NON-INTERVENTIONAL (NI) STUDY INTERIM REPORT

PASS Information

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
Version identifier for the interim study report	1.0
Date	22 June 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
Joint PASS	No
Research question and objectives	Research question: what are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]) among individuals vaccinated with 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 Pfizer-BioNTech COVID-19 vaccine; and • To assess whether sub-cohorts of interest (i.e., immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of 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 Pfizer-BioNTech COVID-19 vaccine. *Secondary study objective:* • To characterize utilization patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA, including estimating the proportion of individuals receiving vaccine, two-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.
Country of study	United States
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Not applicable

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACOS	Associate Chief of Staff
ACIP	Advisory Committee on Immunization Practices
AESI	Adverse event of special interest
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CCI	Charlson comorbidity index
CDC	Centers for Disease Control and Prevention
CDW	Corporate Data Warehouse
CEP	Clinical Epidemiology Program
CHAMPVA	Civilian Health and Medical Program of the Department of Veterans Affairs
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPT	Current Procedural Terminology
CRADA	Cooperative Research and Data Agreement
CRF	Case report form
Tdap	Diphtheria, tetanus and (acellular) pertussis
Td	Diphtheria and tetanus
ED	Emergency department
EMA	European Medicines Agency
EMR	Electronic medical record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUA	Emergency Use Authorization
EU PAS	European Union Post-Authorization Safety
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HBV	Hepatitis B virus
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRU	Healthcare resource utilization
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System

Abbreviation	Definition
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
IRR	Incidence rate ratio
MaxSPRT	Maximized sequential probability ratio test
MenACWY	Meningococcal conjugate
MenB	Serogroup B meningococcal
mRNA	Messenger RiboNucleic Acid
NDC	National Drug Code
NI	Non-interventional
NNERC VAMC	Northern New England Research Consortium Veterans Affairs Medical Centers
OR	Odds ratio
PASS	Post-Authorization Safety Study
PCAFC	Program of Comprehensive Assistance for Family Caregivers
PHI	Protected Health Information
R&D	Research and Development
RCA	Rapid cycle analysis
RPSS	Research Protocol Safety Survey
RR	Relative risk
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCRI	Self-controlled risk interval
SD	Standard deviation
SPEAC	Safety Platform for Emergency vACcines
SRSS	Subcommittee on Research Safety and Security
US	United States
VA	Department of Veterans Affairs
VAIRRS	Veterans Affairs Innovation and Research Review System
VHA	Veterans Health Administration
VINCI	VA Informatics and Computing Infrastructure
VINNE	Veteran's Institutional Review Board of Northern New England
VISN	Veterans Integrated Service Networks
VSD	Vaccine Safety Datalink
WHO	World Health Organization
WOC	Without compensation

3. INVESTIGATORS

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4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date
VHA CRADA execution	8 January 2021
Determination of IRB exemption[1]	10 February 2021
Determination of Research Safety and Security exemption[2]	17 February 2021
Approval by Designated Member Review[3]	26 February 2021
Registration in the EU PAS register	5 March 2021
Start of data collection	11 March 2021[4]
Interim reports	22 June 2021 31 December 2021 30 June 2022 31 December 2022
End of data collection	10 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 the planned date on which Pfizer-BioNTech COVID-19 vaccine exposure data reached 30 months post-EUA approval.

6. 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 May 26, 2021, over 33.1 million COVID-19 cases and 590,000 deaths have been reported in the United States (US) alone.[2] To date, the cumulative incidence of COVID-19 has continued to rise, largely among the elderly and middle-aged individuals, those with comorbid conditions, and in settings with high noncompliance with public health measures.[3,4,5] COVID-19 is a well-adapted highly infectious human pathogen that has evolved over time to develop multiple variants, including those associated with an increased risk of transmission and death that were first identified in late 2020.[3, 6,7,8]

On December 11, 2020, the US Food and Drug Administration (FDA) issued its first emergency use authorization (EUA) for a vaccine for the prevention of COVID-19 disease, indicated for individuals 16 years of age and older.[9] This vaccine, developed by Pfizer and BioNTech (BNT162b2; COMIRNATY®), contains synthetic messenger RNA (mRNA) that instructs cells in the body to produce the virus' distinctive "spike" protein that triggers an immune response against SARS-CoV-2.[9] The EUA for Pfizer-BioNTech COVID-19 vaccine was based on safety and efficacy data from an ongoing Phase 1/2/3 trialsof approximately 44,000 participants aged 12 years and older who were randomized 1:1 to receive Pfizer-BioNTech COVID-19 vaccine or saline control.[10,11] The FDA reviewed safety data from 37,586 of the participants 16 years of age and older who were followed for a median of two months after receiving their second dose, and efficacy data from 36,523 participants 12 years of age and older after Day seven following vaccination with dose 2.[12,13] The efficacy data reviewed by the FDA indicated that Pfizer-BioNTech COVID-19 vaccine was 95% effective in preventing symptomatic COVID-19 disease, while the safety data indicated that the most commonly reported side effects, which typically lasted several days, were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, and fever.[13] No severe adverse events were reported that would preclude Pfizer-BioNTech COVID-19 vaccine to meet the criteria for EUA.[13] 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.[14]

As required by the FDA EUA,[13] 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 among individuals who received the vaccine in both the population at large and in populations of interest (e.g., immunocompromised individuals, elderly, and those with specific comorbidities).[13] Such post-authorization safety evaluations are important for identifying rare, unexpected, 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 monitoring that the favorable benefit-risk ratio of the vaccine is maintained post-trial.

On January 27, 2021, Pfizer, in collaboration with the US Veterans Health Administration (VHA) and Analysis Group, submitted a study protocol (protocol C4591012; Appendix 2) for post-EUA active safety surveillance of safety events of interest among individuals 16 years of age and older in the VHA system. Safety events of interest for the current study include 42 safety outcomes that were selected 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.[15,16]

The study uses data from a large-scale electronic medical record (EMR) database from the VHA to identify and evaluate rapid-cycle, near real-time potential safety signals associated with Pfizer-BioNTech COVID-19 vaccine. The Cooperative Research and Data Agreement (CRADA) was established between Analysis Group and White River Junction VA Medical Center and Veterans Education and Research Association of Northern New England (VINNE) for this study on January 8, 2021. Data included for this analysis commenced on December 11, 2020 and will continue through June 10, 2023 – i.e., 30 months following the issuance of the EUA for Pfizer-BioNTech COVID-19 vaccine. Four interim reports are planned on June 30, 2021; December 31, 2021; June 30, 2022; and December 31, 2022, with a final report to be issued on December 31, 2023.

In this first interim report, the data included for analysis spans from December 11, 2020 to March 12, 2021, and the data were locked on April 26, 2021. This first interim report describes the selection of two samples of individuals within the VHA: individuals who received Pfizer-BioNTech COVID-19 vaccine between December 11, 2020 (EUA approval date by the US FDA) and March 12, 2021 (data cutoff date), and recipients of seasonal influenza vaccine(s) during the five prior influenza seasons (2014/2015 through 2018/2019). The demographic characteristics and vaccine utilization patterns among the two samples of individuals are described pursuant to the secondary study objective. Due to the short time between the data lock date and the first interim report issuance date, this report does not include results from the safety signal analyses pursuant to the primary study objectives. All references to the study protocol in this first interim report pertain to the study protocol Version 1.0 dated January 27, 2021 (see Appendix 2). Meanwhile, a protocol amendment is currently under development to address the FDA's comments on the study protocol Version 1.0, communicated electronically to Pfizer on May 12, 2021.

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

7. 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 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 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 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 Pfizer-BioNTech COVID-19 vaccine.

Secondary study objective:

To characterize utilization patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA including estimating the proportion of individuals receiving vaccine, two-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.

This first interim report pertains to the secondary study objective.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

9.1. Study Design

The methodology to address the primary study objectives has not yet been implemented and thus is not covered in this first interim report. As described in greater detail in the study protocol (Appendix 2), 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 the 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 Pfizer-BioNTech COVID-19 vaccination to pre- or post-vaccination non-risk intervals (“pre-vaccination control interval” and “post-vaccination control interval”, respectively) in the same individual.

- An active comparator design will be used to sequentially monitor the occurrence of safety events of interest among individuals who receive Pfizer-BioNTech COVID-19 vaccinations as compared to recipients of influenza vaccine in the VHA during October 2014 - May 2015 through October 2018 - May 2019 influenza 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.

Thus, analyses to address the study primary objectives will rely on two samples:

1. Recipients of Pfizer-BioNTech COVID-19 vaccine after December 11, 2020, which will be included in both the SCRI and active comparator designs; and

2. Recipients of influenza vaccine(s) between the 2014/2015 influenza season and the 2018/2019 influenza season, which will be only included in the active comparator design.

With both designs, safety events of interest will be monitored sequentially every two weeks, and any signal that is detected will be further evaluated and verified (e.g., by conducting multivariate adjustment using Poisson regression, assessing temporal clusters, conducting medical records review). The rapid cycle analysis (RCA) has not yet been initiated and thus is not included in the current interim report.

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 consists of VHA enrollees, which largely include veterans, and is kept as broad as possible under inclusion and exclusion criteria to be representative of the real-world population at the VHA receiving Pfizer-BioNTech COVID-19 vaccine.

The study relies on secondary data from the Corporate Data Warehouse (CDW) in the National Veterans Affairs Health Care Network. The CDW data, which are updated daily, include standard EMR for all medical encounter information in the VHA system. Information is also available on date of death, COVID-19 infection status, and COVID-19 and seasonal influenza vaccination status.

The VHA oversees the rollout of both COVID-19 and seasonal influenza vaccination among individuals enrolled in the VHA. The VHA delivers vaccines through VHA health care facilities, community urgent care providers in the VHA's network, and community pharmacies in the VHA's network.[17] For seasonal influenza, the VHA vaccination rollout overlaps with the influenza season, which typically starts in October and ends in May of the following year.[18] For COVID-19, the VHA vaccination rollout started on December 15, 2020 and is still ongoing in a phased approach, as follows:[17]

Phase 1a includes the following eligible VHA enrollees: individuals who work or live in VA community living centers and spinal cord units; who live or work in other long-term care or congregate (group living) settings and do not have access to COVID-19 vaccines in those settings; who work in cemeteries, and who work as health care personnel;

Phase 1b includes the following eligible VHA enrollees: veterans who are at least 75 years old; individuals who are essential frontline workers; who experience homelessness; who receive hemodialysis care; who have had a solid organ transplant or who are being considered for transplant; who have spinal cord injuries and disorders; and who receive chemotherapy treatment in a clinic or hospital;

Phase 1c includes the following eligible VHA enrollees: veterans who are 65 to 74 years old; who are younger than 65 years old and have certain health conditions that are deemed by the CDC to be associated with a high risk of severe illness from COVID-19; and individuals who are considered essential workers by the CDC and were not included in Phase 1b;

After Phase 1c is completed, COVID-19 vaccination will be offered free of charge to all veterans enrolled in the VHA, caregivers of eligible veterans under the Program of Comprehensive Assistance for Family Caregivers (PCAFC), and other eligible individuals (e.g., veteran spouses and dependents) under the Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA)[17]

As the VHA's health care delivery system is organized regionally around 18 Veterans Integrated Service Networks (VISNs) across the US, with each VISN responsible for health care planning and resource allocation in a particular geographical region,[17] regional variations may impact the timing of vaccine distribution, particularly for COVID-19 vaccines where supply was not pre-planned.

9.3. Subjects

9.3.1. Inclusion Criteria

9.3.1.1. Pfizer-BioNTech COVID-19 Vaccine Sample

Individuals with at least one record of Pfizer-BioNTech COVID-19 vaccine during the period December 11, 2020 to March 12, 2021; and

Individuals with at least one year of continuous enrollment in VHA benefits (i.e., the baseline period) prior to their first Pfizer-BioNTech COVID-19 vaccination date.

9.3.1.2. Seasonal Influenza Vaccine Sample

Individuals with records of one or more seasonal influenza vaccine from the 2014/2015 influenza season to the 2018/2019 influenza season, where the influenza season was defined as the period from October 1 of one year until May 31 of the following year; and

Individuals with at least one year of continuous enrollment in VHA benefits (i.e., the baseline period) prior to at least one seasonal influenza vaccination date.

9.3.2. Exclusion Criteria

9.3.2.1. Pfizer-BioNTech COVID-19 Vaccine Sample

Individuals who received at least one dose of COVID-19 vaccine from a manufacturer other than Pfizer-BioNTech.

While excluded from the study sample, these individuals were described when characterizing the vaccine utilization patterns of Pfizer-BioNTech COVID-19 vaccine (secondary objective).

9.3.2.2. Seasonal Influenza Vaccine Sample

Individuals who have records for more than one seasonal influenza vaccine in the same influenza season were excluded from that influenza season.

9.3.3. Subgroups

Safety surveillance, which is not included in this first interim report, will be conducted for subgroups of interest (i.e., immunocompromised individuals, different age groups with a focus on elderly, individuals with specific comorbidities, individuals receiving only one dose of Pfizer-BioNTech COVID-19 vaccine, individuals with prior SARS-CoV-2 infection, and individuals likely to receive all their care from VA facilities [i.e., individuals with regular use of VHA medical care, VA priority group 1 veterans]) as outlined in Section 9.2.3 of the study protocol (Appendix 2).

9.4. Variables

This section includes a listing of the key variables for the current study, including outcomes, exposures, and baseline characteristics. For details on the measurement of these variables in the CDW data, please see Section 9.5.2.

9.4.1. Outcomes

Outcomes include 42 safety events of interest (Table 15.2). The list of outcome safety events may be modified over time as new safety information about the COVID-19 vaccines emerges.

Safety events of interest will only be counted as outcomes when observed during a pre-specified risk interval (e.g., within two days of vaccination for anaphylaxis; within 42 days of vaccination for Bell's palsy or thrombocytopenia) without any other diagnosis codes for the same safety event of interest in a pre-specified clean window (e.g., six months before that date for anaphylaxis; one year before that date for Bell's palsy or thrombocytopenia). The duration of the risk interval and the duration of the clean window for a given safety event of interest were determined based on biological plausibility and precedents in the literature when the safety event of interest is vaccine-related (Section 9.3.3 of the study protocol; Appendix 2). Details on the measurement of outcomes in the CDW data are presented in Section 9.5.2 below.

Due to the short time between the data lock date and the first interim report issuance date, this report does not include results from the safety signal analyses pursuant to the primary study objectives.

