan will also be used to conduct specific temporal analyses.

9.7.1. Baseline Characteristics

Baseline demographics and clinical characteristics for individuals receiving Pfizer-BioNTech COVID-19 vaccine and individuals who received seasonal influenza vaccination 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. Incidence rates (i.e., per-patient per-month) for prior hospitalizations may be calculated as the number of events divided by person-time of observation since the length of the baseline period may vary between individuals. Standardized differences will be calculated between Pfizer BioNTech COVID-19 vaccine recipients and active comparators who received seasonal influenza vaccination to evaluate whether there are any major differences in individuals' baseline characteristics. Standardized differences < 10% will indicate that matching has appropriately balanced the characteristics between recipients of the Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine.

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9.7.2. Vaccine Utilization Patterns

Descriptive statistics will also be used to summarize vaccine utilization patterns, including proportion of individuals receiving vaccine, 2-dose completion rate, distribution of time gaps between the first and second dose, and care setting where immunization was received (e.g., outpatient clinic, pharmacy, inpatient ward). Counts of individuals who received a COVID-19 vaccine from a different manufacturer in addition to the Pfizer-BioNTech COVID-19 vaccine will be summarized.

9.7.3. Safety Signal Analyses

Several analyses corresponding to the designs discussed previously will be conducted to detect safety signals associated with Pfizer-BioNTech COVID-19 vaccine. Analyses will be conducted among all individuals receiving the vaccine, individuals who received Pfizer-BioNTech COVID-19 vaccine without seasonal flu vaccine (Cohort A will be used for SCRI; Cohort B+C will be used for active comparator analyses), and individuals receiving Pfizer-BioNTech COVID-19 vaccine and seasonal flu vaccine on the same day (Cohort D), along with sub-cohorts receiving only one dose vs. two doses.

A stepwise process, illustrated below, will be performed for signal detection, evaluation, and verification (Figure 3). This approach has been adapted from the Active Monitoring Protocol of the FDA's COVID-19 Vaccine Safety Surveillance Project.[16] The statistical approach described below may be modified further based on data availability, additional clinical input, and for consistency or to complement similar studies of Pfizer-BioNTech COVID-19 vaccine.

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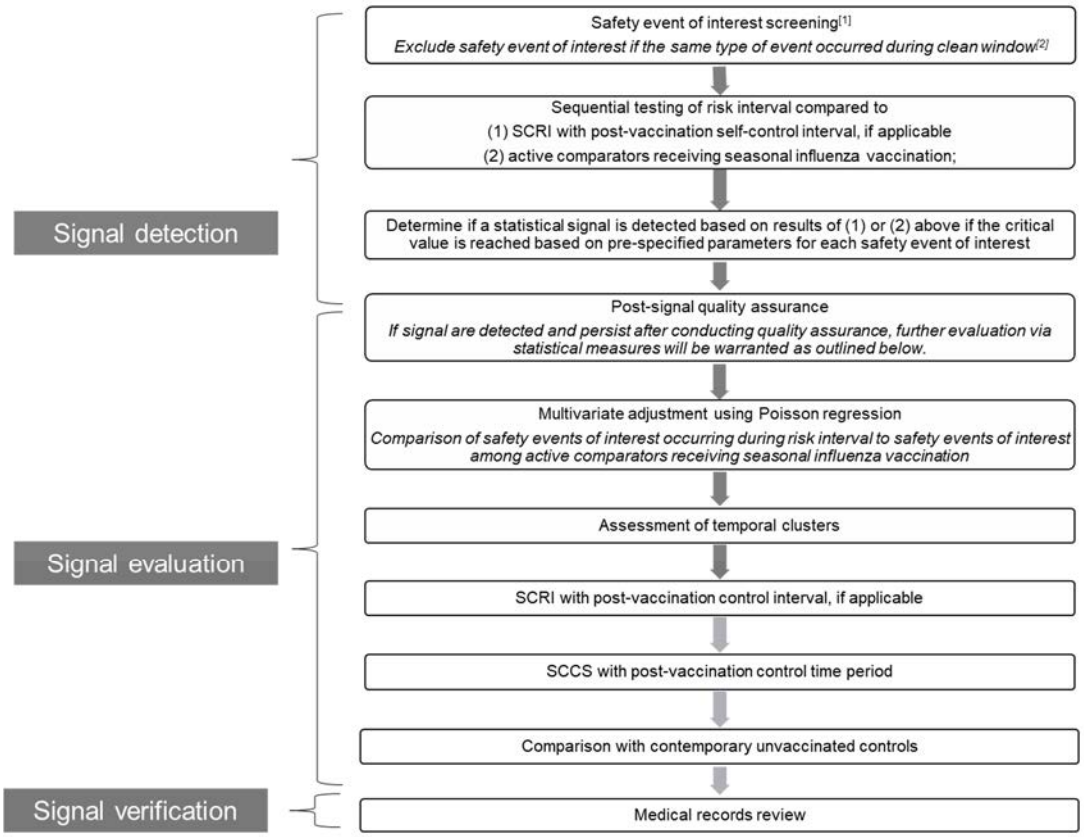
Figure 3. Steps in Signal Detection, Evaluation, and Verification



Notes:
[1] List of safety events of interest and corresponding definitions may be refined as the study progresses based on additional available information.
[2] The risk and control intervals selected for the SCRI analysis for each safety event of interest are based on biological plausibility and precedents in the literature. Only the individual's first instance during the specified clean window (i.e., the interval used to define incident outcomes) will be included. Note that only the first inpatient or outpatient occurrence of a safety event of interest following the clean window will be used to identify incident events (e.g., if an inpatient safety event of interest occurs in the clean window, a repeat occurrence will not be counted in the risk interval). However, event worsening will be counted as a safety event of interest. For example, 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 as a safety event of interest.

9.7.3.1. Signal Detection

Signal detection will rely on SCRI design with comparison to post-vaccination control intervals for the two safety events that require COVID-19 diagnosis (i.e., severe COVID-19 disease, MIS-A) and active comparator design for the remaining safety events. While the active comparator design will be the main analysis for signal detection because it can be performed the fastest, it cannot be used for safety events that require COVID-19 diagnosis because historical controls would not meet the criteria of having a COVID-19 diagnosis.

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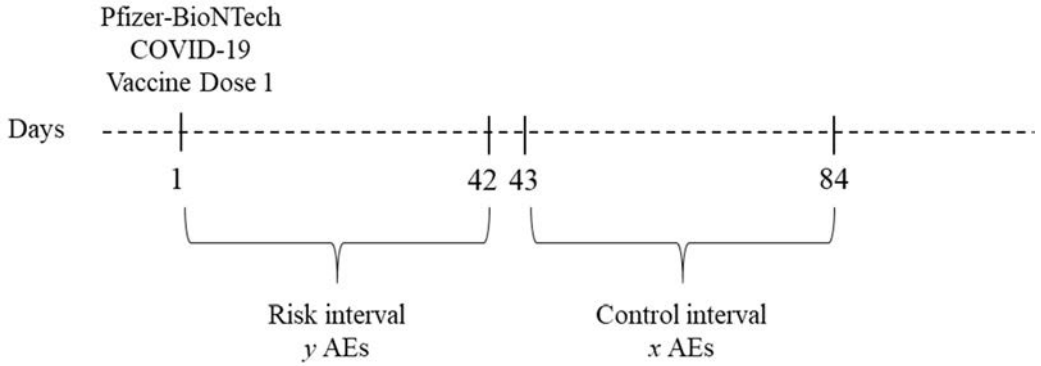
9.7.3.1.1. Sequential Testing - SCRI Design using the Binomial-based MaxSPRT for Comparison to Post-vaccination Control Intervals For the Two Safety Events Requiring COVID-19 Diagnosis

The goal is to provide rapid-cycle, near real-time safety surveillance. In the signal detection phase, the SCRI analysis with post-vaccination control intervals will be used for certain safety events of interest (i.e., severe COVID-19 disease, MIS-A). All other safety events of interest will be assessed in the signal detection phase using the active comparator design. The post-vaccination control period will be assessed once enough post-vaccination time has accumulated.

To account for multiple testing and bi-weekly review of the data, the MaxSPRT using a binomial probability model will be applied. The null hypothesis (H_0) assumes that the risk of a safety event of interest during the risk interval is equivalent to the risk of the same safety event of interest developing during the control interval, accounting for differences in interval duration as needed (e.g., for safety events of interest such as demyelinating disease), meaning a RR of 1 is specified under H_0.[30] The one-sided composite alternative hypothesis (H_a) assumes that the risk of a safety event of interest during the risk interval is greater than the risk of the same safety event of interest developing during the control interval, accounting for differences in interval duration (i.e., RR > 1, H_a is applicable across a range of RRs).[46]

Specifically, for the Pfizer-BioNTech COVID-19 vaccine, let *x* represent the total count of safety events of interest in the control interval (Figure 4), let *y* represent the total count of safety events of interest in the risk interval, and let *r* represent the ratio of *y* to *x* under the null hypothesis. Thus, when the total control interval duration and total risk interval duration are equal, r will be 1. The RR is estimated by $\frac{y}{x}$.[44] The RR and corresponding 99% confidence intervals (CIs) will be calculated.

Figure 4. Example of SCRI Design for a Safety Event of Interest with a 42-day Risk Interval and a Post-vaccination Control Interval



For the binomial model, the log-likelihood ratio (LLR) is calculated as the log probability of observing this distribution of *y* under H_a, divided by the probability of this occurring under H_0.[46] This ratio is calculated whenever new data are received to account for the continuous data stream until the full 42-day risk period is complete.

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$$LLR = \ln \frac{P(y \mid H_a)}{P(y \mid H_0)}$$

Once the LLR test statistic reaches a pre-specified critical value, a signal is detected. Specifically, the null hypothesis will be rejected if the LLR exceeds the critical value. The null hypothesis will not be rejected if the LLR does not reach or exceed the critical value, if the total number of safety events of interest reaches a pre-specified upper limit, or if surveillance ends without reaching this upper limit.[44]

For each safety event of interest (and specific to each age group, if age-stratified analyses are conducted), the critical value of the LLR will be determined based on the safety event of interest specific upper limit of expected safety events of interest and alpha level.[44] Upper limits will be determined based on the expected number of safety events of interest under the null hypothesis, assuming the risk after Pfizer-BioNTech COVID-19 vaccination is no greater than the risk of safety events of interest after seasonal influenza vaccination. Therefore, upper limits will be chosen such that they would not usually be reached.

9.7.3.1.2. Sequential Testing - Poisson-based MaxSPRT for Comparison to Active Comparators who Received Seasonal Influenza Vaccination

For comparison with active comparators who received seasonal influenza vaccination, the Poisson-based MaxSPRT will be applied, following the same statistical approach as described above, but using a Poisson probability distribution. In the Poisson MaxSPRT approach, the event frequency of safety events of interest in the risk interval after Pfizer-BioNTech COVID-19 vaccination will be compared to a background rate of safety events of interest in the risk interval after seasonal influenza vaccination in five prior seasons, ranging from 2014/15 through 2018/19. This approach is particularly important for extremely rare safety events of interest (i.e., less than 50 anticipated based on historical influenza vaccine rates of safety events of interest).[30] Poisson MaxSPRT is used to monitor very rare safety events of interest as binomial MaxSPRT may not detect a signal, despite a clinically meaningful RR.[44] This will also allow for more timely analysis using historical data, as well as improved power and sample size.

