# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## Study information

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| **Title** | A Post-Authorization Safety Study of Atrial Fibrillation Following Respiratory Syncytial Virus Vaccine (ABRYSVO™) Among Older Adults in the Veterans Affairs Health System |
| **Protocol number** | C3671037 |
| **Protocol version identifier** | 1.0 |
| **Date** | 29 November 2023 |
| **EU Post Authorization Study (PAS) register number** | Study to be registered prior to the start of data collection |
| **Active substance** | ABRYSVO™ is a bivalent recombinant stabilized prefusion F protein subunit vaccine (Respiratory Syncytial Virus Vaccine). It consists of equal amounts of prefusion F antigens from the two major RSV subgroups: RSV subgroup A prefusion F (60 µg) and RSV subgroup B prefusion F (60 µg). |
| **Medicinal product** | Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine (ABRYSVO™, Respiratory Syncytial Virus Vaccine) |
| **Research question and objectives** | Research question: What are the incidence rates of atrial fibrillation and supraventricular arrhythmia, overall and in sub-cohorts of interest, among individuals vaccinated with ABRYSVO within the US Veterans Health Administration (VHA) system as compared to expected rates of those events?<br><br>*Primary study objective:*<br><br>• To estimate the incidence of atrial fibrillation following administration of ABRYSVO among adults 60 years of age and older in the VHA system<br><br>*Secondary study objectives:* |

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| | • To estimate the incidence of supraventricular arrhythmia following administration of ABRYSVO among adults 60 years of age and older in the VHA system<br><br>• To assess whether adults 60 years of age and older in the VHA system experience increased risk of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO<br><br>• To estimate the incidence of atrial fibrillation and supraventricular arrhythmia in sub-cohorts of interest (i.e., individuals with specific comorbidities, individuals with weakened immune systems, older age groups, individuals with dual VHA/Medicare coverage, females) in the VHA system following administration of ABRYSVO<br><br>• To assess whether sub-cohorts of interest (i.e., individuals with specific comorbidities, individuals with weakened immune systems, older age groups, individuals with dual VHA/Medicare coverage, females) in the VHA system experience increased risk of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO |
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## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ABRYSVO | Respiratory Syncytial Virus Vaccine |
| AE | Adverse event |
| AEM | Adverse event monitoring |
| AHA | American Heart Association |
| AIDS | Acquired immunodeficiency syndrome |
| AMA | American Medical Association |
| AR | Adverse reaction |
| ATT | Average treatment effect among the treated |
| BMI | Body mass index |
| CAD | Coronary artery disease |
| CBER | Center for Biologics Evaluation and Research |
| CCI | Charlson Comorbidity Index |
| CDC | Centers for Disease Prevention and Control |
| CDW | Corporate Data Warehouse |
| CEP | Clinical Epidemiology Program |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| CMCD | Clinical and Medical Controlled Document |
| CMS | Centers for Medicare & Medicaid Services |
| COPD | Chronic obstructive pulmonary disease |
| COVID-19 | Coronavirus Disease 19 |
| CPT | Current Procedural Terminology |

| Abbreviation | Definition |
|---|---|
| CRF | Case report form |
| CSA | Clinical study agreement |
| CVX | Vaccine administered |
| EC | Ethics Committee |
| ED | Emergency department |
| EHR | Electronic health record |
| EU | European Union |
| EU PAS | European Union Post Authorization Safety |
| EUA | Emergency Use Authorization |
| FDA | Food and Drug Administration |
| GEP | Good Epidemiological Practice |
| GPP | Guidelines for Good Pharmacoepidemiology Practices |
| HBV | Hepatitis B virus |
| HCPCS | Healthcare Common Procedure Coding System |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HPV | Human papillomavirus |
| HSCT | Hematopoietic stem cell transplant |
| ICD-10-CM | International Classification of Diseases, Tenth Revision, Clinical Modification |
| IEA | International Epidemiological Association |
| IP | Inpatient |
| IPTW | Inverse probability treatment weighting |

| Abbreviation | Definition |
|---|---|
| IQR | Interquartile range |
| IRB | Institutional Review Board |
| IRR | Incidence rate ratio |
| LOINC | Logical Observation Identifiers Names and Codes |
| MAH | Marketing Authorization Holder(s) |
| MenACWY | Meningococcal conjugate vaccine |
| MenB | Serogroup B meningococcal vaccine |
| mRNA-1345 | Messenger Ribonucleic Acid-1345 Vaccine |
| MVA-BN-RSV | Modified Vaccinia Ankara-Bavarian Nordic-Respiratory Syncytial Virus Vaccine |
| MVX | Manufacturers of vaccines |
| NDC | National Drug Codes |
| NI | Non-interventional |
| NIS | Non-interventional study |
| NSAID | Nonsteroidal anti-inflammatory drug |
| OP | Outpatient |
| PAS | Post-authorization safety |
| PASS | Post-authorization safety studies |
| PCR | Polymerase chain reaction |
| PI | Primary investigator |
| PPV | Positive predictive value |
| preF | Prefusion F |
| PS | Propensity score |

| Abbreviation | Definition |
|---|---|
| RDC | Research and Development Committee |
| RENOIR | RSV vaccine Efficacy study iN Older adults Immunized against RSV disease |
| RR | Risk ratio |
| RSV | Respiratory syncytial virus |
| RSV F | Respiratory Syncytial Virus Fusion Nanoparticle Vaccine |
| RSVpreF | Respiratory Syncytial Virus Prefusion F |
| SAP | Statistical analysis plan |
| SAS | Statistical Analysis System |
| SCRI | Self-controlled risk interval |
| SD | Standard deviation |
| Td | Tetanus diphtheria and pertussis vaccine |
| Tdap | Tetanus diphtheria and acellular pertussis vaccine |
| US | United States |
| VA | Department of Veterans Affairs |
| VAERS | Vaccine Adverse Event Reporting System |
| VHA | Veterans Health Administration |
| VINCI | VA Informatics and Computing Infrastructure |
| VISN | Veterans Integrated Service Networks |
| VISN 1 | VA New England Healthcare System |
| VISN 17 | VA Heart of Texas Health Care Network |
| VTE | Venous thromboembolism |
| WOC | Without compensation |

| Abbreviation | Definition |
|---|---|
| YRR | Your Reporting Responsibilities |

# 3. RESPONSIBLE PARTIES

## Principal Investigator(s) of the Protocol

| Name, degree(s) | Job Title | Affiliation | Address |
|---|---|---|---|
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| Mei Sheng Duh, ScD, MPH | Managing Principal and Chief Epidemiologist | Analysis Group, Inc. | 111 Huntington Ave 14th Floor Boston, MA 02199 |
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## 4. ABSTRACT

Title: A Post-Authorization Safety Study of Atrial Fibrillation Following Respiratory Syncytial Virus Vaccine (ABRYSVO™) Among Older Adults in the Veterans Affairs Health System

Protocol Version: 1.0; Date of Protocol: 29 November 2023

Authors: Jurandir Dalle Lucca, MD, PhD, White River Junction Veterans Affairs Medical Center; Caroline Korves, ScD, White River Junction Veterans Affairs Medical Center; Joanne Wu, ScD, MS, Pfizer, Inc.; Mei Sheng Duh, ScD, MPH, Analysis Group, Inc.; Maral DerSarkissian, PhD, Analysis Group, Inc.

Rationale and background:

ABRYSVO™ (Respiratory Syncytial Virus Vaccine [Pfizer; Study C3671013]) was authorized by the US FDA on 31 May 2023 for active immunization for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older. ABRYSVO is a bivalent recombinant protein subunit vaccine which consists of equal amounts of stabilized preF antigens from the two major RSV subgroups: RSV A and RSV B (RSVpreF). Pfizer's ongoing pivotal Phase 3 clinical trial, RENOIR (**R**SV vaccine **E**fficacy study i**N** **O**lder adults **I**mmunized against **R**SV disease; Study C3671013) in adults 60 years and older[1,2] reported a vaccine efficacy of 66.7% (96.66% CI: 28.8%-85.8%) in preventing RSV-associated lower respiratory tract illness with at least two signs or symptoms lasting more than one day, and 85.7% (96.66% CI: 32.0%-98.7%) in preventing RSV-associated lower-respiratory tract illness with at least three signs or symptoms. The pivotal Phase 3 study, and the totality of data from the clinical development program for older adults, provides robust evidence of a highly favorable benefit-to-risk profile.

RENOIR reported a numerical imbalance of atrial fibrillation with 10 events in the RSVpreF group (n=17,215) versus 4 events in the placebo group (n=17,069) within one month of vaccination.[2,3] A medical history of atrial fibrillation was reported in 60% and 50% of the cases in the RSVpreF and placebo groups, respectively, and none of the events of atrial fibrillation were considered related to RSVpreF by the investigators.[3] Atrial fibrillation is the most common cardiac arrythmia, where both incidence and prevalence of atrial fibrillation have been shown to increase with age and are higher in males versus females and in those of European versus African descent.[4]

Pfizer in collaboration with the US VHA of the Department of VA and Analysis Group herein propose to conduct a PASS to further evaluate the risk of atrial fibrillation and supraventricular arrhythmia following ABRYSVO administration in the large-scale VHA EHR database among adults 60 years and older.

This non-interventional study is designated as a PASS and is a post-marketing commitment to the US FDA.

Research question and objectives:

Research question: What are the incidence rates of atrial fibrillation and supraventricular arrhythmia, overall and in sub-cohorts of interest, among individuals vaccinated with ABRYSVO within the US VHA system as compared to expected rates of this event?

*Primary study objective:*

- To estimate the incidence of atrial fibrillation following administration of ABRYSVO among adults 60 years of age and older in the VHA system

*Secondary study objectives:*

- To estimate the incidence of supraventricular arrhythmia following administration of ABRYSVO among adults 60 years of age and older in the VHA system
- To assess whether adults 60 years of age and older in the VHA system experience increased risk of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO
- To estimate the incidence of atrial fibrillation and supraventricular arrhythmia in sub-cohorts of interest (i.e., individuals with specific comorbidities, individuals with weakened immune systems, older age groups, individuals with dual VHA/Medicare coverage, females) in the VHA system following administration of ABRYSVO
- To assess whether sub-cohorts of interest (i.e., individuals with specific comorbidities, individuals with weakened immune systems, older age groups, individuals with dual VHA/Medicare coverage, females) in the VHA system experience increased risk of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO

Study design:

This non-interventional PASS will assess the incidence and risk of atrial fibrillation and supraventricular arrhythmia following ABRYSVO among adults 60 years of age and older in the VHA system from earliest date of vaccine availability to 31 May 2026. The following retrospective, longitudinal, observational cohort study designs will be implemented:

- The incidence of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO will be assessed in the pre-specified post-vaccination period for each outcome (e.g., 0-3 days for atrial fibrillation).
- An internal comparator cohort design (i.e., contemporary control design) will serve as the primary study design and will compare the incidence of atrial fibrillation and supraventricular arrhythmia among those who received ABRYSVO to the incidence in two

separate random samples of contemporaneous, index date-matched older adult controls in the VHA system based on information recorded in the VHA database:

1) Primary analysis - individuals who were vaccinated with another vaccine (e.g., influenza vaccine or COVID-19 vaccine on the index date (e.g., +/- 30 days); i.e., contemporaneous vaccinated control cohort)

2) Secondary analysis - individuals who were not vaccinated with any vaccine on the index date but had at least one vaccination record in the year prior to the index date (i.e., contemporaneous unvaccinated control cohort)

- An SCRI design, which will serve as the secondary study design, will be used to compare the incidence of atrial fibrillation and supraventricular arrhythmia during the post-vaccination risk window (e.g., 0-3 days following vaccination) to the post-vaccination control window (e.g., 4-10 days following vaccination) among ABRYSVO vaccinated individuals.

- Medical records review will be conducted as a separate component to validate/adjudicate cases of atrial fibrillation among ABRYSVO vaccinated individuals within the VHA system.

Population: The study population will consist of individuals with a record of at least one dose of ABRYSVO who are at least 60 years of age on the date of vaccination (i.e., index date). Individuals who receive an RSV vaccine from a manufacturer other than Pfizer will be excluded from the study. Contemporary vaccinated controls will be included if they have no record of RSV vaccine and have a record for another vaccine (e.g., influenza vaccine, COVID-19 vaccine, and other pre-specified vaccines such as shingles, hepatitis B) within 30 days of a corresponding ABRYSVO vaccinee's vaccination date; the control's index date will be the date of the control's non-RSV vaccine and they will be required to be at least 60 years of age on the index date. Contemporary unvaccinated controls will be included if they have no record of any vaccine on the index date but had at least one vaccination record in the year prior to the index date; they will be assigned an index date matched to a corresponding ABRYSVO vaccinee's vaccination date and will be required to be at least 60 years of age on the matched index date. All individuals must be enrolled in (i.e., not disenrolled from) VHA benefits during the 2 years prior to the index date (i.e., baseline period).

Variables:

- Exposure: Administration of ABRYSVO will be identified based on the following:
    - CPT code 90678, OR
    - 10 and 11-digit NDCs 0069-0207-01, 0069-0250-01, 0069-0344-01, 0069-0344-05, 0069-0344-10; OR
    - Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (i.e., Pfizer), lot number, injection site, and date(s) of immunization.

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

- Outcomes: The study's primary outcome, new onset atrial fibrillation, will be identified by a diagnosis code for atrial fibrillation in any setting during the 0-3 day risk interval for the primary analysis (or 0-1 day or 0-30 day risk interval for secondary analysis), or day 4-10 post vaccination control interval, followed by a confirmatory diagnosis within 30 days after the initial diagnosis and no diagnosis for atrial fibrillation or other supraventricular arrhythmias in the 2 years prior to the index date (i.e., "clean window," to rule out pre-existing events).[5,6]

  The secondary outcome of the study will be new onset supraventricular arrhythmia, including atrial fibrillation, and will be identified in the same manner as the primary outcome.

  The risk intervals were selected based on published literature and biological plausibility.[7-14] A safety event will be counted if it can be assigned to 1) the risk interval following ABRYSVO, 2) the post-vaccination control interval (SCRI design), or 3) risk interval for the contemporary vaccinated or unvaccinated controls. The risk intervals for outcome evaluation for contemporary vaccinated or unvaccinated controls will be the same as for individuals who received ABRYSVO.

- Key Covariates: Baseline demographic (i.e., age, sex, race/ethnicity, VHA service area, marital status) and clinical characteristics (i.e., smoking, BMI, history of anaphylaxis/allergic reactions including to vaccine components, history of hospitalizations, frailty index, CCI, alcohol abuse, history of atrial fibrillation prior to the baseline period, selected comorbidities, selected concomitant medications, and concurrent immunizations). The final list of baseline characteristics will be defined in the SAP based on feasibility and availability.

- Subgroups: The following subgroups will be analyzed:
  - Individuals with specific comorbidities identified as high risk for severe RSV by the CDC, defined as individuals diagnosed with chronic cardiovascular disease, chronic lung disease, diabetes mellitus, neurologic conditions, kidney disorders, liver disorders, or hematologic disorders; [15,16]
  - Individuals with weakened immune systems;[17]
  - Different age groups defined by age on the index date, e.g., 60 to 69 years, 70 to 79 years, ≥80 years;
  - Individuals enrolled in the VHA with dual insurance coverage who are also identified in the CMS Medicare administrative claims data;
  - Females enrolled in the VHA (pending sufficient sample size).

Data sources: The VHA is the largest integrated health care system in the US, providing both inpatient and outpatient clinical care to over 9 million Veterans enrolled at more than 170 medical

centers and 1,113 community-based outpatient clinics.[18] The objectives of this study will be addressed using data from VHA's CDW, which is an integrated EHR system with a centralized data warehouse that is updated on a daily basis. The CDW lacks information on care received outside of a VHA facility. In a subgroup analysis of individuals with both VHA and Medicare coverage, CDW data will be supplemented and linked with Medicare administrative claims data at the patient level to ensure a more comprehensive evaluation of the care an individual receives.

Study size and power: All individuals who meet the eligibility criteria during the study period in the VHA database will be included. The sample size achieved will depend on the number of individuals administered ABRYSVO identified within the VHA database during the study period, which will increase over time. Data will be analyzed at two different time points to add newly vaccinated individuals and index-matched controls. Analyses using the primary internal comparator cohort design will have sufficient power (80.0%) to detect a 2-fold and 1.5-fold increased risk of safety events associated with ABRYSVO assuming a baseline rate of 33.9 events per 1,000 person-year and 4:1 matching ratio of controls to ABRYSVO vaccinees with a sample size of 47,536 and 147,890 individuals vaccinated with ABRYSVO, respectively.

Data analysis: Baseline demographics and clinical characteristics for individuals administered ABRYSVO and contemporary vaccinated or unvaccinated controls will be summarized using descriptive statistics. Descriptive statistics will also be used to summarize vaccination patterns for ABRYSVO.

Incidence rates per 1,000 patient years (and corresponding 95% CIs) will be calculated for the primary and secondary outcomes and will be compared to rates observed in the following control groups:

- Internal comparator cohorts: two random samples of contemporaneous vaccinated and unvaccinated matched controls in the VHA system. Average treatment effect among the treated (ATT) weighting, based on the propensity score (PS), will be used to ensure baseline comparability between the ABRYSVO vaccinated cohort vs. contemporary vaccinated control cohort and ABRYSVO vaccinated cohort vs. contemporary unvaccinated control cohort. ATT-weighted Cox regression with robust standard errors to account for within-subject correlation will compare the risk of safety events between cohorts. Hazard ratios and corresponding 95% CIs will be summarized.