9.4.2. Exposures of Interest

Vaccination with Pfizer-BioNTech COVID-19 vaccine is the main exposure of interest. Risk of safety events of interest during the pre-specified risk window post-Pfizer-BioNTech COVID-19 vaccine will be compared with risk during pre-defined pre-and/or post-vaccination control intervals within the same individuals (SCRI design) or compared to similar risk intervals post-influenza vaccination among recipients of influenza vaccine(s) between the 2014/2015 through 2018/2019 influenza seasons (active comparator design). Details on the measurement of Pfizer-BioNTech COVID-19 and seasonal influenza vaccine receipt in the CDW data are presented in Section 9.5.2.

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

Some recipients of Pfizer-BioNTech COVID-19 vaccine may have received seasonal influenza vaccine in the 2020/2021 influenza season, which may impact their observed rates of safety events of interest. As described in Section 9.3.1.1 of the study protocol (Appendix 2), additional analyses will be conducted among subsets of the study population based on (1) whether they received the influenza vaccine in the 2020/2021 influenza season, and (2) the timing of the influenza vaccine relative to Pfizer-BioNTech COVID-19 vaccine in the 2020/2021 season.

9.4.3. Baseline Characteristics

The following baseline demographic and clinical characteristics were assessed based on a one-year baseline period prior to the date of vaccination with Pfizer-BioNTech COVID-19 vaccine and prior to the date of seasonal influenza vaccination for active comparators (unless otherwise specified). Operational definitions for baseline characteristics variables listed in this section are provided in Table 15.1, while measurement details are provided in Section 9.5.2.3.

Demographics:

- Age (<16, 16-64, 65-74, ≥74 years)
- Sex
- Race/ethnicity
- VHA service area - US region

Clinical characteristics:

- Smoking status
- Body mass index (BMI; measured based on a two-year baseline period, for reasons described in Section 11.1)
- History of anaphylaxis/allergic reactions
- Previous anaphylaxis of vaccine component
- History of hospitalizations

- Charlson comorbidity index (CCI)
- Selected comorbidities
    - Autoimmune disease
    - Asthma
    - Bleeding diathesis or condition associated with prolonged bleeding
    - Cancer
    - Cardiovascular conditions (e.g., heart failure, coronary artery disease [CAD], cardiomyopathies)
    - Chronic kidney disease/dialysis
    - Chronic obstructive pulmonary disease (COPD)/interstitial lung disease
    - Diabetes mellitus (i.e., Type 1 or Type 2 diabetes)
    - Down syndrome
    - Sickle cell disease
    - Hepatitis B virus infection (HBV)
    - Hepatitis C virus infection (HCV)
    - Human immunodeficiency virus infection (HIV)
    - Hyperlipidemia
    - Hypertension
    - Liver disease
    - Neurological disease
    - Other immune deficiencies
    - Solid organ transplant
    - Venous thromboembolism (VTE)
- Immunization history
    - Seasonal influenza (during the 2020/2021 influenza season; reported for recipients of Pfizer-BioNTech COVID-19 vaccine)
    - Tetanus diphtheria and pertussis (Tdap or Td)
    - Chickenpox (Varicella)
    - Shingles (Herpes zoster recombinant and/or live)
    - Human papillomavirus (HPV)
    - Pneumococcal conjugate
    - Pneumococcal polysaccharide
    - Hepatitis A
    - Hepatitis B
    - Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB)
    - Haemophilus influenza type b

9.5. Data Sources and Measurement

The study relies on secondary EMR data from the VHA CDW, which is a centralized data warehouse that is updated daily. For this first interim report, the study used data from the CDW that were available at the time of data cut-off on March 12, 2021.

9.5.1. VHA EMR Database

The VHA is the largest integrated health care system in the US, providing comprehensive healthcare services, including primary, specialty and inpatient care, rehabilitation, long-term and home care, and other services to over nine million veterans through 1,293 health care facilities, including 171 medical centers and 1,112 outpatient sites of varying care complexity.[19] In addition to veterans, VHA enrollees may also include employees and certain categories of family members of the veterans, but these are a minority among all VHA enrollees.

The CDW consolidates data from the VHA's EMR system and contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions, immunizations, and lab results. Although the VHA may have financially covered/reimbursed care provided at non-VHA facilities, the EMR system (and thus the CDW) does not capture information on visits at non-VHA facilities. The CDW stores data in separate databases based on type of clinical information (e.g., inpatient medication, inpatient admission, outpatient medication, outpatient visit). The VHA also maintains its own mortality data, in which 99% of enrollees' deaths are reported within one month of occurrence and which are based on information collected from multiple sources: family members, VHA hospitals, the National Cemetery Administration, Medicare vital status file, and the Social Security Administration. Death ascertainment from these sources in the VHA data has been shown to have 98% sensitivity.[20]

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

The VHA database is an appropriate data source to provide early data on potential rare safety events of interest associated with Pfizer-BioNTech COVID-19 vaccine. First, given that some groups of veterans were prioritized in the first wave of vaccinations,[17] VHA enrollees were among the first Pfizer-BioNTech COVID-19 vaccine recipients in the US, enabling early safety analyses. Second, the VHA data are refreshed daily, and thus enable rapid data analysis. Third, the VHA population is older and has more comorbid conditions[21] than the general population, thus maximizing the chance of capturing rare safety events of interest in early analyses, following the initial phases of Pfizer-BioNTech COVID-19 vaccine distribution. Finally, subgroup analyses will be performed among individuals who are in the VA priority group 1 (i.e., individuals who have the highest levels of service connected disability[22] and are categorized as the highest priority for VHA care), which will ensure that the individual is more likely to receive all their care from a VA facility, hence minimizing the potential for missing data.

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

9.5.2. Measurement

9.5.2.1. Outcomes

Operational definitions of the 42 safety events of interest, based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes, are detailed in Table 15.2. [23,24,25,26,27] The list of outcome safety events may be modified over time as new safety information about the COVID-19 vaccines emerges.

Outpatient (including emergency department [ED]) and/or inpatient settings will be used to identify safety events of interest, depending on the type of event, as described in Section 9.3.3 of the protocol (Appendix 2). Any record of death will be captured, regardless of whether the individual died in a healthcare or non-healthcare setting.

9.5.2.2. Exposures of Interest

Administration of Pfizer-BioNTech COVID-19 vaccine post-EUA approval and date of immunization for each dose were identified in the CDW data based on any of the following codes:

- Current Procedural Terminology (CPT) codes; or
  - 91300, corresponding to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNALNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted, for intramuscular use) or
- Healthcare Common Procedure Coding System (HCPCS) codes; or
  - 0001A, corresponding to administration of first dose (ADM SARS-CoV-2 30 mcg/0.3mL 1st)
  - 0002A, corresponding to administration of second dose (ADM SARS-CoV-2 30 mcg/0.3mL 2nd)[28,29] or
- National Drug Codes (NDCs) codes; or
  - 10-digit NDCs: 59267-1000-1, 59267-1000-2, 59267-1000-3)
  - 11-digit NDCs: 59267-1000-01, 59267-1000-02, 59267-1000-03[30]

- Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (i.e., Pfizer), lot number, injection site, and date(s) of immunization.[28]

Administration of the seasonal influenza vaccine during 2014/2015 through 2018/2019 influenza seasons and date of immunization were identified in the CDW data based on any of the following (see Table 15.3 for additional details):

- CPT codes; or
- 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.

9.5.2.3. Baseline Characteristics

Operational definitions for all diagnoses, procedures, and immunizations are provided in Table 15.1. In short, diagnoses were identified by ICD-10-CM diagnosis codes, procedures were identified by ICD-10-PCS (procedure coding system) codes, CPT, or HCPCS procedure codes, while vaccines were identified by NDC, CPT, and HCPCS codes, and immunization records. Baseline demographic and clinical characteristics reported in this first interim report were based on a one-year baseline period (with two exceptions, specified below) and included the following:

- Demographic variables included age, sex, race/ethnicity, and VHA service area. Demographic variables were extracted from the CDW data at the time of the receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine (for Pfizer-BioNTech COVID-19 vaccine sample) and at the time of the receipt of the seasonal influenza vaccine (for the seasonal influenza vaccine sample), and were well-populated.
- BMI was extracted from the CDW based on the most recent BMI record for the individual in the year before the receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine and/or receipt of the seasonal influenza vaccine. Given the high proportion of missing values for BMI in Pfizer-BioNTech COVID-19 vaccine sample, which was likely due to a higher utilization of telemedicine encounters during the COVID-19 pandemic,[31] BMI was therefore reported based on the two years prior to the receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine and/or receipt of the seasonal influenza vaccine.
- History of hospitalizations included the number of hospitalizations recorded in the CDW in the year before the receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine and/or receipt of the seasonal influenza vaccine.
- Smoking status, history of anaphylaxis/allergic reactions, previous anaphylaxis of vaccine component, comorbidities included in the CCI,[32] and other relevant

comorbidities were identified in the CDW data (based on diagnosis codes that conform with the ICD-9-CM and ICD-10-CM codes) in the year before the receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine and/or receipt of the seasonal influenza vaccine (see Table 15.1 for more details on the specific codes used).

- Other immunizations were identified in the immunization file from the CDW based on CPT codes, HCPCS codes, NDC codes, and other immunization records (please see Table 15.1 for more details on the specific codes used).

    - Non-seasonal immunizations (i.e., all immunizations other than seasonal influenza) were measured in the year preceding the vaccination; seasonal influenza was measured only among individuals who received Pfizer-BioNTech COVID-19 vaccine during the influenza season (i.e., from October 1 to May 31) that overlaps or precedes the date when the individual received Pfizer-BioNTech COVID-19 vaccine.

9.6. Bias

Several approaches were incorporated in the study design and will be implemented in forthcoming safety signal analyses to reduce bias in this study.

First, the SCRI and active comparator designs complement each other in mitigating bias in the current study. Specifically, the SCRI design will use individuals as their own controls, thus removing any potential confounding bias due to factors that do not change over short periods of time within an individual (e.g., age, sex, chronic conditions). While the SCRI design that uses a pre-vaccination control interval may be subject to detection bias because individuals pay more attention to possible safety events post-vaccination compared to pre-vaccination, the SCRI design that uses a post-vaccination control interval is not subject to this bias because both the risk and control intervals are defined post-vaccination.[33] Despite the ability to adjust for time-invariant confounders, the SCRI design may have limited power to estimate expected rates for very rare safety events of interest.[34] Thus, the SCRI design will be complemented by an active comparator design that will derive expected rates of safety events of interest from historical controls vaccinated for seasonal influenza. To mitigate potential confounding bias in the active comparator design, historical controls will only include individuals vaccinated for seasonal influenza (individuals who are open to vaccination are expected to share similarities) and additional Poisson multivariate adjusted regression models will be implemented for safety events of interest that are detected and persist after conducting quality assurance.

Second, when a signal is detected in the signal detection phase, additional analyses will be performed to evaluate the signal and identify other possible sources of bias. For example, the impact of seasonal variations in the rates of the safety events of interest (e.g., mortality rates vary during the year, with higher rates in winter months and lower rates in summer months[34]) will be assessed using a seasonality-adjusted case-centered analysis that focuses on the subset of individuals in Pfizer-BioNTech COVID-19 vaccine sample who experienced a safety event of interest (i.e., cases). Temporal scan statistics will be calculated to empirically identify temporal clusters of safety events of interest during the risk interval.

Third, for both the SCRI and active comparator designs, bias may result from the misclassification or imprecision of the time interval during which rates of safety events of interest are measured. It is possible that some safety events of interest do not have a precise time interval for which to evaluate risk – for example, if biological plausibility is not well known or the diagnostic time window is more delayed than anticipated. In these cases, misspecification of the risk (and control) intervals could result in outcome 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 the effect when using post-vaccination time intervals for self-control. To address this, the length of the risk intervals may be varied in sensitivity analyses to increase the likelihood that the safety risk is detected accurately.

Finally, if individuals receive Pfizer-BioNTech COVID-19 vaccine or the seasonal influenza vaccine outside of a VHA facility, this information will not be captured in the VHA EMR system, resulting in exposure misclassification. Veterans with secondary insurance and veterans who are 65 years of age or older who have Medicare may be more likely to receive services outside VHA. One study on VHA enrollees in seven different states found that among all individuals admitted to VHA hospitals in 2007, one-fifth also had a non-VHA hospitalization during that year.[35] To mitigate this limitation, subgroups of individuals who receive care regularly at VHA facilities, as well as those with priority group 1 status (i.e., veterans with service-connected disability that is ≥50% disabling, veterans who are unable to work, or veterans who have received the Medal of Honor)[22], will be examined to ensure that their healthcare data are complete to the extent possible in the CDW.

Further discussion of potential sources of bias in the study, including exposure misclassification, is provided in Section 11.2.

9.7. Study Size

A total of 750,999 individuals received at least one dose of Pfizer-BioNTech COVID-19 vaccine from December 11, 2020 to March 12, 2021 in the VHA database. The active comparator group includes a fixed cohort of 4,277,220 historical seasonal influenza vaccine recipients who received a total of 10,529,071 seasonal influenza vaccines across successive influenza seasons between 2014/2015 through 2018/2019.

9.7.1. Power

Power calculations for the safety signal analyses (study primary objective) will be conducted for each safety event of interest using the power calculation feature in the sequential R package for RCA developed by Kulldorff et al.[36] The power calculations are not included in this first interim report as they require the calculation of the background incidence of each safety event of interest among the historical seasonal influenza active comparator group as an input and this analysis has not yet been performed, and will be included in the second interim report .

9.8. Data Transformation

Not applicable.

9.9. Statistical Methods

9.9.1. Main Summary Measures

9.9.1.1. Baseline Characteristics

Baseline demographics and clinical characteristics were summarized using mean, standard deviation (SD), and median (interquartile range [IQR]) values for continuous variables and frequency distributions for categorical variables. Baseline demographics and clinical characteristics were summarized and compared between Pfizer-BioNTech COVID-19 vaccine recipients (at the time of the first dose of Pfizer-BioNTech COVID-19 vaccine) and for active comparators who received seasonal influenza vaccination (at the time of the most recent seasonal influenza vaccine received from the 2014/2015 to the 2018/2019 influenza season to facilitate comparison with Pfizer-BioNTech COVID-19 vaccine recipients). Baseline demographics and clinical characteristics were also summarized at the time of each seasonal influenza vaccine observed in the seasonal influenza sample from the 2014/2015 to the 2018/2019 influenza season (i.e., allowing multiple measurements per individual) as the background incidence of the safety events of interest will be assessed in the risk intervals following all observed seasonal influenza vaccines (to increase the chance of capturing rare safety events of interest).

