NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Post-Authorization Safety Study of Atrial Fibrillation Following Respiratory Syncytial Virus Vaccine (ABRYSVO™) Among Adults Aged 18 Years and Older in the Veterans Affairs Health System
Protocol number	C3671037
Protocol version identifier	2.0
Date	04 December 2024
European Union (EU) Post Authorization Study (PAS) register number	EUPAS1000000290
Active substance	ABRYSVO™ is a bivalent recombinant stabilized prefusion F (preF) protein subunit vaccine (Respiratory Syncytial Virus Vaccine). It consists of equal amounts of preF antigens from the two major respiratory syncytial virus (RSV) subgroups: RSV subgroup A preF (60 µg) and RSV subgroup B preF (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 United States (US) Veterans Health Administration (VHA) system as compared to expected rates of those events? *Primary study objective:* • To estimate the incidence of atrial fibrillation following administration of ABRYSVO among adults 18 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 18 years of age and older in the VHA system • To assess whether adults 18 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 (ie, individuals with specific conditions that increase the risk for severe RSV, older age groups [60 to 69 years, 70 to 79 years, ≥80 years], individuals in VA priority group 1, individuals with dual VHA/Medicare coverage, females, individuals with co-administration with other vaccines) in the VHA system following administration of ABRYSVO • To assess whether sub-cohorts of interest (ie, individuals with specific conditions that increase the risk for severe RSV, older age groups [60 to 69 years, 70 to 79 years, ≥80 years], individuals in VA priority group 1, individuals with dual VHA/Medicare coverage, females, individuals with co-administration with other vaccines) in the VHA system experience increased risk of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO
Country(ies) of study	US
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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
AR	Adverse reaction
ATT	Average treatment effect among the treated
BMI	Body mass index
CAD	Coronary artery disease
CAR	Chimeric antigen receptor
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
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 19
CPT	Current Procedural Terminology
CRF	Case report form
EC	Ethics Committee

Abbreviation	Definition
ED	Emergency department
EHR	Electronic health record
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FFS	Fee-For-Service
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
HBV	Hepatitis B virus
HCPCS	Healthcare Common Procedure Coding System
HCT	Hematopoietic cell transplant
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMA	Heads of Medicines Agencies
HPV	Human papillomavirus
HSCT	Hematopoietic stem cell transplant
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System
IEA	International Epidemiological Association
IP	Inpatient
IQR	Interquartile range
IRB	Institutional Review Board
IRR	Incidence rate ratio

Abbreviation	Definition
LRTD	Lower respiratory tract disease
MBSF	Master Beneficiary Summary File
MenACWY	Meningococcal conjugate vaccine
MenB	Serogroup B meningococcal vaccine
mRNA-1345	Messenger Ribonucleic Acid-1345 Vaccine
MONeT	RSV IMmunizatiON Study for AdulTs at Higher Risk of Severe Illness
MVA-BN-RSV	Modified Vaccinia Ankara-Bavarian Nordic-Respiratory Syncytial Virus Vaccine
NDC	National Drug Codes
NI	Non-interventional
NIS	Non-interventional study
NSAID	Nonsteroidal anti-inflammatory drug
OP	Outpatient
PAS	Post Authorization Study
PASS	Post-authorization safety studies
PCR	Polymerase chain reaction
PDE	Prescription Drug Event
PPV	Positive predictive value
preF	Prefusion F
PS	Propensity score
RDC	Research and Development Committee
RENOIR	RSV vaccine Efficacy study iN Older adults Immunized against RSV disease
RR	Risk ratio

Abbreviation	Definition
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
SNF	Skilled nursing facility
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
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: A Post-Authorization Safety Study of Atrial Fibrillation Following Respiratory Syncytial Virus Vaccine (ABRYSVO™) Among Adults Aged 18 Years and Older in the Veterans Affairs Health System

Protocol Version: 2.0; Date of Protocol: 04 December 2024

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 United States (US) Food and Drug Administration (FDA) on 31 May 2023 for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older. ABRYSVO is a bivalent recombinant protein subunit vaccine which consists of equal amounts of stabilized prefusion F (preF) antigens from the two major RSV subgroups: RSV A and RSV B (Respiratory Syncytial Virus Prefusion F [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% confidence interval [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]

Additionally, Pfizer's pivotal Phase 3 clinical trial, MONeT (RSV I**M**munizati**ON** Study for Adul**T**s at Higher Risk of Severe Illness; Study C3671023 evaluating the safety, tolerability, and immunogenicity of ABRYSVO in adults aged 18 and older at risk of developing severe RSV-associated LRTD is ongoing. The MONeT trial consists of two substudies – a double-blind randomized study among 681 adults aged 18 to 59 years old with certain chronic medical conditions (substudy A) and an open-label study among approximately 200 adults who are immunocompromised (substudy B). Positive top-line safety and immunogenicity

results were announced for substudy A in April 2024 and for substudy B in August 2024[5,6]. Based on the inferred efficacy from the Phase 3 MONeT trial, the FDA approved ABRYSVO for the prevention of LRTD caused by RSV in individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV on 22 October 2024.[7]

Pfizer in collaboration with the US Veterans Health Administration (VHA) of the Department of Veterans Affairs (VA) and Analysis Group herein propose to conduct a post-authorization safety study (PASS) to further evaluate the risk of atrial fibrillation and supraventricular arrhythmia following ABRYSVO administration in the large-scale VHA electronic health record (EHR) database among adults 18 years and older.