GBS is of particular interest relative to the safety profile of Pfizer-BioNTech COVID-19 vaccine. As GBS is an extremely rare safety event of interest, the primary RCA proposed will focus on Poisson MaxSPRT and apply an alpha of 0.05. The Poisson MaxSPRT has increased power to detect a signal with fewer occurrences of the safety event of interest. However, this method cannot fully control for confounding by indication.

9.7.3.1.3. Critical Values and Alpha Spending

Critical values for the LLR test statistic are shown below in Table 3 based on calculations conducted by Kulldorff et al 2011.[46] For example, assuming T = 6 (number of expected events under the null) and RR = 3, which corresponds to a power of 80.0% (See Section 9.5.1), the critical value would be 5.14 using alpha of 0.01 for the Poisson-based MaxSPRT. As noted previously, each safety event of interest will be evaluated separately to

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determine a critical value based on background incidence, alpha, power, and clinically meaningful RR. These details will be addressed in the SAP.

Table 3. Critical Values for Poisson-based MaxSPRT

T	$\alpha = 0.05$	$\alpha = 0.01$	$\alpha = 0.001$
0.1	2.044069	4.119293	6.579669
0.2	2.266893	4.179630	6.754862
0.5	2.637928	4.483740	7.034472
1	2.853937	4.670428	7.172614
1.5	2.964971	4.778944	7.278202
2	3.046977	4.862223	7.341453
2.5	3.110419	4.924475	7.397851
3	3.162106	4.971792	7.445736
4	3.245004	5.040311	7.518319
5	3.297183	5.091907	7.569312
6	3.342729	5.136461	7.608607
8	3.413782	5.206326	7.673013
10	3.467952	5.260513	7.724863
12	3.511749	5.302914	7.767520
15	3.562591	5.351279	7.814719
20	3.628123	5.414770	7.877573
25	3.676320	5.463382	7.924478
30	3.715764	5.502563	7.962688
40	3.774663	5.561620	8.022182
50	3.819903	5.605972	8.067072
60	3.855755	5.642209	8.102340
80	3.910853	5.697631	8.157530
100	3.952321	5.738974	8.199403
120	3.985577	5.772435	8.232827
150	4.025338	5.812121	8.272692
200	4.074828	5.862113	8.322983
250	4.112234	5.899824	8.360938
300	4.142134	5.929897	8.391288
400	4.188031	5.976241	8.438008
500	4.222632	6.011088	8.473183
600	4.250310	6.039013	8.501314
800	4.292829	6.081871	8.544590
1,000	4.324917	6.114225	8.577253

Multiple types of alpha spending functions can be employed to calculate the cumulative rate at which Type 1 error (alpha) probability is spent during sequential testing.[49] To achieve optimal expected time-to-signal, especially when historical Poisson data are used with surveillance data, a power-type convex alpha spending shape will be used based on published literature.[49] Additionally, $\rho = 1.5$ is referenced as a "rule of thumb" as it is suggested to be appropriate in most applications.

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9.7.3.2. Signal Evaluation

Signals are detected when the event frequency of a safety event of interest during the risk interval following vaccination with Pfizer-BioNTech COVID-19 vaccine is significantly increased compared to the event frequency of the same safety events of interest in the control comparator (i.e., the critical value is achieved and surpassed). If signals are indeed detected for safety events of interest based on the analysis described above, further evaluation is warranted to refine and confirm such detections. This will consist of the additional analyses describe in the following sections, which will be conducted every six months.

9.7.3.2.1. Post-Signal Quality Assurance

Quality assurance will first be conducted in order to assess the quality of the data and analysis that produced the signal. While quality control measures will be conducted during the signal detection phase (see Section 9.8), post-signal quality assurance will also be performed during the signal evaluation phase. This will include a comprehensive quality assurance (for example, check for possible duplications of claims or medical records, checking for unusual clustering in claim or medical record accrual by service date for potential coding issues, check for geographical distribution of cases that may be related to lot numbers or diagnostic practice). In addition, for signals detected via active comparison, additional analyses comparing to post-vaccination control intervals may be formed to check for consistency. Signals will also be confirmed across all of the safety studies planned to be performed (i.e., C4591008, C4591011, C4591012) to confirm that specific data sources are not biased.

9.7.3.2.2. Multivariate Adjustment using Poisson Regression

If signals are detected and persist after conducting quality assurance, further evaluation via statistical measures are warranted. Specifically, to investigate whether potential signals identified via Poisson MaxSPRT for the comparison to active comparators with seasonal influenza vaccination are not confounded (i.e., to take into account baseline differences between the Pfizer BioNTech COVID-19 vaccinated and active comparator populations), a multivariate Poisson regression analysis will be conducted to compare the incidence rates of the safety events of interest occurring within the risk intervals. 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 (e.g., age, sex, race, CCI and/or specific comorbidities of interest, state, etc.).[10]

If the signal remains, based on an IRR > 3 with a p-value < 0.01 from the adjusted Poisson regression, further evaluation may be considered via signal verification.

9.7.3.2.3. Assessment of Temporal Clusters

Vaccine safety surveillance must allow for sufficient type I error probability for rapid detection of safety events of interest, and statistically significant signals must be studied further to ensure that a true association is present.[50] Therefore, the presence of temporal clusters will be assessed using the software SaTScan to calculate temporal scan statistic in

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order to further refine safety signals detected from the signal detection analyses.[30] A temporal scan statistic accounts for multiple testing present during overlapping risk intervals. The null hypothesis assumes that there is no association between the safety events of interest and immunization, and safety events of interest are assumed to be distributed independently and uniformly during a period of time subsequent to Pfizer-BioNTech COVID-19 vaccination.[30] A temporal scan statistic will be generated by moving a time interval of fixed length across the risk interval, comparing the number of observed versus expected safety events of interest within the time interval under the null hypothesis.[46]

9.7.3.2.4. Sequential Testing - SCRI Design using the Binomial MaxSPRT for Comparison with Post-Vaccination Control Intervals

Any safety events of interest with signals detected and not already analyzed during the signal detection phase with the SCRI design using the binomial-based MaxSPRT will be analyzed during the signal evaluation phase using SCRI design using the binomial-based MaxSPRT method for post-vaccination control intervals. This will be conducted during the signal evaluation phase in order to allow time to accumulate during the post-vaccination control period. The same statistical methodology as described above will be applied.

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

Similar to the SCRI design with post-vaccination control intervals, SCCS design with post-vaccination control time period will include cases (i.e., 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 with signals detected in the signal detection phase. The SCCS design differs from the SCRI design in that instead of having fixed post-vaccination control intervals of the same duration as the risk interval, it has a time-varying post-vaccination control time period that includes all-non risk interval time from Pfizer-BioNTech COVID-19 vaccination date until the earliest of 183 days after Pfizer-BioNTech COVID-19 vaccination, disenrollment, death, end of data availability.[23]

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. See Figure 5 below for an example of an individual who receives two doses of Pfizer-BioNTech COVID-19 vaccine, where the safety event of interest has a 42-day risk interval window (e.g., Bell's palsy; Table 1 in Section 9.3.3). Figure 5A demonstrates the SCCS design with the second dose received 21 days after the first (i.e., the risk interval for dose 1 overlaps with the risk interval for dose 2), while Figure 5B demonstrates the SCCS design with the second dose received 60 days after the first (i.e., with gaps between the end of dose 1 risk interval and dose 2). The post-vaccination control time period is displayed below as shading with gray lines.

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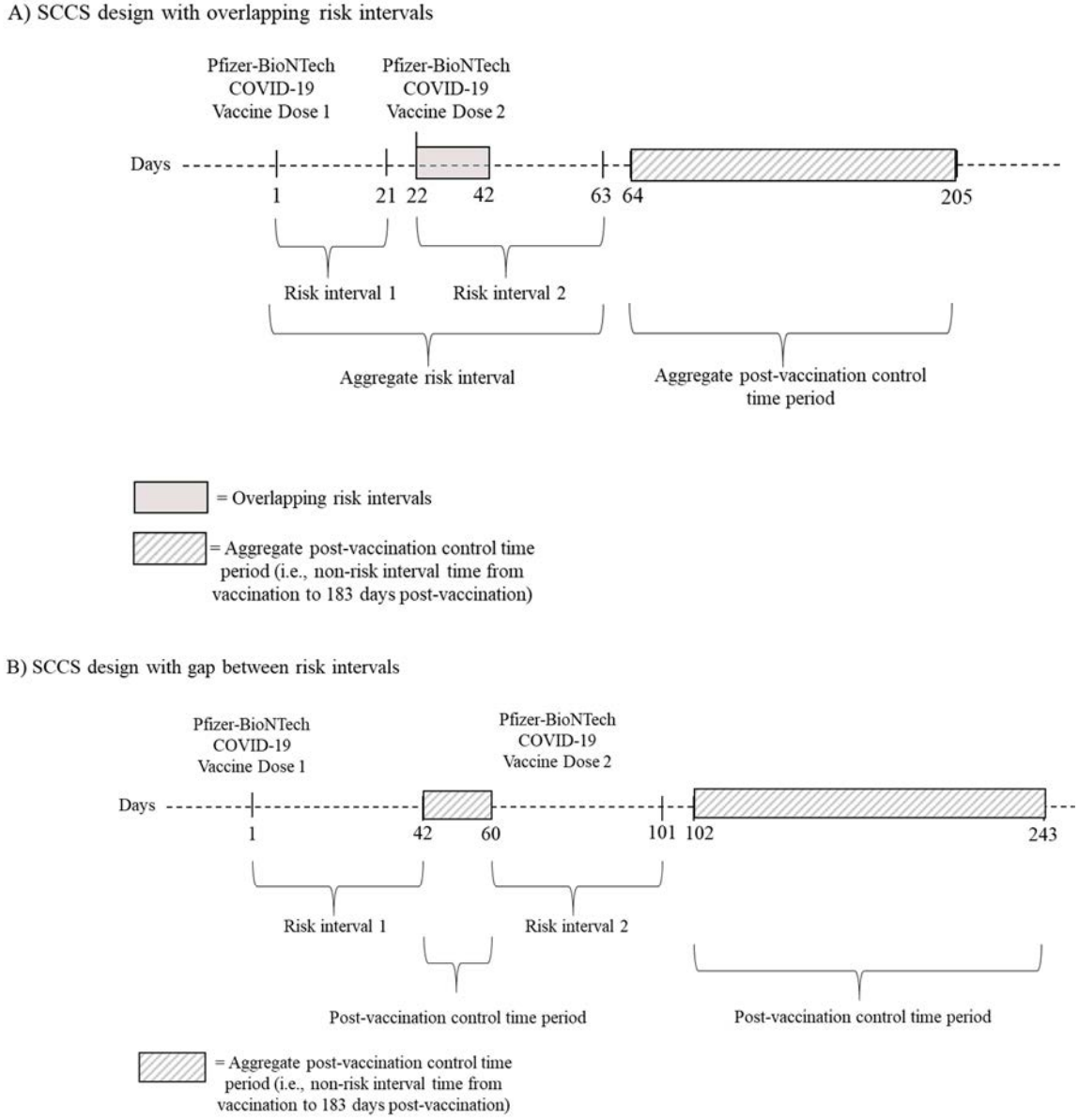
Figure 5. Example of SCCS Design for Safety Event of Interest with a 42-day Risk Interval with Post-vaccination Control Intervals when Two Doses of Pfizer-BioNTech COVID-19 Vaccine are Administered



Compared to the SCRI design, the SCCS design with post-vaccination control time period will have increased statistical power, which is especially useful for the study of rare safety events of interest. 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.