Standardized differences were used to compare baseline demographics and clinical characteristics between individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine (at the time of the first Pfizer-BioNTech COVID-19 vaccine dose) and those vaccinated for seasonal influenza (at the time of the most recent seasonal influenza vaccine). For a given covariate, the standardized difference scales the difference in means between the samples (if the covariate is continuous) or the difference in proportions (if the covariate is binary) by the standard deviation of that covariate in both samples combined. Because the standardized difference is a measure of the magnitude of difference in means/proportions between two groups that does not depend on sample size,[37] it is a more appropriate estimate than statistics that rely on statistical significance (e.g., t-test for continuous variables or chi-square tests for binary variables) for studies with very large samples, such as the current study.

In the current study, a standardized difference >10% was used to identify an imbalance between characteristics of recipients of Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine.[38,39] The study used a conservative threshold to indicate covariate imbalance (other authors proposed thresholds ranging from >10% to >25%[40,41,42,43]) to capture any possible differences between the study samples that need to be accounted for in the signal evaluation phase.

9.9.1.2. Pfizer-BioNTech COVID-19 Vaccine Utilization Patterns

Descriptive statistics were used to summarize Pfizer-BioNTech COVID-19 vaccine utilization patterns, including the proportion of individuals who received the vaccine, two-dose completion rate, distribution of time gaps between the first and second vaccine dose,

and description of care setting where immunization was received (e.g., outpatient clinic, pharmacy, inpatient ward, other). These utilization patterns were summarized using the mean (SD) and median (IQR) values for continuous variables, and frequency distributions for categorical variables. Individuals with at least one healthcare encounter in the VHA from December 11, 2020 to March 12, 2021 served as the expected number of individuals who would be eligible for Pfizer-BioNTech COVID-19 vaccine, as they had been actively receiving care through the VHA during the time period when Pfizer-BioNTech COVID-19 vaccine was available. The count and proportion of individuals who received COVID-19 vaccine(s) from different manufacturers in addition to Pfizer-BioNTech COVID-19 vaccine were also reported.

9.9.1.3. Safety Signal Analysis

Safety signal analysis was not performed in this first interim report. As described in greater detail in Section 9.7 of the study protocol (Appendix 2), the safety signal analysis will rely on the following key measures, as appropriate for each study phase:

The signal detection phase will be conducted every two weeks for all safety events of interest, and will include the following analyses:

- For analyses based on the SCRI design using pre-vaccination control intervals, relative risks (RRs) and corresponding confidence intervals (CIs) will be estimated to compare the risks of safety events of interest during the risk interval immediately following Pfizer-BioNTech COVID-19 vaccination and the risks of safety events of interest during pre-specified control intervals before Pfizer-BioNTech COVID-19 vaccination. Please see Section 9.9.2 for additional methodological details.

- For analyses based on the active comparator design, RRs and corresponding CIs will be estimated to compare the risks of safety events of interest during the risk interval immediately following Pfizer-BioNTech COVID-19 vaccination among Pfizer-BioNTech COVID-19 vaccine recipients and the risk interval immediately following seasonal influenza vaccine among historical seasonal influenza vaccine recipients.

The signal evaluation phase will be conducted after a signal is detected (if the signal persists following post-signal quality assurance), and will include the following analyses:

- For analyses based on the SCRI design, RRs and corresponding CIs will also be calculated using post-vaccination control intervals in order to account for potential detection bias that may impact SCRI analyses using pre-vaccination control intervals (due to enhanced vigilance for safety events after vaccination compared to the pre-vaccination period).

- For analyses based on the active comparator design, incidence rate ratios (IRRs) and corresponding CIs will be calculated using a multivariate adjusted Poisson regression model to account for baseline differences between Pfizer-BioNTech COVID-19 and seasonal influenza vaccinees.

- Temporal scan statistics for each safety event of interest will be estimated to determine whether temporal clusters are present in the occurrence of the safety events of interest post-vaccination.

- Kaplan-Meier (KM) methods will be used to analyze time-to-safety event of interest, with censoring at the end of the risk interval for individuals who did not experience the safety event of interest by the end of the risk interval.

- If a defined COVID-19 season is established,[44] additional analyses will be performed to address seasonality:

    - A seasonality-adjusted case-centered analysis may be conducted to account for bias caused by seasonality of safety events of interest and vaccination.[45,46] From this analysis, odds ratios (ORs) and corresponding CIs will be reported.

    - If it is determined in the literature that the COVID-19 pandemic exhibits seasonality, analyses may be conducted at the end of the defined COVID-19 season. This end-of-season analysis will use data from the SCRI design with post-vaccination control intervals, from which RR and corresponding CIs will be reported. An end-of-season analysis using data from the active comparator design with historical seasonal influenza vaccination recipients may also be conducted, from which RRs and corresponding CIs will be reported.

Finally, the end-of-surveillance safety analysis will be a one-time analysis conducted after the final data lock at the study end (July 14, 2023), for safety events of interest with signals detected, and will include the following analyses:

- Using data from the SCRI design, the RR for safety events of interest with signals detected during the risk interval compared to the control interval and corresponding CIs will be estimated. In addition, using data from the active comparator design, safety events of interest with signals detected in the risk interval among individuals that received Pfizer-BioNTech COVID-19 vaccine will be compared to safety events of interest observed in the risk intervals among individuals that received seasonal influenza vaccination in the five prior seasons to estimate RRs and corresponding CIs.

9.9.2. Main Statistical Methods

Statistical methods for the safety signal analysis have not been implemented in this first interim report. As described in greater detail in the study protocol (Appendix 2), the safety signal analysis will be performed for signal detection, evaluation, and verification.

In the signal detection phase, the SCRI analysis will only include pre-vaccination control intervals as the post-vaccination control intervals will require a longer time to accumulate and will be used in the signal evaluation phase. 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 (active comparator design), the Poisson-based MaxSPRT will be applied.

For each safety event of interest, the safety signal analysis 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.[47] Critical values will be determined for each safety event of interest based on the historical incidence rate, expected upper limit of the number of events under the null hypothesis, and pre-specified significance level and power. Signals will be detected if the critical values are reached via the SCRI or active comparator analysis. Incidence rates will also be calculated, and KM methods will be used to analyze time to safety event of interest.

If signals are detected for safety events of interest based on the analysis described above, signal evaluation will be conducted to refine and confirm such detections. This will include comprehensive quality assurance (e.g., checking 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, checking 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 the active comparator cohort. SCRI analyses using the post-vaccination control intervals will be conducted as an additional inferential analysis once enough post-vaccination time has accumulated. Lastly, the assessment of temporal clustering will also be conducted.

The signal verification phase will include the diagnostic validation of the safety events of interest detected in the signal evaluation phase, and will rely on adjudication of medical records in a representative sample of cases by VHA clinicians for outcome verification. For rare events, potentially all cases may be adjudicated.

End-of-season analyses (over the course of the 30-month period, pending if COVID-19 seasonality is established) and an end-of-surveillance analysis (i.e., at 30 months) will also be conducted.

9.9.2.1. Subgroup Analyses

Separate analyses of baseline characteristics, vaccine utilization patterns, signal detection, signal evaluation, and signal verification in subgroups of interest (defined in Section 9.3.3) will be conducted in subsequent interim reports pending feasibility, sample size, and data availability.

9.9.3. Missing Values

No VHA members had missing date of birth or sex data. A very small minority of individuals had both sexes documented. Those members were categorized as "unknown" (Table 2). Individuals with missing race/ethnicity or BMI data were also categorized as "unknown" (Table 3).

9.9.4. Sensitivity Analyses

No sensitivity analyses were performed in this interim report.

9.9.5. Amendments to the Statistical Analysis Plan

Not applicable.

9.10. Quality Control

For this first interim report, data for the study were extracted from EMR databases in the CDW of the VHA. Each data content area in the CDW was subjected to similar checks, from high-level variable name/type checks, to detailed trending comparisons. As an example, the diagnostic data was subject to the following checks:

- Checked that variables referenced in the data dictionary exist and are of appropriate length and type
- Checked the diagnosis code type (i.e., ICD-9-CM, ICD-10-CM) was correctly matched with the codes defining specific diagnoses of interest;
- Assessed percentages and rates in the light of literature and substantive knowledge;
- Checked percentages and rates of missing data;
- Checked that both inpatient and outpatient (which include emergency room visits) diagnosis codes were captured.

Data retrieval was coordinated by two experienced programmers/analysts. The analyst wrote programming for retrieval of each data element from the electronic databases. Double programming was performed; results/datasets were compared, and discrepancies were resolved. All tables were reviewed by the project manager and the principal investigator and evaluated for internal consistency of counts and totals. All calculated variables were checked against the component variables (cross tabs) to ensure accuracy. For example, categorical age was compared with continuous age to confirm that each category of age contained only individuals of the expected age ranges within that category.

9.11. Protection of Human Subjects

Patient Information and Consent

Protected health information (PHI) will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research, or for other research for which the use or disclosure of PHI would be permitted by applicable regulation. The PHI obtained were the minimum necessary to conduct the research. Information regarding Institutional Review Board (IRB) exemption is provided in the below section. The project is led by the VHA, with Dr. Yinong Young-Xu, Director of the Clinical Epidemiology Program (CEP), serving as the Principal Investigator. The CEP at White River Junction VA Medical Center will conduct this safety surveillance study with sponsorship from Pfizer and assistance from Analysis Group. Analysis Group employees underwent

background checks by the VHA and received without compensation employee (WOC) status to access the CDW VHA data files hosted on the VA servers through the VA Informatics and Computing Infrastructure (VINCI) platform. CDW VHA data will not be transferred off from the VA servers, to either Pfizer or Analysis Group. Only Analysis Group WOC employees have access to de-identified patient-level data on the VINCI platform and they will only share summary statistics based on these data with study investigators who are not WOC employees.

All parties complied and will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure personal data protection. Given the sensitive nature of healthcare data, comprehensive security measures are implemented to ensure the confidentiality, integrity, and protection of individuals enrolled in the VHA's privacy and healthcare data. Only VA employees, including those with 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. Other measures will include omitting individual 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 individual 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, individual-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.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The study protocol that outlined the plan for the signal detection and signal evaluation phases of the study, which includes the analyses presented in this interim study report, was determined on February 10, 2021 to be exempt from IRB review by the VINNE, White River Junction VA Medical Center, White River Junction, VT in accordance with 38 CFR 16. 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 was implemented to expedite the initiation of the project. On February 17, 2021 the study protocol was reviewed and determined to be exempt from future research safety and security review by the Subcommittee on Research Safety and Security (SRSS), VA Innovation and Research Review System (VAIRRS). Finally, on February 26, 2021, the study protocol was granted approval by Designated Member Review of the Northern New England Research Consortium VA Medical Centers (NNERC VAMC) Research and Development Committee and the Associate Chief of Staff for Research and Development (ACOS/R&D). All correspondence with the IRB was retained and forwarded to Pfizer.

Research Standards of the Study Conduct

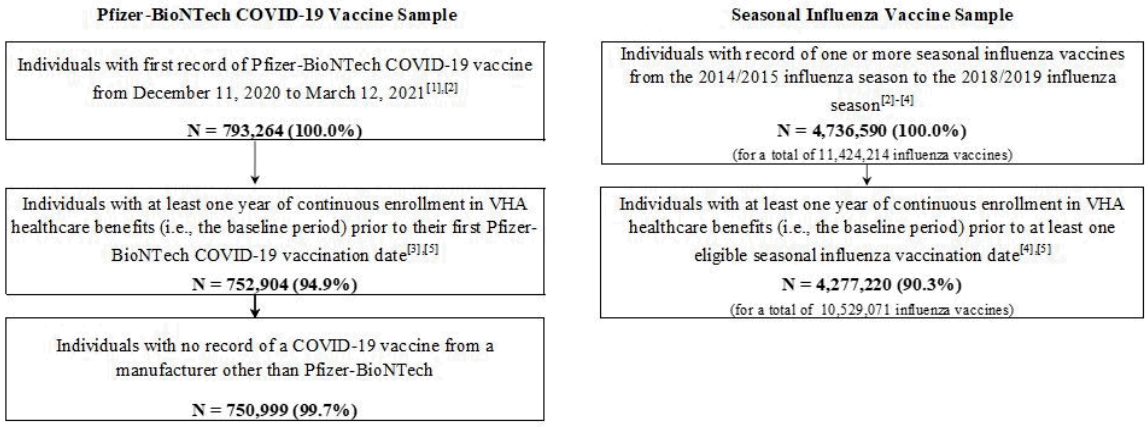
The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices

described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE),[48] Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA),[49] International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.[50]

10. RESULTS

Figure 1 presents a summary of the sample selection for this interim report. After applying all eligibility criteria, the Pfizer-BioNTech COVID-19 vaccine sample consisted of a total of 750,999 eligible individuals who received their first Pfizer-BioNTech COVID-19 vaccination from December 11, 2020 to March 12, 2021. The seasonal influenza vaccine sample consisted of a total of 4,277,220 eligible individuals who received up to five seasonal influenza vaccines from the 2014/2015 influenza season to the 2018/2019 influenza season (i.e., one vaccine per influenza season). Among the individuals in the seasonal influenza sample that satisfied the study eligibility criteria, a total of 10,529,071 seasonal influenza vaccines were observed (for an average of 2.46 seasonal influenza vaccines per individual).

Figure 1. Sample Selection of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine (from December 11, 2020 to March 12, 2021) or Seasonal Influenza Vaccine (from October 1, 2014 to May 31, 2019) in the VHA Database



Abbreviations: COVID-19, Coronavirus Disease 2019; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; VHA, Veterans Health Administration.

Notes:

[1] December 11, 2020 is the date when the FDA issued the EUA for Pfizer-BioNTech COVID-19 Vaccine; March 12, 2021 is the date of data cutoff.

[2] All data records (including vaccination records) observed prior to an individual's date of birth and after an individual's date of death were considered erroneous and were not included.

[3] Influenza seasons started on October 1 of one year and ended on May 31 of the next year (e.g., the 2014/2015 influenza season spanned October 1, 2014 - May 31, 2015).

[4] Individuals who received influenza vaccines in different seasons contributed multiple times to the seasonal influenza sample. For each individual, eligible influenza vaccines included those from influenza seasons in which the individual had only a single influenza vaccine record.

[5] Baseline period was defined as the one year prior to (and not including) the vaccination date.

Table 1 describes the month and year when the first Pfizer-BioNTech COVID-19 vaccines were administered in Pfizer-BioNTech COVID-19 vaccine sample and when the seasonal influenza vaccines were administered in the seasonal influenza vaccine sample. In the Pfizer-BioNTech COVID-19 vaccine sample, most individuals had their first dose of the vaccine in January and February 2021 (39.3% and 37.8%, respectively). In the seasonal influenza sample, the vaccines were distributed similarly across all influenza seasons, but with considerable variation with respect to the month of administration within each influenza season. Specifically, seasonal influenza vaccines administered in October and November accounted for approximately three quarters of all observed seasonal influenza vaccines, while the remaining months (December to May) accounted for only one quarter of all observed vaccines.