- Self-controls: cases who experience safety events following vaccination using the SCRI design to compare the risk interval following vaccination to post-vaccination non-risk intervals in the same individual using a conditional Poisson regression model. From this model, we will report rate ratios and 95% CIs.

Diagnostic validation of identified atrial fibrillation cases among individuals administered ABRYSVO will be conducted in a randomly selected representative sample of up to 100 cases per interim/final report, as available and feasible. PPV will be calculated as the proportion of atrial fibrillation cases deemed as true cases via adjudication among the total number of adjudicated cases. If the lower bound of the 95% CI of the PPV is less than 70% at the interim analysis, the algorithm

used to identify incident atrial fibrillation using codified data may be updated in subsequent analyses and atrial fibrillation cases identified with the new algorithm will be re-adjudicated. If the lower bound of the 95% CI for PPV is equal to or greater than 70% in the interim report, chart adjudication may be waived for the final report.

If an increased risk of atrial fibrillation following ABRYSVO vaccination is observed from the analyses described above, a risk factor analysis will be conducted via logistic regression among individuals vaccinated with ABRYSVO, adjusting for baseline characteristics and co-administration of vaccines selected a priori.

Analyses may also be conducted in the subgroups of interest described above, depending on feasibility, sample size, and data availability.

Various sensitivity analyses may be conducted, including analysis of negative control outcomes. Further details and any additional sensitivity analyses will be described in the SAP.

Milestones:

- Registration in the EU PAS register: To be registered before the start of data collection
- VHA RDC and IRB approval (estimated): 30 June 2024
- Start of data collection (estimated planned date for starting data extraction for analysis): 01 September 2024
- Interim report: 30 June 2026
- End of data collection (planned date for final data cut): 28 February 2027
- Final study report: 29 February 2028

## 5. AMENDMENTS AND UPDATES

None.

## 6. MILESTONES

| Milestone | Planned Date |
|---|---|
| Registration in the EU PAS register | To be registered before the start of data collection |
| VHA RDC and IRB approval (estimated) | 30 June 2024 |
| Start of data collection (estimated) | 01 September 2024 |
| Interim report[1] | 30 June 2026 |
| End of data collection | 28 February 2027 |
| Final study report[2] | 29 February 2028 |

1. Interim report will include data from the 2023-2024 and half of the 2024-2025 RSV season with data through the end of 2024.
2. The final study report will include data from the 2023-2024, 2024-2025, and 2025-2026 RSV seasons.

## 7. RATIONALE AND BACKGROUND

RSV is a major cause of respiratory infection in both infants and older adults.[19] The CDC estimates that among adults 65 years and older in the US, RSV is responsible for approximately 60,000 – 160,000 hospitalizations, 6,000 – 13,000 deaths, and 0.9 – 1.4 million medical encounters annually.[20-26] However, the current documented disease burden of RSV is most likely underestimated due to variable RSV testing rates and surveillance, with routine testing less common in older adults than in children.[23,27,28] Routine testing of suspected RSV cases is essential for accurate estimation of the burden of RSV disease as RSV does not produce a distinctive clinical syndrome in adults.[27,28] Rather, RSV manifestations can be difficult to distinguish from those associated with influenza virus or other respiratory viruses.[29] RSV can lead to mild cold-like symptoms in adults, but more serious presentations are possible including tracheobronchitis, other lower respiratory tract disease (e.g., pneumonia), or severe respiratory distress.[21,29] Traditionally, detection methods such as cell culture and rapid antigen tests for RSV were cumbersome with low sensitivity.[30] The recent development and increased availability of less invasive and highly sensitive multiphasic PCR respiratory panel tests has enabled clinicians to recognize how common and serious RSV is in older adults.[30]

With increased routine PCR testing, epidemiological data have shown that the burden of RSV in older adults is similar to seasonal influenza, with comparable rates of infection and severity of illness.[27] Older adults are at higher risk of RSV illness compared with younger adults, and recent data have shown higher rates of medically attended RSV, as well as hospitalizations and deaths due to RSV, in adults aged 65 years and older.[27,28,31-33] This may be related to immunosenescence with aging related to a weakened immune response to pathogens, decreased strength of the respiratory muscle and diaphragm, and decreased protective mucus levels, lung compliance, and elastin.[31-33] RSV has also been recognized as a significant cause of severe illness in populations with underlying cardiopulmonary disease and those who are immunocompromised, including HSCT recipients, patients undergoing intensive chemotherapy, and lung transplant patients.[19] RSV can trigger exacerbations of underlying comorbid conditions in older adults, such as COPD and CHF.[28] RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans.[34]

RSV is therefore a disease for which a highly effective vaccine could have a large public health impact among older adults, with the potential to avert a similar number of hospitalizations as the seasonal influenza vaccine program in the same age group.[23] Up until 2023 there were no vaccines licensed for the prevention of RSV infection in older adults and treatment for this population consisted primarily of supportive care.[35,36] However, two vaccines have recently been approved by the US FDA including: ABRYSVO™ (Respiratory Syncytial Virus Vaccine [Pfizer; Study C3671013]; authorized on 31 May 2023), and AREXVY™ (Respiratory Syncytial Virus Vaccine, Adjuvanted [GlaxoSmithKline; NCT04886596]; authorized on 03 May, 2023).[37,38] Several additional vaccines, using different technology platforms, are currently under investigation in Phase 3 clinical trials, including ResVax, Respiratory Syncytial Virus Fusion Nanoparticle Vaccine (RSV F [Novavax; NCT02608502]), Messenger Ribonucleic Acid-1345 Vaccine (mRNA-1345 [Moderna; NCT05127434]), and Modified Vaccinia Ankara-Bavarian Nordic Respiratory Syncytial Virus Vaccine (MVA-BN-RSV [Bavarian Nordic; NCT05238025]).[39-41]

ABRYSVO is a bivalent recombinant protein subunit vaccine which consists of equal amounts of stabilized preF antigens from the two major RSV subgroups: RSV A and RSV B (RSVpreF). Pfizer's ongoing pivotal Phase 3 clinical trial, RENOIR (**R**SV vaccine **E**fficacy study i**N** **O**lder adults **I**mmunized against **R**SV disease; Study C3671013), was initiated in September 2021 and evaluates the efficacy, immunogenicity, and safety of a single 120 µg dose of RSVpreF in adults 60 years and older.[1,2] As of 14 July 2022, the cut-off for the pre-planned interim analysis, 77.0% of all participants (N=34,284) had at least 6 months of follow-up post vaccination. Vaccine efficacy in preventing RSV-associated lower respiratory tract illness with at least two signs or symptoms lasting more than one day was reported to be 66.7% (96.66% CI: 28.8%-85.8%), and vaccine efficacy in preventing RSV-associated lower respiratory tract illness with at least three signs or symptoms was reported to be 85.7% (96.66% CI: 32.0%-98.7%). Vaccine efficacy was maintained through the end of the first RSV season following administration (31 August 2021 through 14 July 2022).[2] Efficacy results from a pre-specified interim analysis met the pre-defined success criterion (lower limit of confidence interval exceeding 20%) for a decrease in the incidence of RSV-associated lower respiratory tract illness with at least two signs or symptoms, and a decrease in the incidence of RSV-associated lower respiratory tract illness with at least three signs or symptoms. Most ARs were mild to moderate in severity with resolution within the 1-2 days after vaccination.[25,26] The pivotal Phase 3 study and additional preclinical and clinical data from the older adults development program demonstrate a highly favorable benefit-to-risk profile.

As of 14 July 2022 in RENOIR, there was a numerical imbalance of atrial fibrillation, a condition that causes an irregular and often fast heartbeat, with 10 events in the RSVpreF group (n=17,215) versus 4 events in the placebo group (n=17,069) within 1 month of vaccination, although the rates of overall unsolicited adverse events between RSVpreF and placebo groups were similar.[2,3] A medical history of atrial fibrillation was reported in 60% and 50% of the cases in the RSVpreF and placebo groups, respectively, and none of the events of atrial fibrillation were considered related to RSVpreF by the investigators.[3] Atrial fibrillation is the most common cardiac arrythmia, where both incidence and prevalence of atrial fibrillation have been shown to increase with age and are higher in males versus females and in those of European versus African descent.[4] A background incidence rate of 33.9 per 1,000 person-years for incident atrial fibrillation was reported in 2007 for male versus 24.7

per 1,000 person-years for female Medicare beneficiaries 65 years of age and older.[6] Atrial fibrillation is part of a broader group of supraventricular arrhythmias which are relatively common cardiac rhythm disturbances typically occurring in repetitive bouts.

PASS are important for characterizing and quantifying the risk of serious safety events in larger populations beyond those captured in the clinical trials (either due to sample size or selected study populations) and for ensuring a favorable benefit-risk profile in real world settings. Pfizer in collaboration with the US VHA of the Department of VA and Analysis Group herein propose a PASS to further evaluate the risk of atrial fibrillation and supraventricular arrhythmia following ABRYSVO administration in the large-scale VHA EHR database among adults 60 years and older.

This non-interventional study is designated as a PASS and is a post-marketing commitment to the FDA.

## 8. RESEARCH QUESTION AND OBJECTIVES

Research question: What are the incidence rates of atrial fibrillation and supraventricular arrhythmia, overall and in sub-cohorts of interest, among individuals vaccinated with ABRYSVO within the US VHA system as compared to expected rates of this events?

*Primary study objective:*

- To estimate the incidence of atrial fibrillation following administration of ABRYSVO among adults 60 years of age and older in the VHA system

*Secondary study objectives:*

- To estimate the incidence of supraventricular arrhythmia following administration of ABRYSVO among adults 60 years of age and older in the VHA system
- To assess whether adults 60 years of age and older in the VHA system experience increased risk of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO
- To estimate the incidence of atrial fibrillation and supraventricular arrhythmia in sub-cohorts of interest (i.e., individuals with specific comorbidities, individuals with weakened immune systems, older age groups, individuals with dual VHA/Medicare coverage, females) in the VHA system following administration of ABRYSVO
- To assess whether sub-cohorts of interest (i.e., individuals with specific comorbidities, individuals with weakened immune systems, older age groups, individuals with dual VHA/Medicare coverage, females) in the VHA system experience increased risk of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO

# 9. RESEARCH METHODS

## 9.1. Study Design

This non-interventional PASS will assess the incidence and risk of atrial fibrillation and supraventricular arrhythmia following receipt of ABRYSVO among adults 60 years of age and older in the VHA system from earliest date of vaccine availability to 31 May 2026. The following retrospective, longitudinal, observational cohort study designs will be implemented:

- The incidence of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO will be assessed in the pre-specified post-vaccination period for each outcome (e.g., 0-3 days for atrial fibrillation).

- An internal comparator cohort design (i.e., contemporary control design) will serve as the primary study design and will compare the incidence of atrial fibrillation and supraventricular arrhythmia among those who received ABRYSVO to the incidence in two random samples of contemporaneous, index date-matched older adult controls in the VHA system based on information recorded in the VHA database:

  1) Primary analysis - individuals who were vaccinated with another vaccine (e.g., influenza vaccine or COVID-19 vaccine on the index date (e.g., +/- 30 days); i.e., contemporaneous vaccinated control cohort)

  2) Secondary analysis - individuals who were not vaccinated with any vaccine on the index date but had at least one vaccination record in the year prior to the index date (i.e., contemporaneous unvaccinated control cohort).

  This will provide additional context for the interpretation for any potential observed excess risk as the controls will reflect the background rate of atrial fibrillation and supraventricular arrhythmia among vaccinated and unvaccinated individuals in the VHA population.

- An SCRI design, which will serve as the secondary study design, will be used to compare the incidence of atrial fibrillation and supraventricular arrhythmia during the post-vaccination risk window (e.g., 0-3 days following vaccination) to the post-vaccination control window (e.g., 4-10 days following vaccination) among ABRYSVO vaccinated individuals within the VHA system.

- Medical records review will be conducted as a separate component (see Section 9.7.2.4 "Case Validation/Adjudication via Medical Records Review" for further details) to validate/adjudicate cases of atrial fibrillation among ABRYSVO vaccinated individuals within the VHA system.

### 9.1.1. Primary Design - Internal Comparator Cohort Design (Contemporary Control Design)

To examine atrial fibrillation and supraventricular arrhythmia following ABRYSVO vaccination, days 0-3 will be used to define the risk interval, comprising a length of 4 days (i.e., from the day of vaccination through the 3 days that follow, as only the date and not exact timing of vaccination will

be known) for the primary analysis. This risk interval was selected based on post-marketing reports indicating atrial fibrillation onset less than one day after ABRYSVO administration, while accounting for a potential delay between the actual event onset and when individuals seek care. As secondary analyses, days 0-1 comprising a length of 2 days (i.e., the day of vaccination and the day following) will be used to define the risk interval, and days 0-30 comprising a length of 31 days (i.e., the date of vaccination through the 30 days that follow) will be used to define the risk interval, similar to other studies that evaluated the risk for cardiac events (e.g., myocarditis and pericarditis) to assess the safety profile of COVID-19 vaccines.[7-11] To reduce outcome misclassification, a confirmed case will require a diagnosis of atrial fibrillation (or supraventricular arrythmia) in the risk interval, with a confirmatory diagnosis within the subsequent 30 days (see Section 9.3.2).[5,6]

Multivariable adjusted analyses will be performed comparing individuals who received ABRYSVO to individuals who received another vaccine (e.g., influenza vaccine, COVID-19 vaccine, and other pre-specified vaccines such as shingles, hepatitis B listed in Section 9.3.3) at that point in time (+/- 30 days) [i.e., contemporary vaccinated controls] in the primary analysis. The vaccinated controls' index date will be defined as the date on which the individual received another vaccine that is within 30 days of a corresponding ABRYSVO vaccinee's vaccination date; these individuals can later receive ABRYSVO and enter the vaccination group if all eligibility criteria are met.

As a secondary analysis, individuals who received ABRYSVO will be compared to individuals not receiving any vaccinations at that point in time but had at least one vaccination record in the year prior to the index date (i.e., contemporary unvaccinated controls). The unvaccinated controls will be assigned an index date matched to a corresponding ABRYSVO vaccinee's vaccination date; these individuals can later receive ABRYSVO and enter the vaccination group if all eligibility criteria are met. To address possible selection bias due to health seeking behaviors, the unvaccinated controls will be randomly selected from a population of patients who have regular use of preventive medical care within the VHA system, defined as at least one vaccination record in the year prior to the index date. The index date for the contemporary unvaccinated controls will be selected based on the observed index dates in the vaccinated cohort. If ABRYSVO vaccination is associated with a regular healthcare encounter, the contemporary unvaccinated control will be required to have an encounter within 30 days of the assigned index date, and the date of encounter will be set as the index date to ensure comparability of covariate measurement.

In the primary analysis, the ABRYSVO vaccinated, contemporary vaccinated control, and contemporary unvaccinated control cohorts will be followed for up to 34 days post-index (i.e., 0-3 day risk interval plus 30-day diagnosis confirmation window) to assess and confirm the occurrence of atrial fibrillation and supraventricular arrhythmia. In secondary analyses, the cohorts will be followed up to 32 days post-index (i.e., 0-1 day risk interval plus 30-day diagnosis confirmation window) and up to 61 days post-index (i.e., 0-30 day risk interval plus 30-day diagnosis confirmation window). Individuals will be censored upon the earliest occurrence of disenrollment, death, date of RSV vaccination (for controls who later receive any RSV vaccine only), or end of the risk window. The date of the first atrial fibrillation (or supraventricular arrythmia) case will be considered date of onset.

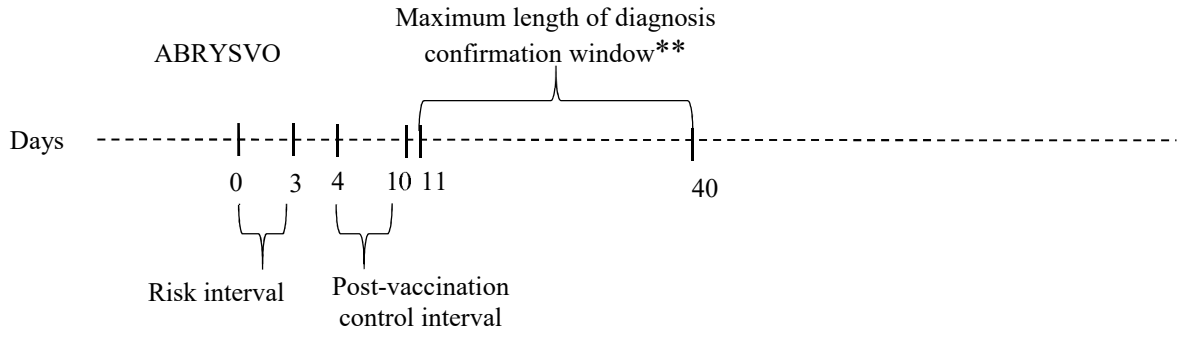
### 9.1.2. Secondary Design - SCRI Design with Post-Vaccination Control Interval

In addition, the SCRI design uses information from cases (i.e., individuals who experience a safety event following vaccination) to compare the risk interval following vaccination to post-vaccination non-risk intervals ("post-vaccination control interval") in the same individual.[42,43] Only ABRYSVO vaccinated individuals who experience an outcome of interest within the risk or control interval will contribute to the SCRI analysis. As the SCRI design is a within person analysis, it implicitly controls for time fixed confounders. Time varying confounders still need to be controlled for, but with short, defined risk windows the risk of time varying confounding is limited.