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9.7.3.2.6. Comparison with Contemporary Unvaccinated Controls

To address period effects that could impact the appropriateness of using the historical comparator cohort, 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 selected from a population of patients who have regular use of VHA medical care, defined as at least two outpatient (excluding ED, as ED visits may not be considered regular) or inpatient encounters in the one year prior to vaccination. The encounters must be separated by > 30 days (for inpatient, by admission date), and at least one must be within six months prior to index date. This approach is consistent with the Center for Biologics Evaluation and Research (CBER) Surveillance Program, Draft Master Protocol Assessment of Risk of Safety Outcomes Following COVID-19 Vaccination.[23]

Inverse probability treatment weighting (IPTW) will be used to ensure 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.[51] 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. 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, as the weight will be applied for both doses.[23] Initial inverse probability weights 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 Pr (Pfizer-BioNTech COVID-19 = 1) / PS for individuals who received the Pfizer-BioNTech COVID-19 vaccine and 1 - Pr (Pfizer-BioNTech COVID-19 = 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. Signal Verification

9.7.3.3.1. Medical Records Review

As part of the signal evaluation process, diagnostic validation of the detected safety events of interest (i.e., cases) via adjudication of patient medical records by VHA clinicians for outcome verification in a representative sample of cases will be conducted. 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 for safety events of interest where a small number of events

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result in signal detection and a representative sub-sample may be reviewed for safety events of interest where a larger number of events results in signal detection.[52] For rare events, potentially all cases may be adjudicated. An adjudication charter will be developed to govern signal evaluation and medical records review. Specifically, validation of detected safety events of interest will be performed through patient medical chart review in collaboration with an adjudication committee comprised of the treating or trained healthcare professionals.[52]

9.7.4. Seasonality-Adjusted Cases-Centered Method

A case-centered analysis for specific safety events of interest for which signals were detected may also be conducted in order to account for bias caused by seasonality of safety events of interest and vaccination.[30,53]

This method will use data on all safety event of interest cases that occur after vaccination with Pfizer-BioNTech COVID-19 vaccine. Logistic regression will be used to compare the number of safety event of interest cases that were vaccinated inside versus outside a pre-specified risk interval, as of the date of the safety events, where the total number of vaccinations given inside versus outside the risk interval (in the population of all vaccinees) is used as the offset term.[44] Specifically, the association of vaccination with risk of safety events of interest will be estimated from a logistic regression model that includes summarized data with one record per risk set. The key independent variable will be the proportion of the risk set who were in the risk interval on the date of the safety event of interest occurrence. In this way, risk sets are anchored to calendar dates, and confounding by seasonality of the safety events of interest and vaccination is addressed.[53] Note that other confounders may also be adjusted for by restricting risk sets to vaccinees similar with respect to select characteristics (i.e., through stratification).

9.7.5. End-of-Season and End-of-Surveillance Analyses

For any safety event of interest with signals detected, end-of-season analyses (over the course of the 30-month period) and an end-of-surveillance analysis (i.e., at 30 months, after the end of surveillance) will be conducted. Similar methodology will be applied for the end-of-surveillance analysis and end-of-season analysis conducted for seasonal influenza vaccine in order to adjust for the seasonality of both disease and vaccine administration.[10] This approach will be able to define the true risk intervals after each dose and estimate the risk for potential safety events of interest after both dose 1 and 2 of the Pfizer-BioNTech COVID-19 vaccine, as well as the ability to discern whether or not one or two doses of seasonal influenza vaccine were administered during the same period.

The number of events in the sum of three distinct risk intervals will be compared to the control interval, adjusting for potential differences in interval length, to estimate the RR of Pfizer-BioNTech COVID-19 vaccine compared to the influenza vaccine. In order to monitor the safety after the first and full course of the vaccine, the number of potential safety events of interest occurring in three separate risk intervals (P_1, P_2, P_3) will be estimated (Figure 6). P_1 represents the risk interval after the first dose only, excluding any overlap in risk intervals with the second dose. P_2 represents the overlapping risk intervals for first and second dose of

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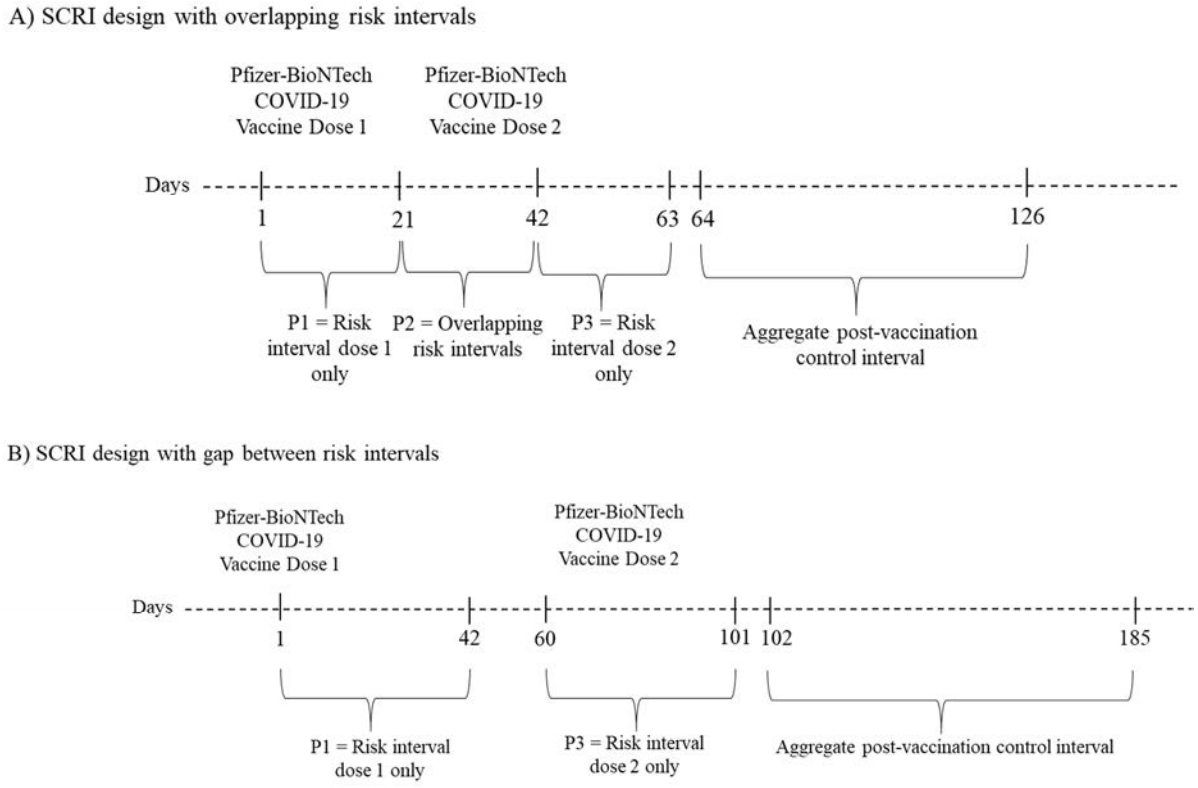
the vaccine. P_3 represents the risk interval of the second dose of the vaccine, excluding the overlapping risk interval already captured in P_2. This design will allow for the assessment of risk during the appropriate periods, regardless of the time interval between vaccine doses. As multiple endpoints will be assessed, 99% CIs will be calculated around the RR in order to ascertain whether the Pfizer-BioNTech COVID-19 vaccine is associated with safety events of interest.

Figure 6. Example of Risk (P1, P2, P3) and Aggregate Post-vaccination Control Intervals for the SCRI End-of-surveillance Analyses of 1 or 2 Doses of Pfizer-BioNTech COVID-19 Vaccine



In Figure 6A, $P_1 + P_2 + P_3$ represent the risk intervals where a safety event of interest may occur. In Figure 6B, there is no overlapping risk interval so that $P_1 + P_3$ represent the risk intervals where a safety event of interest may occur. The timing of the risk and control intervals may be adjusted for in order to control for the effect of seasonality across the intervals assessed.

9.7.6. Subgroup Analysis

Separate analyses of baseline characteristics, vaccine utilization patterns, signal detection, signal evaluation, and signal verification in subgroups of interest may be conducted based on feasibility, sample size, and data available.

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

Incidence rates (and corresponding CIs) will be calculated from safety event of interest signal detection analyses. Kaplan-Meier methods will be used to analyze time-to-event (i.e., time to safety event of interest). If individuals do not experience the safety events 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 summarized.

9.7.8. Prioritized Safety Analysis of Myocarditis/Pericarditis

Notably, CDC recently investigated the occurrence of myocarditis/pericarditis following mRNA COVID-19 vaccinations.[17] 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. Therefore, separate analyses will be prioritized and conducted to better understand the risk of myocarditis/pericarditis following Pfizer-BioNTech COVID-19 vaccination in the VHA. This 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.[17,18] 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 (i.e., 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 (i.e., 1-7 days, 1-21 days, and 1-42 days). This definition and the statistical approach differ from the primary analysis described in this protocol, but will facilitate comparison with the results presented by ACIP.[16,17]

This analysis will include all individuals in the primary analysis 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 (e.g., 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. 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 (i.e., risk vs. comparison interval) and for adjustment variables (i.e., age group, sex, race/ethnicity, and VHA 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 VHA service area. The log of the number of individuals

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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.[19] 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 details will be provided in the SAP.

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 (i.e., 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 dose (first and second) and onset of myocarditis/pericarditis; echocardiogram information; lab troponin information; symptoms (e.g., 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 (e.g., 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).

9.8. Quality Control

Data for the study will be extracted from electronic databases in the CDW of the VHA. Each data content area in the CDW is subjected to similar checks, from high level variable name/type checks, 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

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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 (i.e., 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 SCRI method of signal detection offers some key advantages. The SCRI approach inherently adjusts for within-individual confounders, such as age, sex, and confounding by indication. While control intervals can be defined both pre- and post- vaccination, the current study will only use a post-vaccination control period because individuals may be more vigilant for the reporting of possible safety events after they receive a vaccine than before vaccination, which may bias the comparison between a post-vaccine risk interval with a pre-vaccine control interval.[54] 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. Lastly, SCRI allows for near real-time monitoring of safety risks associated with the Pfizer-BioNTech COVID-19 vaccine. Similar considerations apply to the SCCS design with post-vaccination control interval that will be used in the signal evaluation phase.