Table 1. Calendar Time Distribution for the Receipt of Pfizer-BioNTech COVID-19 Vaccine (from December 11, 2020 to March 12, 2021) or Seasonal Influenza Vaccine (from 2014/2015 to 2018/ 2019 influenza seasons) in the VHA Database

Calendar time	**Pfizer-BioNTech COVID-19 Vaccine Sample N = 750,999**	**Seasonal Influenza Vaccine Sample N = 4,277,220**	
	First Pfizer-BioNTech COVID-19 vaccine dose from December 11, 2020 to March 12, 2021 **N = 750,999**	*Most recent seasonal influenza vaccine from 2014/2015 to 2018/2019 influenza seasons* **N = 4,277,220**	*All seasonal influenza vaccines from 2014/2015 to 2018/2019 influenza seasons*[1] **N = 10,529,071**
Pfizer-BioNTech COVID-19 vaccine			
Month when vaccine was received, n (%)			
December 2020 (from December 11; 21 days)	12,880 (1.7)	-	-
Average number of individuals vaccinated per day[2]	613	-	-
January 2021 (31 days)	295,028 (39.3)	-	-
Average number of individuals vaccinated per day[2]	9,517	-	-
February 2021 (28 days)	283,780 (37.8)	-	-
Average number of individuals vaccinated per day[2]	10,135	-	-

Table 1. Calendar Time Distribution for the Receipt of Pfizer-BioNTech COVID-19 Vaccine (from December 11, 2020 to March 12, 2021) or Seasonal Influenza Vaccine (from 2014/2015 to 2018/ 2019 influenza seasons) in the VHA Database

Calendar time	**Pfizer-BioNTech COVID-19 Vaccine Sample N = 750,999**	**Seasonal Influenza Vaccine Sample N = 4,277,220**	
	First Pfizer-BioNTech COVID-19 vaccine dose from December 11, 2020 to March 12, 2021 **N = 750,999**	*Most recent seasonal influenza vaccine from 2014/2015 to 2018/2019 influenza seasons* **N = 4,277,220**	*All seasonal influenza vaccines from 2014/2015 to 2018/2019 influenza seasons*[1] **N = 10,529,071**
March 2021 (until March 12; 12 days)	159,311 (21.2)	-	-
Average number of individuals vaccinated per day[2]	13,276	-	-
Seasonal influenza vaccine			
Month when vaccine was received (regardless of year/influenza season) [3], n (%)			
October	-	2,419,380 (56.6)	5,898,719 (56.0)
November	-	886,076 (20.7)	2,269,903 (21.6)
December	-	381,404 (8.9)	1,005,034 (9.5)
January	-	285,623 (6.7)	672,769 (6.4)
February	-	159,617 (3.7)	373,925 (3.6)
March	-	94,714 (2.2)	208,398 (2.0)
April	-	36,244 (0.8)	73,480 (0.7)
May	-	14,162 (0.3)	26,843 (0.3)

Table 1. Calendar Time Distribution for the Receipt of Pfizer-BioNTech COVID-19 Vaccine (from December 11, 2020 to March 12, 2021) or Seasonal Influenza Vaccine (from 2014/2015 to 2018/ 2019 influenza seasons) in the VHA Database

Calendar time	**Pfizer-BioNTech COVID-19 Vaccine Sample N = 750,999**	**Seasonal Influenza Vaccine Sample N = 4,277,220**	
	First Pfizer-BioNTech COVID-19 vaccine dose from December 11, 2020 to March 12, 2021 **N = 750,999**	*Most recent seasonal influenza vaccine from 2014/2015 to 2018/2019 influenza seasons* **N = 4,277,220**	*All seasonal influenza vaccines from 2014/2015 to 2018/2019 influenza seasons*[1] **N = 10,529,071**
Influenza season when vaccine was received[3], n (%)			
2014/2015	-	328,509 (7.7)	2,005,782 (19.0)
2015/2016	-	391,729 (9.2)	2,066,378 (19.6)
2016/2017	-	478,070 (11.2)	2,018,667 (19.2)
2017/2018	-	796,513 (18.6)	2,155,845 (20.5)
2018/2019	-	2,282,399 (53.4)	2,282,399 (21.7)

Abbreviations: COVID-19, Coronavirus Disease 2019; SD, standard deviation.

Notes:

[1] Individuals who received influenza vaccines in different seasons contributed multiple times to the seasonal influenza sample. For each individual, eligible influenza vaccines included those from influenza seasons in which the individual had only a single influenza vaccine record.

[2] The average number of individuals vaccinated per day was based on all first dose Pfizer-BioNTech COVID-19 vaccinations received in a specific month divided by the total number of days in the specific month, irrespective of holidays and weekends.

[3] Influenza seasons started on October 1 of one year and ended on May 31 of the next year (e.g., the 2014/2015 influenza season spanned October 1, 2014 - May 31, 2015).

10.1. Descriptive Data

10.1.1. Baseline Characteristics

10.1.1.1. Pfizer-BioNTech COVID-19 Vaccine Sample

Table 2 and Table 3 describe the baseline demographic and clinical characteristics, respectively, of individuals who received Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccines. The mean age of the recipients of Pfizer-BioNTech COVID-19 vaccine from December 11, 2020 to March 12, 2021 was 69.8 years (median: 72.0 years) and the sample included 93.2% males and 64.2% White, non-Hispanics, with the largest proportion of individuals residing in the South (Table 2). Previous and existing smoking status was documented in the EMR records for 11.4% of individuals and 33.6% had a BMI ≥30 (obese and severe obesity) (Table 2). History of anaphylaxis/allergic reactions was rare (<1%) . The mean CCI score was 1.0 (median: 0.0), and 8.9% individuals were hospitalized in the year preceding Pfizer-BioNTech COVID-19 vaccine. Comorbidities affecting >10% of the sample included hypertension (57.8%), hyperlipidemia (49.1%), diabetes (30.8%), cardiovascular conditions (16.3%; excludes hypertension), cancer (12.5%), COPD/interstitial lung disease (12.0%), and chronic kidney disease/dialysis (11.7%). Approximately one-third of the individuals in the Pfizer-BioNTech COVID-19 vaccine sample were immunized for seasonal influenza between October 1, 2020 and the date of their first Pfizer-BioNTech COVID-19 vaccination. Non-seasonal immunizations were rare (<5% users) in the year before Pfizer-BioNTech COVID-19 vaccine, except for the Shingles vaccine which was received by 14.2% of the individuals in this sample (Table 3).

10.1.1.2. Seasonal Influenza Vaccine Sample

Baseline demographic and clinical characteristics of recipients of the seasonal influenza vaccine (at the time of their most recent seasonal influenza vaccine during the 2014/2015 through 2018/2019 influenza seasons) were generally similar to those of recipients of Pfizer-BioNTech COVID-19 vaccine sample at the time of their first dose (standardized difference <10%). However, a few exceptions with standardized differences ≥10% were noted, as summarized below. With respect to demographic characteristics, compared to the Pfizer-BioNTech COVID-19 vaccine sample, the seasonal influenza vaccine sample (assessed at the time of their most recent seasonal influenza vaccine) had a lower proportion of individuals between 65 and 74 years of age (33.8% vs. 41.2%; standardized difference 15.3%) and 75 years of age or older (25.9% vs. 31.6%; standardized difference 12.5%), a lower proportion of Blacks (15.4% vs. 20.7%; standardized difference 14.0%), and a higher proportion of individuals received care in the “Other” (i.e., Puerto Rico) VHA service area (1.1% vs. 0.2%; standardized difference 10.6%) (Table 2).Differences were also observed in the history of other immunizations. The Pfizer-BioNTech COVID-19 vaccine sample had comparable proportions of comorbidities compared to the seasonal influenza vaccine sample, with the exception of HBV, which was higher among seasonal influenza vaccine recipients (1.5% vs. 0.2%; standardized difference 13.6%). As compared to the Pfizer-BioNTech COVID-19 vaccine sample, the seasonal influenza vaccine sample had a higher proportion of individuals immunized with Tdap or Td, pneumococcal conjugate and pneumococcal

polysaccharide vaccines (7.5% vs. 3.5%, 7.7% vs. 0.8% and 6.7% vs. 4.3%, respectively; standardized differences 17.5%, 35.2% and 10.4%, respectively) and a lower proportion immunized for Shingles (4.8% vs. 14.2%; standardized difference 32.6%) (Table 3).

The baseline demographic and clinical characteristics assessed across all seasonal influenza vaccinations observed in the seasonal influenza vaccine sample, (i.e., N = 10,529,071 vaccinations) were numerically similar to those assessed at the time of the most recent seasonal influenza vaccine for individuals in this sample (e.g., mean age: 65.7 years vs. 65.4 years; males 93.1% vs. 92.6%; White, non-Hispanics: 70.6% vs. 69.6%; South VHA service area: 43.2 vs. 43.6% [Table 2]; smoking status: 13.1% vs. 12.4%; mean BMI: 30.1 vs. 29.9; history of anaphylaxis/allergic reactions: 0.7% vs. 0.6%; hospitalization in prior year: 8.9% vs 9.6%, mean CCI: 0.8 vs. 0.9, respectively [Table 3]).

Table 2. Baseline Demographic Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N = 750,999 individuals	**N = 4,277,220 individuals**		**N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Age (years), mean ± SD [median][4]	69.8 ± 12.3 [72.0]	65.4 ± 15.9 [68.4]	31.1%*	65.7 ± 14.5 [67.9]
Categorical, n (%)				
<16	0 (0.0)	1 (0.0)	0.1%	2 (0.0)
16–64	204,189 (27.2)	1,719,739 (40.2)	27.8%*	4,102,639 (39.0)
65–74	309,699 (41.2)	1,447,722 (33.8)	15.3%*	3,926,315 (37.3)
≥75	237,111 (31.6)	1,109,758 (25.9)	12.5%*	2,500,115 (23.7)

Table 2. Baseline Demographic Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N = 750,999 individuals	**N = 4,277,220 individuals**		**N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Sex, n (%)				
Male	700,029 (93.2)	3,959,260 (92.6)	2.5%	9,803,257 (93.1)
Female	50,969 (6.8)	317,955 (7.4)	2.5%	725,802 (6.9)
Unknown	1 (0.0)	5 (0.0)	0.0%	12 (0.0)
Race/ethnicity[5], n (%)				
White, non-Hispanic	481,895 (64.2)	2,975,670 (69.6)	11.5%*	7,434,793 (70.6)
Black	155,552 (20.7)	656,649 (15.4)	14.0%*	1,571,550 (14.9)
Hispanic ethnicity, any race	43,650 (5.8)	274,025 (6.4)	2.5%	662,903 (6.3)
Asian	7,212 (1.0)	44,223 (1.0)	0.7%	98,871 (0.9)
Native Hawaiian or Pacific Islander	5,196 (0.7)	32,487 (0.8)	0.8%	80,001 (0.8)
American Indian or Alaskan Native	3,903 (0.5)	28,289 (0.7)	1.8%	67,039 (0.6)
Two or more races	5,122 (0.7)	31,388 (0.7)	0.6%	74,922 (0.7)
Unknown	48,469 (6.5)	234,489 (5.5)	4.1%	538,992 (5.1)

Table 2. Baseline Demographic Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	Pfizer-BioNTech COVID-19 Vaccine Sample	Seasonal Influenza Vaccine Sample[2]	Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample	Seasonal Influenza Vaccine Sample[2]
	N = 750,999 individuals	N = 4,277,220 individuals		N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
VHA service area - US region[6], n (%)				
South	321,699 (42.8)	1,864,584 (43.6)	1.5%	4,551,767 (43.2)
Midwest	174,882 (23.3)	941,190 (22.0)	3.1%	2,418,497 (23.0)
West	149,526 (19.9)	867,589 (20.3)	0.9%	2,090,837 (19.9)
Northeast	103,061 (13.7)	551,532 (12.9)	2.4%	1,318,221 (12.5)
Other (i.e., Puerto Rico)	1,831 (0.2)	47,366 (1.1)	10.6%*	142,471 (1.4)
Unknown	0 (0.0)	4,959 (0.1)	4.8%	7,278 (0.1)

Abbreviations: SD, standard deviation; Std. Diff., standardized difference; US, United States; VHA, Veterans Health Administration.
Notes:
[1] Baseline period was defined as the one year prior to (and not including) the vaccination date.
[2] The findings presented for the seasonal influenza vaccine sample for all vaccines observed is informative given that this is the unit of analysis that will be used in the rapid-cycle safety signal analyses. Standardized differences between the seasonal influenza vaccine sample for all vaccines observed and the Pfizer-BioNTech COVID-19 vaccine sample were not calculated given that they rely on two separate units of analysis (i.e., at the vaccine level vs. at the individual level). Two individuals in the seasonal influenza vaccine sample did not have all information fully extracted at the time of the data lock. These two individuals are currently classified as "Unknown", "Missing", or "No" (i.e., as not having the specific characteristic) when data was unavailable. Their information will be updated in subsequent analyses.
[3] Individuals who received influenza vaccines in different seasons contributed multiple times to the seasonal influenza sample. For each individual, eligible influenza vaccines included those from influenza seasons in which the individual had only a single influenza vaccine record.
[4] Age on the date of Pfizer-BioNTech COVID-19 vaccination (for Pfizer-BioNTech COVID-19 vaccine recipients) or date of seasonal influenza vaccination (for active comparators), was reported.

Table 2. Baseline Demographic Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N = 750,999 individuals	**N = 4,277,220 individuals**		**N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*

[5] If multiple categories were noted in the data, individuals were classified as two or more races, with the exception of Hispanic ethnicity. If Hispanic ethnicity was recorded for any individual, they were classified as Hispanic. Individuals with both known and unknown race categories recorded in the data were classified into their known category.
[6] The region information associated with the most recent healthcare encounter prior to index date was used. Midwest included IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; Northeast included CT, ME, MA, NH, NJ, NY, PA, RI, VT; South included AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; West included AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY; Other included Puerto Rico.