This non-interventional study (NIS) 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 those events?

Primary study objective:

- To estimate the incidence of atrial fibrillation following administration of ABRYSVO among adults 18 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 18 years of age and older in the VHA system
- To assess whether adults 18 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 (ie, individuals with specific conditions that increase the risk for severe RSV, older age groups [60 to 69 years, 70 to 79 years, ≥80 years], individuals in VA priority group 1, individuals with dual VHA/Medicare coverage, females, individuals with co-administration with other vaccines) in the VHA system following administration of ABRYSVO
- To assess whether sub-cohorts of interest (ie, individuals with specific conditions that increase the risk for severe RSV, older age groups [60 to 69 years, 70 to 79 years, ≥80 years], individuals in VA priority group 1, individuals with dual VHA/Medicare coverage, females, individuals with co-administration with other vaccines) in the VHA system experience increased risk of atrial fibrillation and supraventricular arrhythmia following administration of ABRYSVO

Study design:

This NI PASS will assess the incidence and risk of atrial fibrillation and supraventricular arrhythmia following ABRYSVO among adults 18 years of age and older in the VHA system from 31 May 2023 to 31 May 2026. All analyses will be conducted separately for individuals 18-59 years of age and for those at least 60 years of age. Pooled analysis using combined individual-level data from both age groups may be conducted. 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 (eg, 0-3 days for atrial fibrillation).

- An internal comparator cohort design (ie, 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 controls in the VHA system based on information recorded in the VHA database:

    1) Primary analysis - individuals who were vaccinated with another vaccine (eg, influenza vaccine or Coronavirus Disease 19 (COVID-19) vaccine on the index date (eg, +/- 30 days); ie, 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 (ie, contemporaneous unvaccinated control cohort)

- An self-controlled risk interval (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 (eg, 0-3 days following vaccination) to the post-vaccination control window (eg, 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 18 years of age on the date of vaccination (ie, 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 (eg, 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 18 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 18 years of age on the matched index date. All individuals must be enrolled in (ie, not disenrolled from) VHA benefits during the 2 years prior to the index date (ie, baseline period) and have complete follow-up (ie, no disenrollment from VHA benefits, death, or receipt of RSV vaccination [for controls who may later receive any RSV vaccine only]) during the risk interval and confirmatory diagnosis window. Eligible individuals will be further classified into either the 18-59 years old age group or 60 years and older age group based on their age on the index date; contemporary vaccinated or unvaccinated controls in the 18-59 years old age group are further required to have a record for specific conditions that increase the risk for severe RSV as defined by the Centers for Disease Prevention and Control (CDC) during the baseline period (see "Subgroups" below for specific conditions).

Variables:

- Exposure: Administration of ABRYSVO will be identified based on the following:
    - Current Procedural Terminology (CPT) code 90678, OR
    - 10 and 11-digit National Drug Codes (NDC) 0069-0207-01, 0069-0250-01, 0069-0344-01, 0069-0344-05, 0069-0344-10, 0069-0651-01, 0069-1265-10, 0069-1265-20, 0069-2465-19, 0069-2465-01, 0069-2465-10; OR
    - Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (ie, 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 arrhythmia in the 2 years prior to the index date (ie, "clean window," to rule out pre-existing events).[8,9]

  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.[10-17] 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 (ie, age, sex, race/ethnicity, VHA service area, marital status) and clinical characteristics (ie, smoking, body mass index [BMI], history of anaphylaxis/allergic reactions including to vaccine components, history of hospitalizations, frailty index, Charlson Comorbidity Index [CCI], alcohol abuse, prior infections, history of atrial fibrillation prior to the baseline period, selected comorbidities, selected concomitant medications, history of immunizations, and co-administered immunizations). The final list of baseline characteristics will be defined in the statistical analysis plan (SAP) based on feasibility and availability.