The comparison of vaccinated to contemporary unvaccinated controls yields a more interpretable result than other planned analyses using SCRI and active comparators who receive seasonal influenza vaccination (i.e., the increased risk of experiencing a specific safety event due to Pfizer-BioNTech COVID-19 vaccination). The potential for selection bias (i.e., 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 at least 1 year of enrollment in and no disenrollment from VHA benefits prior to their match date. This design is also not limited to assumptions required by SCCS and SCRI, and can also be completed rapidly as it does not require post-vaccination control intervals. 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 VHA.

The VHA CDW provides a range of benefits, including its comprehensive structure, large number of variables, and electronic accessibility. The VHA CDW also includes EMR data that include structured fields (which will be used for signal detection) and open fields (such as physician notes, which will be used for signal verification and case validation, as needed). Importantly, the VHA CDW retains electronic immunization records that include

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manufacturer name and lot numbers, facilitating the identification of brand-specific vaccines, such as the Pfizer-BioNTech COVID-19 vaccine. Moreover, the VHA CDW data are updated on a daily basis, enabling near real-time rapid monitoring of potential safety signals.

However, there are several limitations when relying on VHA that should be noted. First, there could be gaps in the data since individuals may receive healthcare services outside of VHA facilities. As such, if individuals receive the Pfizer-BioNTech COVID-19 vaccine outside of a VHA facility, this information will not be captured in the VHA EMR system. Similarly, individuals may have also received past seasonal influenza vaccinations outside of the VHA system, and thus would be misclassified as not having received vaccine in the current analysis. For example, veterans with secondary insurance or veterans who are 65 years of age or older who have Medicare may receive health care services outside of VHA facilities. One study on VHA enrollees in seven different states found that of all individuals admitted to VHA hospitals in 2007, one fifth also had a non VHA hospitalization during that year.[55] Another study reported that about 53% of Veterans 65 years of age and older who were dually eligible for VHA and Medicare services in 2003 2004 used both.[56] Hence, it is important to note that data on vaccination status may be incomplete. However, this limitation will be addressed by examining subgroups of individuals who receive care regularly at VHA facilities, as well as those with Priority group 1 status, to ensure that their healthcare data are complete to the extent possible in the CDW. The results from these subgroup analyses will be compared to the overall population results from the VHA CDW to confirm consistent findings such that if there are missing data for individuals in the overall population, the missing data can be assumed to be missing at random and not biasing the results in any direction. This will be evaluated in the context of evaluating the relative risk of safety events of interest in the comparative analyses. However, if there are discrepancies that suggest data are not missing at random and could bias results, subgroup analyses will be conducted for individuals with dual coverage in the VHA and Medicare. The CDW data will be supplemented and linked with Medicare administrative claims data at the patient level to ensure a more comprehensive evaluation of the care an individual receives. Linking variables are available in the data to allow for patient-level linking of the two data sources. Given the older age of many veterans, it is likely that these individuals have secondary coverage with Medicare.

Lastly, to the extent that the individuals in the VHA database are different from individuals outside of the VHA, the results may not be generalizable to the broader US population. For example, since the VHA includes predominantly male Veterans (approximately 90% male), findings from this study may not be generalizable to women in the US.

9.10. Other Aspects

Not applicable.

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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.

To protect the rights and freedoms of natural individuals with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of individuals' personal data consistent with the vendor contract, and applicable privacy laws.

No personal data is planned to be transferred off the VA servers. Specifically, the Clinical Epidemiology Program (CEP) at White River Junction VA Medical Center will conduct this safety surveillance study with sponsorship from Pfizer and assistance from Analysis Group, Inc. The project will be led by the VA, with Dr. Yinong Young-Xu, Director of CEP, serving as the Principal Investigator. Data access will be granted through VA Informatics and Computing Infrastructure (VINCI). VHA data will not be provided to Pfizer or Analysis Group. Rather, only VA employees, including those with research service without compensation (WOC) employee status, who have completed necessary VA training and have proper clearance will access and analyze data on secure VA servers and behind necessary firewalls, under the direction and supervision of Dr. Young-Xu. Given the sensitive nature of healthcare data, comprehensive security measures will be implemented to ensure the confidentiality, integrity, and protection of Veterans' privacy and healthcare data.

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 IRB of the VA Medical Center, White River Junction, VT.

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,[57] the FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting, Pharmacoepidemiologic Safety Studies

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Using Electronic Healthcare Data[58] and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).[59]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Signal Detection and Signal Evaluation

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

Signal Verification

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 of interest on the non-interventional study (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 data collection tool (e.g., chart abstraction form) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

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

For 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.

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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 (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

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

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

- Your Reporting Responsibilities (YRR) Training for Vendors Working on Pfizer Studies

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 (e.g., 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

N/A

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18. ANNEX 3. ADDITIONAL INFORMATION

Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
Demographic Characteristics		
Age	Continuous variable; Categorical variable: • ≤16 • 16–64 • 65–74 • ≥75	Age on the date of Pfizer-BioNTech COVID-19 vaccination (and/or date of seasonal influenza vaccination for active comparators)
Sex	Categorical variable: • Male • Female • Unknown	
Race/ethnicity	Categorical variable: • White, non-Hispanic • Black • Hispanic ethnicity, any race • Asian • Native Hawaiian or Pacific Islander • American Indian or Alaskan native • Two or more races • Unknown	
VHA service area	Geographic regions in the US; Categorical variable: • South • Midwest • West • Northeast • Other • Unknown	Region associated with the most recent healthcare encounter prior to index date
Clinical Characteristics		
Smoking Status	Dichotomous variable	ICD-9-CM codes: • 305.1, Tobacco use disorder • V15.82, History of tobacco use

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Appendix Table 1. 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–<25) • Overweight (25–<30) • Obese (30–<40) • Severe obesity (≥40) • Unknown	Calculated from height and weight data (kg/m^2)
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 • 525.66, Allergy to existing dental restorative material • 995, 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		• 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 • 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	Dichotomous variable	ICD-9-CM code: • 999.42, Anaphylactic reaction due to vaccination

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
vaccine component		• 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
History of hospitalizations	Dichotomous variable; Continuous variable	Defined by having any hospitalizations (dichotomous) and number of hospitalizations (continuous)
Frailty index[60]	Continuous variable	ICD-9-CM codes available in Appendix Table 1 of Segal et al, 2017. ICD-9-CM codes mapped to ICD-10-CM codes.
Charlson Comorbidity Index (CCI)[61]	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

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Appendix Table 1. 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		• 196.x–199.x, Metastatic solid tumor • 042.x–044.x, Acquired immunodeficiency syndrome (AIDS)/Human immunodeficiency virus (HIV) 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–

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		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, 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,

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		K72.9x, K76.5, K76.6, K76.7, Moderate or severe liver disease • C77.x–C80.x, C77.xx–C80.xx, Metastatic solid tumor • B20, B97.35, AIDS/HIV
Comorbidities	Categorical variable: • Autoimmune disease • Asthma • Bleeding diathesis or condition associated with prolonged bleeding • Cancer • Cardiovascular conditions (e.g., heart failure, CAD, cardiomyopathies) • Chronic kidney disease/dialysis • COPD/interstitial lung disease • Diabetes mellitus • Down syndrome • Sickle cell disease • HBV • HCV • HIV • Hyperlipidemia • Hypertension • Liver disease • Neurological disease • Other immune deficiencies • Solid organ transplant • VTE	Autoimmune disease (immunocompromised state [weakened immune system] from solid organ transplant): ICD-9-CM codes: • 245.2, Chronic lymphocytic thyroiditis • 340, Multiple sclerosis • 357, Acute infective polyneuritis • 357.4, Polyneuropathy in other diseases classified elsewhere • 696.1, Other psoriasis • 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		• 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 • 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 • N05.9, Glomerulonephritis • D84.9, Immunodeficiency, unspecified Asthma: • ICD-9-CM codes: o 493.xx, Asthma • ICD-10-CM codes: o J45.2x–J45.3x, Mild intermittent asthma o J45.4x, Moderate persistent asthma o J45.5x, Severe persistent asthma o J45.9x, Other and unspecified asthma Bleeding diathesis or condition associated with prolonged bleeding: • ICD-9-CM codes:

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		o 286.x, Coagulation defects o 289.8x, Other specified diseases of blood and blood-forming organs o 287, 287.x, 287.xx, Purpura and other hemorrhagic conditions • ICD-10-CM codes: o D65, Disseminated intravascular coagulation o D66, Hereditary factor VIII deficiency o D67, Hereditary factor IX deficiency o D68, D68.x, D68.xx, Other coagulation defects o D69, D69.x, D69.xx, Purpura and other hemorrhagic conditions Cancer: • ICD-9-CM codes: o 140.x–149.x, Malignant neoplasm of lip, oral cavity, and pharynx o 150.x–159.x, Malignant neoplasm of digestive organs and peritoneum o 160.x–165.x, Malignant neoplasm of respiratory and intrathoracic organs o 170.x–176.x, Malignant neoplasm

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		of bone, connective tissue, skin, and breast o 179.x–189.x, Malignant neoplasm of genitourinary organs o 190.x–199.x, Malignant neoplasm of other unspecified sites o 200.xx–208.xx, Malignant neoplasm of lymphatic and hematopoietic tissue o 209.0x–209.3x, Malignant neuroendocrine tumors o 230.x–234.x, Carcinoma in situ of digestive organs • ICD-10-CM codes: o 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 o C76–C80, C76.x–C80.x, C76.xx–C80.xx, Malignant

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		neoplasms of ill-defined, other secondary and unspecified sites o C81–-C96, C81.x–C96.x, C81.xx–C96.xx, Malignant neoplasms of lymphoid, hematopoietic and related tissue Cardiovascular conditions (e.g., heart failure, coronary artery disease [CAD], cardiomyopathies): • ICD-9-CM codes: o 428.xx, Heart failure o 414.01, 429.2, 411.1, 413.9, 414.11, 414.12, 414.05, 414.02, 414.03, 414.04, 414.06, 414.07, 414.2, 411.81, 411.89, CAD o 425.xx, Cardiomyopathy • ICD-10-CM codes: o 150.x, 150.xx, Heart failure o 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, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750,

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		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 o I42.x, Cardiomyopathy Chronic kidney disease/dialysis: • ICD-9-CM codes: o 283.11, Hemolytic-uremic syndrome o 403, 403.x, 403.xx, Hypertensive chronic kidney disease o 404, 404.x, 404.xx, Hypertensive heart and chronic kidney disease o 440.1, Atherosclerosis of renal artery o 442.1, Aneurysm of renal artery o 572.4, Hepatorenal syndrome o 274.1, Gouty nephropathy, unspecified o 710, Systemic lupus erythematosus o 710.2, Sicca syndrome o 580, 580.x, 580.xx, Acute glomerulonephritis o 581.x, 581.xx, Nephrotic syndrome