To ensure all individuals have the same chance of having a confirmed diagnosis, the SCRI analysis will require individuals to have continuous enrollment in VHA benefits for an additional 30 days following the risk and post-vaccination control interval (e.g., a total of 40 days of follow-up comprised of the day 0-3 risk interval [including the day of ABRYSVO vaccination], day 4-10 control interval, and additional 30 days of follow up). Note that a longer control interval of 7 days (i.e., day 4-10 corresponding to the day 0-3 risk interval and day 2-8 corresponding to the day 0-1 risk interval) will be used to increase power of detecting an association should one truly exist by providing a more statistically stable estimate of the baseline risk while avoiding the confounding impact of time-varying covariates (e.g., seasonality, other vaccination, medication use).[44,45] Since the required post-vaccination follow-up period is short, this requirement is not expected to produce any appreciable selection bias in the analysis.

The SCRI design with a post-vaccination control interval is presented in Figure 1 below.

**Figure 1. SCRI Design for Assessment of Atrial Fibrillation or Supraventricular Arrhythmia with a 0-3-day Risk Interval in an Individual who Receives ABRYSVO, with Post-vaccination Control Interval***




* Day 0 is defined as the date of vaccination.
** The diagnosis confirmation window allows everyone the same chance of having a confirmed diagnosis of atrial fibrillation or supraventricular arrhythmia. Day 40 reflects the last possible date for the confirmatory diagnosis of atrial fibrillation or supraventricular arrhythmia based on cases occurring at the end of the control interval.

### 9.1.3. Medical Records Review

Cases of atrial fibrillation among individuals vaccinated with ABRYSVO will be validated/adjudicated (see Section 9.7.2.4 Case Validation/Adjudication via Medical Records Review for further details). VA analysts will produce a line listing of cases for medical records data abstraction. The listing will contain an identifier and other relevant information that is sufficient to identify the correct electronic health record for each patient (detailed in Section 9.6.1 "Case Report Forms"). The listing will also include sex, date of birth, date of vaccination with ABRYSVO, date of atrial fibrillation diagnosis, age at diagnosis of atrial fibrillation, days lapsed since vaccination, and concurrent vaccines.

## 9.2. Setting

The study population will consist of individuals aged 60 and older within the VHA system from earliest date of vaccine availability to 31 May 2026.

### 9.2.1. Inclusion Criteria

Three cohorts will be defined for the main analyses.

A. A cohort of individuals who received ABRYSVO will form the ABRYSVO cohort and must have:
    - A record for at least one dose of ABRYSVO in the study period from earliest date of vaccine availability to 31 May 2026; the date of ABRYSVO vaccination will define the index date for this cohort
    - No record of an RSV vaccine from a manufacturer other than Pfizer

B. A cohort of individuals who did not receive ABRYSVO but received another vaccine will form the contemporary vaccinated control cohort and must have:
    - A record for another vaccine (e.g., influenza vaccine, COVID-19 vaccine, and other pre-specified vaccines such as shingles, hepatitis B listed in Section 9.3.3) within 30 days of a corresponding ABRYSVO vaccinee's vaccination date; the control's index date will be the date of the control's non-RSV vaccine
    - No record for any RSV vaccine on the index date or in the baseline period (i.e., 2 years prior to the index date)
        - Individuals in the vaccinated control cohort who go on to receive an RSV vaccine following their index date will be censored at the time of RSV vaccination. If the RSV vaccine is ABRYSVO, these individuals will contribute to the ABRYSVO cohort starting from the date of ABRYSVO receipt.

C. A cohort of individuals who did not receive ABRYSVO or another vaccine on the index date but had at least one vaccination record in the year prior to the index date will form the contemporary unvaccinated control cohort and must have:

    - No record for any RSV or other vaccine (e.g., those listed in Section 9.3.3) on the index date

        - This cohort will be assigned an index date matched to a corresponding ABRYSVO vaccinee's vaccination date. If the vaccination is associated with a healthcare encounter (i.e., inpatient or outpatient visit), the unvaccinated control will be required to have a healthcare encounter within 30 days of the assigned index date, and the date of the healthcare encounter will be set as the index date for the unvaccinated control.

        - Individuals in the unvaccinated control cohort who go on to receive an RSV vaccine following their index date will be censored at the time of RSV vaccination. If the RSV vaccine is ABRYSVO, these individuals will contribute to the ABRYSVO cohort starting from the date of ABRYSVO receipt.

    - Regular use of preventive medical care, defined as at least one vaccination record in the year prior to the index date.

In addition, individuals in all cohorts must meet the following inclusion criteria to be eligible for the study:

- At least 60 years of age on the index date
- At least 2 years of continuous enrollment in (i.e., no disenrollment from) VHA benefits (i.e., the baseline period) prior to the index date

### 9.2.2. Exclusion Criteria

Individuals meeting any of the following criteria will be excluded from the study:

- Individuals with a record for atrial fibrillation or other supraventricular arrhythmias during the baseline period

### 9.2.3. Subgroups

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

- Individuals with specific comorbidities identified as high risk for severe RSV by the CDC, defined as individuals diagnosed with chronic cardiovascular disease (CHF and coronary artery disease), chronic lung disease (COPD and asthma), diabetes mellitus, neurologic conditions, kidney disorders, liver disorders, or hematologic disorders;[15,16]

- Individuals with weakened immune systems (i.e., individuals diagnosed with symptomatic HIV/AIDS, hematologic malignancy, or other immune conditions; individuals diagnosed with solid malignancy, organ transplant, or rheumatologic/inflammatory conditions, all of whom were administered chemotherapy or immune modulators; individuals diagnosed with rheumatologic/inflammatory conditions and administered systemic corticosteroids; or individuals who were administered chemotherapy, immune modulators, or systematic steroids for at least 14 days);[17]

- Different age groups defined by age on the index date, e.g., 60 to 69 years, 70 to 79 years, ≥80 years;

- Individuals enrolled in the VHA with dual coverage who are also identified in the CMS Medicare administrative claims data, which will be linked to the CDW to supplement the data for a more complete evaluation of healthcare encounters;

- Females enrolled in the VHA (pending sufficient sample size).

Additional subgroups of interest may be assessed as additional information becomes available from ongoing clinical trials, VAERS, and other sources that will inform the ABRYSVO safety profile.

## 9.3. Variables

### 9.3.1. Exposure of Interest

Administration of ABRYSVO post-approval will be identified based on the following (see Annex 3 Table A-1 for additional details):

- CPT code 90678, OR

- 10 and 11-digit NDCs 0069-0207-01, 0069-0250-01, 0069-0344-01, 0069-0344-05, 0069-0344-10; OR

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

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

### 9.3.2. Outcomes

The study's primary outcome, new onset atrial fibrillation, will be identified by a diagnosis code for atrial fibrillation in any setting during the 0-3 day risk interval (or 0-1 day or 0-30 day risk interval for secondary analysis), or corresponding control interval, followed by a confirmatory diagnosis within 30 days after the initial diagnosis. To be considered an incident case, no diagnosis for atrial fibrillation or other supraventricular arrhythmias should be observed in the 2 years prior to the index date (i.e., "clean window," the occurrence-free baseline period used to define incident outcomes during which individuals enter the study cohort only if the safety event did not occur during this period).[5,6]

The secondary outcome of the study will be new onset supraventricular arrhythmia, including atrial fibrillation, and will be identified in the same manner as the primary outcome (i.e., a diagnosis code for the event in any setting during the risk interval, or control interval, followed by a confirmatory diagnosis within 30 days after the initial diagnosis, and no diagnosis code for atrial fibrillation or other supraventricular arrhythmias in the 2-year clean window).

The study outcomes and operational definitions of the outcome variables based on ICD-10-CM diagnosis codes are outlined in Table 1. ICD-10-CM diagnosis codes occurring in any position (i.e., primary or secondary) in outpatient (including ED) and/or inpatient settings will be used to identify safety events.

**Table 1. Safety events, including outcome algorithms and risk and control intervals**

| Safety Event | Operational Definition<br>Defined by the presence of any of the following **ICD-10-CM** codes (inclusive): | Setting (IP, OP) | Clean Window | Risk Interval (Days) | Post-Vaccination Control Interval (Days) |
|---|---|---|---|---|---|
| Atrial fibrillation (primary outcome)[46] | • I48.0, Paroxysmal atrial fibrillation<br>• I48.19, Other persistent atrial fibrillation<br>• I48.20, Chronic atrial fibrillation, unspecified<br>• I48.91, Unspecified atrial fibrillation | IP or OP | 2 years | Primary: 0-3<br>Secondary: 0-1 and 0-30 | Primary: 4-10<br>Secondary: 2-8 and 31-61 |
| Supraventricular arrhythmia, including atrial fibrillation (secondary outcome)[46] | Paroxysmal tachycardia<br>• I47.0, Re-entry ventricular arrhythmia<br>• I47.10, Supraventricular tachycardia, unspecified<br>• I47.11, Inappropriate sinus tachycardia<br>• I47.19, Other supraventricular tachycardia<br>• I47.9, Paroxysmal tachycardia, unspecified<br><br>Atrial fibrillation:<br>• See "Atrial fibrillation (primary outcome)" above<br><br>Atrial flutter:<br>• I48.3, Atrial flutter<br>• I48.4, Atypical atrial flutter<br>• I48.92, Unspecified atrial flutter | IP or OP | 2 years | Primary: 0-3<br>Secondary: 0-1 and 0-30 | Primary: 4-10<br>Secondary: 2-8 and 31-61 |

**Table 1. Safety events, including outcome algorithms and risk and control intervals**

| Safety Event | Operational Definition<br>Defined by the presence of any of the following **ICD-10-CM** codes (inclusive): | Setting (IP, OP) | Clean Window | Risk Interval (Days) | Post-Vaccination Control Interval (Days) |
|---|---|---|---|---|---|
| | Other cardiac arrhythmias:<br>• I49.1, Atrial premature depolarization<br>• I49.5, Sick sinus syndrome<br>• I49.8, Other specified cardiac arrhythmias including Brugada syndrome, coronary sinus rhythm disorder, ectopic rhythm disorder, nodal rhythm disorder | | | | |

**Abbreviations:** ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IP, inpatient; OP, outpatient.

The risk intervals were selected based on published literature and biological plausibility.[7-14] A safety event will be counted if it can be assigned to 1) the risk interval following ABRYSVO, 2) the post-vaccination control interval (SCRI design), or 3) risk interval for the contemporary vaccinated or unvaccinated controls. The risk intervals for outcome evaluation for contemporary vaccinated or unvaccinated controls will be the same as for individuals who received ABRYSVO.

Events outside these intervals will not be counted. Only the individual's first instance of a safety event following the 2-year clean window will be included; this means that if a safety event is identified but diagnosis codes corresponding to the safety event are also observed during the clean window, it will not be counted to rule out pre-existing events.

### 9.3.3. Baseline Characteristics

Data elements regarding baseline demographic and clinical characteristics will be assessed at index or based on a 2-year baseline period prior to the index date (i.e., date of vaccination with ABRYSVO for ABRYSVO vaccinated individuals, date of vaccination with another vaccine for contemporary vaccinated controls, and assigned index date for contemporary unvaccinated controls). The demographic and clinical characteristics that will be assessed may include, but are not limited to, those that are listed below. The final list of baseline characteristics will be defined in the SAP based on feasibility and availability. All diagnoses, procedures, and medications will be identified by the ICD-10-CM diagnosis codes, ICD-10-PCS (procedure coding system) codes, CPT, or HCPCS procedure codes, and generic drug names, as appropriate (Annex 3 Table A-2 and Annex 3 Table A-3; codes listed in the Annexes will be reviewed and updated in the SAP as necessary).

**Demographics:**

- Age
- Sex
- Race/ethnicity
- VHA service area (i.e., US region)
- Marital status

**ABRYSVO characteristics:**

- Month and year of vaccination
- Care setting of vaccination

**Clinical characteristics:**

- Smoking status
- BMI
- History of atrial fibrillation prior to baseline period (based on all available data rather than 2-year baseline)
- History of anaphylaxis/allergic reactions
- Previous anaphylaxis of vaccine component
- History of hospitalizations
- Frailty index
- CCI
- Alcohol abuse
- Alcohol dependence (excluding alcohol abuse)*
- Selected comorbidities
    - Cardiovascular
        - Cardiomyopathy
        - CAD
        - Cardiac valvular disease*
        - CHF
        - Conduction disorder
        - Congenital heart disease*
        - Heart failure
        - Hypertension
        - Myocarditis*
        - Pericarditis*
        - Stroke/Transient ischemic attack
    - Hematological
        - Bleeding diathesis or condition associated with prolonged bleeding
        - Hematologic malignancy
        - Sickle cell disease
        - VTE
    - Hepatic

        - HBV
        - HCV
        - Liver disease
    - Immunological
        - Autoimmune disease
        - Immunocompromising conditions[17]
            - Solid organ transplant
            - HSCT
            - Hematologic or solid malignancy
            - HIV/AIDS
            - Other immune deficiencies
    - Neurological
        - Dementia (i.e., Alzheimer's disease and related disorders, senile dementia)
        - Neurological disease
    - Respiratory
        - Asthma
        - Chronic bronchiectasis
        - COPD/interstitial lung disease
        - Obstructive sleep apnea*
        - Pneumonia*
    - Other
        - Cancer
        - Chronic kidney disease/dialysis
        - Diabetes mellitus
        - Down syndrome
        - Gout
        - Hyperlipidemia
        - Hyperthyroidism (excluding autoimmune thyroiditis)*
        - Illicit drug use (e.g., cocaine)*
        - Stimulant use (e.g., amphetamines, caffeine)*
        - Metabolic syndrome*
        - Panic disorders*
        - Reaction to stress*
- Concomitant medications**
    - Antineoplastic (i.e., 7-con-o-methylnogaril, aclacinomycin a, , cisplatin, doxorubicin, etaracizumab, ifosfamide, melphalan, mitoxantrone, trastuzumab)
    - Bisphosphonates (i.e., alendronate)
    - Cardiovascular (i.e., adenosine, dobutamine)
    - Central nervous system (i.e., clozapine, morphine)
- Other medications (identified outside of the AHA criteria)
    - Nonsteroidal anti-inflammatory drugs (NSAID)
    - Respiratory (i.e., theophylline)
    - Ivabradine
    - Digitalis

- Concurrent immunizations
  - Seasonal influenza vaccine
  - COVID-19
  - Tetanus diphtheria and pertussis (Tdap or Td)
  - Chickenpox (varicella)
  - Shingles (herpes zoster recombinant and/or live)
  - HPV
  - Pneumococcal conjugate
  - Pneumococcal polysaccharide
  - Hepatitis A
  - Hepatitis B
  - MenACWY and MenB
  - Haemophilus influenzae type b

* ICD-10-CM diagnosis codes, ICD-10-PCS codes, CPT, or HCPCS procedure codes will be provided in the SAP.
** The list of concomitant medications was derived from the AHA's scientific statement regarding drug-induced arrhythmias, which is based on a literature search.[47] Since the level of evidence varies substantially across articles and reports identified by the AHA, only drugs with relative risk (i.e., incidence rate ratio, hazard ratio, or odds ratio) or 95% confidence interval upper limit greater than 3 or incidence/proportion of patients experiencing atrial fibrillation greater than 10% were included to ensure a higher degree of certainty that the drug is actually associated with atrial fibrillation. Drugs with evidence based on case reports only were not included. Note that alcohol was not included despite meeting the criteria as it is included as a clinical characteristic.

### 9.4. Data Sources

The VHA is the largest integrated health care system in the US, providing both inpatient and outpatient clinical care to over 9 million Veterans enrolled at more than 170 medical centers and 1,113 community-based outpatient clinics.[18] VHA's health care delivery system is organized regionally around 18 VISNs across the US. Each VISN is responsible for health care planning and resource allocation in a particular geographical region. For example, VISN 1 covers VHA facilities in Massachusetts, Connecticut, New Hampshire, Maine, and Rhode Island, while VISN 17 oversees the facilities in Texas. The VHA also maintains its own mortality data where 99% of enrollees' deaths are reported within one month of occurrence.

The objectives of this study will be addressed using data from VHA's CDW, which is an integrated EHR system with a centralized data warehouse that is updated on a daily basis. The CDW stores data in separate databases, one for each type of clinical information (e.g., inpatient medication, inpatient admission, outpatient medication, outpatient visit). Individual demographic information such as date of birth and gender are also available. Immunization records include information on manufacturer, lot number, injection site, and concurrent immunizations. The CDW lacks information on care received outside of a VHA facility.

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

The VHA database is an appropriate data source to evaluate the safety of the ABRYSVO vaccine for the following reasons. First, VHA data are refreshed daily and would thus enable early data analysis. Second, the VHA population is on average older than the general US population.[48] Of these, about 30% (roughly 1,000,000 individuals) use VHA health services almost exclusively (i.e., those with a priority group of 1 or 4; Veterans assigned to Priority group 4 are either accepting VA assistance or housebound benefits, or have been determined to be "catastrophically disabled" by the VA.[49]), which lends itself to having complete, longitudinal healthcare data for such individuals who may be at higher risk of RSV due to older age.[50,51] These priority groups include Veterans with the highest levels of service-connected disability and are therefore, the highest priority for VHA care.[49] Finally, the VHA population has, on average, more comorbid conditions than the general population, which also indicates that these individuals may be at higher risk of RSV.[52] While the VHA population is predominantly male (approximately 90%), and thus lacks generalizability to females, it will still provide a useful setting to examine real-world vaccine safety.