- Subgroups:

  The following subgroups will be analyzed for the 18-59 years old age group and the 60 years and older age group:

  - Individuals in VA priority group 1;
  - Females enrolled in the VHA (pending sufficient sample size);
  - Individuals with co-administration with other vaccines (ie, influenza vaccine, COVID-19 vaccine, or other pre-specified vaccines [eg, shingles, hepatitis B]) on the same day.[18]

  The following subgroups will be analyzed for the 60 years and older age group only:

  - Individuals with specific conditions that increase the risk for severe RSV as defined by the CDC during the baseline period, identified as those with chronic cardiovascular disease, chronic lung or respiratory disease, end-stage renal disease or dependence on hemodialysis or other renal replacement therapy, diabetes mellitus with complications, neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness, chronic liver disease, chronic hematologic conditions, severe obesity, moderate or severe immune compromise, residence in a nursing home, or other chronic medical conditions or risk factors that a health care provider determines would increase the risk for severe disease due to viral respiratory infection (eg, frailty);[19] list of conditions may be updated to align with the most current CDC definition at the time of data analysis;
  - Different age groups defined by age on the index date, eg, 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 Centers for Medicare & Medicaid Services (CMS) Medicare administrative claims data;

Data sources: The VHA is the largest integrated health care system in the US, providing both inpatient (IP) and outpatient (OP) clinical care to over 9 million Veterans enrolled at more than 170 medical centers and 1,113 community-based OP clinics.[20] The objectives of this study will be addressed using data from VHA's Corporate Data Warehouse (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 37,444 and 116,493 individuals at least 60 years of age vaccinated with ABRYSVO, respectively. For individuals 18-59 years of age, based on an expected background rate of 4.4 per 1,000 person-years for incident atrial fibrillation and assuming the same matching rate of controls to ABRYSVO vaccinated individuals (ie, 4:1 ratio), a sample size of 286,730 and 892,049 individuals vaccinated with ABRYSVO is needed to detect a 2-fold and 1.5-fold increase in the incidence rate ratio (IRR), respectively with a power of 80% and a one-sided alpha level of 0.05.

Data analysis: All analyses will be conducted separately among individuals at least 60 years of age and older and among individuals 18-59 years of age. Pooled analyses among individuals 18 years of age or older may be conducted using combined individual-level data from both age groups. If heterogeneity in patient characteristics (other than age) is not observed and characteristics are considered to be sufficiently similar, then individual-level data from both age groups will be combined, and the descriptive analyses of characteristics and outcomes will be conducted using the combined dataset. If sample size is sufficient to allow comparative cohort analyses to be performed separately among individuals 18-59 years of age and individuals 60 years and older, then comparative analyses will also be performed in the pooled population.

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. Positive predictive value (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 Heads of Medicines Agencies (HMA)-European Medicines Agency (EMA) Catalogues of Real-world Data (RWD) studies: 16 August 2024

- VHA Research and Development Committee (RDC) and Institutional Review Board (IRB) approval (estimated): 31 December 2024
- Start of data collection (estimated planned date for starting data extraction for analysis): 24 February 2025
- Interim report: 25 September 2026
- End of data collection (planned date for final data cut): 30 November 2027
- Final study report: 26 May 2028

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	04 December 2024	Administrative	Study information, Section 4 Abstract	The study title has been updated to reflect the expansion of the study population to include individuals 18-59 years of age who are at increased risk for LRTD caused by RSV. Other study information (ie, protocol version identifier, date, European Union [EU] Post Authorization Study [PAS] register number, research question and objectives, Country[ies] of study, author) has been updated to reflect the updated information as of the amendment.	To reflect the expansion of the study population to include individuals 18-59 years of age who are at increased risk for LRTD caused by RSV given FDA's recent approval of this indication. To update study information.
2.0	04 December 2024	Administrative	Study Information, Section 4 Abstract, Section 7 Rationale and Background, Section 8 Research Question and Objectives, Section 9 Research Methods, Section 10 Protection of Human Participants, Section 11 Management and Reporting of Adverse Events/Adverse Reactions, Section 12 Plans for Disseminating and	Abbreviations have been updated or formatted according to Pfizer's template.	To update abbreviations.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
			Communicating Study Results		
2.0	04 December 2024	Administrative	Section 2 List of Abbreviations	List of Abbreviations has been updated to include additional abbreviations used in the protocol and to remove ones not referenced.	To reflect the abbreviations used in the protocol.
2.0	04 December 2024	Administrative	Section 3 Responsible Parties	Updated to include additional principal investigators of the protocol.	To align with the Authors of the protocol as reflected on the Title page (study information).
2.0	04 December 2024	Administrative	Section 4 Abstract, Section 6 Milestones	Milestones dates have been updated.	To update milestone dates.
2.0	04 December 2024	Substantial	Section 4 Abstract, Section 7 Rationale and Background, Section 8 Research Question and Objectives, Section 9 Research Methods	Text has been updated to reflect the inclusion of the 18-59 years old age group. Text in the Abstract, Research Question and Objectives sections has been updated to reflect the inclusion of the 18-59 years old age group and to reflect the updated subgroups of interest for the 18-59 years old age group and the 60 years and older age group. Specifically, for both age groups, subgroup analysis will be conducted in individuals in VA priority group 1, females enrolled in the VHA (pending sufficient sample size), and individuals with co-administration with other vaccines; for the 60 years and older age group only, subgroup analysis will be conducted in individuals with specific conditions that increase the risk for severe RSV, different age groups defined by age on the index date (60 to 69 years, 70 to 79 years, ≥80 years), and individuals enrolled in the VHA with dual coverage with Medicare.	To reflect the expansion of the study population to include individuals 18-59 years of age who are at increased risk for LRTD caused by RSV given FDA's recent approval of this indication, and to update subgroups of interest associated with the newly added 18-59 years old age group and the 60 years and older age group.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				The text in the Research Methods section has been updated to reflect the updated analysis associated with the inclusion of the additional 18-59 years old age group, specifically: • Section 9.1: text specifying analysis will be conducted separately in the 18-59 years old age group and the 60 years or older age group has been added. • Section 9.2.1 and Section 9.2.2: inclusion/exclusion criteria for the 18-59 years old age group have been added. Across all ages, missing data on age was also added as a specific exclusion criterion and complete follow-up has been added as a specific inclusion criterion. Additional clarification around the timeframe of assessment of RSV and other vaccines and around the regular use of preventive medical care has been added to the contemporary unvaccinated control cohort. • Section 9.7: text specifying analysis will be conducted separately in the 18-59 years old age group and the 60 years or older age group has been added. Text describing the method and condition when pooled analysis using individual level data from both age	