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 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 ○ 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		and chronic kidney disease o I70.1, Atherosclerosis of renal artery o I72.2 Aneurysm of renal artery o K76.7, Hepatorenal syndrome o M10.30–M10.39, M10.30x–M10.37x, Gout due to renal impairment o M32.14, Glomerular disease in systemic lupus erythematosus o M32.15, Tubulo-interstitial nephropathy in systemic lupus erythematosus o M35.04, Sicca syndrome with tubulo-interstitial nephropathy o N00.x–N07.x, N08, Glomerular diseases o N13.1, N13.2, N13.3x, Obstructive and reflux uropathy o N14.x, Nephropathy o N15.x, Other renal tubulo-interstitial diseases o N16, Renal tubulo-interstitial disorders in diseases classified elsewhere o N17.x, N18.x, N19, Acute kidney failure and chronic kidney disease

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 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 ○ 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:

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 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: ○ Q90.x, Down syndrome Sickle cell disease: • ICD-9-CM codes: ○ 282.xx, Sickle-cell disease • ICD-10-CM codes:

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 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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Appendix Table 1. Demographic and Clinical Characteristics Definitions

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 HIV: • ICD-9-CM codes: ○ 42, HIV disease ○ 79.53, HIV type 2 • ICD-10-CM codes: ○ B20, HIV disease ○ B97.35, HIV type 2 as the cause of diseases classified elsewhere 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 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 ○ 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 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 ○ 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

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FDA-CBER-2021-5683-1077437

Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		symptoms or syndromes, not elsewhere classified o 300.9, Unspecified nonpsychotic mental disorder o 308.9, Unspecified acute reaction to stress o 307.9, Other and unspecified special symptoms or syndromes, not elsewhere classified o V62.85, Homicidal ideation o V62.84, Suicidal ideation o 799.24, Emotional lability o 799.23, Impulsiveness o 799.29, Other signs and symptoms involving emotional state o V40.39, Other specified behavioral problem • ICD-10-CM codes: o R41, R41.x, R41.xx, Other symptoms and signs involving cognitive functions and awareness o R42, Dizziness and giddiness o R43, R43.x, Disturbances of smell and taste o R44, R44.x, Other symptoms and signs

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		involving general sensations and perceptions o R45, R45.x, R45.xx, Symptoms and signs involving emotional state o R46, R46.x, R46.xx, Symptoms and signs involving appearance and behavior Other immune deficiencies: • ICD-9-CM codes: o 279.x, 279.xx, Deficiency of humoral immunity o 135, Sarcoidosis o 273.x, Disorders of plasma protein metabolism • ICD-10-CM codes: o D80, D80.x, Immunodeficiency with predominantly antibody defects o D81, D81.x, D81.xx, Combined immunodeficiencies o D82, D82.x, Immunodeficiency associated with other major defects o D83, D83.x, Common variable immunodeficiency o D84, D84.x, D84.xx, Other immunodeficiencies o D86, D86.x, D86.xx, Sarcoidosis

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ D89, D89.x, D89.xx, Other disorders involving the immune mechanism, not elsewhere classified 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, 50360, 50365, 50370, 50380, Renal transplantation • ICD-9-PCS codes: ○ 00.91–00.93, Transplant from donor or cadaver ○ 37.51, Heart transplantation ○ 33.51, Unilateral lung transplantation ○ 33.52, Bilateral lung transplantation

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 0FY00Z0, 0FY00Z1, Transplantation of liver ○ 0FYG0Z0, 0FYG0Z1, Transplantation of pancreas ○ 0TY00Z0, 0TY00Z1, 0TY10Z0, 0TY10Z1, Transplantation of kidney VTE: • ICD-9-CM codes: ○ 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
Immunization history	Categorical variable: • Seasonal influenza • Tetanus diphtheria and pertussis (Tdap or Td) • Chickenpox (Varicella)	Seasonal influenza: • See Appendix Table 3 Tetanus diphtheria and pertussis (Tdap or Td): • CPT codes:

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
	• 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	○ 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 ○ 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 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 Pneumococcal polysaccharide: • CPT code: ○ 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 ○ 90632, Hepatitis A vaccine, adult dosage, for intramuscular use

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		○ 90633, Hepatitis A vaccine (HepA), pediatric/adolescent dosage-2 dose schedule, for intramuscular use ○ 90634, Hepatitis A vaccine (HepA), pediatric/adolescent dosage-3 dose schedule, for intramuscular use ○ 90730, Hepatitis A vaccine ○ 90636, Hepatitis A and hepatitis B vaccine (HepA-HepB), adult dosage, for intramuscular use Hepatitis B • CPT codes: ○ 90731, Hepatitis B vaccine ○ 90739, Hepatitis B vaccine (HepB), adult dosage, 2 dose schedule, for intramuscular use ○ 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

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		dosage, 4 dose schedule, for intramuscular use • HCPCS codes: o G0010, Administration of Hepatitis B vaccine Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB) • CPT codes: o 90619, Meningococcal conjugate vaccine, serogroups A, C, W, Y, quadrivalent, tetanus toxoid carrier (MenACWY-TT), for intramuscular use o 90620, Meningococcal recombinant protein and outer membrane vesicle vaccine, serogroup B (MenB-4C), 2 dose schedule, for intramuscular use o 90621, Meningococcal recombinant lipoprotein vaccine, serogroup B (MenB-FHbp), 2 or 3 dose schedule, for intramuscular use o 90733, Meningococcal polysaccharide vaccine, serogroups A, C, Y, W-135, quadrivalent (MPSV4), for subcutaneous use o 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: o 90645, Hemophilus influenza b vaccine (Hib), HbOC conjugate

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Appendix Table 1. Demographic and Clinical Characteristics Definitions

Variable	Description	Operational definition
		(4 dose schedule), for intramuscular use o 90646, Hemophilus influenza b vaccine (Hib), PRP-D conjugate, for booster use only, intramuscular use o 90647, Haemophilus influenzae type b vaccine (Hib), PRP-OMP conjugate, 3 dose schedule, for intramuscular use o 90648, Haemophilus influenzae type b vaccine (Hib), PRP-T conjugate, 4 dose schedule, for intramuscular use o 90737, Hemophilus influenza B o 90748, Hepatitis B and Haemophilus influenzae type b vaccine (Hib-HepB), for intramuscular use

*BMI was assessed within the 1-year and 2-year baseline periods, respectively. BMI at the time of the most recent encounter within the baseline period prior to vaccination date was included and was calculated based on patient height and weight data as dividing weight in kilograms (kg) by height in meters (m) squared. Patients with missing BMI or those with BMI <15 or >60 were categorized as "Unknown".

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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		
Aseptic meningitis[8]	• 047.0, Meningitis due to coxsackle virus • 047.1, Meningitis due to echo virus • 047.8, Other specified viral meningitis • 047.9, Unspecified viral meningitis • 072.1, Mumps meningitis • 321.1, Meningitis due to viruses not elsewhere classified • 322.0, Nonpyogenic meningitis	• A27.81, Aseptic meningitis in leptospirosis • A87.0, Enteroviral meningitis • A87.1, Adenoviral meningitis • A87.2, Lymphocytic choriomeningitis • A87.8, Other viral meningitis • A87.9, Viral meningitis, unspecified • B26.1, Mumps meningitis • G03.0, Nonpyogenic meningitis
Bell's palsy[10,30]	• 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
Cerebrovascular non-hemorrhagic stroke[10,30]	• 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 • 433.31, 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	• 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I63.039, Cerebral infarction due to thrombosis of unspecified carotid artery • I63.09, Cerebral infarction due to thrombosis of other precerebral artery • I63.10, Cerebral infarction due to embolism of unspecified precerebral artery • I63.111, Cerebral infarction due to embolism of right vertebral artery • I63.112, Cerebral infarction due to embolism of left vertebral artery • I63.113, Cerebral infarction due to embolism of bilateral vertebral arteries • I63.119, Cerebral infarction due to embolism of unspecified vertebral artery • I63.12, Cerebral infarction due to embolism of basilar artery • I63.131, Cerebral infarction due to embolism of right carotid artery

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I63.132, Cerebral infarction due to embolism of right carotid artery • I63.133, Cerebral infarction due to embolism of carotid artery • I63.139, Cerebral infarction due to embolism of right carotid artery • I63.19, Cerebral infarction due to embolism of other precerebral artery • I63.20, Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries • I63.211, Cerebral infarction due to unspecified occlusion or stenosis of right vertebral arteries • I63.212, Cerebral infarction due to unspecified occlusion or stenosis of left vertebral arteries • I63.213, Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I63.219, Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries • I63.22, Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries • I63.231, Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries • I63.232, Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries • I63.233, Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries • I63.239, Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries • I63.29, Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• 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 • I63.322, Cerebral infarction due to thrombosis of left anterior cerebral artery

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• 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 • I63.40, Cerebral infarction due to embolism of unspecified cerebral artery • I63.411, Cerebral infarction due to embolism of right middle cerebral artery • I63.412, Cerebral infarction due to embolism of left middle cerebral artery • I63.413, Cerebral infarction due to embolism of bilateral middle cerebral arteries • I63.419, Cerebral infarction due to embolism of unspecified middle cerebral artery

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I63.421, Cerebral infarction due to embolism of right anterior cerebral artery • I63.422, Cerebral infarction due to embolism of left anterior cerebral artery • I63.423, Cerebral infarction due to embolism of bilateral anterior cerebral arteries • I63.429, Cerebral infarction due to embolism of unspecified anterior cerebral artery • I63.431, Cerebral infarction due to embolism of right posterior cerebral artery • I63.432, Cerebral infarction due to embolism of left posterior cerebral artery • I63.433, Cerebral infarction due to embolism of bilateral posterior cerebral arteries

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I63.439, Cerebral infarction due to embolism of unspecified posterior cerebral artery • I63.441, Cerebral infarction due to embolism of right cerebellar artery • I63.442, Cerebral infarction due to embolism of left cerebellar artery • I63.443, Cerebral infarction due to embolism of bilateral cerebellar arteries • I63.449, Cerebral infarction due to embolism of unspecified cerebellar artery • I63.49, Cerebral infarction due to embolism of other cerebral artery • I63.50, Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery • I63.511, Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I63.512, Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery • I63.513, Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries • I63.519, Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery • I63.521, Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery • I63.522, Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery • I63.523, Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries • I63.529, Cerebral infarction due to unspecified occlusion or stenosis

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		of unspecified anterior cerebral artery • I63.531, Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery • I63.532, Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery • I63.533, Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries • I63.539, Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery • I63.541, Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery • I63.542, Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I63.543, Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries • I63.549, Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery • I63.59, Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery • I63.6, Cerebral infarction due to cerebral venous thrombosis, nonpyogenic • I63.81, Other cerebral infarction due to occlusion or stenosis of small artery • I63.89, Other cerebral infarction • I63.9, Cerebral infarction, unspecified
Convulsions/seizures in individuals with controlled epilepsy[35]	Controlled epilepsy: ≥ 1 diagnosis of epilepsy or ≥ 2 diagnoses of nonfebrile convulsions occurring ≥ 30 days apart, no change in AED for 365 days from baseline period, and no epilepsy-related IP or ED for 365 days from baseline period.	Controlled epilepsy: ≥ 1 diagnosis of epilepsy or ≥ 2 diagnoses of nonfebrile convulsions occurring ≥ 30 days apart, no change in AED for 365 days from