Table 3. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N = 750,999 individuals	**N = 4,277,220 individuals**		**N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Smoking, n (%)	85,251 (11.4)	532,001 (12.4)	3.4%	1,379,342 (13.1)
BMI[4]				
BMI known within one-year baseline period, n (%)	296,073 (39.4)	3,018,783 (70.6)	65.9%*	7,571,414 (71.9)
BMI known within two-year baseline period, n (%)	558,911 (74.4)	3,548,170 (83.0)	21.0%*	8,865,904 (84.2)
BMI (kg/m^2), mean ± SD [median]	30.0 ± 5.9 [29.3]	29.9 ± 6.0 [29.2]	2.7%	30.1 ± 6.0 [29.4]
BMI category within two-year baseline period, n (%)				
Underweight (<18.5)	4,352 (0.6)	37,046 (0.9)	3.4%	71,330 (0.7)
Normal weight (18.5–<25)	98,857 (13.2)	681,747 (15.9)	7.9%	1,571,978 (14.9)
Overweight (25–<30)	203,416 (27.1)	1,269,378 (29.7)	5.8%	3,206,893 (30.5)
Obese (30–<40)	219,554 (29.2)	1,346,430 (31.5)	4.9%	3,464,843 (32.9)
Severe obesity (≥40)	32,732 (4.4)	213,569 (5.0)	3.0%	550,860 (5.2)
Unknown	192,088 (25.6)	729,050 (17.0)	21.0%*	1,663,167 (15.8)

Table 3. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N = 750,999 individuals	**N = 4,277,220 individuals**		**N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
History of anaphylaxis/allergic reactions, n (%)	6,755 (0.9)	24,739 (0.6)	3.7%	76,642 (0.7)
Previous anaphylaxis to vaccine component, n (%)	95 (0.0)	233 (0.0)	0.8%	430 (0.0)
History of hospitalizations				
Individuals with at least one hospitalization, n (%)	67,009 (8.9)	412,028 (9.6)	2.4%	934,257 (8.9)
Number of hospitalizations, mean ± SD [median]	0.2 ± 0.7 [0.0]	0.2 ± 0.7 [0.0]	2.1%	0.2 ± 0.6 [0.0]
CCI, mean ± SD [median]	1.0 ± 1.6 [0.0]	0.9 ± 1.5 [0.0]	8.3%	0.8 ± 1.4 [0.0]
Comorbidities, n (%)				
Hypertension	433,785 (57.8)	2,302,502 (53.8)	7.9%	5,941,440 (56.4)
Hyperlipidemia	368,981 (49.1)	2,037,504 (47.6)	3.0%	5,376,106 (51.1)
Diabetes mellitus (i.e., Type 1 or 2 diabetes)	231,010 (30.8)	1,200,288 (28.1)	5.9%	3,125,904 (29.7)
Cardiovascular conditions	122,304 (16.3)	618,950 (14.5)	5.0%	1,395,072 (13.2)
Cancer	93,790 (12.5)	418,659 (9.8)	8.6%	1,078,501 (10.2)

Table 3. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N = 750,999 individuals	**N = 4,277,220 individuals**		**N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
COPD/interstitial lung disease	90,343 (12.0)	543,528 (12.7)	2.1%	1,320,902 (12.5)
Chronic kidney disease/dialysis	87,644 (11.7)	427,083 (10.0)	5.4%	1,012,975 (9.6)
Neurological disease	51,180 (6.8)	298,956 (7.0)	0.7%	740,193 (7.0)
Liver disease	31,965 (4.3)	133,576 (3.1)	6.0%	297,481 (2.8)
Asthma	28,173 (3.8)	143,231 (3.3)	2.2%	372,693 (3.5)
Autoimmune disease	24,858 (3.3)	134,384 (3.1)	1.0%	401,245 (3.8)
VTE	15,927 (2.1)	70,287 (1.6)	3.5%	167,542 (1.6)
Bleeding diathesis or condition associated with prolonged bleeding	14,647 (2.0)	76,822 (1.8)	1.1%	181,649 (1.7)
HCV	11,925 (1.6)	91,774 (2.1)	4.1%	212,734 (2.0)
HIV	4,936 (0.7)	22,635 (0.5)	1.7%	63,363 (0.6)
Other immune deficiencies	3,955 (0.5)	18,354 (0.4)	1.4%	52,978 (0.5)
HBV	1,793 (0.2)	63,746 (1.5)	13.6%*	439,674 (4.2)
Sickle cell disease	592 (0.1)	3,356 (0.1)	0.0%	11,220 (0.1)
Solid organ transplant	124 (0.0)	289 (0.0)	0.9%	716 (0.0)
Down syndrome	0 (0.0)	88 (0.0)	0.6%	619 (0.0)

Table 3. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N = 750,999 individuals	**N = 4,277,220 individuals**		**N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*
Immunization history, n (%)				
Seasonal influenza vaccine (2020/2021 influenza season)[5]	283,162 (37.7)	-	-	-
Shingles (Herpes zoster recombinant and/or live)	106,441 (14.2)	203,315 (4.8)	32.6%*	486,479 (4.6)
Pneumococcal polysaccharide	32,542 (4.3)	286,451 (6.7)	10.4%*	759,757 (7.2)
Tdap or Td	26,338 (3.5)	319,721 (7.5)	17.5%*	878,651 (8.3)
Hepatitis B	6,522 (0.9)	35,223 (0.8)	0.5%	85,445 (0.8)
Pneumococcal conjugate	5,682 (0.8)	331,447 (7.7)	35.2%*	1,156,793 (11.0)
Hepatitis A	4,059 (0.5)	25,874 (0.6)	0.9%	58,301 (0.6)
MenACWY and MenB	676 (0.1)	5,230 (0.1)	1.0%	9,189 (0.1)
HPV	442 (0.1)	3,300 (0.1)	0.7%	5,437 (0.1)
Haemophilus influenza type b	194 (0.0)	890 (0.0)	0.3%	2,016 (0.0)
Chickenpox (Varicella)	134 (0.0)	1,567 (0.0)	1.1%	5,581 (0.1)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; ICD-9/10-CM: International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification; MenACWY, meningococcal conjugate; MenB, serogroup B meningococcal; SD, standard deviation; Std. Diff., standardized difference; Tdap, diphtheria, tetanus and (acellular) pertussis; Td, diphtheria and tetanus; VHA, Veterans Health Administration; VTE, venous thromboembolism.

Table 3. Baseline Clinical Characteristics of Individuals who Received Pfizer-BioNTech COVID-19 Vaccine or Seasonal Influenza Vaccine[1]

Characteristics	**Pfizer-BioNTech COVID-19 Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**	**Std. Diff. (%) Pfizer-BioNTech COVID-19 vs. Seasonal Influenza Vaccine Sample**	**Seasonal Influenza Vaccine Sample[2]**
	N = 750,999 individuals	**N = 4,277,220 individuals**		**N = 10,529,071 vaccines (average 2.46 vaccines/individual[3])**
	At first dose	*At most recent vaccine observed*		*At each vaccine observed*

Notes:
[1] Baseline period was defined as the one year prior to (and not including) the vaccination date.
[2] Two individuals in the seasonal influenza vaccine sample did not have all information fully extracted at the time of the data lock. These two individuals are currently classified as "Unknown", "Missing", or "No" (i.e., as not having the specific characteristic) when data was unavailable. Their information will be updated in subsequent analyses.
[3] Individuals who received influenza vaccines in different seasons contributed multiple times to the seasonal influenza sample. For each individual, eligible influenza vaccines included those from influenza seasons in which the individual had only a single influenza vaccine record.
[4] Most recent BMI record during the baseline period prior to vaccination date was included and was calculated based on individuals height and weight data as dividing weight in kilograms (kg) by height in meters (m) squared. Individuals with missing BMI or those with BMI <15 or >60 were categorized as "Unknown".
[5] Vaccinations that were received during the 2020/2021 influenza season between October 1, 2020 and the date of individuals' first Pfizer-BioNTech COVID-19 vaccination were included.

10.2. Vaccination utilization patterns

The month and year of first Pfizer-BioNTech COVID-19 vaccination from December 11 2020 to March 12 2021 were described in Table 1 in Section 10.1.

Table 4 presents additional details on Pfizer-BioNTech COVID-19 vaccine utilization. Individuals with at least one healthcare encounter in the VHA from December 11, 2020 to March 12, 2021 served as the expected number of individuals who would be eligible for Pfizer-BioNTech COVID-19 vaccine, as they had been actively receiving care through the VHA during the time period when Pfizer-BioNTech COVID-19 vaccine was available. Among 4,648,524 individuals with at least one healthcare encounter during

the period when administration of Pfizer-BioNTech COVID-19 vaccines was assessed for this first interim report (i.e., December 11, 2020 to March 12, 2021 assessment period), 793,264 individuals (17.1%) received at least one Pfizer-BioNTech COVID-19 vaccine dose. Among the latter, 752,904 (94.9%) individuals satisfied the one year of continuous enrollment in VHA healthcare benefits eligibility criteria, of which most (N = 750,999; 99.7%) only received COVID-19 vaccine(s) from Pfizer-BioNTech and a minority (N = 1,905; 0.3%) received COVID-19 vaccine(s) from both Pfizer-BioNTech and other manufacturer(s) (96.8% Moderna; 2.9% Johnson & Johnson; and 0.5% AstraZeneca [Table 4]).

Table 4. Vaccine Utilization Patterns among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine

Individuals with at least one healthcare encounter in the VHA from December 11, 2020 to March 12, 2021	**N = 4,648,524**
Individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine, n (%)	793,264 (17.1)
Individuals who satisfy the one year of continuous enrollment in VHA healthcare benefits sample eligibility criteria, n (% with at least one dose)	752,904 (94.9)
Individuals who received COVID-19 vaccine from Pfizer-BioNTech only, n (% with continuous enrollment)	750,999 (99.7)
Individuals who received COVID-19 vaccine from both Pfizer-BioNTech and another manufacturer[1], n (% with continuous enrollment)	1,905 (0.3)
Moderna, n (% with COVID-19 vaccine from multiple manufacturers)	1,844 (96.8)
Johnson & Johnson (Janssen), n (% with COVID-19 vaccine from multiple manufacturers)	55 (2.9)
AstraZeneca, n (% with COVID-19 vaccine from multiple manufacturers)	10 (0.5)

Abbreviations: COVID-19, Coronavirus Disease 2019; VHA, Veterans Health Administration.
Note:
[1] Individuals may have had multiple records of COVID-19 vaccines from other manufacturers, which could have been administered either before or after vaccination with Pfizer-BioNTech COVID-19 vaccine.

Table 5 describes the care setting where Pfizer-BioNTech COVID-19 vaccine doses were received, as well as the two-dose completion rate and timing of doses among Pfizer-BioNTech COVID-19 vaccine recipients. The most common care setting where the first and second doses of Pfizer-BioNTech COVID-19 vaccine were received was in outpatient clinics (85.3% and 84.8%, respectively). While only 64.6% individuals in the Pfizer-BioNTech COVID-19 vaccine sample received both doses during the December 11, 2020 to March 12, 2021 assessment period, most (94.1%) of those without a second dose had <21 days follow-up after the first dose (i.e., less than manufacturer recommended gap between doses) and are therefore considered censored. The two-dose completion rate among individuals who had ≥21 days of observation after the first dose was 95.3%. Of the 485,410 individuals who

completed two Pfizer-BioNTech COVID-19 vaccine doses, 70.2% received the second dose exactly 21 days after the first dose, as recommended per the product label. Extreme values for the gaps between the two doses (i.e., ≤16 days or ≥43 days) were observed for fewer than 1% of Pfizer-BioNTech COVID-19 vaccine recipients.

Table 5. Vaccine Doses among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine

Pfizer-BioNTech COVID-19 Vaccine Dose 1[1]	**N = 750,999**
Care setting where first Pfizer-BioNTech COVID-19 vaccine was received, n (%)	
Outpatient clinic	640,526 (85.3)
Inpatient ward	1,647 (0.2)
Pharmacy	2 (0.0)
Unknown[2]	108,824 (14.5)
Two-dose completion rate[3]	
All individuals with first dose, n	750,999
Individuals *with* two doses observed, n (%)	485,410 (64.6)
Individuals *without* two doses observed, n (%)	265,589 (35.4)
Individuals with first dose and ≥21 days of follow-up between the first dose and data cut-off, n	507,438
Individuals *with* two doses observed, n (%)	483,555 (95.3)
Individuals *without* two doses observed, n (%)	23,883 (4.7)
Pfizer-BioNTech COVID-19 Vaccine Dose 2[1]	**N = 485,410**
Care setting where second Pfizer-BioNTech COVID-19 vaccine was received, n (%)	
Care setting type for second dose	
Outpatient clinic	411,644 (84.8)
Inpatient ward	867 (0.2)
Pharmacy	0 (0.0)
Unknown[2]	72,899 (15.0)
Different settings for first and second doses, n (%)[4]	671 (0.1)
Time gap between first and second Pfizer-BioNTech COVID-19 vaccine doses (days)	

Table 5. Vaccine Doses among Individuals who Received Pfizer-BioNTech COVID-19 Vaccine

Pfizer-BioNTech COVID-19 Vaccine Dose 1[1]	**N = 750,999**
Mean ± SD	21.3 ± 2.7
Median [IQR]	21.0 [21.0, 21.0]
Categorical, n (%)[5]	
≤16 days	2,494 (0.5)
17-20 days	63,809 (13.1)
21 days	340,789 (70.2)
22-27 days	62,161 (12.8)
28 days	4,833 (1.0)
29-35 days	8,657 (1.8)
36-42 days	1,878 (0.4)
≥43 days	789 (0.2)

Abbreviations: CDC: US Centers for Disease Control and Prevention; COVID-19, Coronavirus Disease 2019; IQR, interquartile range; SD, standard deviation.

Notes:

[1] Individuals' first record of Pfizer-BioNTech COVID-19 vaccination was categorized as the first dose. Among individuals with only two Pfizer-BioNTech COVID-19 vaccination records, the second vaccination record was categorized as the second dose. Among individuals with more than two records of Pfizer-BioNTech COVID-19 vaccination, the vaccination date closest to 21 days after the first vaccination dose was categorized as the second dose. Among the 750,999 individuals in the Pfizer-BioNTech COVID-19 vaccine sample, 1,111 (0.1%) individuals had more than two records of Pfizer-BioNTech COVID-19 vaccinations.

[2] This category included individuals with vaccination records without care setting information available or individuals who had documentation of receiving one vaccination dose in several different care settings so the care setting could not be determined.

[3] Individuals who received their first COVID-19 vaccine dose in the three weeks prior to March 12, 2021 may not have had sufficient follow-up time for their second vaccine dose to be observed.

[4] Individuals who received one of their two vaccine doses in an unknown setting were excluded from this count.