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				groups will be performed has been added. • In Section 9.2.3 and Section 9.7.3, text has been updated to reflect the updated subgroups of interest for the 18-59 years old age group and the 60 years and older age group. Text clarifying that subgroup analyses will be conducted to each age group as applicable has been added.	
2.0	04 December 2024	Administrative	Section 4 Abstract, Section 7 Rationale and Background, Section 9.2.2, Section 9.3.2, Section 9.3.3, Section 9.9	Corrected typo in "arrhythmia".	To correct typos.
2.0	04 December 2024	Administrative	Section 4 Abstract, Section 8 Research Question and Objectives	Corrected typo in "those events".	To correct typos.
2.0	04 December 2024	Substantial	Section 4 Abstract, Section 9.1, Section 9.2, Section 9.2.1, Section 9.3.1	Earliest date of vaccine availability has been updated to 31 May 2023.	To reflect the approval date of ABRYSVO.
2.0	04 December 2024	Substantial	Section 4 Abstract, Section 9.3.1	Additional codes to identify ABRYSVO.	To ensure a comprehensive code list for ABRYSVO.
2.0	04 December 2024	Substantial	Section 4 Abstract, Section 9.3.3	Baseline characteristics have been added to include additional covariates of interest, including comorbidities associated with conditions that increase the risk of LRTD caused by RSV	To reflect the baseline characteristics of interest with the inclusion of individuals 18-59 years of age who are at increased risk for LRTD caused by RSV

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	04 December 2024	Substantial	Section 4 Abstract, Section 9.5.1	Sample size calculation has been updated to include separate calculation for the 18-59 years old age group using the internal comparator cohort design. Sample size calculation using the SCRI design has also been added for both age groups.	To reflect the addition of the 18-59 years old age group in sample size calculations.
2.0	04 December 2024	Substantial	Section 9.1.1	Clarifying text on lengths of confirmatory diagnosis window and on the index date for the ABRYSVO cohort has been added.	To specify lengths of confirmatory diagnosis window and the index date for the ABRYSVO cohort.
2.0	04 December 2024	Substantial	Section 9.1.2	Figure 1 has been updated to clarify the SCRI study design.	To clarify the SCRI study design.
2.0	04 December 2024	Substantial	Section 9.1.3	Information in line listing of atrial fibrillation cases from the chart review has been clarified.	To specify all variables that will be provided in the line listing of atrial fibrillation cases from the chart review.
2.0	04 December 2024	Substantial	Section 9.3.2	Clarified post-vaccination control interval in Table 1 is defined for SCRI design.	To provide clarification of the post-vaccination control interval for SCRI design.
2.0	04 December 2024	Substantial	Section 9.4	Text has been updated to include additional information of the CMS Medicare claims along with minor clarification edits of the data elements available in CDW.	To provide comprehensive information around the CMS Medicare claims and CDW.
2.0	04 December 2024	Administrative	Section 9.7.2.3	Corrected typo in “41 days”.	To correct typo.
2.0	04 December 2024	Substantial	Section 9.9	Text updated to incorporate additional strengths associated with the subgroup analysis of the individuals in the VA priority group 1 subgroup among those 18-59 years old.	To ensure comprehensive description of study strengths and limitations.
2.0	04 December 2024	Administrative	Section 12	Replaced references to “EU PAS Register” with “HMA-EMA Catalogues of RWD Studies”.	To incorporate updated Pfizer protocol template.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	04 December 2024	Substantial	Annex 3 Table A-1	Additional codes to identify ABRYSVO have been added.	To ensure a comprehensive code list for ABRYSVO is used.
2.0	04 December 2024	Substantial	Annex 3 Table A-2	Additional ABRYSVO characteristics and clinical characteristics and associated codes have been added	To reflect the baseline characteristics of interest with the inclusion of individuals 18-59 years of age who are at increased risk for LRTD caused by RSV.
2.0	04 December 2024	Substantial	Annex 3 Table A-3	Additional codes to identify other vaccinations have been added.	To ensure a comprehensive code list for other vaccinations is used.