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	Uncontrolled convulsions/seizures: At least two of the following criteria: First change in AED ≤ 30 days following index date, second change in AED ≥ 30 days following the first change in AED, epilepsy-related IP or ED following a change in AED up to 90 days after the index date Epilepsy • 345.00, Generalized nonconvulsive epilepsy, without mention of intractable epilepsy • 345.01, Generalized nonconvulsive epilepsy, with intractable epilepsy • 345.10, Generalized convulsive epilepsy, without mention of intractable epilepsy • 345.11, Generalized convulsive epilepsy, with intractable epilepsy • 345.2, Petit mal status • 345.3, Grand mal status • 345.40, Localization-related (focal) (partial) epilepsy and epileptic syndromes with	baseline period, no epilepsy-related IP or ED for 365 days from baseline period. Uncontrolled convulsions/seizures: At least two of the following criteria: First change in AED ≤ 30 days following index date, second change in AED ≥ 30 days following the first change in AED, epilepsy-related IP or ED following a change in AED up to 90 days after the index date Epilepsy • G40.A01, Absence epileptic syndrome, not intractable, with status epilepticus • G40.A09, Absence epileptic syndrome, not intractable, without status epilepticus • G40.A11, Absence epileptic syndrome, intractable, with status epilepticus • G40.A19, Absence epileptic syndrome, intractable, without status epilepticus

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	complex partial seizures, without mention of intractable epilepsy • 345.41, Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, with intractable epilepsy • 345.50, Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures, without mention of intractable epilepsy • 345.51, Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures, with intractable epilepsy • 345.60, Infantile spasms, without mention of intractable epilepsy • 345.61, Infantile spasms, with intractable epilepsy • 345.70, Epilepsia partialis continua, without mention of intractable epilepsy • 345.71, Epilepsia partialis continua, with intractable epilepsy	• G40.309, Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus • 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 • G40.311, Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus • G40.411, Other generalized epilepsy and epileptic syndromes, intractable, with status epilepticus • G40.419, Other generalized epilepsy and epileptic syndromes, intractable, without status epilepticus

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 345.80, Other forms of epilepsy and recurrent seizures, without mention of intractable epilepsy • 345.81, Other forms of epilepsy and recurrent seizures, with intractable epilepsy • 345.90, Epilepsy, unspecified, without mention of intractable epilepsy • 345.91, Epilepsy, unspecified, with intractable epilepsy Nonfebrile convulsions • 780.33, Post traumatic seizures • 780.39, Other convulsions AED Medication • See operational definition for AED Medication in the next column	• G40.301, Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus • G40.201, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, with status epilepticus • G40.209, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, without status epilepticus • G40.211, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, with status epilepticus • G40.219, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures,

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		intractable, without status epilepticus • G40.101, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, with status epilepticus • G40.109, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus • G40.111, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, with status epilepticus • G40.119, Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• G40.821, Epileptic spasms, not intractable, with status epilepticus • G40.822, Epileptic spasms, not intractable, without status epilepticus • G40.823, Epileptic spasms, intractable, with status epilepticus • G40.824, Epileptic spasms, 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• G40.901, Epilepsy, unspecified, not intractable, with status epilepticus • G40.909, Epilepsy, unspecified, not intractable, without status epilepticus • G40.911, Epilepsy, unspecified, intractable, with status epilepticus • G40.919, Epilepsy, unspecified, intractable, without status epilepticus Nonfebrile convulsions: • R56.1, Post traumatic seizures • R56.9, Unspecified convulsions AED medication • HCPCS o C9254, Injection, lacosamide, 1 mg o J1953, Injection, levetiracetam, 10 mg

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		○ J2560, Injection, phenobarbital sodium, up to 120 mg ○ J1165, Injection, phenytoin sodium, per 50 mg ○ Q2009, Injection, fosphenytoin, 50 mg phenytoin equivalent
Encephalitis/encephalomyelitis[10,30]	• 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 • 323.41, Other encephalitis and encephalomyelitis due to infection classified elsewhere	• G04.00, Acute disseminated encephalitis and encephalomyelitis, unspecified • G04.02, Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis • G04.81, Other encephalitis and encephalomyelitis • G04.90, Encephalitis and encephalomyelitis, unspecified • G05.3, Encephalitis and encephalomyelitis in diseases classified elsewhere
Guillain-Barré syndrome (GBS)[10,30]	• 357.0, Guillain-Barre syndrome	• G61.0, Guillain-Barre syndrome

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
Generalized convulsions/seizure[10,30]	• 345.2, Petit mal status • 345.3, Grand mal status • 780.31, Febrile convulsions (simple), unspecified • 780.39, Other convulsions • 780.32, Complex febrile 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• R56.00, Simple febrile convulsions • R56.01, Complex febrile convulsions • R56.9, Unspecified convulsions
Multiple sclerosis (MS)[10,30]	• 340, Multiple sclerosis	• G35, Multiple sclerosis
Optic neuritis (ON)[10,30]	• 341.0, Neuromyelitis optica • 377.30, Optic neuritis, unspecified • 377.31, Optic papillitis • 377.32, Retrobulbar neuritis (acute) • 377.34, Toxic optic neuropathy • 377.39, Other optic neuritis	• G36.0, Neuromyelitis optica [Devic] • H46.00, Optic papillitis, unspecified eye • H46.01, Optic papillitis, right eye • H46.02, Optic papillitis, left eye • H46.03, Optic papillitis, bilateral • H46.10, Retrobulbar neuritis, unspecified eye • H46.11, Retrobulbar neuritis, right eye • H46.12, Retrobulbar neuritis, left eye • H46.13, Retrobulbar neuritis, bilateral

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• H46.3, Toxic optic neuropathy • H46.8, Other optic neuritis • H46.9, Unspecified optic neuritis
Other acute demyelinating diseases (excluding those limited as separate outcomes)[10,30]	• 341.1, Schilder's disease • 341.8, Other demyelinating diseases of central nervous system • 341.9, Demyelinating disease of central nervous system, unspecified • 357.81, Chronic inflammatory demyelinating polyneuritis	• G37.1, Central demyelination of corpus callosum • G37.2, Central pontine myelinolysis • G37.8, Other specified demyelinating diseases of central nervous system • G37.9, Demyelinating disease of central nervous system, unspecified • G61.81, Chronic inflammatory demyelinating polyneuritis
Transverse myelitis (TM)[10,30]	• 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
Immunologic		

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
Anaphylaxis[10,30]	• 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
Arthritis and arthralgia/joint pain (not osteoarthritis or traumatic arthritis)[62]	• 713.6, Arthropathy associated with hypersensitivity reaction • 999.52, Other serum reaction due to vaccination	• M02.20, Postimmunization arthropathy, unspecified site • M02.211, Postimmunization arthropathy, right shoulder • M02.212, Postimmunization arthropathy, left shoulder • M02.219, Postimmunization arthropathy, unspecified shoulder • M02.221, Postimmunization arthropathy, right elbow • M02.222, Postimmunization arthropathy, left elbow • M02.229, Postimmunization arthropathy, unspecified elbow • M02.231, Postimmunization arthropathy, right wrist

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• M02.232, Postimmunization arthropathy, left wrist • M02.239, Postimmunization arthropathy, unspecified wrist • M02.241, Postimmunization arthropathy, right hand • M02.242, Postimmunization arthropathy, left hand • M02.249, Postimmunization arthropathy, unspecified hand • M02.251, Postimmunization arthropathy, right hip • M02.252, Postimmunization arthropathy, left hip • M02.259, Postimmunization arthropathy, unspecified hip • M02.261, Postimmunization arthropathy, right knee • M02.262, Postimmunization arthropathy, left knee • M02.269, Postimmunization arthropathy, unspecified knee

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• M02.271, Postimmunization arthropathy, right ankle and foot • M02.272, Postimmunization arthropathy, left ankle and foot • M02.279, Postimmunization arthropathy, unspecified ankle and foot • M02.28, Postimmunization arthropathy, vertebrae • M02.29, Postimmunization arthropathy, multiple sites • M15.8, Other polyosteoarthritis • M15.9, Polyosteoarthritis, unspecified • M19.90, Unspecified osteoarthritis, unspecified site • M19.91, Primary osteoarthritis, unspecified site • M19.93, Secondary osteoarthritis, unspecified site
Autoimmune thyroiditis[62]	• N/A	• E06.3, Autoimmune thyroiditis

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
Fibromyalgia[62]	• 729.1, Myalgia and myositis, unspecified	• M79.7, Fibromyalgia
Kawasaki disease (KD)[62]	• 446.1, Acute febrile mucocutaneous lymph node syndrome [MCLS]	• M30.3, Mucocutaneous lymph node syndrome [Kawasaki]
Multisystem inflammatory syndrome in adults (MIS-A)[62]	• 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
Vasculitides (excluding those limited as separate outcomes)[63,64]	• 136.1, Behcet's disease • 273.2, Other paraproteinemias • 287.0, Allergic purpura (Henoch-Schonlein Purpura)	• D69.0, Allergic purpura (Henoch-Schonlein Purpura) • D89.1, Cryoglobulinemia

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 443.1, Thromboangiitis obliterans (Buerger's disease) • 446.0, Polyarteritis nodosa • 446.4, Wegener's granulamatosis • 446.5, Giant cell arteritis • 446.7, Takayasu's disease • 447.6, Arteritis, unspecified	• I73.1, Thromboangiitis obliterans (Buerger's disease) • I77.6, Arteritis, unspecified • M30.0, Polyarteriitis nodosa • M30.1, Polyarteritis with lung involvement (Churg-Strauss) • M31.3, Wegener's granulomatosis • M31.4, Aortic arch syndrome (Takayasu's disease) • M31.5, Giant cell arteritis with other polymyalgia rheumatica • M31.6, Other giant cell arteritis • M31.7, Microscopic polyangiitis • M35.2, Behcet's disease • M35.3, Polymyalgia rheumatica
Cardiac		
Acute myocardial infarction (AMI)[62]	• 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	• I21.01, ST elevation (STEMI) myocardial infarction involving left main coronary artery

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 410.21, 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 • 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	• I21.02, ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery • I21.09, ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall • I21.11, ST elevation (STEMI) myocardial infarction involving right coronary artery • I21.19, ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall • I21.21, ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery • I21.29, ST elevation (STEMI) myocardial infarction involving other sites