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

### 9.5. Study Size

All individuals in the VHA database who meet the eligibility criteria as described in Section 9.2 will be included. The sample size achieved will depend on the number of individuals administered ABRYSVO identified within the VHA database during the study period, which will increase over time as the data will be analyzed at two different time points to add newly vaccinated individuals and matched controls.

#### 9.5.1. Power

The study population will consist of VHA enrollees 60 years of age and older without a prior history of atrial fibrillation as assessed during a 2-year baseline period. Of the nine million VHA enrollees,[18] it is estimated that 56% are at least 60 years of age[53] and one million VHA enrollees have a prior history of atrial fibrillation.[54] Based on previous studies using VHA data, it is further estimated that 85% of the eligible population will have continuous enrollment during a 2-year baseline period.[55]

This results in approximately 3.8 million VHA enrollees estimated as eligible for inclusion in the study.

Table 2 illustrates the estimated sample size required for the weighted Cox regression using the internal comparator cohort design. Based on an expected background rate of 33.9 per 1,000 person-years for incident atrial fibrillation reported for male Medicare beneficiaries 65 years of age and older,[6] assuming controls (vaccinated or unvaccinated) will be matched to ABRYSVO vaccinated individuals on a 4:1 ratio, a sample size of 47,536 and 147,890 individuals vaccinated with ABRYSVO is needed to detect a 2-fold and 1.5-fold increase in the IRR with a power of 80% and an alpha level of 0.05, respectively.[56] Power of ≥ 80% is typically desirable in drug safety research and the FDA views a RR of >3 as meaningful, so these have also been used for the power calculations.[57] The secondary objective's comparative analyses will only be conducted when a sufficient number of atrial fibrillation events have been observed for the analyses to be adequately powered.

Vaccine uptake will be monitored during the course of the study. If a sufficient number of atrial fibrillation events are not observed by the end of the planned study period, Pfizer will discuss contingency plans with the FDA to achieve the target sample size.

**Table 2. Sample Size Calculations for the Weighted Cox Regression Using the Internal Comparator Cohort Design**

| Matching ratio (controls: ABRYSVO vaccinated) | Incidence Rate Ratio | Number of controls needed in each comparator cohort (N) | Number of ABRYSVO vaccinated individuals needed (N) |
|---|---|---|---|
| 4:1 | 1.5 | 591,560 | 147,890 |
| | 2.0 | 190,145 | 47,536 |
| | 3.0 | 68,664 | 17,166 |
| 2:1 | 1.5 | 338,035 | 169,018 |
| | 2.0 | 105,636 | 52,818 |
| | 3.0 | 36,973 | 18,487 |

**Notes:**
The power calculations are based on assuming two sided α=0.05, a power of 80%, and a risk interval of 4 days corresponding to the 0-3 day risk interval. A background rate of 33.9 incident atrial fibrillation events per 1,000 person years as observed among male Medicare beneficiaries 65 years of age and older was used.

### 9.6. Data Management

Data for this study will be stored and extracted from the VHA database (previously described in Section 9.4) that contains information about patient demographics, vaccinations, procedures, diagnoses, and death. Personal data will reside on VHA servers only and will not be transferred off the VHA servers to third parties (see Section 10.1 for further details).

### 9.6.1. Case Report Forms

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

For case validation/adjudication via the medical records review study component, a CRF will be used to abstract data from VA CDW EHRs, as necessary, for atrial fibrillation cases among individuals vaccinated with ABRYSVO who are identified in the safety analyses (see Section 9.7.2.4 for further details). CRFs will include the encrypted study ID and will not contain any identifiable information. A CRF is required and should be completed for each included patient described above. The completed original CRFs will not be made available in any form. The CRF will consist of two parts: (1) a chart review CRF that will be populated based on a direct extraction of relevant information from the VA CDW for review by the adjudicators; (2) an adjudication page that will be completed by an adjudicator after reviewing data in the completed CRFs. The VA shall ensure that the CRFs are securely stored at White River Junction VA in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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

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

### 9.6.2. Record Retention

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

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

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

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

### 9.7. Data Analysis

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

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

#### 9.7.1. Baseline Characteristics

Baseline demographics and clinical characteristics for individuals administered ABRYSVO, contemporary vaccinated controls, and contemporary unvaccinated controls will be summarized using descriptive statistics, consisting of the mean, SD, median, and IQR values for continuous variables and frequency distributions for categorical variables. Standardized differences will be calculated between individuals who received ABRYSVO and contemporary vaccinated controls, and between individuals who received ABRYSVO and contemporary unvaccinated controls. Standardized differences <10% will indicate that the characteristics between recipients of ABRYSVO and the comparator cohort are balanced.

Descriptive statistics will also be used to summarize ABRYSVO characteristics, including calendar year and month of vaccination and care setting of vaccination (e.g., outpatient clinic, pharmacy, inpatient ward).

#### 9.7.2. Safety Analyses

Several analyses corresponding to the internal comparator cohort and SCRI designs will be conducted to evaluate safety events associated with ABRYSVO. Analyses will be conducted among all individuals meeting the study eligibility criteria.

Incidence rates for the primary and secondary outcomes will be compared to rates observed in the following control groups:

- Internal comparator cohorts: two random samples of contemporaneous vaccinated and unvaccinated matched controls in the VHA system.
- Self-controls: cases who experience safety events following vaccination using the SCRI design to compare the risk interval following vaccination to post-vaccination non-risk intervals in the same individual.

##### 9.7.2.1. Incidence Rates of Safety Events

Incidence rates per 1,000 patient-years (and corresponding 95% CIs) will be calculated for atrial fibrillation and supraventricular arrhythmia observed in the risk interval as the total number of incident events divided by the total observation time.

#### 9.7.2.2. Comparison with Contemporary Controls

ATT weighting will be used to ensure baseline comparability between the ABRYSVO vaccinated cohort vs. contemporary vaccinated control cohort and between the ABRYSVO vaccinated cohort vs. contemporary unvaccinated control cohort. ATT weighting creates a "pseudo-population" in which the distribution of covariates is, on average, the same in each cohort.[58] Specifically, ATT weights will be calculated to allow for estimation of the average treatment effect among individuals receiving ABRYSVO.[59] This approach will be taken to ensure that inference from the analysis will be applicable to this population. Individuals receiving ABRYSVO will receive an ATT weight of one. Individuals not receiving ABRYSVO will receive an ATT weight equal to the odds of receiving ABRYSVO conditional on their demographic and clinical characteristics as of the index date, which will be calculated based on the PS. The PS is defined as an individual's probability of receiving ABRYSVO, conditional on observed baseline covariates, and will be calculated using a logistic regression model. The logistic regression model will include the cohort variable (i.e., ABRYSVO vs. vaccinated or unvaccinated control) as the dependent variable, and the independent variables will include variables deemed clinically important and baseline covariates that have standardized differences ≥10% between the two cohorts. Specifically, ATT weights will be PS/(1-PS) for individuals with no record of ABRYSVO. The distribution of weights will be examined to assess extreme values, and truncation will be considered if necessary.

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

#### 9.7.2.3. SCRI Design using the Conditional Poisson Regression for Comparison to Post-vaccination Control Intervals

SCRI design with post-vaccination control time period will include cases (i.e., individuals vaccinated with ABRYSVO who experience safety events following vaccination) who have at least 40 days (or 38 days or 91 days for secondary analysis) of enrollment post-index to compare the incidence of safety events occurring in the risk interval following vaccination with the incidence of safety events occurring during the post-vaccination control interval.

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

#### 9.7.2.4. Case Validation/Adjudication via Medical Records Review

Diagnostic validation of identified atrial fibrillation cases among individuals administered ABRYSVO will be conducted in a randomly selected representative sample of up to 100 cases per interim/final report, as available and feasible.

An adjudication charter will be developed to govern medical records review and case validation/adjudication. Specifically, validation of atrial fibrillation cases will be performed through

patient medical chart review in collaboration with an adjudication committee consisting of trained healthcare professionals.[60] Further details will be described in the SAP.

PPV will be calculated based on adjudication results as the proportion of atrial fibrillation cases deemed as true cases among the total number of adjudicated cases. Generally, PPV of 70% or greater is considered as sufficiently high.[61] To be conservative, if the lower bound of the 95% CI of the PPV is less than 70% at the interim analysis, the algorithm used to identify incident atrial fibrillation using codified data may be updated in subsequent analyses and atrial fibrillation cases identified with the new algorithm will be re-adjudicated. If the lower bound of the 95% CI for PPV is equal to or greater than 70% in the interim report, chart adjudication may be waived for the final report.

#### 9.7.2.5. Analysis of Risk Factors for Atrial Fibrillation

If an increased risk of atrial fibrillation following ABRYSVO vaccination is observed from the analyses described above, a risk factor analysis will be conducted via logistic regression among individuals vaccinated with ABRYSVO. Specifically, up to ten baseline characteristics will be selected a priori (e.g., age, sex, race/ethnicity, history of atrial fibrillation prior to baseline period, co-administration of influenza vaccine, COVID-19 vaccine, or other pre-specified vaccines such as shingles, hepatitis B] listed in Section 9.3.3) and included in a multivariable logistic regression model with atrial fibrillation as the outcome to determine if any of the select baseline characteristics may be risk factors associated with atrial fibrillation.

Co-administration with other vaccines and patient characteristics during the two-year baseline period (or based on all available data for history of atrial fibrillation) will also be described to enhance understanding of the healthcare profiles of atrial fibrillation cases. Co-administration will be defined as receipt of ABRYSVO and another vaccine (i.e., influenza vaccine, COVID-19 vaccine, or other pre-specified vaccines [e.g., shingles, hepatitis B] listed in Section 9.3.3) on the same day.[62]

### 9.7.3. Subgroup Analysis

Separate analyses of baseline characteristics and safety analyses in subgroups of interest may be conducted based on feasibility, sample size, and data availability. These analyses will be performed for all subgroups listed in Section 9.2.3. For each subgroup, a new set of ATT weights will be generated in the comparison with contemporary vaccinated and unvaccinated controls, and analyses will be conducted as described above.

### 9.7.4. Sensitivity Analysis

The following sensitivity analysis will be conducted. Further details and any additional sensitivity analyses that may be conducted will be described in the SAP.

#### 9.7.4.1. Safety Analyses of Negative Control Outcomes

A negative control outcome is defined as an outcome that shares the same potential sources of bias with the primary outcome (i.e., atrial fibrillation) but cannot plausibly be related to the exposure of interest (i.e., vaccination with ABRYSVO).[63] As such, assessment of negative control outcomes has

been used as a helpful tool to detect unmeasured confounding, selection bias, and misclassification bias in epidemiological studies.[64,65]

Risk of select negative control outcomes associated with ABRYSVO will be assessed following the same methodology described in Section 9.7.2. A null association between ABRYSVO and a negative control outcome suggests the observed association between ABRYSVO and atrial fibrillation is unlikely to be due to confounding or other bias, thus providing additional support for the validity of the analysis.

The specific negative control outcome for this study will be specified in the SAP and will be based on the FDA-suggested negative health seeking behavior outcomes, such as cataracts, hemorrhoids, and appendicitis, evaluated in past vaccine studies conducted by the CDC and FDA.[66-68]

### 9.8. Quality Control

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

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

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

### 9.9. Strengths and Limitations of the Research Methods

To identify individuals who experienced safety events associated with ABRYSVO, there will be a comparison of individuals vaccinated with ABRYSVO to contemporary vaccinated or unvaccinated controls which yields a more interpretable result than other planned analyses using SCRI (i.e., the increased risk of experiencing a specific safety event due to ABRYSVO). The potential for selection bias (i.e., confounding by indication, healthy user bias) will be mitigated by comparing baseline

demographic and clinical characteristics between those administered ABRYSVO and the vaccinated or unvaccinated controls. Potential confounders can be accounted for in the statistical analysis to achieve balance between cohorts, using methods such as ATT weighting.[69] Unmeasured confounding may remain, for instance due to lack of information on clinically important covariates such as family history of atrial fibrillation and left ventricular hypertrophy, but will be assessed through sensitivity analysis of a negative control outcome. To further reduce the potential for healthy user bias, unvaccinated controls will be required to have similar healthcare-seeking behaviors as ABRYSVO vaccinees, including at least 2 years of enrollment in and no disenrollment from VHA benefits prior to their matched index date and at least one vaccination record during the one year prior to their matched index date.

In addition, the SCRI method offers some key advantages. The SCRI approach inherently adjusts for within-individual time-stable confounders, such as age, sex, and confounding by indication. While control intervals can be defined both pre- and post- vaccination, the current study will only use a post-vaccination control period because individuals may be more vigilant for the reporting of possible safety events after they receive a vaccine than before vaccination, which may bias the comparison between a post-vaccine risk interval with a pre-vaccine control interval.[70] Specifically, safety events may be more likely to be reported, or care sought for, after vaccination with ABRYSVO than before, which may result in bias against ABRYSVO. The SCRI design is based on several assumptions including that the occurrence of risk of the event in one risk interval is independent of the occurrence in the subsequent or previous interval.

To reduce possible outcome misclassification, confirmatory diagnosis of atrial fibrillation and supraventricular arrhythmias will be required within 30 days of the initial diagnosis. In addition, chart review adjudication will be used to ensure a high PPV for identifying atrial fibrillation. If the PPV is not considered high enough, the algorithm used to identify incident atrial fibrillation using codified data may be updated in subsequent analyses.

The study population has been kept as broad as possible in order to capture safety events that occur among all individuals vaccinated with ABRYSVO. However, individuals who ever had a record of RSV vaccine from a different manufacturer are excluded to ensure that safety signals are not attributable to different RSV vaccines. Thus, the study results are not generalizable to patients who received RSV vaccines from different manufacturers.

The VHA CDW provides a range of benefits, including its comprehensive structure, large number of variables, and electronic accessibility. The VHA CDW also includes EHR data that include structured fields and open fields (such as physician notes, which will be used for case validation, as needed). Importantly, the VHA CDW retains electronic immunization records that include manufacturer name and lot numbers, facilitating the identification of brand-specific vaccines, such as ABRYSVO. Moreover, the VHA CDW data are updated on a daily basis.

However, there are several limitations when relying on VHA data that should be noted. First, there could be gaps in the data since individuals may receive healthcare services outside of VHA facilities. As such, if individuals receive ABRYSVO outside of a VHA facility, this information will not be captured in the VHA EHR system. Other medical information may be similarly under-captured in the VHA EHR system if the individuals seek care in non-VHA facilities, resulting in potential

residual confounding. For example, veterans with secondary insurance or veterans who are 65 years of age and older who have Medicare may receive health care services outside of VHA facilities. One study on VHA enrollees in seven different states found that of all individuals admitted to VHA hospitals in 2007, one fifth also had a non VHA hospitalization during that year.[71] Another study reported that about 53% of Veterans 65 years of age or older who were dually eligible for VHA and Medicare services in 2003 and 2004 used both.[72] Hence, it is important to note that data on vaccination status and clinical information may be incomplete. As such, the CDW data will be supplemented and linked with Medicare administrative claims data at the patient level to ensure a more comprehensive evaluation of the care an individual receives. Linking variables are available in the data to allow for patient-level linking of the two data sources. Given the older age of many veterans, it is likely that these individuals have secondary coverage with Medicare.

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

### 9.10. Other Aspects

Not applicable.

## 10. PROTECTION OF HUMAN PARTICIPANTS

### 10.1. Patient Information

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

The personal data will be stored at VA in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. VA will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, VA shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, no identifiable nor de-identified data will be transferred outside the VA. Rather, only aggregate data will be transferred. High standards of confidentiality and protection of patients' personal data consistent with the vendor contract and applicable privacy laws will be maintained.

No personal data is planned to be transferred off the VA servers. Specifically, the Clinical Epidemiology Program of the White River Junction Veterans Affairs Medical Center will conduct this safety surveillance study with sponsorship from Pfizer and assistance from Analysis Group, Inc. The project will be led by the VA, with Dr. Dalle Lucca serving as the Principal Investigator. Data access will be granted through VINCI. VHA data will not be provided to Pfizer or Analysis

Group. Rather, only VA employees, including those with research service 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. Dalle Lucca. Given the sensitive nature of healthcare data, comprehensive security measures will be implemented to ensure the confidentiality, integrity, and protection of Veterans' privacy and healthcare data.

### 10.2. Patient Consent

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

### 10.3. Institutional Review Board (IRB)/Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer. The study protocol will be reviewed by the IRB of White River Junction Veterans Affairs Medical Center.

### 10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for GPP issued by the International Society for Pharmacoepidemiology,[73] the FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting, Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data[74] and GEP guidelines issued by the IEA.[75]

## 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Structured Data Analysis

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

Human Review of Unstructured Data

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

The requirements for reporting safety events on the NIS AEM Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the data collection tool (e.g., chart abstraction form) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

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

- For exposure during pregnancy in studies of pregnant women, data on the exposure to ABRYSVO during pregnancy, are not reportable unless associated with serious or non-serious AEs.