6. MILESTONES

Milestone	Planned Date
Registration in the Heads of Medicines Agencies-European Medicines Agency (HMA-EMA) Catalogues of Real-world Data (RWD)	16 August 2024 Registration number: EUPAS1000000290
Veterans Health Administration (VHA) Research and Development Committee (RDC) and Institutional Review Board (IRB) approval (estimated)	31 December 2024
Start of data collection (estimated)	24 February 2025
Interim report[1]	25 September 2026
End of data collection	30 November 2027
Final study report[2]	26 May 2028

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

7. RATIONALE AND BACKGROUND

Respiratory syncytial virus (RSV) is a major cause of respiratory infection and significant contributor to morbidity and mortality in infants, older adults, and adults at higher risk for lower respiratory tract disease (LRTD), such as those who are immunocompromised or have chronic cardiopulmonary conditions.[21,22] The Centers for Disease Prevention and Control (CDC) estimates that among adults 65 years and older in the United States (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.[23-29] RSV infection has been estimated to affect 3%-7% of the elderly population and 4%-10% of adults at high-risk.[22] 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.[26,30,31] 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.[30,31] Rather, RSV manifestations can be difficult to distinguish from those associated with influenza virus or other respiratory viruses.[32] RSV can lead to mild cold-like symptoms in adults, but more serious presentations are possible including tracheobronchitis, other LRTD (eg, pneumonia), or severe respiratory distress.[24,32] Traditionally, detection methods such as cell culture and rapid antigen tests for RSV were cumbersome with low sensitivity.[33] The recent development and increased availability of less invasive and highly sensitive multiphasic polymerase chain reaction (PCR) respiratory panel tests has enabled clinicians to recognize how common and serious RSV is in older adults.[33]

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.[30] 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.[30,31,34-36] 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.[34-36] RSV has also been recognized as a significant cause of severe illness in populations with underlying cardiopulmonary disease and those who are immunocompromised, including hematopoietic stem cell transplant (HSCT) recipients, patients undergoing intensive chemotherapy, and lung transplant patients.[21] Studies suggest that people less than 65 years with chronic medical conditions were 1.2−28 times more likely to be hospitalized for RSV depending on risk condition.[37] RSV can trigger exacerbations of underlying comorbid conditions in older adults, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF).[31] RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans.[38]

RSV is therefore a disease for which a highly effective vaccine could have a large public health impact among older adults and high-risk adults, with the potential to avert a similar number of hospitalizations as the seasonal influenza vaccine program in the same age group.[26] 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.[39,40] However, two vaccines have recently been approved by the US Food and Drug Administration (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).[41,42] 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]).[43-45]

ABRYSVO is a bivalent recombinant protein subunit vaccine which consists of equal amounts of stabilized Prefusion F (preF) antigens from the two major RSV subgroups: RSV A and RSV B (Respiratory Syncytial Virus Prefusion F [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% confidence interval [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 CI 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 adverse reactions (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 (AE) 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.[9] Atrial fibrillation is part of a broader group of supraventricular arrhythmia which are relatively common cardiac rhythm disturbances typically occurring in repetitive bouts.

Additionally, Pfizer's pivotal Phase 3 clinical trial, MONeT (RSV I**M**munizati**ON** Study for Adul**T**s at Higher Risk of Severe Illness; Study C3671023 evaluating the safety, tolerability, and immunogenicity of ABRYSVO in adults aged 18 and older at risk of developing severe RSV-associated LRTD is ongoing. The MONeT trial consists of two substudies – a double-blind randomized study among 681 adults aged 18 to 59 years old with certain chronic medical conditions (substudy A) and an open-label study among approximately 200 adults who are immunocompromised (substudy B). Positive top-line safety and immunogenicity results were announced for substudy A in April 2024 and for substudy B in August 2024.[5,6] Based on the inferred efficacy from the Phase 3 MONeT trial, the FDA approved ABRYSVO for the prevention of LRTD caused by RSV in individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV on 22 October, 2024.[7]

Post-authorization safety studies (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 Veterans Health Administration (VHA) of the Department of Veterans Affairs (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 electronic health record (EHR) database among adults 18 years and older.

This NIS 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 those events?

Primary study objective:

- To estimate the incidence of atrial fibrillation following administration of ABRYSVO among adults 18 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 18 years of age and older in the VHA system
- To assess whether adults 18 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 (ie, individuals with specific conditions that increase the risk for severe RSV, older age groups [60 to 69 years, 70 to 79 years, ⩾80 years], individuals in VA priority group 1, individuals with dual VHA/Medicare coverage, females, individuals with co-administration with other vaccines) in the VHA system following administration of ABRYSVO
- To assess whether sub-cohorts of interest (ie, individuals with specific conditions that increase the risk for severe RSV, older age groups [60 to 69 years, 70 to 79 years, ⩾ 80 years], individuals in VA priority group 1, individuals with dual VHA/Medicare coverage, females, individuals with co-administration with other vaccines) 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 NI PASS will assess the incidence and risk of atrial fibrillation and supraventricular arrhythmia following receipt of ABRYSVO among adults 18 years of age and older in the VHA system from 31 May 2023 to 31 May 2026. All analyses will be conducted separately for individuals 18-59 years of age and for those at least 60 years of age. Pooled analysis using combined individual-level data from both age groups may be conducted (see Section

9.7 for further details). 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 (eg, 0-3 days for atrial fibrillation).