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I21.3, ST elevation (STEMI) myocardial infarction of unspecified site • I21.4, Non-ST elevation (NSTEMI) myocardial infarction • I21.9, Acute myocardial infarction, unspecified • I21.A1, Myocardial infarction type 2 • I21.A9, Other myocardial infarction type • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I22.9, Subsequent ST elevation (STEMI) myocardial infarction of unspecified site
Arrhythmia[62]	• 427.0, Paroxysmal supraventricular tachycardia • 427.1, Paroxysmal ventricular tachycardia • 427.2, Paroxysmal tachycardia, unspecified • 427.31, Atrial fibrillation • 427.32, Atrial flutter • 427.89, Other specified cardiac dysrhythmias • 427.9, Cardiac dysrhythmia, unspecified	• I47.1, Supraventricular tachycardia • I47.2, Ventricular tachycardia • I47.9, Paroxysmal tachycardia, unspecified • I48.0, Paroxysmal atrial fibrillation • I48.3, Typical atrial flutter • I48.4, Atypical atrial flutter • I48.91, Unspecified atrial fibrillation • I48.92, Unspecified atrial flutter • I49.8, Other specified cardiac arrhythmias • I49.9, Cardiac arrhythmia, unspecified
Coronary artery disease (CAD)[62]	• 411.81, Acute coronary occlusion without myocardial infarction	• I24.0, Acute coronary thrombosis not resulting in myocardial infraction

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 411.89, Other acute and subacute forms of ischemic heart disease, other • 414.01, Coronary atherosclerosis of native coronary artery • 429.2, Cardiovascular disease, unspecified • 411.1, Intermediate coronary syndrome • 413.9, Other and unspecified angina pectoris • 414.11, Aneurysm of coronary vessels • 414.12, Dissection of coronary artery • 414.05, Coronary atherosclerosis of unspecified bypass graft • 414.02, Coronary atherosclerosis of autologous vein bypass graft • 414.04, Coronary atherosclerosis of artery bypass graft • 414.03, Coronary atherosclerosis of nonautologous biological bypass graft • 414.06, Coronary atherosclerosis of native coronary artery of transplanted heart • 414.07, Coronary atherosclerosis of bypass graft (artery) (vein) of transplanted heart	• I24.8, Other forms of acute ischemic heart disease • I24.9, Acute ischemic heart disease, unspecified • I25.10, Atherosclerotic heart disease of native coronary artery without angina pectoris • I25.110, Atherosclerotic heart disease of native coronary artery with unstable angina pectoris • I25.111, Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm • I25.118, Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris • I25.119, Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris • I25.41, Coronary artery aneurysm • I25.42, Coronary artery dissection

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I25.700, Atherosclerosis of coronary artery bypass graft(s), unspecified, with unstable angina pectoris • I25.701, Atherosclerosis of coronary artery bypass graft(s), unspecified, with angina pectoris with documented spasm • I25.708, Atherosclerosis of coronary artery bypass graft(s), unspecified, with other forms of angina pectoris • I25.709, Atherosclerosis of coronary artery bypass graft(s), unspecified, with unspecified angina pectoris • I25.710, Atherosclerosis of autologous vein coronary artery bypass graft(s) with unstable angina pectoris • I25.711, Atherosclerosis of autologous vein coronary artery bypass graft(s) with angina pectoris with documented spasm

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I25.718, Atherosclerosis of autologous vein coronary artery bypass graft(s) with other forms of angina pectoris • I25.719, Atherosclerosis of autologous vein coronary artery bypass graft(s) with unspecified angina pectoris • I25.720, Atherosclerosis of autologous artery coronary artery bypass graft(s) with unstable angina pectoris • I25.721, Atherosclerosis of autologous artery coronary artery bypass graft(s) with angina pectoris with documented spasm • I25.728, Atherosclerosis of autologous artery coronary artery bypass graft(s) with other forms of angina pectoris • I25.729, Atherosclerosis of autologous artery coronary artery bypass graft(s) with unspecified angina pectoris

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I25.730, Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unstable angina pectoris • I25.731, Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with angina pectoris with documented spasm • I25.738, Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with other forms of angina pectoris • I25.739, Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unspecified angina pectoris • I25.750, Atherosclerosis of native coronary artery of transplanted heart with unstable angina • I25.751, Atherosclerosis of native coronary artery of transplanted heart with angina pectoris with documented spasm

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I25.758, Atherosclerosis of native coronary artery of transplanted heart with other forms of angina pectoris • I25.759, Atherosclerosis of native coronary artery of transplanted heart with unspecified angina pectoris • I25.760, Atherosclerosis of bypass graft of coronary artery of transplanted heart with unstable angina • I25.761, Atherosclerosis of bypass graft of coronary artery of transplanted heart with angina pectoris with documented spasm • I25.768, Atherosclerosis of bypass graft of coronary artery of transplanted heart with other forms of angina pectoris • I25.769, Atherosclerosis of bypass graft of coronary artery of transplanted heart with unspecified angina pectoris

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I25.790, Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris • I25.791, Atherosclerosis of other coronary artery bypass graft(s) with angina pectoris with documented spasm • I25.798, Atherosclerosis of other coronary artery bypass graft(s) with other forms of angina pectoris • I25.799, Atherosclerosis of other coronary artery bypass graft(s) with unspecified angina pectoris • I25.810, Atherosclerosis of coronary artery bypass graft(s) without angina pectoris • I25.811, Atherosclerosis of native coronary artery of transplanted heart without angina pectoris • I25.812, Atherosclerosis of bypass graft of coronary artery of

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		transplanted heart without angina pectoris
Heart failure and cardiogenic shock[62]	• 428.0, Congestive heart failure, unspecified • 428.20, Systolic heart failure, unspecified • 428.21, Acute systolic heart failure • 428.23, Acute on chronic systolic heart failure • 428.30, Diastolic heart failure, unspecified • 428.31, Acute diastolic heart failure • 428.33, Acute on chronic diastolic heart failure • 428.40, Combined systolic and diastolic heart failure, unspecified • 428.41, Acute combined systolic and diastolic heart failure • 428.43, Acute on chronic combined systolic and diastolic heart failure • 428.9, Heart failure, unspecified • 785.51, Cardiogenic shock	• I50.1, Left ventricular failure, unspecified • I50.20, Unspecified systolic (congestive) heart failure • I50.21, Acute systolic (congestive) heart failure • I50.23, Acute on chronic systolic (congestive) heart failure • I50.30, Unspecified diastolic (congestive) heart failure • I50.31, Acute diastolic (congestive) heart failure • I50.33, Acute on chronic diastolic (congestive) heart failure • I50.40, Unspecified combined systolic (congestive) and diastolic (congestive) heart failure • I50.41, Acute combined systolic (congestive) and diastolic (congestive) heart failure

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I50.43, Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure • I50.810, Right heart failure, unspecified • I50.811, Acute right heart failure • I50.813, Acute on chronic right heart failure • I50.814, Right heart failure due to left heart failure • I50.82, Biventricular heart failure • I50.89, Other heart failure • I50.9, Heart failure, unspecified • R57.0, Cardiogenic shock
Pericarditis[10,30]	• 420.90, Acute pericarditis, unspecified • 420.91, Acute idiopathic pericarditis • 420.99, Other acute pericarditis • 420.0, Acute pericarditis in diseases classified elsewhere • 074.21, Coxsackie pericarditis	• I30.0, Acute nonspecific idiopathic pericarditis • I30.1, Infective pericarditis • I30.8, Other forms of acute pericarditis • I30.9, Acute pericarditis, unspecified

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I32, Pericarditis in diseases classified elsewhere • B33.23, Viral pericarditis
Microangiopathy[62]	• 446.6, Thrombotic microangiopathy	• M31.1, Thrombotic microangiopathy
Myocarditis[10,30]	• 422, Acute myocarditis in diseases classified elsewhere • 422.9, Acute myocarditis, unspecified • 422.91, Idiopathic myocarditis • 422.99, Other acute myocarditis • 074.23, Coxsackie myocarditis • 429.0, Myocarditis, unspecified	• B33.22, Viral myocarditis • I40.0, Infective myocarditis • I40.1, Isolated myocarditis • I40.8, Other acute myocarditis • I40.9, Acute myocarditis, unspecified • I41, Myocarditis in diseases classified elsewhere • I51.4, Myocarditis, unspecified
Stress cardiomyopathy[62]	• 425.9, Secondary cardiomyopathy, unspecified • 425.4, Other primary cardiomyopathies • 429.83, Takotsubo syndrome	• I42.7, Cardiomyopathy due to drug and external agent • I42.8, Other cardiomyopathies • I42.9, Cardiomyopathy, unspecified • I51.81, Takotsubo syndrome

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
Hematologic		
Cerebrovascular hemorrhagic stroke[10,30]	• 431, Intracerebral hemorrhage • 432.1, Subdural hemorrhage • 432.9, Unspecified intracranial hemorrhage	• I61.0, Nontraumatic intracerebral hemorrhage in hemisphere, subcortical • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I61.9, Nontraumatic intracerebral hemorrhage, unspecified • I62.00, Nontraumatic subdural hemorrhage, unspecified • I62.01, Nontraumatic acute subdural hemorrhage • I62.02, Nontraumatic subacute subdural hemorrhage • I62.9, Nontraumatic intracranial hemorrhage, unspecified
Chilblain-like lesions[62]	• 991.5, Chilblains	• T69.1XXA, Chilblains, initial encounter
Disseminated intravascular coagulation (DIC)[62]	• 286.6, Defibrination syndrome	• D65, Disseminated intravascular coagulation [defibrination syndrome]
Deep vein thrombosis (DVT) [62]	• 453.2, Other venous embolism and thrombosis of inferior vena cava • 453.3, Other venous embolism and thrombosis of renal vein	• I82.220, Acute embolism and thrombosis of inferior vena cava • I82.3, Embolism and thrombosis of renal vein

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 453.40, 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	• I82.401, 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 • I82.413, Acute embolism and thrombosis of femoral vein, bilateral • I82.419, Acute embolism and thrombosis of unspecified femoral vein

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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 • I82.441, Acute embolism and thrombosis of right tibial vein • I82.442, Acute embolism and thrombosis of left tibial vein

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.443, 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 • I82.461, Acute embolism and thrombosis of right calf muscular vein • I82.462, Acute embolism and thrombosis of left calf muscular vein

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.463, 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.4Y2, 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.4Z9, Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower 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
Hemolytic anemia[62]	• 283.9, Acquired hemolytic anemia, unspecified	• D59.9, Acquired hemolytic anemia, unspecified
Hemorrhagic disease (excluding those limited as separate outcomes)[62]	• 287.8, Other specified hemorrhagic conditions • 287.9, Unspecified hemorrhagic conditions • 65.3, Other tick-borne hemorrhagic fever	• D69.8, Other specified hemorrhagic conditions • D69.9, Hemorrhagic condition, unspecified