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

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

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

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

- *“Your Reporting Responsibilities (YRR) with Supplemental Topics.”*

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

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This protocol will be posted on publicly available registers (i.e., EU PAS) prior to the start of data collection. The final study results will be made publicly available and may be submitted for publication in a peer reviewed medical journal.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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## 14. LIST OF TABLES



## 15. LIST OF FIGURES

## ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

## ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

N/A

## ANNEX 3. ADDITIONAL INFORMATION

### Annex 3 Table A-1. RSV Vaccine Exposure CPT and NDC Codes

| Code Type | Code | Manufacturer/Descriptions |
|---|---|---|
| NDC | 0069-0207-01 | Pfizer, Inc. |
| | 0069-0250-01 | Pfizer, Inc. |
| | 0069-0344-01 | Pfizer, Inc. |
| | 0069-0344-05 | Pfizer, Inc. |
| | 0069-0344-10 | Pfizer, Inc. |
| CPT | 90678 | A bivalent preF vaccine product administered into the muscle to protect against respiratory syncytial virus |

**Note:**
Additional codes will be added for RSV vaccines as they become available.

### Annex 3 Table A-2. Demographic and Clinical Characteristics Definitions

| Variable | Description | Operational definition |
|---|---|---|
| **Demographic Characteristics** | | |
| Age | Continuous variable;<br>Categorical variable:<br>• 60-64<br>• 65–69<br>• 70-74<br>• 75-79<br>• 80-84<br>• 85-89<br>• ≥90 | Age on the date of ABRYSVO vaccination for ABRYSVO vaccinated individuals, date of vaccination with another vaccine for contemporary vaccinated controls, or assigned index date for contemporary unvaccinated controls |
| Sex | Categorical variable:<br>• Male<br>• Female<br>• Unknown | |

| Variable | Description | Operational definition |
|---|---|---|
| Race/ethnicity | Categorical variable:<br>• White, non-Hispanic<br>• Black<br>• Hispanic ethnicity, any race<br>• Asian<br>• Native Hawaiian or Pacific Islander<br>• American Indian or Alaskan native<br>• Two or more races<br>• Unknown | |
| Service area | Geographic regions in the US;<br>Categorical variable:<br>• South<br>• Midwest<br>• West<br>• Northeast<br>• Other<br>• Unknown | Region associated with the most recent healthcare encounter prior to index date |
| Marital status | Categorical variable:<br>• Currently married<br>• Not currently married | |
| **Clinical Characteristics** | | |
| Smoking Status | Dichotomous variable | ICD-10-CM codes:<br>• F17.200, Nicotine dependence, unspecified, uncomplicated<br>• Z7.20, Tobacco use<br>• Z87.891, Personal history of nicotine dependence |
| Body mass index (BMI) | Continuous variable;<br>Categorical variable:<br>• Underweight (<18.5)<br>• Normal weight (18.5–<25)<br>• Overweight (25–<30)<br>• Obese (30–<40)<br>• Severe obesity (≥40)<br>• Unknown | Calculated from height and weight data ($kg/m^2$) |

| Variable | Description | Operational definition |
|---|---|---|
| History of anaphylaxis/ allergic reactions | Dichotomous variable | ICD-10-CM code:<br>• Z87.892 Personal history of anaphylaxis<br>• Z88.0–Z88.6, Z88.8, Z88.9, Allergy status to drugs, medications and biological substances, excluding serum and vaccine<br>• T78.00xx–T78.09xx, Anaphylactic reaction due to food, initial encounter, subsequent encounter and sequela<br>• T78.2xxx, Anaphylactic shock, initial encounter, subsequent encounter and sequela<br>• T78.3xxx, Angioneurotic edema, initial encounter, subsequent encounter and sequela<br>• T78.41xx, Arthus phenomenon<br>• T80.51xx, Anaphylactic reaction due to administration of blood and blood products, initial encounter, subsequent encounter and sequela<br>• T80.59xx, Anaphylactic reaction due to other serum, initial encounter, subsequent encounter and sequela<br>• T88.6xxx, Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter, subsequent encounter and sequela |
| Previous anaphylaxis of vaccine component | Dichotomous variable | ICD-10-CM codes:<br>• T80.52xx, Anaphylactic reaction due to vaccination, initial encounter, subsequent encounter and sequela<br>• Z28.04, Immunization not carried out because of patient allergy to vaccine or component |

| Variable | Description | Operational definition |
|---|---|---|
| | | • Z88.7, Allergy status to serum and vaccine |
| History of hospitalizations | Dichotomous variable; Continuous variable | Defined by having any hospitalizations (dichotomous) and number of hospitalizations (continuous) |
| Frailty index[76] | Continuous variable | ICD-9-CM codes available in Appendix Table 1 of Segal et al, 2017. ICD-9-CM codes mapped to ICD-10-CM codes. |
| Charlson Comorbidity Index (CCI)[77] | Continuous variable | ICD-10-CM codes:<br>• I21.x, I21.xx, I22.x, I25.2, Myocardial infarction<br>• 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<br>• 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<br>• 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<br>• F00.x–F03.x, F00.xx–F03.xx, F05, F05.1, G30.x, G31.1, Dementia<br>• 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<br>• 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<br>• K25.x–K28.x, Peptic ulcer disease |

| Variable | Description | Operational definition |
|---|---|---|
| | | • 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<br>• E10.0, E10.1x, E10.6x, E10.6xx, E10.8, E10.9, E11.0x, E11.1x, E11.6x, E11.6xx, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0x, E13.1x, E13.6x, E13.6xx, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9, Diabetes without chronic complication<br>• 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<br>• 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<br>• 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<br>• 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 |

| Variable | Description | Operational definition |
|---|---|---|
| | | • 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<br>• C77.x–C80.x, C77.xx–C80.xx, Metastatic solid tumor<br>• B20, B97.35, AIDS/HIV |
| Alcohol abuse | Categorical variable | ICD-10-CM codes<br>• F10, Alcohol related disorders |
| History of atrial fibrillation prior to baseline period based on all available data | Categorical variable | ICD-10-CM codes, identified prior to the baseline period based on all available data<br>• I48.0, Paroxysmal atrial fibrillation<br>• I48.19, Other persistent atrial fibrillation<br>• I48.20, Chronic atrial fibrillation, unspecified<br>• I48.91, Unspecified atrial fibrillation |
| Comorbidities | Categorical variable<br>*Cardiovascular*<br>• Cardiomyopathy<br>• CAD<br>• CHF<br>• Cardiac valvular disease*<br>• Heart failure<br>• History of congenital heart disease*<br>• Hypertension<br>• Myopericarditis*<br>• Stroke/Transient ischemic attack<br>*Hematological*<br>• Bleeding diathesis or condition associated with prolonged bleeding<br>• Hematologic malignancy<br>• Sickle cell disease | *Cardiovascular*<br>Cardiomyopathy:<br>▪ ICD-10-CM codes:<br>o I42.x, Cardiomyopathy<br>CAD:<br>▪ ICD-10-CM codes:<br>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, I25.811, I25.812, CAD |

| Variable | Description | Operational definition |
|---|---|---|
| | • VTE<br>*Hepatic*<br>• HBV<br>• HCV<br>• Liver disease<br>*Immunological*<br>• Autoimmune disease<br>• Immunocompromising conditions<br>o Solid organ transplant<br>o HSCT<br>o Hematologic or solid malignancy<br>o HIV/AIDS<br>o Other immune deficiencies<br>*Neurological*<br>• Dementia (i.e., Alzheimer's disease and related disorders, senile dementia)<br>• Neurological disease<br>*Respiratory*<br>• Asthma<br>• Chronic bronchiectasis<br>• COPD/interstitial lung disease<br>• Obstructive sleep apnea*<br>• Pneumonia*<br>*Other*<br>• After cardiac and other surgery, including pulmonary esophageal, and childhood cardiac surgery*<br>• Cancer<br>• Chronic kidney disease/dialysis<br>• Diabetes mellitus<br>• Down syndrome<br>• Emotional and other stress*<br>• Gout<br>• Hyperlipidemia<br>• Hyperthyroidism (excluding autoimmune thyroiditis)* | CHF:<br>▪ ICD-10-CM codes:<br>o I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I43.x, I50.x, I50.xx, CHF<br>Heart failure:<br>▪ ICD-10-CM codes:<br>o 150.x, 150.xx, Heart failure<br>Hypertension:<br>▪ ICD-10-CM codes:<br>o H35.03x, Hypertensive retinopathy<br>o I10, I11.x–I16.x, I13.xx, Hypertensive diseases<br>o I67.4, Hypertensive encephalopathy diseases<br>Stroke/transient ischemic attack:<br>▪ ICD-10-CM codes:<br>o G43.601, G43.609, G43.611, G43.619, I60.9, I62.00, I61.9, I62.1, I62.9, I63.019, I63.119, I63.139, I63.20, I63.219, I63.22, I63.239, I63.30, I63.40, I63.50, I63.59, I66.09, I66.19, I66.29, I66.9, I67.89, I69.898, I69.90, I69.910, I69.911, I69.912, I69.913, I69.914, I69.915, I69.918, I69.919, I69.920, I69.921, I69.922, I69.923, I69.928, I69.941, I69.942, I69.943, I69.944, I69.949, I69.951, I69.952, I69.953, I69.954, I69.959, I69.961, I69.962, I69.963, I69.964, I69.965, I69.969, I69.990, I69.991, I69.992, I69.993, I69.998, Stroke<br>o G45, Transient ischemic attack<br>*Hematological*<br>Bleeding diathesis or condition associated with prolonged bleeding: |

| Variable | Description | Operational definition |
|---|---|---|
| | • Illicit drug use (e.g., cocaine)*<br>• Metabolic syndrome*<br>• Panic disorders*<br>• Stimulant use (e.g., amphetamines, caffeine)*<br><br>* ICD-10-CM diagnosis codes, ICD-10-PCS codes, CPT, or HCPCS procedure codes will be provided in the SAP. | ▪ ICD-10-CM codes:<br>o D65, Disseminated intravascular coagulation<br>o D66, Hereditary factor VIII deficiency<br>o D67, Hereditary factor IX deficiency<br>o D68, D68.x, D68.xx, Other coagulation defects<br>o D69, D69.x, D69.xx, Purpura and other hemorrhagic conditions<br>Hematologic malignancy:<br>▪ ICD-10-CM codes:<br>o C81, C82, C83, C88, C89, C90, C91, C92, C93, C94, C95, C96, Hematologic malignancy<br>Sickle cell disease:<br>▪ ICD-10-CM codes:<br>o D57, D57.x, D57.xx, D57.xxx, Sickle-cell disorders<br>VTE:<br>▪ ICD-10-CM codes:<br>o I26, I26.x, I26.xx, Pulmonary embolism<br>o I80, I80.x, I80.xx, I80.xxx, Phlebitis and thrombophlebitis<br>o I81, Portal vein thrombosis<br>o I82, I82.x, I82.xx, I82.xxx Other venous embolism and thrombosis<br>*Hepatic*<br>HBV:<br>▪ ICD-10-CM codes:<br>o B18.0, B18.1, Chronic viral hepatitis B<br>o B19.1, B19.1x, Unspecified viral hepatitis B<br>HCV:<br>▪ ICD-10-CM codes: |

| Variable | Description | Operational definition |
|---|---|---|
| | | ○ B18.2, Chronic viral hepatitis C<br>○ B19.2x, Unspecified viral hepatitis C<br>Liver disease:<br>▪ ICD-10-CM codes:<br>○ K70.x, K70.xx, Alcoholic fatty liver<br>○ K71.x, K71.xx, Toxic liver disease<br>○ K72.xx, Hepatic failure, not elsewhere classified<br>○ K73.x, Chronic hepatitis, not elsewhere specified<br>○ K74.x, K74.xx, Fibrosis and cirrhosis of liver<br>○ K75.x, K75.xx, Other inflammatory liver diseases<br>○ K76.x, K76.xx, Other diseases of liver<br>○ K77, Liver disorders in diseases classified elsewhere<br>*Immunological*<br>Autoimmune disease:<br>▪ ICD-10-CM codes:<br>○ D69.3, Immune thrombocytopenic purpura<br>○ E06.3, Autoimmune thyroiditis<br>○ G35, Multiple sclerosis<br>○ G61.0 and G65.0, GBS and sequelae of GBS<br>○ L40.x, L40.5x, Psoriasis<br>○ L93.x, Lupus erythematosus<br>○ M05.x, M05.xx, M05.xxx, Rheumatoid arthritis with rheumatoid factor<br>○ M06.x, M06.xx, M06.xxx, Other rheumatoid arthritis<br>○ M31.5, M31.6, Giant cell arteritis<br>○ M35.0x, Sicca (Sjogren's) syndrome |

| Variable | Description | Operational definition |
|---|---|---|
| | | ○ N05.9, Glomerulonephritis<br>○ D84.9, Immunodeficiency, unspecified<br>Immunocompromising conditions:<br>▪ Solid organ transplant<br>○ CPT codes:<br>▪ 32850–32856, Transplantation of lung<br>▪ 33930–33945, Transplantation of heart<br>▪ 44132, 44133, 47133, 47135, 47140–47147, Transplantation of liver<br>▪ 44135–44137, 44715, 44720, 44721, Transplantation of intestine<br>▪ 48160, 48550–48552, 48554, 48556, Transplantation of pancreas<br>▪ 50300, 50320, 50323, 50325, 50327, 50328, 50329, 50340, 50360, 50365, 50370, 50380, Renal transplantation<br>○ ICD-10-PCS codes:<br>▪ 02YA0Z0, 02YA0Z1, Transplantation of heart<br>▪ 0BYC0Z0, 0BYC0Z1, 0BYD0Z0, 0BYD0Z1, 0BYF0Z0, 0BYF0Z1, 0BYG0Z0, 0BYG0Z1, 0BYH0Z0, 0BYH0Z1, 0BYJ0Z0, 0BYJ0Z1, 0BYK0Z0, 0BYK0Z1, 0BYL0Z0, 0BYL0Z1, 0BYM0Z0, 0BYM0Z1, Transplantation of lung<br>▪ 0DY60Z0, 0DY60Z1, Transplantation of stomach |

| Variable | Description | Operational definition |
|---|---|---|
| | | ▪ 0DY80Z0, 0DY80Z1, Transplantation of small intestine<br>▪ 0DYE0Z0, 0DYE0Z1, Transplantation of large intestine<br>▪ 0FY00Z0, 0FY00Z1, Transplantation of liver<br>▪ 0FYG0Z0, 0FYG0Z1, Transplantation of pancreas<br>▪ 0TY00Z0, 0TY00Z1, 0TY10Z0, 0TY10Z1, Transplantation of kidney<br>▪ HSCT:<br>o CPT codes:<br>▪ 38240, 38241, 38242, 38243<br>o HCPCS:<br>▪ S2150, S2142<br>o ICD-10-PCS:<br>▪ 30230Y0, 30230Y1, 30230Y2, 30230Y3, 30230Y4, 30233Y0, 30233Y1, 30233Y2, 30233Y3, 30233Y4, 30240Y0, 30240Y1, 30240Y2, 30240Y3, 30240Y4, 30243Y0, 30243Y1, 30243Y2, 30243Y3, 30243Y4, 30250X0, 30250X1, 30250Y0, 30250Y1, 30253X0, 30253X1, 30253Y0, 30253Y1, 30260X0, 30260X1, 30260Y0, 30260Y1, 30263X0, 30263X1, 30263Y0, 30263Y1, 30230AZ, 30230G1, 30230G2, 30230G3, 30230G4, 30230X1, |

| Variable | Description | Operational definition |
|---|---|---|
| | | 30230X2, 30230X3, 30230X4, 30233AZ, 30233G1, 30233G2, 30233G3, 30233G4, 30233X1, 30233X2, 30233X3, 30233X4, 30240AZ, 30240G1, 30240G2, 30240G3, 30240G4, 30240X1, 30240X2, 30240X3, 30240X4, 30243AZ, 30243G1, 30243G2, 30243G3, 30243G4, 30243X1, 30243X2, 30243X3, 30243X4, 30250G1, 30253G1, 30260G1, 30263G1, 38240, 38241, 38242, 38243, 30230G0, 30230U2, 30230U3, 30230U4, 30230X0, 30233G0, 30233U2, 30233U3, 30233U4, 30233X0, 30240G0, 30240U2, 30240U3, 30240U4, 30240X0, 30243G0, 30243U2, 30243U3, 30243U4, 30243X0<br>▪ Hematologic or solid malignancy:<br>o ICD-10-CM codes:<br>▪ C81, C82, C83, C88, C89, C90, C91, C92, C93, C94, C95, C96, Hematologic malignancy<br>▪ C00, C01, C02, C03, C04, C05, C06, C07, C11, C12, C13, C14, C15, C16, C17, C18, C19, C22, C23, C24, C25, C26, C27, C28, C29, C30, C31, C32, C33, C34, C35, C36, C37, C38, C39, |

| Variable | Description | Operational definition |
|---|---|---|
| | | C40, C41, C42, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C59, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, Z85, C7A, C7B, D3A, D00, D01, D02, D03, D04, D05, D06, D07, D08, D09, D10, D11, D12, D13, D14, D15, D16, D17, D18, D19, D20, D21, D22, D23, D24, D25, D26, D27, D28, D29, D30, D31, D32, D33, D34, D35, D36, D37, D38, D39, D40, D41, D42, D43, D44, D45, D46, D47, D48, D49, Solid malignancy<br>▪ HIV/AIDs:<br>o ICD-10-CM codes:<br>▪ B20, HIV disease<br>▪ B97.35, HIV type 2 as the cause of diseases classified elsewhere<br>▪ B21, B22, B23, B24, HIV/AIDs disease<br>▪ Other immune deficiencies:<br>o ICD-10-CM codes:<br>▪ D80, D80.x, Immunodeficiency with predominantly antibody defects<br>▪ D81, D81.x, D81.xx, Combined immunodeficiencies<br>▪ D82, D82.x, Immunodeficiency associated with other major defects |