[5] According to the CDC's Interim Clinical Considerations for Use of COVID-19 Vaccines, the second dose of Pfizer-BioNTech COVID-19 vaccine should be administered as close to the recommended 21 days after the first dose as possible, but not earlier than 21 days. However, second doses administered within a grace period of 4 days earlier than the recommended date for the second dose are still considered valid. If it is not feasible to adhere to the recommended interval and a delay in vaccination is unavoidable, the second dose of Pfizer-BioNTech COVID-19 vaccine may be administered up to 6 weeks (42 days) after the first dose.[51]

10.3. Safety signal analyses

This interim report focused on baseline demographic and clinical characteristics among individuals who received Pfizer-BioNTech COVID-19 vaccine or seasonal influenza vaccine, and vaccine utilization patterns among individuals who received Pfizer-BioNTech COVID-19 vaccine. Results obtained from the real-time, rapid-cycle safety signal analyses for Pfizer-BioNTech COVID-19 vaccine have not yet been initiated and thus are not included in this first interim report.

10.4. Main results

This interim report focused on baseline demographic and clinical characteristics among individuals who received Pfizer-BioNTech COVID-19 vaccine or seasonal influenza vaccine, and vaccine utilization patterns among individuals who received Pfizer-BioNTech COVID-19 vaccine. Results obtained from the real-time, rapid-cycle safety signal analyses for Pfizer-BioNTech COVID-19 vaccine have not yet been initiated due to the short time interval between the data receipt date and the interim report date, and thus are not included in this first interim report.

10.5. Other analyses

None.

10.6. Adverse events / adverse reactions

This interim report relies solely on structured data. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met. For additional information regarding adverse event management and reporting, please see Section 11 of the study protocol (Appendix 2).

11. DISCUSSION

11.1. Summary of key results

This interim report based on the first three months of the post-EUA experience of Pfizer-BioNTech COVID-19 vaccine in VHA included 750,999 individuals who received Pfizer-BioNTech COVID-19 vaccine from December 11, 2020 through March 12, 2021. The comparator cohort included 4,277,220 individuals who received the seasonal influenza vaccine from the 2014/2015 influenza season to the 2018/2019 influenza season. In the Pfizer-BioNTech COVID-19 vaccine sample, 72.8% were at least 65 years of age, 93.2% were males and 64.2% were white, non-Hispanics. While the distribution of sex was comparable between the two samples (standardized difference 2.5%), individuals in the Pfizer-BioNTech COVID-19 vaccine sample were older than those in the seasonal influenza vaccine sample (standardized difference 31.1%). These results are consistent with the CDC COVID-19 vaccine distribution recommendations, given that the current report covers only the first three months of Pfizer-BioNTech COVID-19 vaccine roll out in the VHA, when older individuals were prioritized for vaccination. The proportion of individuals who were at least 65 years of age in the seasonal influenza vaccine sample (59.7%) is consistent with that reported by Luo et al. (2021) in the overall VHA population (59.7%).[52] As the COVID-19

vaccination continues to be expanded to younger individuals, it is expected that the age gap will narrow between the Pfizer-BioNTech COVID-19 vaccine sample and seasonal influenza sample. Nevertheless, if differences in ages between samples persist, they will be accounted for in the safety signal analyses (e.g., by conducting age-stratified safety analyses or using standardization methods to age-adjust the expected rates for the adverse events of interest extracted from the seasonal influenza sample).

While standardized differences for white non-Hispanic and Black categories indicated imbalance for race/ethnicity between the Pfizer-BioNTech COVID-19 vaccine sample and the seasonal influenza vaccine sample, the overall race/ethnicity breakdown was largely similar in the two samples (White, non-Hispanic: 64.2% vs 69.6%, standardized difference 11.5%; Black: 20.7% vs 15.4%, standardized difference 14.0%; all other race/ethnicity categories: standardized differences <10%).

A recently published systematic review reported that the COVID-19 pandemic decreased healthcare resource utilization (HRU) by approximately one-third.[53] The reduction in HRU and enhanced use of telehealth in the US during the COVID-19 pandemic could have contributed to the higher proportion of individuals with unknown BMI in the Pfizer-BioNTech COVID-19 vaccine sample in the one-year period prior to vaccination compared to the seasonal influenza vaccine sample (standardized difference: 65.9%), as weight and height cannot be measured in telehealth settings.[54] Therefore, a two-year baseline period was implemented for BMI, which yielded comparable proportions of obese and severe obesity categorizations for the two samples (29.2% and 4.4% for the Pfizer-BioNTech COVID-19 vaccine sample and 31.5% and 5.0% for the seasonal influenza samples, respectively).

Among the estimated 4.6 million individuals with at least one healthcare encounter during the December 11, 2020 to March 12, 2021 assessment period, the Pfizer-BioNTech COVID-19 vaccination rate (at least one dose) was 17.1%. While this proportion is lower than the CDC-reported proportion of individuals greater than 18 years of age in the US who received at least one dose of any COVID-19 vaccine up until March 12, 2021 in the US (25.5%),[55] in the current study only Pfizer-BioNTech COVID-19 was considered whereas the US statistics included any COVID-19 vaccine. The two-dose completion rate among individuals who had ≥21 days of observation after the first dose was 95.3%. The majority of individuals in the VHA system received Pfizer-BioNTech COVID-19 vaccination in the outpatient setting (84.8%). Most individuals in the VHA system who received two doses of Pfizer-BioNTech COVID-19 vaccine (70.2%) received the second dose precisely 21 days following the first dose, which is consistent with the manufacturer's guidelines for the Pfizer-BioNTech COVID-19 vaccine schedule.

11.2. Limitations

While the VHA CDW provides a range of benefits, including its comprehensive structure, large number of variables, and electronic accessibility, there may be gaps in the data since individuals may receive healthcare services outside of VHA facilities that are not recorded in the CDW. For example, veterans with secondary insurance (e.g., TRICARE through Department of Defense, Medicare for those aged 65 years of age or older, or Medicaid for

low socioeconomic group) may receive health care services outside of VHA facilities. One study on VHA enrollees in seven states found that of all individuals admitted to VHA hospitals in 2007, one fifth also had a non-VHA hospitalization during that year.[35] 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] As such, if individuals received Pfizer-BioNTech COVID-19 vaccine outside of a VHA facility, this information would not be captured in the data. Similarly, individuals might 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 descriptive analysis. Hence, data on vaccination status may be incomplete. However, this limitation will be addressed in future study reports by examining subgroups of individuals who receive care regularly at VHA facilities, as well as those with VA priority group 1 status, to minimize healthcare services rendered outside of the VHA system. Results from the overall VHA group will be compared to these subgroups with more complete data to examine the extent to which missingness may bias the study findings. Linkage to Medicare claims data may be sought or the base study population may be further restricted to the subgroup of individuals who utilized VHA services regularly.

The reduction in HRU during the COVID-19 pandemic may also impact the detection of safety events of interest and comorbidities identified in the outpatient setting. Given that none of the safety events of interest examined in this study will be identified only in the outpatient setting, the potential for underestimating outcomes in the Pfizer-BioNTech COVID-19 sample is limited. However, prevalence of some underlying comorbidities identified in the outpatient setting may be underestimated in the Pfizer-BioNTech COVID-19 sample.

As with any large EMR or claims database, occasional data entry errors may result in misclassification of exposures, outcomes, or covariates for some individuals. However, these are expected to only affect a minority of individuals. Furthermore, intensive quality checks will be performed in the signal evaluation phase for safety events of interest for which a signal is detected in the signal detection phase.

The active comparator study design requires the selection of a historical comparator sample to calculate the expected rates for each of the safety events of interest. Similar to prior studies that conducted post-vaccination safety surveillance (e.g., for H1N1), this study will use seasonal influenza recipients as historical active comparators.[46,57] The current study will rely on individuals who received the seasonal influenza vaccine in the five prior seasons in the VHA system to calculate the expected rates for each of the safety events of interest. While seasonal influenza vaccine recipients were deemed to be an appropriate comparison group due to similarities in preventative healthcare behaviors and the large number of vaccine recipients each year, differences in secular trends, coding practices or diagnostic techniques could lead to potential bias.[46] To address this, a multivariate Poisson regression analysis will be conducted as part of signal evaluation to account for potential baseline differences between Pfizer-BioNTech COVID-19 and seasonal influenza vaccinees. Stratified analyses will also be used to address confounding and possible heterogeneity in the risk of adverse events across specific populations of interest.

11.3. Generalizability

The VHA population included in this interim report is largely male and elderly. Therefore, this population may not be generalizable to younger men or to women and children in the US. These findings may also not be generalizable beyond individuals enrolled in the VHA, who were eligible to receive the initial distribution of Pfizer-BioNTech COVID-19 vaccine.[17] Further, the results of this study are specific to Pfizer-BioNTech COVID-19 vaccine and are not generalizable to COVID-19 vaccines from a manufacturer other than Pfizer-BioNTech.

11.4. Interpretation

This interim report describes sample selection, baseline characteristics and vaccine utilization patterns among individuals who received Pfizer-BioNTech COVID-19 vaccine within the VHA system and a historical sample of individuals who received seasonal influenza vaccine before the COVID-19 pandemic. Most baseline characteristics were well-balanced between the study samples, suggesting that seasonal influenza vaccine from the five prior seasons is an appropriate active comparator for the safety surveillance of Pfizer-BioNTech COVID-19 vaccine.

Since CDC's COVID-19 vaccine rollout recommendations gave priority to individuals 65 years and older in phases 1a through 1c, the higher proportion of older individuals with Pfizer-BioNTech COVID-19 vaccine in the current sample was expected.[58] This distribution of age will likely change in subsequent interim reports as younger individuals become eligible to be vaccinated in the VHA. The higher proportion of men in this study was also expected, as the VHA population is predominantly male (approximately 90%). The lower proportion of individuals from Puerto Rico in the Pfizer-BioNTech COVID-19 vaccine sample can be attributed to delays in vaccine distribution to Puerto Rico, which was delayed by one month as compared to other VHA service areas, with access to COVID-19 vaccinations starting in January 2021 rather than December 2020.[59]

Recipients of Pfizer-BioNTech COVID-19 vaccine from December 11, 2020 to March 12, 2021 had a higher prevalence of the Shingles vaccine during the one-year prior to Pfizer-BioNTech COVID-19 vaccination, as compared to the seasonal influenza comparator sample. Given the higher proportion of older individuals in the Pfizer-BioNTech COVID-19 vaccine sample, the higher proportion of individuals with concurrent Shingles immunization is not surprising, as the Shingles vaccine is recommended for adults 50 years of age or older.[60] Conversely, seasonal influenza vaccinees had a higher prevalence of Tdap or Td and pneumococcal conjugate vaccines during the one-year prior to seasonal influenza vaccination, as compared to the Pfizer-BioNTech COVID-19 sample. These differences are likely explained by changes over time in immunization guidelines for the elderly.[61,62]

The demographic and clinical characteristics of the Pfizer-BioNTech COVID-19 vaccine sample were consistent with existing data in the US population, which suggests that vaccine administration within the VHA system aligned with CDC's vaccine rollout recommendations to prioritize the elderly population and individuals with underlying medical conditions.[58]

12. OTHER INFORMATION

While this interim report focused on baseline demographic and clinical characteristics among individuals who received Pfizer-BioNTech COVID-19 vaccine or seasonal influenza vaccine, and vaccine utilization patterns among individuals who received Pfizer-BioNTech COVID-19 vaccine, results for the real-time, rapid-cycle safety signal analyses are forthcoming in the next report. The second interim report, to be submitted in December 2021, will include updated baseline descriptive data (with the additionally accrued data), updated vaccination utilization patterns, and results from the safety signal analysis, which will come from both the signal detection and safety evaluation analyses. Additionally, findings from the signal verification phase are expected to be included in the third interim report, to be submitted in June 2022.

13. CONCLUSIONS

Among the 750,999 eligible VHA enrollees who received at least one dose of Pfizer-BioNTech COVID-19 vaccine from December 11, 2020 to March 12, 2021, 64.6% were administered two doses, with the two-dose vaccination completion rate among individuals with ≥21 days of observation after the first dose was 95.3%. Most individuals in the VHA received Pfizer-BioNTech COVID-19 vaccine in the outpatient setting (84.8%). The majority of individuals who received two doses of the vaccine received the second dose precisely 21 days following the first dose (70.2%). Very few individuals (N = 1,905; 0.3%) of VHA enrollees received mixed doses of COVID-19 vaccines - receiving a different vaccine brand as a second dose from the first dose of Pfizer-BioNTech COVID-19 vaccine. Overall, Pfizer-BioNTech COVID-19 and seasonal influenza vaccinees within the VHA system were comparable based on both baseline demographic and clinical characteristics, supporting the use of seasonal influenza vaccinees from the five prior seasons as an appropriate active comparator group for the safety surveillance of Pfizer-BioNTech COVID-19 vaccine.

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15. LIST OF SOURCE TABLES AND FIGURES

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

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 ICD-10-CM codes:

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		• 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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

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:

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
vaccine component		• 999.42, Anaphylactic reaction due to vaccination • V14.7, Personal history of allergy to serum or vaccine ICD-10-CM codes: • T80.52xx, Anaphylactic reaction due to vaccination, initial encounter, subsequent encounter and sequela • Z28.04, Immunization not carried out because of patient allergy to vaccine or component • Z88.7, Allergy status to serum and vaccine
History of hospitalizations	Dichotomous variable; Continuous variable	Defined by having any hospitalizations (dichotomous) and number of hospitalizations (continuous)
Charlson Comorbidity Index (CCI)[32]	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 • 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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		• 416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8, Chronic pulmonary disease • 446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x, Rheumatic disease • 531.x–534.x, Peptic ulcer disease • 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7, Mild liver disease • 250.0–250.3, 250.8, 250.9, Diabetes without chronic complication • 250.4–250.7, Diabetes with chronic complication • 334.1, 342.x, 343.x, 344.0–344.6, 344.9, Hemiplegia or paraplegia • 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x, Renal disease • 140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6, Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin • 456.0–456.2, 572.2–572.8, Moderate or severe liver disease • 196.x–199.x, Metastatic solid tumor • 042.x–044.x, Acquired immunodeficiency syndrome (AIDS)/Human immunodeficiency virus (HIV) ICD-10-CM codes:

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		E13.1x, E13.6x, E13.6xx, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9, Diabetes without chronic complication • E10.2x–E10.5x, E10.2xx–E10.5xx, E10.7, E11.2x–E11.5x, E11.2xx–E11.5xx, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5x, E13.7, E14.2–E14.5, E14.7, Diabetes with chronic complication • G04.1, G11.4, G80.1, G80.2, G81.x, G81.xx, G82.x, G82.xx, G83.0, G83.1–G83.3, G83.1x–G83.3x, G83.4, G83.9, Hemiplegia or paraplegia • I12.0, I13.1x, N03.2–N03.7, N05.2–N05.7, N18.x, N19, N25.0, Z49.0x–Z49.3x, Z94.0, Z99.2, Renal disease • C00–C75, C00.x–C75.x, C00.xx–C75.xx (excluding C44, C44.x and C44.xx), C7A., C7A.x, C7A.xx, C7B., C7B.x, C7B.xx, C76–C80, C76.x–C80.x, C76.xx–C80.xx, C81–C96, C81.x–C96.x, C81.xx–C96.xx, Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin • I85.0, I85.9, I86.4, I98.2, K70.4x, K71.1x, K72.1x, K72.9x, K76.5, K76.6, K76.7, Moderate or severe liver disease • C77.x–C80.x, C77.xx–C80.xx, Metastatic solid tumor • B20, B97.35, AIDS/HIV
Comorbidities	Categorical variable: • Autoimmune disease	Autoimmune disease (immunocompromised state [weakened