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 78.6, Hemorrhagic nephrosonephritis	• A98.8, Other specified viral hemorrhagic fevers • A99, Unspecified viral hemorrhagic fever • A98.5, Hemorrhagic fever with renal syndrome • G04.39, Other acute necrotizing hemorrhagic encephalopathy
Limb ischemia[62]	• 459.89, Other specified disorders of circulatory system	• I99.8, Other disorder of circulatory system
Pulmonary embolus[62]	• 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I26.94, Multiple subsegmental pulmonary emboli without acute cor pulmonale • I26.99, Other pulmonary embolism without acute cor pulmonale
Single organ cutaneous vasculitis[62]	• 709.1, Vascular disorders of skin	• L95.8, Other vasculitis limited to the skin • L95.9, Vasculitis limited to the skin, unspecified
Thrombocytopenia[8]	• 287.31, Immune thrombocytopenic purpura • 287.39, Other primary thrombocytopenia	• D69.3, Immune thrombocytopenic purpura
Thrombosis 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.[65] Acute venous or arterial thromobosis[62] • 411.81, Acute coronary occlusion without myocardial infarction • 429.89, Other ill-defined heart diseases	Diagnosis of both acute venous or arterial thromobsis AND new onset thrombocytopenia AND no history of receipt of heparin within 100 days.[65] Acute venous or arterial thromobosis[62] • I24.0, Acute coronary thrombosis not resulting in myocardial infarction

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 433.91, 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 • 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	• 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 444.22, Arterial embolism and thrombosis of lower extremity • 444.81, Embolism and thrombosis of iliac artery • 444.89, Embolism and thrombosis of other specified artery • 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	• I63.033, 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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 • 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	• I63.319, Cerebral infarction due to thrombosis of unspecified middle cerebral artery • I63.321, Cerebral infarction due to thrombosis of right anterior cerebral artery • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 455.7, Unspecified thrombosed hemorrhoids • 607.89, Other specified disorders of penis Thrombocytopenia[8] • 287.31, Immune thrombocytopenic purpura • 287.39, Other primary thrombocytopenia Heparin[62] • See operational definition in the previous column	• I63.333, Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• 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 • I74.5, Embolism and thrombosis of iliac artery • I74.8, Embolism and thrombosis of other arteries • I74.9, Embolism and thrombosis of unspecified artery

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.411, 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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 • I82.453, Acute embolism and thrombosis of peroneal vein, bilateral

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.459, 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 • I82.492, Acute embolism and thrombosis of other specified deep vein of left lower extremity

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.493, 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 • I82.4Y9, Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.4Z1, 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 • I82.602, Acute embolism and thrombosis of unspecified veins of left upper extremity

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.603, 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• I82.622, 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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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.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 • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)[*]:
		• I82.812, Embolism and thrombosis of superficial veins of left lower extremity • I82.813, Embolism and thrombosis of superficial veins of lower extremities, bilateral • 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[8] • D69.3, Immune thrombocytopenic purpura

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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[62]
		• HCPCS
		  ○ J1642, Injection, heparin sodium, (heparin lock flush), per 10 units
		  ○ J1644, Injection, heparin sodium, per 1000 units
		  ○ E1520, Heparin infusion pump for hemodialysis

Other		
Acute kidney injury[66]	• 584.9, Acute kidney failure, unspecified • See operational definition for laboratory result in the next column.	• N17.9, Acute kidney failure, unspecified Laboratory result:[67] • Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; or • Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days; or

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• Urine volume ≤0.5 ml/ kg/ hour for 6 hours
Appendicitis[62]	• 540.9, Acute appendicitis without mention of peritonitis • 541, Appendicitis, unqualified	• K35.20, Acute appendicitis with generalized peritonitis, without abscess • 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

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• K35.890, Other acute appendicitis without perforation or gangrene • K35.891, Other acute appendicitis without perforation, with gangrene K37, Unspecified appendicitis
Death	• Defined by individual having "date of death" information.	
Erythema multiforme[62]	• 695.10, Erythema multiforme, unspecified • 695.11, Erythema multiforme minor • 695.12, Erythema multiforme major • 695.19, Other erythema multiforme	• L51.0, Nonbullous erythema multiforme • L51.8, Other erythema multiforme • L51.9, Erythema multiforme, unspecified
Liver injury[68]	• 571.9, Unspecified chronic liver disease without mention of alcohol • 573.9, Unspecified disorder of liver • 789.1, Hepatomegaly • 789.2, Splenomegaly • 790.4, Nonspecific elevation of levels of transaminase or lactic acid dehydrogenase (LDH) • 573.3, Hepatitis, unspecified	• K76.8, Other specified diseases of liver • K76.9, Liver disease, unspecified • R17, Unspecified jaundice, excludes neonatal • R16.0, Hepatomegaly, not elsewhere classified

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 572.2, Hepatic encephalopathy • 572.8, Other sequelae of chronic liver disease • 570, Acute and subacute necrosis of liver See operational definition for laboratory result in the next column. The presence of any of the following codes will not result in the safety events of interest being considered an event: • 070, Viral hepatitis • 155, Malignant neoplasm of liver and intrahepatic bile ducts • 570, Acute and subacute hepatic failure paired with any of the following: ○ 458, Hypotension • 573.8, Other specified disorders of liver	• R16.2, Hepatomegaly with splenomegaly, not elsewhere classified • R74.0, Nonspecific elevation of transaminase and lactic acid dehydrogenase • K71.0, Toxic liver disease with cholestasis • K71.1, Toxic liver disease with hepatic necrosis • K71.10, Toxic liver disease with hepatic necrosis, without coma • K71.11, Toxic liver disease with hepatic necrosis, with coma • K71.2, Toxic liver disease with acute hepatitis • K71.6, Toxic liver disease with hepatitis, not elsewhere classified • K71.9, Toxic liver disease, unspecified • K72.9, Hepatic failure, unspecified

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
		• K72.90, Hepatic failure, unspecified without coma • K72.91, Hepatic failure, unspecified with coma • K75.9, Inflammatory liver disease • K76.2, Central hemorrhagic necrosis of liver Laboratory result: [68] • > 3-fold elevation above the upper normal limit for alanine transaminase (ALT) or aspartate transaminase (AST;) or • > 2-fold above the upper normal limit for total serum bilirubin or gamma-glutamyl transferase (GGT) or alkaline phosphatase (ALP) The presence of any of the following codes will not result in the safety events of interest being considered an event: • B15-B19, Viral hepatitis

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:

		• C22, Malignant neoplasm of liver and intrahepatic bile ducts
		• K72.0, Acute and subacute hepatic failure paired with any of the following:
		  ○ I50.811, Acute right heart failure
		  ○ I95, Hypotension
		• K77, Liver disorders in diseases classified elsewhere

Narcolepsy/cataplexy[62]	• 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
Non-anaphylactic allergic reactions[10,30]	• 708, Allergic urticaria • 708.1, Idiopathic urticaria	• L50.0, Allergic urticaria • L50.1, Idiopathic urticaria

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Appendix Table 2. Operational Definitions of Safety Events of Interest

Variable	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)*:
	• 708.9, Urticaria, unspecified • 995.1, Angioneurotic edema, not elsewhere classified • 995.3, Allergy, unspecified, not elsewhere classified	• L50.9, Urticaria, unspecified • T78.3XXA, Angioneurotic edema, initial encounter • T78.40XA, Allergy, unspecified, initial encounter
Severe COVID-19 disease[62]	• N/A	• U07.1, COVID-19 • B97.29*, Other coronavirus as the cause of diseases classified elsewhere *This code is only used before 4/1/2020
Stevens-Johnson syndrome/Toxic epidermal necrolysis[62]	• 695.13, Stevens-Johnson syndrome • 695.15, Toxic epidermal necrolysis • 695.14, Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome	• L51.1, Stevens-Johnson syndrome • L51.2, Toxic epidermal necrolysis (Lyell) • L51.3, Stevens-Johnson synd-tox epdrml necrolysis overlap syndrome

*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.

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
COVID-19	CPT	91300	Pfizer
		91301	Moderna
		91302	AstraZeneca
		91303	Janssen
	HCPCS	0001A	Pfizer
		0002A	Pfizer
		0011A	Moderna
		0012A	Moderna
		0021A	AstraZeneca
		0022A	AstraZeneca
		0031A	Janssen
	NDC	5926710001	Pfizer
		59267100001	Pfizer
		5926710002	Pfizer
		59267100002	Pfizer
		5926710003	Pfizer
		59267100003	Pfizer
		00310122210	AstraZeneca
		00310122215	AstraZeneca
		0310122210	AstraZeneca
		0310122215	AstraZeneca
		59676058005	Janssen
		59676058015	Janssen
		5967658005	Janssen
		5967658015	Janssen
		80777027310	Moderna

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
		80777027399	Moderna
		8077727310	Moderna
		8077727399	Moderna
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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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)

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	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
	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

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Appendix Table 3. COVID-19 and Seasonal Influenza Vaccine Exposure CPT, HCPCS, NDC Codes

Vaccine	Code Type	Code[16]	Manufacturer/Descriptions
	NDC	70461012003	FLUAD QUADRIVALENT
	NDC	70461031903	FLUCELVAX QUADRIVALENT
	NDC	70461032003	FLUCELVAX QUADRIVALENT
	NDC	70461041910	FLUCELVAX QUADRIVALENT
	NDC	70461042010	FLUCELVAX QUADRIVALENT

Appendix Table 4. COVID-19 RT-PCR Test LOINC

LOINC[16]	Long Common Name
94745-7	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection
94746-5	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Unspecified specimen by NAA with probe detection
94819-0	SARS-CoV-2 (COVID-19) RNA [Log #/volume] (viral load) in Unspecified specimen by NAA with probe detection
94565-9	SARS coronavirus 2 RNA [Presence] in Nasopharynx by NAA with non-probe detection
94759-8	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection
94500-6	SARS coronavirus 2 RNA [Presence] in Respiratory specimen by NAA with probe detection
94845-5	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection
94660-8	SARS-CoV-2 (COVID-19) RNA [Presence] in Serum or Plasma by NAA with probe detection
94309-2	SARS Coronavirus 2 RNA [Presence] in Unspecified specimen Qualitative by NAA with probe detection
41458-1	SARS coronavirus RNA [Presence] in Unspecified specimen by NAA with probe detection
94534-5	SARS coronavirus 2 RdRp gene [Presence] in Respiratory specimen by NAA with probe detection
95608-6	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with non-probe detection
94533-7	SARS-CoV-2 (COVID19) N gene [Presence] in Respiratory specimen by NAA with probe detection
94640-0	SARS coronavirus 2 S gene [Presence] in Respiratory specimen by NAA with probe detection
94559-2	SARS coronavirus 2 ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection

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Appendix Table 4. COVID-19 RT-PCR Test LOINC

LOINC[16]	Long Common Name
94502-2	SARS-related coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection
95423-0	Influenza virus A + B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection
95409-9	SARS coronavirus 2 (COVID19) N gene [Presence] in Nose by NAA with probe detection
95425-5	SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by NAA with probe detection
94760-6	SARS coronavirus 2 N gene [Presence] in Nasopharynx by NAA with probe detection
95406-5	SARS-CoV-2 (COVID19) RNA [Presence] in Nose by NAA with probe detection
94758-0	SARS-related coronavirus E gene [Presence] in Respiratory specimen by NAA with probe detection
96091-4	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Saliva (oral fluid) by NAA with probe detection
94316-7	SARS-CoV-2 (COVID-19) N gene [Presence] in Specimen by NAA with probe detection

Abbreviations: LOINC, Logical Observation Identifiers Names and Codes; RT-PCR, Reverse Transcription Polymerase Chain Reaction.

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