| Variable | Description | Operational definition |
|---|---|---|
| | | ▪ D83, D83.x, Common variable immunodeficiency<br>▪ D84, D84.x, D84.xx, Other immunodeficiencies<br>▪ D86, D86.x, D86.xx, Sarcoidosis<br>▪ D89, D89.x, D89.xx, Other disorders involving the immune mechanism, not elsewhere classified<br>*Neurological*<br>Dementia (i.e., Alzheimer's disease and related disorders, senile dementia):<br>▪ ICD-10-CM codes:<br>o F00.x–F03.x, F00.xx–F03.xx, F05, F05.1, G30.x, G31.1, Dementia<br>Neurological disease:<br>▪ ICD-10-CM codes:<br>o R41, R41.x, R41.xx, Other symptoms and signs involving cognitive functions and awareness<br>o R42, Dizziness and giddiness<br>o R43, R43.x, Disturbances of smell and taste<br>o R44, R44.x, Other symptoms and signs involving general sensations and perceptions<br>o R45, R45.x, R45.xx, Symptoms and signs involving emotional state<br>o R46, R46.x, R46.xx, Symptoms and signs involving appearance and behavior<br>*Respiratory*<br>Asthma:<br>▪ ICD-10-CM codes:<br>o J45.2x–J45.3x, Mild intermittent asthma<br>o J45.4x, Moderate persistent asthma |

| Variable | Description | Operational definition |
|---|---|---|
| | | o J45.5x, Severe persistent asthma<br>o J45.9x, Other and unspecified asthma<br>Chronic bronchiectasis:<br>▪ ICD-10-CM codes:<br>o J47.0, J47.1, J47.9, Bronchiectasis<br>COPD/interstitial lung disease:<br>▪ ICD-10-CM codes:<br>o J41.x Simple and mucopurulent chronic bronchitis<br>o J42, Unspecified chronic bronchitis<br>o J43.x, Emphysema<br>o J44.x, Other COPD<br>o J80, J81.x, J82.xx, J84.xx, J84.xxx, Other respiratory diseases principally affecting the interstitium<br>o M05.10, Rheumatoid lung disease with rheumatoid arthritis of unspecified site<br>*Other*<br>Cancer:<br>▪ ICD-10-CM codes:<br>o C00–C75, C00.x–C75.x, C00.xx–C75.xx, C7A., C7A.x, C7A.xx, C7B., C7B.x, C7B.xx, Malignant neoplasms, stated or presumed to be primary (of specified sites), and certain specified histologies, except neuroendocrine, and of lymphoid, hematopoietic and related tissue<br>o C76–C80, C76.x–C80.x, C76.xx–C80.xx, Malignant neoplasms of ill-defined, other |

| Variable | Description | Operational definition |
|---|---|---|
| | | secondary and unspecified sites<br>o C81–-C96, C81.x–C96.x, C81.xx–C96.xx, Malignant neoplasms of lymphoid, hematopoietic and related tissue<br>Chronic kidney disease/dialysis:<br>▪ ICD-10-CM codes:<br>o D59.3, Hemolytic-uremic syndrome<br>o I12.x, Hypertensive chronic kidney disease<br>o I13.x, I13.xx, Hypertensive heart and chronic kidney disease<br>o I70.1, Atherosclerosis of renal artery<br>o I72.2 Aneurysm of renal artery<br>o K76.7, Hepatorenal syndrome<br>o M10.30–M10.39, M10.30x–M10.37x, Gout due to renal impairment<br>o M32.14, Glomerular disease in systemic lupus erythematosus<br>o M32.15, Tubulo-interstitial nephropathy in systemic lupus erythematosus<br>o M35.04, Sicca syndrome with tubulo-interstitial nephropathy<br>o N00.x–N07.x, N08, Glomerular diseases<br>o N13.1, N13.2, N13.3x, Obstructive and reflux uropathy<br>o N14.x, Nephropathy<br>o N15.x, Other renal tubulo-interstitial diseases<br>o N16, Renal tubulo-interstitial disorders in diseases classified elsewhere |

| Variable | Description | Operational definition |
|---|---|---|
| | | ○ N17.x, N18.x, N19, Acute kidney failure and chronic kidney disease<br>○ N25.x, N26.x, N25.xx, Other disorders of kidney and ureter<br>○ Q61.02, Q61.11x, Q61.2–Q61.9, Cystic kidney disease<br>○ Q62.x, Q62.xx, Congenital obstructive defects of renal pelvis and congenital malformation of ureter<br>Diabetes mellitus:<br>▪ ICD-10-CM codes:<br>○ E10.x, E10.xx, E10.xxx, Type 1 diabetes mellitus<br>○ E11.x, E11.xx, E11.xxx, Type 2 diabetes mellitus<br>Down syndrome:<br>▪ ICD-10-CM codes:<br>○ Q90.x, Down syndrome<br>Gout:<br>▪ ICD-10-CM codes:<br>○ M10.00, M1A.9XX0, M1A.00X1, M1A.20X1, M1A.30X1, M1A.40X1, M1A.9XX1, M10.30, N20.0, M10.9, M10.40, M11.80, M11.819, M11.829, M11.839, M11.849, M11.859, M11.869, M11.879, M11.88, M11.89, M11.20, M11.219, M11.229, M11.239, M11.249, M11.259, M11.269, M11.279, M11.28, M11.29, M11.9, Gout or other crystal induced arthropathy<br>Hyperlipidemia<br>▪ ICD-10-CM codes:<br>○ E78.0–E78.5, E78.0x, E78.4x, Hyperlipidemia |
| Concomitant medications | Categorical variable: | Medications will be identified by string searching the specific medication names |

| Variable | Description | Operational definition |
|---|---|---|
| | • Antineoplastic (i.e., 7-con-o-methylnogaril, aclacinomycin a, cisplatin, doxorubicin, etaracizumab, ifosfamide, melphalan, mitoxantrone, trastuzumab)<br>• Bisphosphonates (i.e., alendronate)<br>• Cardiovascular (i.e., adenosine, dobutamine)<br>• Central nervous system (i.e., clozapine, morphine)<br>• Respiratory (i.e., theophylline)<br>• NSAIDs<br>• Ivabradine<br>• Digitalis | and using NDC codes that will be described in the SAP. |
| Immunization history | Categorical variable:<br>• Seasonal influenza<br>• COVID-19<br>• Tetanus diphtheria and pertussis (Tdap or Td)<br>• Chickenpox (Varicella)<br>• Shingles (Herpes Zoster recombinant and/or live)<br>• Human papillomavirus (HPV)<br>• Pneumococcal conjugate<br>• Pneumococcal polysaccharide<br>• Hepatitis A<br>• Hepatitis B<br>• Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB)<br>• Haemophilus influenzae type b | See Annex 3 Table A-3 for vaccine codes |

**Annex 3 Table A-3. Immunization history and Vaccine Co-administration CPT, HCPCS, and NDC Codes**

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| COVID-19 | CPT | 91300 | Pfizer |
| | | 91305 | Pfizer |
| | | 91307 | Pfizer |
| | | 91308 | Pfizer |
| | | 91315 | Pfizer (bivalent) |
| | | 91317 | Pfizer (bivalent) |
| | | 91312 | Pfizer (bivalent) |
| | | 91301 | Moderna |
| | | 91306 | Moderna |
| | | 91309 | Moderna |
| | | 91311 | Moderna |
| | | 91314 | Moderna (bivalent) |
| | | 91316 | Moderna (bivalent) |
| | | 91313 | Moderna (bivalent) |
| | | 91302 | AstraZeneca |
| | | 91303 | Janssen |
| | | 91304 | Novavax |
| | HCPCS | 0001A | Pfizer |
| | | 0002A | Pfizer |
| | | 0003A | Pfizer |
| | | 0004A | Pfizer |
| | | 0051A | Pfizer |
| | | 0052A | Pfizer |
| | | 0053A | Pfizer |
| | | 0054A | Pfizer |
| | | 0071A | Pfizer |
| | | 0072A | Pfizer |
| | | 0073A | Pfizer |
| | | 0074A | Pfizer |
| | | 0081A | Pfizer |
| | | 0082A | Pfizer |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | | 0083A | Pfizer |
| | | 0121A | Pfizer (bivalent) |
| | | 0124A | Pfizer (bivalent) |
| | | 0151A | Pfizer (bivalent) |
| | | 0154A | Pfizer (bivalent) |
| | | 0171A | Pfizer (bivalent) |
| | | 0172A | Pfizer (bivalent) |
| | | 0173A | Pfizer (bivalent) |
| | | 0174A | Pfizer (bivalent) |
| | | 0011A | Moderna |
| | | 0012A | Moderna |
| | | 0013A | Moderna |
| | | 0064A | Moderna |
| | | 0091A | Moderna |
| | | 0092A | Moderna |
| | | 0093A | Moderna |
| | | 0094A | Moderna |
| | | 0111A | Moderna |
| | | 0112A | Moderna |
| | | 0113A | Moderna |
| | | 0134A | Moderna (bivalent) |
| | | 0141A | Moderna (bivalent) |
| | | 0142A | Moderna (bivalent) |
| | | 0144A | Moderna (bivalent) |
| | | 0164A | Moderna (bivalent) |
| | | 0021A | AstraZeneca |
| | | 0022A | AstraZeneca |
| | | 0031A | Janssen |
| | | 0034A | Janssen |
| | | 0041A | Novavax |
| | | 0042A | Novavax |
| | | 0044A | Novavax |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | | M0201[b] | Covid-19 vaccine administration inside a patient's home; reported only once per individual home per date of service when only covid-19 vaccine administration is performed at the patient's home |
| | NDC | 5926710001 | Pfizer |
| | | 59267100001 | Pfizer |
| | | 5926710002 | Pfizer |
| | | 59267100002 | Pfizer |
| | | 5926710003 | Pfizer |
| | | 59267100003 | Pfizer |
| | | 5926710251 | Pfizer |
| | | 59267102501 | Pfizer |
| | | 5926710253 | Pfizer |
| | | 5926710254 | Pfizer |
| | | 0069100001[a] | Pfizer |
| | | 0069100002[a] | Pfizer |
| | | 0069100003[a] | Pfizer |
| | | 0069202510 | Pfizer |
| | | 0069202525 | Pfizer |
| | | 0069202501 | Pfizer |
| | | 5926710551 | Pfizer |
| | | 59267105501 | Pfizer |
| | | 59267102503 | Pfizer |
| | | 5926710252 | Pfizer |
| | | 59267102502 | Pfizer |
| | | 59267102504 | Pfizer |
| | | 00069202501 | Pfizer |
| | | 00069202510 | Pfizer |
| | | 00069202525 | Pfizer |
| | | 5926700781 | Pfizer |
| | | 59267007801 | Pfizer |
| | | 5926700784 | Pfizer |
| | | 59267007804 | Pfizer |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | | 5926710552 | Pfizer |
| | | 59267105502 | Pfizer |
| | | 5926710554 | Pfizer |
| | | 59267105504 | Pfizer |
| | | 5926705651 | Pfizer (bivalent) |
| | | 59267056501 | Pfizer (bivalent) |
| | | 5926705652 | Pfizer (bivalent) |
| | | 59267056502 | Pfizer (bivalent) |
| | | 5926706091 | Pfizer (bivalent) |
| | | 59267060901 | Pfizer (bivalent) |
| | | 5926706092 | Pfizer (bivalent) |
| | | 59267060902 | Pfizer (bivalent) |
| | | 5926703042 | Pfizer (bivalent) |
| | | 59267030402 | Pfizer (bivalent) |
| | | 5926703041 | Pfizer (bivalent) |
| | | 59267030401 | Pfizer (bivalent) |
| | | 5926714042 | Pfizer (bivalent) |
| | | 59267140402 | Pfizer (bivalent) |
| | | 5926714041 | Pfizer (bivalent) |
| | | 59267140401 | Pfizer (bivalent) |
| | | 0310122210 | AstraZeneca |
| | | 0310122215 | AstraZeneca |
| | | 00310122210 | AstraZeneca |
| | | 00310122215 | AstraZeneca |
| | | 59676058005 | Janssen |
| | | 59676058015 | Janssen |
| | | 5967658005 | Janssen |
| | | 5967658015 | Janssen |
| | | 80631010210 | Novavax |
| | | 8063110210 | Novavax |
| | | 80631010201 | Novavax |
| | | 8063110201 | Novavax |
| | | 80631100001 | Novavax |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | | 8063110010 | Novavax |
| | | 80631010010 | Novavax |
| | | 8063110001 | Novavax |
| | | 80631010001 | Novavax |
| | | 8077710099 | Moderna |
| | | 80777010099 | Moderna |
| | | 8077710098[a] | Moderna |
| | | 80777010098[a] | Moderna |
| | | 80777027705[a] | Moderna |
| | | 8077727705[a] | Moderna |
| | | 80777027799[a] | Moderna |
| | | 8077727799[a] | Moderna |
| | | 80777027905 | Moderna |
| | | 8077727905 | Moderna |
| | | 80777027999 | Moderna |
| | | 8077727999 | Moderna |
| | | 8077710015[a] | Moderna |
| | | 80777027310 | Moderna |
| | | 80777027399 | Moderna |
| | | 8077727398 | Moderna |
| | | 80777027398 | Moderna |
| | | 8077727315 | Moderna |
| | | 80777027315 | Moderna |
| | | 8077710011 | Moderna |
| | | 80777010011 | Moderna |
| | | 8077727599 | Moderna |
| | | 80777027599 | Moderna |
| | | 8077727505 | Moderna |
| | | 80777027505 | Moderna |
| | | 8077727310 | Moderna |
| | | 8077727399 | Moderna |
| | | 80777028302 | Moderna (bivalent) |
| | | 8077728302 | Moderna (bivalent) |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | | 80777028399 | Moderna (bivalent) |
| | | 8077728399 | Moderna (bivalent) |
| | | 8077728299 | Moderna (bivalent) |
| | | 80777028299 | Moderna (bivalent) |
| | | 8077728205 | Moderna (bivalent) |
| | | 80777028205 | Moderna (bivalent) |
| Seasonal Influenza[c] | CPT | 90470 | H1N1 Immunization administration (intramuscular, intranasal), including counseling when performed |
| | CPT | 90630 | Vaccine for influenza for injection into skin, quadrivalent, preservative free |
| | CPT | 90653 | Vaccine for influenza for injection into muscle, inactivated, subunit, adjuvanted |
| | CPT | 90654 | Vaccine for influenza injection into skin, trivalent, preservative free |
| | CPT | 90655 | Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent, split virus, preservative free |
| | CPT | 90656 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, preservative free |
| | CPT | 90657 | Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent (pediatric use) |
| | CPT | 90658 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent |
| | CPT | 90659 | Influenza virus vaccine, whole virus, for intramuscular or jet injection use |
| | CPT | 90660 | Vaccine for influenza for nasal administration, trivalent |
| | CPT | 90661 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, cell culture-based, preservative and antibiotic free |
| | CPT | 90662 | Vaccine for influenza for injection into muscle, split virus, enhanced immunogenicity via increased antigen content |
| | CPT | 90663 | Influenza virus vaccine, pandemic formulation, H1N1 |
| | CPT | 90664 | Vaccine for influenza for nasal administration, pandemic formulation |
| | CPT | 90666 | Vaccine for influenza for injection into muscle, pandemic formulation |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | CPT | 90667 | Vaccine for influenza for injection into muscle, pandemic formulation |
| | CPT | 90668 | Vaccine for influenza for injection into muscle, pandemic formulation |
| | CPT | 90672 | Vaccine for influenza for nasal administration, tetravalent |
| | CPT | 90673 | Vaccine for influenza administered into muscle, preservative and antibiotic free, trivalent, recombinant DNA, hemagglutinin (HA) protein only |
| | CPT | 90674 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, tetravalent, cell-culture based, preservative and antibiotic free |
| | CPT | 90682 | Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free |
| | CPT | 90685 | Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent, preservative free |
| | CPT | 90686 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, preservative free |
| | CPT | 90687 | Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent (pediatric use) |
| | CPT | 90688 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent |
| | CPT | 90694 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, inactivated, adjuvanted, preservative free |
| | 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) |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | HCPCS | Q2034 | Influenza virus vaccine, split virus, for intramuscular use (agriflu) |
| | HCPCS | Q2035 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (afluria) |
| | HCPCS | Q2036 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (flulaval) |
| | HCPCS | Q2037 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluvirin) |
| | HCPCS | Q2038 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluzone) |
| | HCPCS | Q2039 | Influenza virus vaccine, not otherwise specified |
| | NDC | 70461031803 | FLUCELVAX |
| | NDC | 70461031804 | FLUCELVAX |
| | NDC | 70461041810 | FLUCELVAX |
| | NDC | 70461041811 | FLUCELVAX |
| | 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 |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | NDC | 49281065010 | Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul |
| | NDC | 66521020002 | Influenza virus vaccine (IIV), pandemic formulation, split virus, for intramuscular use |
| | NDC | 49281064015 | Influenza virus vaccine (IIV), pandemic formulation, split virus, for intramuscular use |
| | NDC | 66019020010 | Influenza virus vaccine, live (LAIV), pandemic formulation, for intranasal use |
| | NDC | 66019020001 | Influenza virus vaccine, live (LAIV), pandemic formulation, for intranasal use |
| | NDC | 76420048301 | Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.5 mL dosage, for int |
| | NDC | 76420048201 | Influenza virus vaccine, quadrivalent (IIV4), split virus, preservative free, 0.5 mL dosage, for int |
| | NDC | 58160080815 | Influenza A (H5N1) Monovalent Vaccine, Adjuvanted |
| | NDC | 58160080401 | Influenza A (H5N1) Monovalent Vaccine, Adjuvanted |
| | NDC | 58160080202 | Influenza A (H5N1) Monovalent Vaccine, Adjuvanted |
| | NDC | 33332051901 | Influenza virus vaccine (IIV), pandemic formulation, split virus, preservative free, for intramuscul |
| | NDC | 19515081652 | Flulaval Quadrivalent |
| | NDC | 19515084511 | FLULAVAL |
| | NDC | 19515085052 | FLULAVAL |
| | 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 |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | NDC | 33332032001 | Afluria Quadrivalent |
| | NDC | 33332041610 | AFLURIA QUADRIVALENT |
| | NDC | 33332041810 | AFLURIA QUADRIVALENT |
| | NDC | 33332041910 | Afluria Quadrivalent |
| | NDC | 33332042010 | Afluria Quadrivalent |
| | NDC | 49281012065 | FLUZONE High-Dose Quadrivalent Northern Hemisphere |
| | NDC | 49281018125 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 49281032050 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 49281033615 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 49281040565 | FLUZONE High-Dose |
| | NDC | 49281041810 | FLUZONE QUADRIVALENT |
| | NDC | 49281041850 | FLUZONE QUADRIVALENT |
| | NDC | 49281041910 | FLUZONE QUADRIVALENT |
| | NDC | 49281041950 | FLUZONE QUADRIVALENT |
| | 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 |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | 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 |
| | NDC | 19515080852 | Flulaval Quadrivalent - 2022-23 Outer Carton |
| | NDC | 49281037950 | FLUZONE High-Dose Quadrivalent Southern Hemisphere |
| | NDC | 49281035515 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 66019030910 | FluMist Quadrivalent - 2022-23 |
| | NDC | 49281042210 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 |
| | NDC | 49281032350 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 49281042250 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 Syringe |
| | NDC | 33332042210 | Afluria Quadrivalent - 2022-23 |
| | NDC | 49281063715 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 |
| | NDC | 49281032250 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE - 2022-23 |
| | NDC | 58160089052 | FLUARIX QUADRIVALENT - 2022-23 |
| | NDC | 70461012203 | FLUAD QUADRIVALENT - 2022-23 |
| | NDC | 70461042210 | Flucelvax Quadrivalent - 2022-23 |
| | NDC | 33332032203 | Afluria Quadrivalent - 2022-23 |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| | NDC | 49281012265 | FLUZONE High-Dose Quadrivalent Northern Hemisphere - 2022-23 |
| | NDC | 70461032203 | Flucelvax Quadrivalent - 2022-23 |
| | NDC | 49281072210 | Flublok Quadrivalent Northern Hemisphere - 2022-23 |
| | NDC | 49281033915 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE - 2022-2023 |
| Tetanus diphtheria and pertussis (Tdap or Td) | CPT | 90714 | Tetanus and diphtheria toxoids adsorbed (Td), preservative free, when administered to individuals 7 years or older, for intramuscular use |
| | CPT | 90715 | Tdap administered to individuals 7 years or older, for intramuscular use |
| | CPT | 90718 | Tetanus and diphtheria toxoids (Td) adsorbed when administered to individuals 7 years or older, for intramuscular use |
| Chickenpox (Varicella) | CPT | 90396 | Varicella-zoster immune globulin, human, for intramuscular use |
| | CPT | 90716 | Varicella virus vaccine, live, for subcutaneous use |
| Shingles (Herpes Zoster recombinant and/or live) | CPT | 90396 | Varicella-zoster immune globulin, human, for intramuscular use |
| | CPT | 90736 | Zoster (shingles) vaccine (HZV), live, for subcutaneous injection |
| | CPT | 90750 | Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use |
| Human papillomavirus (HPV) | CPT | 90649 | Human Papillomavirus vaccine, types 6, 11, 16, 18, quadrivalent (4vHPV), 3 dose schedule, for intramuscular use |
| | CPT | 90650 | Human Papillomavirus vaccine, types 16, 18, bivalent (2vHPV), 3 dose schedule, for intramuscular use |
| | CPT | 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 | 90669 | Pneumococcal conjugate vaccine, 7 valent, for intramuscular use |
| | CPT | 90670 | Pneumococcal conjugate vaccine, 13 valent (PCV13), for intramuscular use |
| | HCPCS | G0009 | Administration of pneumococcal vaccine |
| | HCPCS | G8864 | Code for Pneumococcal vaccine administered or previously received |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| Pneumococcal polysaccharide | CPT | 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 | 90632 | Hepatitis A vaccine, adult dosage, for intramuscular use |
| | CPT | 90633 | Hepatitis A vaccine (HepA), pediatric/adolescent dosage-2 dose schedule, for intramuscular use |
| | CPT | 90634 | Hepatitis A vaccine (HepA), pediatric/adolescent dosage-3 dose schedule, for intramuscular use |
| | CPT | 90730 | Hepatitis A vaccine |
| | CPT | 90636 | Hepatitis A and hepatitis B vaccine (HepA-HepB), adult dosage, for intramuscular use |
| Hepatitis B | CPT | 90371 | Hepatitis B immune globulin (HBIg), human, for intramuscular use |
| | CPT | 90739 | Hepatitis B vaccine (HepB), adult dosage, 2 dose schedule, for intramuscular use |
| | CPT | 90740 | Hepatitis B vaccine (HepB), dialysis or immunosuppressed patient dosage, 3 dose schedule, for intramuscular use |
| | CPT | 90743 | Hepatitis B vaccine (HepB), adolescent, 2 dose schedule, for intramuscular use |
| | CPT | 90744 | Hepatitis B vaccine (HepB), pediatric/adolescent dosage, 3 dose schedule, for intramuscular use |
| | CPT | 90745 | Hepatitis B vaccine, adolescent/high risk infant dosage, for intramuscular use |
| | CPT | 90746 | Hepatitis B vaccine (HepB), adult dosage, 3 dose schedule, for intramuscular use |
| | CPT | 90747 | Hepatitis B vaccine (HepB), dialysis or immunosuppressed patient dosage, 4 dose schedule, for intramuscular use |
| | HCPCS | G0010 | Administration of Hepatitis B vaccine |
| Meningococcal conjugate (MenACWY) and serogroup B | CPT | 90619 | Meningococcal conjugate vaccine, serogroups A, C, W, Y, quadrivalent, tetanus toxoid carrier (MenACWY-TT), for intramuscular use |
| | CPT | 90620 | Meningococcal recombinant protein and outer membrane vesicle vaccine, serogroup B (MenB-4C), 2 dose schedule, for intramuscular use |