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
	• 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	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 • 446.5, Giant cell arteritis • 710.2, Sicca syndrome ICD-10-CM codes: • D69.3, Immune thrombocytopenic purpura • E06.3, Autoimmune thyroiditis • G35, MS

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		• 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: 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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		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 of bone, connective tissue, skin, and breast o 179.x–189.x, Malignant neoplasm of genitourinary organs

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 190.x–199.x, Malignant neoplasm of other unspecified sites ○ 200.xx–208.xx, Malignant neoplasm of lymphatic and hematopoietic tissue ○ 209.0x–209.3x, Malignant neuroendocrine tumors ○ 230.x–234.x, Carcinoma in situ of digestive organs • ICD-10-CM codes: ○ C00–C75, C00.x–C75.x, C00.xx–C75.xx, C7A., C7A.x, C7A.xx, C7B., C7B.x, C7B.xx, Malignant neoplasms, stated or presumed to be primary (of specified sites), and certain specified histologies, except neuroendocrine, and of lymphoid, hematopoietic and related tissue ○ C76–C80, C76.x–C80.x, C76.xx–C80.xx, Malignant neoplasms of ill-defined, other secondary and unspecified sites ○ C81–-C96, C81.x–C96.x, C81.xx–

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		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, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810,

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		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 o 582, 582.x, 582.xx, Chronic glomerulonephritis o 583, 583.x, 583.xx, Nephritis and nephropathy, not

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		specified as acute or chronic o 591, Hydronephrosis o 593.3, Stricture or kinking of ureter o 592, Calculus of kidney o 592.1, Calculus of ureter o 590.9, Infection of kidney, unspecified o 584.x, Acute kidney failure o 585.x, Chronic kidney disease o 588.x, 588.xx, Disorders resulting from impaired renal function o 587, Renal sclerosis, unspecified o 753.1x, Cystic kidney disease o 753.2, 753.2x, Obstructive defects of renal pelvis and ureter • ICD-10-CM codes: o D59.3, Hemolytic-uremic syndrome o I12.x, Hypertensive chronic kidney disease o I13.x, I13.xx, Hypertensive heart and chronic kidney disease o I70.1, Atherosclerosis of renal artery

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		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 o N25.x, N26.x, N25.xx, Other disorders of kidney and ureter

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 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: ○ J41.x Simple and mucopurulent chronic bronchitis ○ J42, Unspecified chronic bronchitis

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 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: ○ D57, D57.x, D57.xx, D57.xxx, Sickle-cell disorders HBV: • ICD-9-CM codes:

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 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 ○ 70.71, Unspecified viral hepatitis C with hepatic coma ○ 70.54, Chronic hepatitis C without mention of hepatic coma

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition

		• ICD-10-CM codes:
		  o B18.2, Chronic viral hepatitis C
		  o B19.2x, Unspecified viral hepatitis C
		HIV:
		• ICD-9-CM codes:
		  o 42, HIV disease
		  o 79.53, HIV type 2
		• ICD-10-CM codes:
		  o B20, HIV disease
		  o B97.35, HIV type 2 as the cause of diseases classified elsewhere
		Hyperlipidemia
		• ICD-9-CM codes:
		  o 272.0x, Pure hypercholesterolemia
		  o 272.1x, Pure hyperglyceridemia
		  o 272.2x, Mixed hyperlipidemia
		  o 272.4x, Hyperlipidemia, NOS
		• ICD-10-CM codes:
		  o E78.0–E78.5, E78.0x, E78.4x, Hyperlipidemia
		Hypertension:
		• ICD-9-CM codes:
		  o 401.1, Benign essential hypertension
		  o 401.9, Essential hypertension, NOS
		  o 405.1, Benign secondary hypertension

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 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 ○ K74.x, K74.xx, Fibrosis and cirrhosis of liver

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 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 symptoms or

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 37.51, Heart transplantation ○ 33.51, Unilateral lung transplantation ○ 33.52, Bilateral lung transplantation ○ 46.97, Transplant of intestine ○ 50.59, Other transplant of intestine ○ 52.82, Homotransplant of pancreas ○ 55.69, Other kidney transplant • ICD-10-PCS codes: ○ 02YA0Z0, 02YA0Z1, Transplantation of heart ○ 0BYC0Z0, 0BYC0Z1, 0BYD0Z0, 0BYD0Z1, 0BYF0Z0, 0BYF0Z1, 0BYG0Z0, 0BYG0Z1, 0BYH0Z0, 0BYH0Z1, 0BYJ0Z0, 0BYJ0Z1, 0BYK0Z0, 0BYK0Z1, 0BYL0Z0, 0BYL0Z1, 0BYM0Z0, 0BYM0Z1, Transplantation of lung

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 0DY60Z0, 0DY60Z1, Transplantation of stomach ○ 0DY80Z0, 0DY80Z1, Transplantation of small intestine ○ 0DYE0Z0, 0DYE0Z1, Transplantation of large intestine ○ 0FY00Z0, 0FY00Z1, Transplantation of liver ○ 0FYG0Z0, 0FYG0Z1, Transplantation of pancreas ○ 0TY00Z0, 0TY00Z1, 0TY10Z0, 0TY10Z1, Transplantation of kidney 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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 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) • Shingles (Herpes Zoster recombinant and/or live) • Human papillomavirus (HPV) • Pneumococcal conjugate • Pneumococcal polysaccharide • Hepatitis A • Hepatitis B • Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB) • Haemophilus influenza type b	Seasonal influenza: • See Table 15.3 Tetanus diphtheria and pertussis (Tdap or Td): • CPT codes: ○ 90714, Tetanus and diphtheria toxoids adsorbed (Td), preservative free, when administered to individuals 7 years or older, for intramuscular use ○ 90715, Tdap administered to individuals 7 years or older, for intramuscular use ○ 90718, Tetanus and diphtheria toxoids (Td) adsorbed when administered to individuals 7 years or older, for intramuscular use Chickenpox (Varicella) • CPT codes: ○ 90396, Varicella-zoster immune globulin, human, for intramuscular use ○ 90716, Varicella virus vaccine, live, for subcutaneous use Shingles (Herpes Zoster recombinant and/or live) • CPT codes:

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 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 ○ 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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		○ 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 ○ 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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

Variable	Description	Operational definition
		immunosuppressed patient dosage, 3 dose schedule, for intramuscular use o 90743, Hepatitis B vaccine (HepB), adolescent, 2 dose schedule, for intramuscular use o 90744, Hepatitis B vaccine (HepB), pediatric/adolescent dosage, 3 dose schedule, for intramuscular use o 90745, Hepatitis B vaccine, adolescent/high risk infant dosage, for intramuscular use o 90746, Hepatitis B vaccine (HepB), adult dosage, 3 dose schedule, for intramuscular use o 90747, Hepatitis B vaccine (HepB), dialysis or immunosuppressed patient 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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

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

Table 15.1. Operational Definitions of Demographic and Clinical Characteristics

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

*BMI was assessed within the one-year and two-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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Table 15.2. Operation 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		
Generalized convulsions/seizures[44,57]	• 345, Epilepsy and recurrent seizures • 780.3, Convulsions • 780.31, Febrile convulsions (simple), unspecified • 780.39, Other convulsions • 780.32, Complex febrile convulsions	• 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 • 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

Table 15.2. Operation 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 • G40.111, 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 • 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

Table 15.2. Operation 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)*:
		• G40.211, 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, intractable, without status epilepticus • G40.309, Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus • G40.311, Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus • G40.401, Other generalized epilepsy and epileptic syndromes, not intractable, with status epilepticus • G40.409, Other generalized epilepsy and epileptic syndromes,

Table 15.2. Operation 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)*:
		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 • G40.802, Other epilepsy, not intractable, without status epilepticus • G40.804, Other epilepsy, intractable, without status epilepticus

Table 15.2. Operation 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 • G40.901, Epilepsy, unspecified, not intractable, with status epilepticus • G40.909, Epilepsy, unspecified, not intractable, without status epilepticus • R56.00, Simple febrile convulsions • R56.01, Complex febrile convulsions • R56.9, Unspecified convulsions
Guillain-Barré syndrome (GBS)[44,57]	• 357.0, Guillain-Barre syndrome	• G61.0, Guillain-Barre syndrome

Table 15.2. Operation 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)*:
Aseptic meningitis[29]	• 322.1, Eosinophilic meningitis • 322.9, Meningitis, unspecified	• G03.8, Meningitis due to other specified causes • G03.9, Meningitis, unspecified
Encephalitis/encephalomyelitis[44,57]	• 323.5, Encephalitis, myelitis, and encephalomyelitis following immunization procedures • 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

Table 15.2. Operation 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)*:
Other acute demyelinating diseases (excluding those limited as separate outcomes)[44,57]	• 341.0, Neuromyelitis optica • 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)[44,57]	• 341.2, Acute (transverse) myelitis	• G37.3, Acute transverse myelitis in demyelinating disease of central nervous system
Multiple sclerosis (MS)[44,57]	• 340, Multiple sclerosis	• G35, Multiple sclerosis
Optic neuritis (ON)[44,57]	• 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

Table 15.2. Operation 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)*:
		• H46.02, 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 • H46.3, Toxic optic neuropathy • H46.8, Other optic neuritis • H46.9, Unspecified optic neuritis
Bell's palsy[44,57]	• 351.0, Bell's Palsy • 351.8, Other facial nerve disorders • 351.9, Facial nerve disorder, unspecified	• G51.0, Bell's palsy • G51.8, Other disorders of facial nerve • G51.9, Disorder of facial nerve, unspecified
Immunologic		
Anaphylaxis[44,57]	• 999.4, Anaphylactic shock due to serum not elsewhere specified	• T78.2XXA, Anaphylactic shock, unspecified, initial encounter

Table 15.2. Operation 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)*:
	• 995.0, Other anaphylactic reaction	• T80.52XA, Anaphylactic reaction due to vaccination, initial encounter
Vasculitides (excluding those limited as separate outcomes)[23,24]	• 136.1, Behcet's disease • 273.2, Other paraproteinemias • 287.0, Allergic purpura (Henoch-Schonlein Purpura) • 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	• D69.0, Allergic purpura (Henoch-Schonlein Purpura) • D89.1, Cryoglobulinemia • 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

Table 15.2. Operation 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)*:
Arthritis and arthralgia/joint pain (not osteoarthritis or traumatic arthritis)[29]	• 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 • M02.232, Postimmunization arthropathy, left wrist • M02.239, Postimmunization arthropathy, unspecified wrist • M02.241, Postimmunization arthropathy, right hand

Table 15.2. Operation 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)*:
		• M02.242, 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 • M02.271, Postimmunization arthropathy, right ankle and foot • M02.272, Postimmunization arthropathy, left ankle and foot • M02.279, Postimmunization arthropathy, unspecified ankle and foot

Table 15.2. Operation 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)*:
		• M02.28, Postimmunization arthropathy, vertebrae • M02.29, Postimmunization arthropathy, multiple sites • M15.8, Other polyosteoarthritis • M15.9, Polyosteoarthritis, unspecified • M19.9, Unspecified osteoarthritis, unspecified site
Multisystem inflammatory syndrome in adults (MIS-A)[29]	N/A	≥1 diagnosis code for COVID-19 and ≥1 diagnosis code for other specified systemic involvement of connective tissue or multisystem inflammatory syndrome up to 8 weeks 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

Table 15.2. Operation 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)*:
Kawasaki disease (KD)[29]	• 446.1, Acute febrile mucocutaneous lymph node syndrome [MCLS]	• M30.3, Mucocutaneous lymph node syndrome [Kawasaki]
Fibromyalgia[29]	• 729.1, Myalgia and myositis, unspecified	• M79.7, Fibromyalgia
Autoimmune thyroiditis[29]	N/A	• E06.3, Autoimmune thyroiditis
Cardiac		
Myocarditis[44,57]	• 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
Pericarditis[44,57]	• 420.90, Acute pericarditis, unspecified • 420.91, Acute idiopathic pericarditis • 420.99, Other acute pericarditis	• I30.0, Acute nonspecific idiopathic pericarditis • I30.1, Infective pericarditis

Table 15.2. Operation 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)*:
	• 420.0, Acute pericarditis in diseases classified elsewhere • 074.21, Coxsackie pericarditis	• I30.8, Other forms of acute pericarditis • I30.9, Acute pericarditis, unspecified • I32, Pericarditis in diseases classified elsewhere • B33.23, Viral pericarditis
Acute myocardial infarction (AMI)[29]	• 410.01, Acute myocardial infarction of anterolateral wall, initial episode of care • 410.11, Acute myocardial infarction of other anterior wall, initial episode of care • 410.21, Acute myocardial infarction of inferolateral wall, initial episode of care • 410.31, Acute myocardial infarction of inferoposterior wall, initial episode of care • 410.41, Acute myocardial infarction of other inferior wall, initial episode of care • 410.51, Acute myocardial infarction of other lateral wall, initial episode of care • 410.61, True posterior wall infarction, initial episode of care	• I21.01, ST elevation (STEMI) myocardial infarction involving left main coronary artery • 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

Table 15.2. Operation 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)*:
	• 410.71, 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	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 • 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

Table 15.2. Operation 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)*:
		• I22.1, Subsequent ST elevation (STEMI) myocardial infarction of inferior wall • I22.2, Subsequent non-ST elevation (NSTEMI) myocardial infarction • I22.8, Subsequent ST elevation (STEMI) myocardial infarction of other sites • I22.9, Subsequent ST elevation (STEMI) myocardial infarction of unspecified site
Hematologic		
Thrombocytopenia[29]	• 287.31, Immune thrombocytopenic purpura • 287.39, Other primary thrombocytopenia	• D69.3, Immune thrombocytopenic purpura
Disseminated intravascular coagulation (DIC) [29]	• 286.6, Defibrination syndrome	• D65, Disseminated intravascular coagulation [defibrination syndrome]