- An internal comparator cohort design (ie, 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 controls in the VHA system based on information recorded in the VHA database:

  1) Primary analysis - individuals who were vaccinated with another vaccine (eg, influenza vaccine or Coronavirus Disease 19 (COVID-19) vaccine on the index date (eg, +/- 30 days); ie, 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 (ie, 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.

- A self-controlled risk interval (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 (eg, 0-3 days following vaccination) to the post-vaccination control window (eg, 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 (ie, 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 (ie, 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 (ie, 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 (eg, myocarditis and pericarditis) to assess the safety profile of COVID-19 vaccines.[10-14] 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 for the primary and secondary analyses with different risk interval lengths (see Section 9.3.2).[8,9]

Multivariable adjusted analyses will be performed comparing individuals who received ABRYSVO to individuals who received another vaccine (eg, 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) [ie, contemporary vaccinated controls] in the primary analysis. The ABRYSVO cohort's index date will be defined as the date of vaccination with ABRYSVO. 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 (ie, 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 (ie, 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 (ie, 0-1 day risk interval plus 30-day diagnosis confirmation window) and up to 61 days post-index (ie, 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.

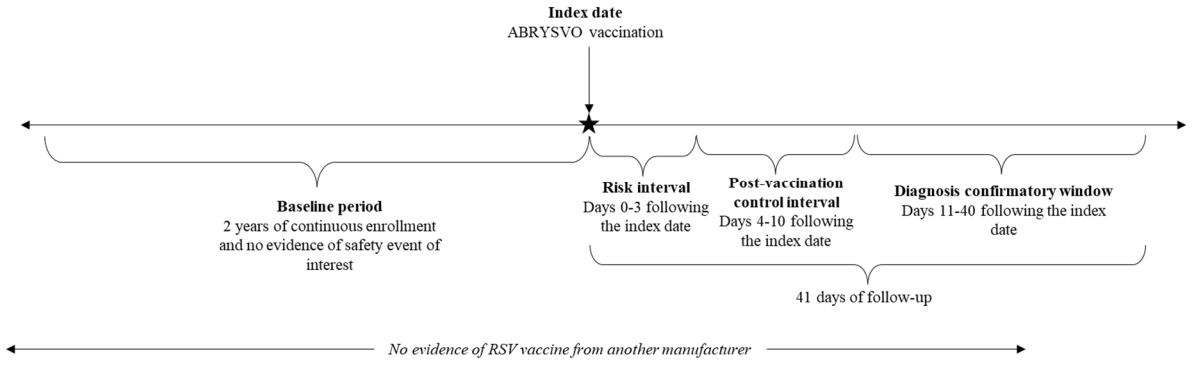
9.1.2. Secondary Design - SCRI Design with Post-Vaccination Control Interval

In addition, the SCRI design uses information from cases (ie, 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.[46,47] 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 (eg, 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 (ie, 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 (eg, seasonality, other vaccination, medication use).[48,49] 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. Example of SCRI Design for Assessment of a Safety Event with a 0-3 Days Risk Interval in the ABRYSVO Cohort*



* Figure is not drawn to scale.

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 EHR for each patient (detailed in Section 9.6.1 "Case Report Forms (CRF)"). 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 co-administered vaccines.

9.2. Setting

The study population will consist of individuals aged 18 years and older within the VHA system from 31 May 2023 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 31 May 2023 (or earliest date of vaccine availability for the indicated population) 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 (eg, 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 (ie, 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 vaccine on or within 30 days of the index date or in the baseline period (ie, 2 years prior to the index date)

- No record for any other vaccine (eg, those listed in Section 9.3.3) on or within 30 days of 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 (ie, inpatient [IP] or outpatient [OP] 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 between 365 to 31 days 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 2 years of continuous enrollment in (ie, no disenrollment from) VHA benefits (ie, the baseline period) prior to the index date

- Complete follow-up (ie, no disenrollment from VHA benefits, death, or receipt of RSV vaccination [for controls who may later receive any RSV vaccine only]) during the risk interval and confirmatory diagnosis window (eg, 34 days of complete follow-up for 0-3 days primary risk interval plus 30-day confirmatory diagnosis window; or 32 days or 61 days for secondary analysis with 0-1 days and 0-30 days risk intervals plus 30-day confirmatory diagnosis window, respectively).