| Vaccine | Code Type | Code | Manufacturer/Description |
|---|---|---|---|
| meningococcal (MenB) | CPT | 90621 | Meningococcal recombinant lipoprotein vaccine, serogroup B (MenB-FHbp), 2 or 3 dose schedule, for intramuscular use |
| | CPT | 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 |
| | CPT | 90734 | Meningococcal conjugate vaccine, serogroups A, C, Y and W-135 (tetravalent), for intramuscular use |
| Haemophilus influenza type b | CPT | 90645 | Hemophilus influenza b vaccine (Hib), HbOC conjugate (4 dose schedule), for intramuscular use |
| | CPT | 90646 | Hemophilus influenza b vaccine (Hib), PRP-D conjugate, for booster use only, intramuscular use |
| | CPT | 90647 | Haemophilus influenzae type b vaccine (Hib), PRP-OMP conjugate, 3 dose schedule, for intramuscular use |
| | CPT | 90648 | Haemophilus influenzae type b vaccine (Hib), PRP-T conjugate, 4 dose schedule, for intramuscular use |
| | CPT | 90737 | Hemophilus influenza B |
| | CPT | 90748 | Hepatitis B and Haemophilus influenzae type b vaccine (Hib-HepB), for intramuscular use |

**Notes:**

a. Codes that will not be manufactured or not available in the near term according to CDC Immunization Information Systems (IIS) - COVID-19 Vaccine Related Codes (https://www.cdc.gov/vaccines/programs/iis/COVID-19-related-codes.html)
b. COVID-19 vaccine home administration. This code must be accompanied by the appropriate CPT code for the product
c. Additional codes will be added for influenza vaccines as they become available.