Table 15.2. Operation 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)*:
COVID-19	Note that ICD-9-CM codes are not included for COVID-19 related endpoints as all must be identified in 2020 or later. To be counted as a COVID-19 related endpoint, the diagnosis code for each safety event of interest must be identified in combination with an inpatient diagnosis for COVID-19; in addition, COVID-19 related safety events of interest will only be evaluated using data from 2020 onward using the SCRI design.	
Severe COVID-19 disease[29]	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
Microangiopathy[29]	N/A	• M31.1, Thrombotic microangiopathy
Heart failure and cardiogenic shock[29]	N/A	• 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

Table 15.2. Operation 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)*:
		• I50.30, 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 • 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

Table 15.2. Operation 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)*:
		• I50.82, Biventricular heart failure • I50.89, Other heart failure • I50.9, Heart failure, unspecified • R57.0, Cardiogenic shock
Stress cardiomyopathy[29]	N/A	• I42.7, Cardiomyopathy due to drug and external agent • I42.8, Other cardiomyopathies • I42.9, Cardiomyopathy, unspecified • I51.81, Takotsubo syndrome
Coronary artery disease (CAD)[29]	N/A	• I24.0, Acute coronary thrombosis not resulting in myocardial infraction • 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

Table 15.2. Operation 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)*:
		• I25.110, 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 • I25.700, Atherosclerosis of coronary artery bypass graft(s), unspecified, with unstable angina pectoris • I25.701, Atherosclerosis of coronary artery bypass graft(s),

Table 15.2. Operation 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)*:
		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 • 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

Table 15.2. Operation 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)*:
		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 • I25.730, Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unstable angina pectoris • I25.731, Atherosclerosis of nonautologous biological coronary

Table 15.2. Operation 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)*:
		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 • 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

Table 15.2. Operation 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)*:
		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 • I25.790, Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris • I25.791, Atherosclerosis of other coronary artery bypass graft(s)

Table 15.2. Operation 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)*:
		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 transplanted heart without angina pectoris
Arrhythmia[29]	N/A	• I47.1, Supraventricular tachycardia • I47.2, Ventricular tachycardia

Table 15.2. Operation 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)*:
		• 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
Deep vein thrombosis (DVT)[29]	N/A	• I82.220, Acute embolism and thrombosis of inferior vena cava • I82.3, Embolism and thrombosis of renal vein • I82.401, Acute embolism and thrombosis of unspecified deep veins of right lower extremity

Table 15.2. Operation 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)*:
		• I82.402, 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 • I82.421, Acute embolism and thrombosis of right iliac vein

Table 15.2. Operation 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)*:
		• I82.422, 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 • I82.443, Acute embolism and thrombosis of tibial vein, bilateral

Table 15.2. Operation 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)*:
		• I82.449, 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 • I82.463, Acute embolism and thrombosis of calf muscular vein, bilateral

Table 15.2. Operation 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)*:
		• I82.469, 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 • I82.4Y2, Acute embolism and thrombosis of unspecified deep

Table 15.2. Operation 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)*:
		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 • I82.4Z9, Acute embolism and thrombosis of unspecified deep

Table 15.2. Operation 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)*:
		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
Pulmonary embolus[29]	N/A	• 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

Table 15.2. Operation 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)*:
		• I26.93, Single subsegmental pulmonary embolism without acute cor pulmonale • I26.94, Multiple subsegmental pulmonary emboli without acute cor pulmonale • I26.99, Other pulmonary embolism without acute cor pulmonale
Cerebrovascular hemorrhagic stroke[44,57]	N/A	• 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

Table 15.2. Operation 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)*:
		• I61.5, Nontraumatic intracerebral hemorrhage, intraventricular • I61.6, Nontraumatic intracerebral hemorrhage, multiple localized • I61.8, Other nontraumatic intracerebral hemorrhage • 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
Cerebrovascular non-hemorrhagic stroke[44,57]	N/A	• I63.00, Cerebral infarction due to thrombosis of unspecified precerebral artery • I63.011, Cerebral infarction due to thrombosis of right vertebral artery

Table 15.2. Operation 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)*:
		• I63.012, 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 • I63.039, Cerebral infarction due to thrombosis of unspecified carotid artery • I63.09, Cerebral infarction due to thrombosis of other precerebral artery

Table 15.2. Operation 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)*:
		• I63.10, 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 • 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

Table 15.2. Operation 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)*:
		• I63.19, 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 • 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

Table 15.2. Operation 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)*:
		• I63.231, 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 • I63.30, Cerebral infarction due to thrombosis of unspecified cerebral artery • I63.311, Cerebral infarction due to thrombosis of right middle cerebral artery

Table 15.2. Operation 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)*:
		• I63.312, 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 • I63.323, Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries • I63.329, Cerebral infarction due to thrombosis of unspecified anterior cerebral artery

Table 15.2. Operation 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)*:
		• I63.331, 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 • I63.343, Cerebral infarction due to thrombosis of bilateral cerebellar arteries • I63.349, Cerebral infarction due to thrombosis of unspecified cerebellar artery

Table 15.2. Operation 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)*:
		• I63.39, 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 • I63.421, Cerebral infarction due to embolism of right anterior cerebral artery • I63.422, Cerebral infarction due to embolism of left anterior cerebral artery

Table 15.2. Operation 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)*:
		• I63.423, 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 • 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

Table 15.2. Operation 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)*:
		• I63.443, 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 • 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

Table 15.2. Operation 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 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 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

Table 15.2. Operation 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)*:
		• I63.533, 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 • 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

Table 15.2. Operation 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)*:
		• I63.6, 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
Limb ischemia[29]	N/A	• I99.8, Other disorder of circulatory system
Hemorrhagic disease (excluding those limited as separate outcomes)[29]	N/A	• D69.8, Other specified hemorrhagic conditions • D69.9, Hemorrhagic condition, unspecified • A98.8, Other specified viral hemorrhagic fevers • A99, Unspecified viral hemorrhagic fever • A98.5, Hemorrhagic fever with renal syndrome

Table 15.2. Operation 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)*:
		• G04.39, Other acute necrotizing hemorrhagic encephalopathy

Acute kidney injury[25]	N/A	• N17.9, Acute kidney failure, unspecified
		
		Laboratory result:[26]
		• Grade 3:
		  ○ Estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) 29 -15 ml/min/1.73 m2
		• Grade 4:
		  ○ eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated
		• Grade 5:
		  ○ Death

Liver injury[27]	N/A	• K76.8, Other specified diseases of liver • K76.9, Liver disease, unspecified

Table 15.2. Operation 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)*:
		• R17, Unspecified jaundice, excludes neonatal • R16.0, Hepatomegaly, not elsewhere classified • 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

Table 15.2. Operation 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)*:
		• K71.9, Toxic liver disease, unspecified • K72.9, Hepatic failure, unspecified • 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:[26] • Grade 3: o Aspartate transaminase (AST) or alanine transaminase (ALT): >5.0 - 20.0x upper LN (ULN) if baseline was normal; >5.0-20.0x baseline if baseline was abnormal o Blood bilirubin: >3.0-10.0x ULN if baseline was

Table 15.2. Operation 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)*:
		normal; >3.0-10.0x baseline if baseline was abnormal • Grade 4: o AST or ALT: >20.0x ULN if baseline was normal; >20.0x if baseline was abnormal o Blood bilirubin: >10.0x ULN if baseline was normal; >10.0x baseline if baseline was abnormal • Grade 5: o Death 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 • C22, Malignant neoplasm of liver and intrahepatic bile ducts • K72.0, Acute and subacute hepatic failure paired with any of the following:

Table 15.2. Operation 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)*:
		○ 50.811, Acute right heart failure ○ I95, Hypotension • K77, Liver disorders in diseases classified elsewhere
Chilblain-like lesions[29]	N/A	• T69.1XXA, Chilblains, initial encounter
Single organ cutaneous vasculitis[29]	N/A	• L95.8, Other vasculitis limited to the skin • L95.9, Vasculitis limited to the skin, unspecified
Erythema multiforme[29]	N/A	• L51.0, Nonbullous erythema multiforme • L51.8, Other erythema multiforme • L51.9, Erythema multiforme, unspecified • L51.1, Stevens-Johnson syndrome • L51.2, Toxic epidermal necrolysis [Lyell]

Table 15.2. Operation 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)*:
		• L51.3, Stevens-Johnson synd-tox epdrml necrolysis overlap syndrome
Other		
Death	• Defined by individual having "date of death" information.	
Narcolepsy/cataplexy[29]	• 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[44,57]	• 708, Allergic urticaria • 708.1, Idiopathic urticaria • 708.9, Urticaria, unspecified	• L50.0, Allergic urticaria • L50.1, Idiopathic urticaria • L50.9, Urticaria, unspecified

Table 15.2. Operation 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)*:
	• 995.1, Angioneurotic edema, not elsewhere classified • 995.3, Allergy, unspecified, not elsewhere classified	• T78.3XXA, Angioneurotic edema, initial encounter • T78.40XA, Allergy, unspecified, initial encounter
Appendicitis[29]	• 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

Table 15.2. Operation 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)*:
		• K35.80, Unspecified acute appendicitis • K35.890, Other acute appendicitis without perforation or gangrene • K35.891, Other acute appendicitis without perforation, with gangrene • K37, Unspecified appendicitis

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

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	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
		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

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	Manufacturer/Descriptions
	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
	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

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	Manufacturer/Descriptions
	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)
	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

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	Manufacturer/Descriptions
	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
	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

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	Manufacturer/Descriptions
	NDC	58160090141	FLUARIX QUAD 2014-2015
	NDC	58160090152	FLUARIX QUAD 2014-2015
	NDC	58160090341	FLUARIX QUAD 2015 2016
	NDC	58160090352	FLUARIX QUAD 2015 2016
	NDC	58160090541	FLUARIX QUAD 2016 2017
	NDC	58160090552	FLUARIX QUAD 2016 2017
	NDC	58160090741	FLUARIX QUAD 2017 2018
	NDC	58160090752	FLUARIX QUAD 2017 2018
	NDC	62577061301	FLUCELVAX 2014-2015
	NDC	62577061311	FLUCELVAX 2014-2015
	NDC	62577061401	FLUCELVAX 2015 2016
	NDC	62577061411	FLUCELVAX 2015 2016
	NDC	70461020001	FLUCELVAX QUADRIVALENT 2016 2017
	NDC	70461020011	FLUCELVAX QUADRIVALENT 2016 2017
	NDC	70461020101	FLUCELVAX QUADRIVALENT 2017 2018
	NDC	70461020111	FLUCELVAX QUADRIVALENT 2017 2018
	NDC	70461030110	FLUCELVAX QUADRIVALENT 2017 2018
	NDC	70461030112	FLUCELVAX QUADRIVALENT 2017 2018
	NDC	70461031803	FLUCELVAX
	NDC	70461031804	FLUCELVAX
	NDC	70461041810	FLUCELVAX
	NDC	70461041811	FLUCELVAX
	NDC	66019030101	FLUMIST QUAD 2014 2015
	NDC	66019030110	FLUMIST QUAD 2014 2015
	NDC	66019030201	FLUMIST QUAD 2015 2016
	NDC	66019030210	FLUMIST QUAD 2015 2016
	NDC	66019030301	FLUMIST QUAD 2016 2017
	NDC	66019030310	FLUMIST QUAD 2016 2017
	NDC	66019030401	FLUMIST QUAD 2017 2018
	NDC	66019030410	FLUMIST QUAD 2017 2018
	NDC	66521000001	FLUAD 2015 2016
	NDC	66521000011	FLUAD 2015 2016
	NDC	70461000101	FLUAD 2016 2017
	NDC	70461000111	FLUAD 2016 2017
	NDC	70461000201	FLUAD 2017 2018
	NDC	70461000211	FLUAD 2017 2018
	NDC	42874001401	FLUBLOK 2014 2015
	NDC	42874001410	FLUBLOK 2014 2015
	NDC	42874001501	FLUBLOK 2015 2016
	NDC	42874001510	FLUBLOK 2015 2016

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	Manufacturer/Descriptions
	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
	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
	NDC	49281070840	FLUZONE INTRADERMAL QUADRIVALENT 2014 15
	NDC	49281070848	FLUZONE INTRADERMAL QUADRIVALENT 2014 15

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	Manufacturer/Descriptions
	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
	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

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	Manufacturer/Descriptions
	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
	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

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

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

Table 15.3. COVID-19 and Seasonal Influenza Vaccine Exposure Codes[47]

Vaccine	Code Type	Code	Manufacturer/Descriptions
	NDC	49281033615	FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE
	NDC	49281040565	FLUZONE High-Dose
	NDC	49281041810	FLUZONE QUADRIVALENT
	NDC	49281041850	FLUZONE QUADRIVALENT
	NDC	49281041910	FLUZONE QUADRIVALENT
	NDC	49281041950	FLUZONE QUADRIVALENT
	NDC	49281042010	FLUZONE QUADRIVALENT
	NDC	49281042050	FLUZONE QUADRIVALENT
	NDC	49281051825	FLUZONE QUADRIVALENT
	NDC	49281051925	FLUZONE QUADRIVALENT
	NDC	49281052025	FLUZONE QUADRIVALENT
	NDC	49281062915	FLUZONE QUADRIVALENT
	NDC	49281063115	FLUZONE QUADRIVALENT
	NDC	49281063315	FLUZONE QUADRIVALENT
	NDC	49281064015	INFLUENZA A (H1N1) 2009 MONOVALENT VACCINE
	NDC	49281071810	Flublok Quadrivalent
	NDC	49281071910	Flublok Quadrivalent
	NDC	49281072010	Flublok Quadrivalent Northern Hemisphere
	NDC	58160080815	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
	NDC	58160080815	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
	NDC	58160088352	FLUARIX
	NDC	58160088552	FLUARIX QUADRIVALENT
	NDC	58160089652	FLUARIX QUADRIVALENT
	NDC	58160089852	FLUARIX QUADRIVALENT
	NDC	63851061301	FLUCELVAX
	NDC	66019030510	FluMist Quadrivalent
	NDC	66019030610	FluMist Quadrivalent
	NDC	66019030710	FluMist Quadrivalent
	NDC	70461001803	FLUAD
	NDC	70461001903	FLUAD
	NDC	70461002003	FLUAD
	NDC	70461012003	FLUAD QUADRIVALENT
	NDC	70461031903	FLUCELVAX QUADRIVALENT
	NDC	70461032003	FLUCELVAX QUADRIVALENT
	NDC	70461041910	FLUCELVAX QUADRIVALENT
	NDC	70461042010	FLUCELVAX QUADRIVALENT

Document Approval Record

Document Name:	C4591012 NI Study Interim Report
Document Title:	C4591012

Signed By:	Date(GMT)	Signing Capacity
De Bernardi, Barbara	22-Jun-2021 19:47:39	EUQPPV Approval
Campbell, Ulka	23-Jun-2021 02:25:51	Final Approval