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| COVID-19 | CPT | 91300 | Pfizer |
| | | 91305 | Pfizer |
| | | 91307 | Pfizer |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | | 91308 | Pfizer |
| | | 91315 | Pfizer (bivalent) |
| | | 91317 | Pfizer (bivalent) |
| | | 91312 | Pfizer (bivalent) |
| | | 91301 | Moderna |
| | | 91306 | Moderna |
| | | 91309 | Moderna |
| | | 91311 | Moderna |
| | | 91314 | Moderna (bivalent) |
| | | 91316 | Moderna (bivalent) |
| | | 91313 | Moderna (bivalent) |
| | | 91302 | AstraZeneca |
| | | 91303 | Janssen |
| | | 91304 | Novavax |
| | HCPCS | 0001A | Pfizer |
| | | 0002A | Pfizer |
| | | 0003A | Pfizer |
| | | 0004A | Pfizer |
| | | 0051A | Pfizer |
| | | 0052A | Pfizer |
| | | 0053A | Pfizer |
| | | 0054A | Pfizer |
| | | 0071A | Pfizer |
| | | 0072A | Pfizer |
| | | 0073A | Pfizer |
| | | 0074A | Pfizer |
| | | 0081A | Pfizer |
| | | 0082A | Pfizer |
| | | 0083A | Pfizer |
| | | 0121A | Pfizer (bivalent) |
| | | 0124A | Pfizer (bivalent) |
| | | 0151A | Pfizer (bivalent) |
| | | 0154A | Pfizer (bivalent) |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | | 0171A | Pfizer (bivalent) |
| | | 0172A | Pfizer (bivalent) |
| | | 0173A | Pfizer (bivalent) |
| | | 0174A | Pfizer (bivalent) |
| | | 0011A | Moderna |
| | | 0012A | Moderna |
| | | 0013A | Moderna |
| | | 0064A | Moderna |
| | | 0091A | Moderna |
| | | 0092A | Moderna |
| | | 0093A | Moderna |
| | | 0094A | Moderna |
| | | 0111A | Moderna |
| | | 0112A | Moderna |
| | | 0113A | Moderna |
| | | 0134A | Moderna (bivalent) |
| | | 0141A | Moderna (bivalent) |
| | | 0142A | Moderna (bivalent) |
| | | 0144A | Moderna (bivalent) |
| | | 0164A | Moderna (bivalent) |
| | | 0021A | AstraZeneca |
| | | 0022A | AstraZeneca |
| | | 0031A | Janssen |
| | | 0034A | Janssen |
| | | 0041A | Novavax |
| | | 0042A | Novavax |
| | | 0044A | Novavax |
| | | M0201[b] | Covid-19 vaccine administration inside a patient's home; reported only once per individual home per date of service when only covid-19 vaccine administration is performed at the patient's home |
| | NDC | 5926710001 | Pfizer |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | | 59267100001 | Pfizer |
| | | 5926710002 | Pfizer |
| | | 59267100002 | Pfizer |
| | | 5926710003 | Pfizer |
| | | 59267100003 | Pfizer |
| | | 5926710251 | Pfizer |
| | | 59267102501 | Pfizer |
| | | 5926710253 | Pfizer |
| | | 5926710254 | Pfizer |
| | | 0069100001[a] | Pfizer |
| | | 0069100002[a] | Pfizer |
| | | 0069100003[a] | Pfizer |
| | | 0069202510 | Pfizer |
| | | 0069202525 | Pfizer |
| | | 0069202501 | Pfizer |
| | | 5926710551 | Pfizer |
| | | 59267105501 | Pfizer |
| | | 59267102503 | Pfizer |
| | | 5926710252 | Pfizer |
| | | 59267102502 | Pfizer |
| | | 59267102504 | Pfizer |
| | | 00069202501 | Pfizer |
| | | 00069202510 | Pfizer |
| | | 00069202525 | Pfizer |
| | | 5926700781 | Pfizer |
| | | 59267007801 | Pfizer |
| | | 5926700784 | Pfizer |
| | | 59267007804 | Pfizer |
| | | 5926710552 | Pfizer |
| | | 59267105502 | Pfizer |
| | | 5926710554 | Pfizer |
| | | 59267105504 | Pfizer |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | | 5926705651 | Pfizer (bivalent) |
| | | 59267056501 | Pfizer (bivalent) |
| | | 5926705652 | Pfizer (bivalent) |
| | | 59267056502 | Pfizer (bivalent) |
| | | 5926706091 | Pfizer (bivalent) |
| | | 59267060901 | Pfizer (bivalent) |
| | | 5926706092 | Pfizer (bivalent) |
| | | 59267060902 | Pfizer (bivalent) |
| | | 5926703042 | Pfizer (bivalent) |
| | | 59267030402 | Pfizer (bivalent) |
| | | 5926703041 | Pfizer (bivalent) |
| | | 59267030401 | Pfizer (bivalent) |
| | | 5926714042 | Pfizer (bivalent) |
| | | 59267140402 | Pfizer (bivalent) |
| | | 5926714041 | Pfizer (bivalent) |
| | | 59267140401 | Pfizer (bivalent) |
| | | 0310122210 | AstraZeneca |
| | | 0310122215 | AstraZeneca |
| | | 00310122210 | AstraZeneca |
| | | 00310122215 | AstraZeneca |
| | | 59676058005 | Janssen |
| | | 59676058015 | Janssen |
| | | 5967658005 | Janssen |
| | | 5967658015 | Janssen |
| | | 80631010210 | Novavax |
| | | 8063110210 | Novavax |
| | | 80631010201 | Novavax |
| | | 8063110201 | Novavax |
| | | 80631100001 | Novavax |
| | | 8063110010 | Novavax |
| | | 80631010010 | Novavax |
| | | 8063110001 | Novavax |
| | | 80631010001 | Novavax |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | | 8077710099 | Moderna |
| | | 80777010099 | Moderna |
| | | 8077710098[a] | Moderna |
| | | 80777010098[a] | Moderna |
| | | 80777027705[a] | Moderna |
| | | 8077727705[a] | Moderna |
| | | 80777027799[a] | Moderna |
| | | 8077727799[a] | Moderna |
| | | 80777027905 | Moderna |
| | | 8077727905 | Moderna |
| | | 80777027999 | Moderna |
| | | 8077727999 | Moderna |
| | | 8077710015[a] | Moderna |
| | | 80777027310 | Moderna |
| | | 80777027399 | Moderna |
| | | 8077727398 | Moderna |
| | | 80777027398 | Moderna |
| | | 8077727315 | Moderna |
| | | 80777027315 | Moderna |
| | | 8077710011 | Moderna |
| | | 80777010011 | Moderna |
| | | 8077727599 | Moderna |
| | | 80777027599 | Moderna |
| | | 8077727505 | Moderna |
| | | 80777027505 | Moderna |
| | | 8077727310 | Moderna |
| | | 8077727399 | Moderna |
| | | 80777028302 | Moderna (bivalent) |
| | | 8077728302 | Moderna (bivalent) |
| | | 80777028399 | Moderna (bivalent) |
| | | 8077728399 | Moderna (bivalent) |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | | 8077728299 | Moderna (bivalent) |
| | | 80777028299 | Moderna (bivalent) |
| | | 8077728205 | Moderna (bivalent) |
| | | 80777028205 | Moderna (bivalent) |
| Seasonal Influenza[c] | CPT | 90470 | H1N1 Immunization administration (intramuscular, intranasal), including counseling when performed |
| | CPT | 90630 | Vaccine for influenza for injection into skin, quadrivalent, preservative free |
| | CPT | 90653 | Vaccine for influenza for injection into muscle, inactivated, subunit, adjuvanted |
| | CPT | 90654 | Vaccine for influenza injection into skin, trivalent, preservative free |
| | CPT | 90655 | Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent, split virus, preservative free |
| | CPT | 90656 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, preservative free |
| | CPT | 90657 | Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent (pediatric use) |
| | CPT | 90658 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent |
| | CPT | 90659 | Influenza virus vaccine, whole virus, for intramuscular or jet injection use |
| | CPT | 90660 | Vaccine for influenza for nasal administration, trivalent |
| | CPT | 90661 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, cell culture-based, preservative and antibiotic free |
| | CPT | 90662 | Vaccine for influenza for injection into muscle, split virus, enhanced immunogenicity via increased antigen content |
| | CPT | 90663 | Influenza virus vaccine, pandemic formulation, H1N1 |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | CPT | 90664 | Vaccine for influenza for nasal administration, pandemic formulation |
| | CPT | 90666 | Vaccine for influenza for injection into muscle, pandemic formulation |
| | CPT | 90667 | Vaccine for influenza for injection into muscle, pandemic formulation |
| | CPT | 90668 | Vaccine for influenza for injection into muscle, pandemic formulation |
| | CPT | 90672 | Vaccine for influenza for nasal administration, tetravalent |
| | CPT | 90673 | Vaccine for influenza administered into muscle, preservative and antibiotic free, trivalent, recombinant DNA, hemagglutinin (HA) protein only |
| | CPT | 90674 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, tetravalent, cell-culture based, preservative and antibiotic free |
| | CPT | 90682 | Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free |
| | CPT | 90685 | Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent, preservative free |
| | CPT | 90686 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, preservative free |
| | CPT | 90687 | Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent (pediatric use) |
| | CPT | 90688 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent |
| | CPT | 90694 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, inactivated, adjuvanted, preservative free |
| | CPT | 90724 | Immunization, active; influenza virus vaccine |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | CPT | 90756 | Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free |
| | HCPCS | G0008 | Administration of influenza virus vaccine |
| | HCPCS | G9141 | Influenza a (H1N1) immunization administration (includes the physician counseling the patient/family) |
| | HCPCS | G9142 | Influenza a (H1N1) vaccine, any route of administration |
| | HCPCS | Q2033 | Influenza vaccine, recombinant hemagglutinin antigens, for intramuscular use (flublok) |
| | HCPCS | Q2034 | Influenza virus vaccine, split virus, for intramuscular use (agriflu) |
| | HCPCS | Q2035 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (afluria) |
| | HCPCS | Q2036 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (flulaval) |
| | HCPCS | Q2037 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluvirin) |
| | HCPCS | Q2038 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluzone) |
| | HCPCS | Q2039 | Influenza virus vaccine, not otherwise specified |
| | NDC | 70461031803 | FLUCELVAX |
| | NDC | 70461031804 | FLUCELVAX |
| | NDC | 70461041810 | FLUCELVAX |
| | NDC | 70461041811 | FLUCELVAX |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | 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 |
| | 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 |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | 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 |
| | NDC | 49281033615 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | 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 | 49281071810 | Flublok Quadrivalent |
| | NDC | 49281071910 | Flublok Quadrivalent |
| | NDC | 49281072010 | Flublok Quadrivalent Northern Hemisphere |
| | 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 |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | NDC | 19515080852 | Flulaval Quadrivalent - 2022-23 Outer Carton |
| | NDC | 49281037950 | FLUZONE High-Dose Quadrivalent Southern Hemisphere |
| | NDC | 49281035515 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 49281042210 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 |
| | NDC | 49281032350 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 49281042250 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 Syringe |
| | NDC | 33332042210 | Afluria Quadrivalent - 2022-23 |
| | NDC | 49281063715 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 |
| | NDC | 49281032250 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE - 2022-23 |
| | NDC | 58160089052 | FLUARIX QUADRIVALENT - 2022-23 |
| | NDC | 70461012203 | FLUAD QUADRIVALENT - 2022-23 |
| | NDC | 70461042210 | Flucelvax Quadrivalent - 2022-23 |
| | NDC | 33332032203 | Afluria Quadrivalent - 2022-23 |
| | NDC | 49281012265 | FLUZONE High-Dose Quadrivalent Northern Hemisphere - 2022-23 |
| | NDC | 70461032203 | Flucelvax Quadrivalent - 2022-23 |
| | NDC | 49281072210 | Flublok Quadrivalent Northern Hemisphere - 2022-23 |
| | NDC | 49281033915 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE - 2022-2023 |
| | NDC | 19515080841 | Flulaval Quadrivalent - 2022-23 Outer Carton |
| | NDC | 49281037988 | FLUZONE High-Dose Quadrivalent Southern Hemisphere |
| | NDC | 49281035578 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 49281042258 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | NDC | 49281032388 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE |
| | NDC | 49281042288 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 Syringe |
| | NDC | 33332042211 | Afluria Quadrivalent - 2022-23 |
| | NDC | 49281063778 | FLUZONE QUADRIVALENT NORTHERN HEMISPHERE - 2022-23 |
| | NDC | 49281032288 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE - 2022-23 |
| | NDC | 58160089041 | FLUARIX QUADRIVALENT - 2022-23 |
| | NDC | 70461012204 | FLUAD QUADRIVALENT - 2022-23 |
| | NDC | 70461042211 | Flucelvax Quadrivalent - 2022-23 |
| | NDC | 33332032204 | Afluria Quadrivalent - 2022-23 |
| | NDC | 49281012288 | FLUZONE High-Dose Quadrivalent Northern Hemisphere - 2022-23 |
| | NDC | 70461032204 | Flucelvax Quadrivalent - 2022-23 |
| | NDC | 49281072288 | Flublok Quadrivalent Northern Hemisphere - 2022-23 |
| | NDC | 49281033978 | FLUZONE QUADRIVALENT SOUTHERN HEMISPHERE - 2022-2023 |
| Tetanus diphtheria and pertussis (Tdap or Td) | CPT | 90714 | Tetanus and diphtheria toxoids adsorbed (Td), preservative free, when administered to individuals 7 years or older, for intramuscular use |
| | CPT | 90715 | Tdap administered to individuals 7 years or older, for intramuscular use |
| | CPT | 90718 | Tetanus and diphtheria toxoids (Td) adsorbed when administered to individuals 7 years or older, for intramuscular use |
| | NDC | 49281040015 | Adacel |
| | NDC | 49281040088 | Adacel |
| | NDC | 14362011104 | TDVAX |
| | NDC | 14362011103 | TDVAX |
| | NDC | 49281021515 | TENIVAC |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | NDC | 49281021588 | TENIVAC |
| | NDC | 49281040005 | Adacel |
| | NDC | 58160084252 | BOOSTRIX |
| | NDC | 49281029183 | DECAVAC |
| | NDC | 17478013101 | Tetanus and Diphtheria Toxoids Adsorbed |
| | NDC | 49281029110 | DECAVAC |
| | NDC | 21695041301 | Tetanus and Diphtheria Toxoids Adsorbed |
| | NDC | 58160084234 | BOOSTRIX |
| | NDC | 49281040010 | Adacel |
| | NDC | 49281040020 | Adacel |
| | NDC | 49281021510 | TENIVAC |
| | NDC | 58160084251 | BOOSTRIX |
| | NDC | 13533013101 | TDVAX |
| | NDC | 58160084211 | BOOSTRIX |
| | NDC | 00006413341 | Tetanus and Diphtheria Toxoids Adsorbed |
| | NDC | 49281040058 | Adacel |
| | NDC | 58160084243 | BOOSTRIX |
| | NDC | 17478013100 | Tetanus and Diphtheria Toxoids Adsorbed |
| | NDC | 58160084205 | BOOSTRIX |
| | NDC | 49281040089 | Adacel |
| | NDC | 49281021558 | TENIVAC |
| | NDC | 58160084241 | BOOSTRIX |
| | NDC | 13533013100 | TDVAX |
| | NDC | 58160084201 | BOOSTRIX |
| | NDC | 00006413301 | Tetanus and Diphtheria Toxoids Adsorbed |
| Chickenpox (Varicella) | CPT | 90396 | Varicella-zoster immune globulin, human, for intramuscular use |
| | CPT | 90716 | Varicella virus vaccine, live, for subcutaneous use |
| | NDC | 00006482700 | VARIVAX |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | NDC | 00006482600 | VARIVAX |
| | NDC | 00006482701 | VARIVAX |
| | NDC | 00006482601 | VARIVAX |
| Shingles (Herpes Zoster recombinant and/or live) | CPT | 90396 | Varicella-zoster immune globulin, human, for intramuscular use |
| | CPT | 90736 | Zoster (shingles) vaccine (HZV), live, for subcutaneous injection |
| | CPT | 90750 | Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use |
| | NDC | 00006496300 | ZOSTAVAX |
| | NDC | 00006496341 | ZOSTAVAX |
| | NDC | 58160081912 | Shingrix |
| | NDC | 58160082311 | Shingrix |
| | NDC | 50090514700 | Shingrix |
| | NDC | 00006496301 | ZOSTAVAX |
| | NDC | 58160082801 | Shingrix |
| | NDC | 58160082803 | Shingrix |
| Pneumococcal conjugate | CPT | 90669 | Pneumococcal conjugate vaccine, 7 valent, for intramuscular use |
| | CPT | 90670 | Pneumococcal conjugate vaccine, 13 valent (PCV13), for intramuscular use |
| | HCPCS | G0009 | Administration of pneumococcal vaccine |
| | HCPCS | G8864 | Code for Pneumococcal vaccine administered or previously received |
| | NDC | 00005197105 | PREVNAR 13 |
| | NDC | 00005197104 | PREVNAR 13 |
| | NDC | 00005197102 | PREVNAR 13 |
| | NDC | 00006432902 | VAXNEUVANCE |
| | NDC | 00006432903 | VAXNEUVANCE |
| | NDC | 00005200010 | Prevnar 20 |
| | NDC | 00005197050 | Prevnar |
| | NDC | 00005200002 | Prevnar 20 |
| | NDC | 50090602600 | PREVNAR 20 |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | NDC | 00005197101 | PREVNAR 13 |
| | NDC | 00006432901 | VAXNEUVANCE |
| | NDC | 00005200001 | Prevnar 20 |
| | NDC | 00005197049 | Prevnar |
| | NDC | 50090602601 | PREVNAR 20 |
| Pneumococcal polysaccharide | CPT | 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 |
| | NDC | 00006473900 | PNEUMOVAX 23 |
| | NDC | 00006483703 | PNEUMOVAX 23 |
| | NDC | 00006494300 | PNEUMOVAX 23 |
| | NDC | 54868432000 | PNEUMOVAX 23 |
| | NDC | 54868333901 | PNEUMOVAX 23 |
| | NDC | 00006483702 | PNEUMOVAX 23 |
| | NDC | 00006473901 | PNEUMOVAX 23 |
| | NDC | 00006483701 | PNEUMOVAX 23 |
| | NDC | 00006494301 | PNEUMOVAX 23 |
| | NDC | 54868432009 | PNEUMOVAX 23 |
| | NDC | 54868333909 | PNEUMOVAX 23 |
| Hepatitis A | CPT | 90632 | Hepatitis A vaccine, adult dosage, for intramuscular use |
| | CPT | 90730 | Hepatitis A vaccine |
| | CPT | 90636 | Hepatitis A and hepatitis B vaccine (HepA-HepB), adult dosage, for intramuscular use |
| | NDC | 58160081552 | TWINRIX |
| | NDC | 00006484100 | VAQTA |
| | NDC | 58160081534 | TWINRIX |
| | NDC | 58160082652 | HAVRIX |
| | NDC | 58160081511 | TWINRIX |
| | NDC | 58160082611 | HAVRIX |
| | NDC | 58160082634 | HAVRIX |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | NDC | 55045384101 | HAVRIX |
| | NDC | 00006409609 | VAQTA |
| | NDC | 00006409602 | VAQTA |
| | NDC | 00006484141 | VAQTA |
| | NDC | 50090150200 | HAVRIX |
| | NDC | 58160081548 | TWINRIX |
| | NDC | 58160081546 | TWINRIX |
| | NDC | 58160081543 | TWINRIX |
| | NDC | 00006484101 | VAQTA |
| | NDC | 58160081505 | TWINRIX |
| | NDC | 58160082643 | HAVRIX |
| | NDC | 58160081501 | TWINRIX |
| | NDC | 58160082601 | HAVRIX |
| | NDC | 58160082605 | HAVRIX |
| | NDC | 00006409601 | VAQTA |
| | NDC | 50090150209 | HAVRIX |
| | NDC | 58160081541 | TWINRIX |
| Hepatitis B | CPT | 90371 | Hepatitis B immune globulin (HBIg), human, for intramuscular use |
| | CPT | 90739 | Hepatitis B vaccine (HepB), adult dosage, 2 dose schedule, for intramuscular use |
| | CPT | 90740 | Hepatitis B vaccine (HepB), dialysis or immunosuppressed patient dosage, 3 dose schedule, for intramuscular use |
| | CPT | 90746 | Hepatitis B vaccine (HepB), adult dosage, 3 dose schedule, for intramuscular use |
| | CPT | 90747 | Hepatitis B vaccine (HepB), dialysis or immunosuppressed patient dosage, 4 dose schedule, for intramuscular use |
| | HCPCS | G0010 | Administration of Hepatitis B vaccine |
| | NDC | 00006499200 | RECOMBIVAX HB |
| | NDC | 00006409402 | RECOMBIVAX HB |
| | NDC | 00006499541 | RECOMBIVAX HB |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | NDC | 58160082134 | ENGERIX-B |
| | NDC | 00006499500 | RECOMBIVAX HB |
| | NDC | 00006409409 | RECOMBIVAX HB |
| | NDC | 58160082152 | ENGERIX-B |
| | NDC | 54868073400 | ENGERIX-B |
| | NDC | 58160082111 | ENGERIX-B |
| | NDC | 54868221900 | RECOMBIVAX HB |
| | NDC | 54868221901 | RECOMBIVAX HB |
| | NDC | 00006499201 | RECOMBIVAX HB |
| | NDC | 00006409401 | RECOMBIVAX HB |
| | NDC | 00006499501 | RECOMBIVAX HB |
| | NDC | 58160082105 | ENGERIX-B |
| | NDC | 58160082143 | ENGERIX-B |
| | NDC | 58160082101 | ENGERIX-B |
| | NDC | 50090346900 | HEPLISAV-B |
| | NDC | 43528000305 | HEPLISAV-B |
| | NDC | 75052000110 | PREHEVBRIO |
| | NDC | 43528000205 | HEPLISAV-B |
| | NDC | 50090346909 | HEPLISAV-B |
| | NDC | 43528000301 | HEPLISAV-B |
| | NDC | 75052000101 | PREHEVBRIO |
| | NDC | 43528000201 | HEPLISAV-B |
| Meningococcal conjugate (MenACWY) and serogroup B meningococcal (MenB) | CPT | 90619 | Meningococcal conjugate vaccine, serogroups A, C, W, Y, quadrivalent, tetanus toxoid carrier (MenACWY-TT), for intramuscular use |
| | CPT | 90620 | Meningococcal recombinant protein and outer membrane vesicle vaccine, serogroup B (MenB-4C), 2 dose schedule, for intramuscular use |
| | CPT | 90621 | Meningococcal recombinant lipoprotein vaccine, serogroup B (MenB-FHbp), 2 or 3 dose schedule, for intramuscular use |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | CPT | 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 |
| | CPT | 90734 | Meningococcal conjugate vaccine, serogroups A, C, Y and W-135 (tetravalent), for intramuscular use |
| | NDC | 49281048991 | MENOMUNE - A/C/Y/W-135 COMBINED |
| | NDC | 49281048901 | MENOMUNE - A/C/Y/W-135 COMBINED |
| | NDC | 49281048878 | MENOMUNE - A/C/Y/W-135 COMBINED |
| | NDC | 49281048758 | MENOMUNE - A/C/Y/W-135 COMBINED |
| | NDC | 49281059005 | MenQuadfi |
| | NDC | 50090618000 | MENQUADFI |
| | NDC | 49281059058 | MenQuadfi |
| | NDC | 50090618001 | MENQUADFI |
| Haemophilus influenzae type b | CPT | 90645 | Hemophilus influenza b vaccine (Hib), HbOC conjugate (4 dose schedule), for intramuscular use |
| | CPT | 90646 | Hemophilus influenza b vaccine (Hib), PRP-D conjugate, for booster use only, intramuscular use |
| | CPT | 90647 | Haemophilus influenzae type b vaccine (Hib), PRP-OMP conjugate, 3 dose schedule, for intramuscular use |
| | CPT | 90648 | Haemophilus influenzae type b vaccine (Hib), PRP-T conjugate, 4 dose schedule, for intramuscular use |
| | CPT | 90737 | Hemophilus influenza B |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | CPT | 90748 | Hepatitis B and Haemophilus influenzae type b vaccine (Hib-HepB), for intramuscular use |
| | NDC | 49281051005 | PENTACEL |
| | NDC | 58160080111 | Menhibrix |
| | NDC | 58160080605 | HIBERIX |
| | NDC | 58160081811 | Hiberix |
| | NDC | 49281054503 | ActHIB |
| | NDC | 63361024315 | VAXELIS |
| | NDC | 58160080905 | MENHIBRIX |
| | NDC | 49281051105 | PENTACEL |
| | NDC | 00006489700 | PedvaxHIB |
| | NDC | 49281054505 | ActHIB |
| | NDC | 63361024510 | VAXELIS |
| | NDC | 63361024310 | VAXELIS |
| | NDC | 00006489800 | COMVAX |
| | NDC | 58160081605 | Hiberix |
| | NDC | 49281056005 | PENTACEL |
| | NDC | 49281054515 | PENTACEL |
| | NDC | 49281054858 | PENTACEL |
| | NDC | 58160080901 | Menhibrix |
| | NDC | 58160080601 | HIBERIX |
| | NDC | 49281054758 | ActHIB |
| | NDC | 63361024388 | VAXELIS |
| | NDC | 49281056101 | PENTACEL |
| | NDC | 49281054458 | PENTACEL |
| | NDC | 00006489701 | PedvaxHIB |
| | NDC | 63361024558 | VAXELIS |
| | NDC | 63361024358 | VAXELIS |
| | NDC | 00006489801 | COMVAX |
| | NDC | 58160081601 | Hiberix |

| Vaccine | Code Type | Code | Manufacturer/Descriptions |
|---|---|---|---|
| | | | |

**Notes:**

a. Codes that will not be manufactured or not available in the near term according to CDC Immunization Information Systems (IIS) - COVID-19 Vaccine Related Codes (https://www.cdc.gov/vaccines/programs/iis/COVID-19-related-codes.html).
b. COVID-19 vaccine home administration. This code must be accompanied by the appropriate CPT code for the product.
c. Additional codes will be added for influenza vaccines as they become available.

# Document Approval Record

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