Based on age on the index date, eligible individuals will be further classified into the following two age groups with the following additional inclusion criteria:

- 18-59 years old age group

  - 18-59 years of age on the index date

  - For individuals in cohorts B and C, a record for specific conditions that increase the risk for severe RSV as defined by the CDC during the baseline period, identified as those with chronic cardiovascular disease, chronic lung or respiratory disease, end-stage renal disease or dependence on hemodialysis or other renal replacement therapy, diabetes mellitus with complications, neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness, chronic liver disease, chronic hematologic

conditions, severe obesity, moderate or severe immune compromise, residence in a nursing home, or other chronic medical conditions or risk factors that a health care provider determines would increase the risk for severe disease due to viral respiratory infection (eg, frailty); list of conditions may be updated to align with the most current CDC definition at the time of data analysis[19]

- Moderate and severe immunocompromising conditions will include solid tumor and hematologic malignancies, receipt of solid-organ transplant or an islet transplant, receipt of chimeric antigen receptor (CAR) T-cell therapy or hematopoietic cell transplant (HCT) (within 2 years of transplantation), moderate or severe primary immunodeficiency, and human immunodeficiency virus [HIV] infection)[19]

- 60 years and older age group
  - At least 60 years of age on 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 arrhythmia during the baseline period
- Individuals with missing date of birth

For the analyses using the SCRI design, a subset of eligible individuals from the ABRYSVO cohort that experienced atrial fibrillation or other supraventricular arrhythmia in the risk or control intervals will be included.

9.2.3. Subgroups

Safety surveillance may be conducted for subgroups of interest as applicable to each age group, including, but not limited to the ones described below.

The following subgroups will be analyzed for the 18-59 years old age group and the 60 years and older age group:

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

- Individuals with co-administration with other vaccines (ie, influenza vaccine, COVID-19 vaccine, or other pre-specified vaccines [eg, shingles, hepatitis B] listed in Section 9.3.3) on the same day.[18]

The following subgroups will be analyzed for the 60 years and older age group only:

- Individuals with specific conditions that increase the risk for severe RSV as defined by the CDC during the baseline period; list of conditions may be updated to align with the most current CDC definition at the time of data analysis (see Section 9.2.1);

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

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

Additional subgroups of interest may be assessed as additional information becomes available from ongoing clinical trials, Vaccine Adverse Event Reporting System (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 (ie, 31 May 2023) will be identified based on the following (see Annex 3 Table A-1 for additional details):

- Current Procedural Terminology (CPT) code 90678, OR

- 10 and 11-digit National Drug Codes (NDCs) 0069-0207-01, 0069-0250-01, 0069-0344-01, 0069-0344-05, 0069-0344-10, 0069-0651-01, 0069-1265-10, 0069-1265-20, 0069-2465-19, 0069-2465-01, 0069-2465-10; OR

- Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (ie, 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 arrhythmia should be observed in the 2 years prior to the index date (ie, "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).[8,9]

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 (ie, 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 arrhythmia in the 2-year clean window).

The study outcomes and operational definitions of the outcome variables based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes are outlined in Table 1. ICD-10-CM diagnosis codes occurring in any position (ie, primary or secondary) in OP (including emergency department [ED]) and/or IP settings will be used to identify safety events.

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

Safety Event	**Operational Definition** 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 for SCRI Design (Days)**
Atrial fibrillation (primary outcome)[50]	• I48.0, Paroxysmal atrial fibrillation • I48.19, Other persistent atrial fibrillation • I48.20, Chronic atrial fibrillation, unspecified • I48.91, Unspecified atrial fibrillation	IP or OP	2 years	Primary: 0-3 Secondary: 0-1 and 0-30	Primary: 4-10 Secondary: 2-8 and 31-61
Supraventricular arrhythmia, including atrial fibrillation (secondary outcome)[50]	Paroxysmal tachycardia • I47.0, Re-entry ventricular arrhythmia • I47.10, Supraventricular tachycardia, unspecified • I47.11, Inappropriate sinus tachycardia • I47.19, Other supraventricular tachycardia • I47.9, Paroxysmal tachycardia, unspecified Atrial fibrillation:	IP or OP	2 years	Primary: 0-3 Secondary: 0-1 and 0-30	Primary: 4-10 Secondary: 2-8 and 31-61

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

Safety Event	Operational Definition 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 for SCRI Design (Days)
	• See "Atrial fibrillation (primary outcome)" above Atrial flutter: • I48.3, Atrial flutter • I48.4, Atypical atrial flutter • I48.92, Unspecified atrial flutter Other cardiac arrhythmia: • I49.1, Atrial premature depolarization • I49.5, Sick sinus syndrome • 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.[10-17] 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 (ie, 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 statistical analysis plan (SAP) based on feasibility and availability. All diagnoses, procedures, and medications will be identified by the ICD-10-CM diagnosis codes, International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS) codes, CPT, or Healthcare Common Procedure Coding System [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 (ie, US region)
- Marital status

ABRYSVO characteristics:

- Month and year of vaccination
- Care setting of vaccination

Clinical characteristics:

- Smoking status
- Body mass index (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
- Charlson Comorbidity Index (CCI)
- Alcohol abuse
- Alcohol dependence (excluding alcohol abuse)
- Prior infections within 90 days of the index date[51,52]
- Selected comorbidities

- Cardiovascular
  - Cardiomyopathy
  - Coronary artery disease (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§
  - Thalassemia§
  - Venous thromboembolism (VTE)
- Hepatic
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Liver disease§
- Immunological
  - Autoimmune disease
  - Immunocompromising conditions§
    - Islet transplant§
    - Solid organ transplant§
    - HSCT§
    - Hematologic or solid malignancy§
    - HIV/Acquired immunodeficiency syndrome (AIDS)§
    - Moderate or severe primary immunodeficiency§
    - Rheumatologic/inflammatory conditions
    - Other immune deficiencies
- Neurological/neuromuscular
  - Dementia (ie, Alzheimer's disease and related disorders, senile dementia)
  - Neurological disease
    - Neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness*§
    - Other neurologic diseases
- Respiratory
  - Asthma§
  - Chronic bronchiectasis
  - COPD/interstitial lung disease/emphysema§
  - Cystic fibrosis§

        - Obstructive sleep apnea
        - Pneumonia
    - Other
        - Cancer
        - Chronic kidney disease/dialysis§
        - Diabetes mellitus without complications
        - Diabetes mellitus with complications§
        - Down syndrome
        - End-stage renal disease§
        - Gout
        - Hyperlipidemia
        - Hyperthyroidism (excluding autoimmune thyroiditis)
        - Illicit drug use (eg, cocaine)
        - Severe obesity (BMI ≥40 kg/m^2)§
        - Stimulant use (eg, amphetamines, caffeine)
        - Metabolic syndrome
        - Panic disorders
        - Reaction to stress
- Concomitant medications†
    - Antineoplastic (ie, 7-con-o-methylnogaril, aclacinomycin a, cisplatin, doxorubicin, etaracizumab, ifosfamide, melphalan, mitoxantrone, trastuzumab)
    - Bisphosphonates (ie, alendronate)
    - Cardiovascular (ie, adenosine, dobutamine)
    - Central nervous system (ie, clozapine, morphine)
- Other medications/procedures (identified outside of the American Heart Association [AHA] criteria)
    - Nonsteroidal anti-inflammatory drugs (NSAID)
    - Ivabradine
    - Respiratory (ie, theophylline)
    - Digitalis
    - CAR T-cell therapy*§
- History of immunizations
    - Seasonal influenza vaccine
    - COVID-19
    - Tetanus diphtheria and pertussis (tetanus diphtheria and acellular pertussis vaccine [Tdap] or tetanus diphtheria and pertussis vaccine [Td])
    - Chickenpox (varicella)
    - Shingles (herpes zoster recombinant and/or live)
    - Human papillomavirus (HPV)
    - Pneumococcal conjugate
    - Pneumococcal polysaccharide
    - Hepatitis A
    - Hepatitis B

    - Meningococcal conjugate vaccine (MenACWY) and serogroup B meningococcal vaccine (MenB)
    - Haemophilus influenzae type b
- Co-administered immunization (same list as history of immunizations)
- Residing in a nursing home*§

* ICD-10-CM diagnosis codes, ICD-10-PCS codes, CPT, HCPCS procedure codes, or operational definition based on other data available in VHA's CDW will be provided in the SAP.
† The list of concomitant medications was derived from the AHA's scientific statement regarding drug-induced arrhythmia, which is based on a literature search.[53] Since the level of evidence varies substantially across articles and reports identified by the AHA, only drugs with relative risk (ie, incidence rate ratio [IRR], hazard ratio, or odds ratio) or 95% CI 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.
§ Conditions that increase the risk of RSV as defined according to CDC.[19]

9.4. Data Sources

The VHA is the largest integrated health care system in the US, providing both IP and OP clinical care to over 9 million Veterans enrolled at more than 170 medical centers and 1,113 community-based OP clinics.[20] VHA's health care delivery system is organized regionally around 18 Veterans Integrated Service Networks (VISNs) across the US. Each VISN is responsible for health care planning and resource allocation in a particular geographical region. For example, VA New England Healthcare System (VISN 1) covers VHA facilities in Massachusetts, Connecticut, New Hampshire, Maine, and Rhode Island, while VA Heart of Texas Health Care Network (VISN 17) oversees the facilities in Texas. The VHA also maintains its own mortality data where 99% of enrollees' deaths are reported within one month of occurrence.

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 (eg, IP medication, IP admission, OP medication, OP 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 history of 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 IP 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 IP 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.[54] Of these, about 30% (roughly 1,000,000 individuals) use VHA health services almost exclusively (ie, 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.[55]), which lends itself to having complete, longitudinal healthcare data for such individuals who may be at higher risk of RSV.[56,57] These priority groups include Veterans with the highest levels of service-connected disability and are therefore, the highest priority for VHA care.[55] 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.[58] 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 Fee-For-Service (FFS) billable healthcare services received in the IP and OP setting, as well as skilled nursing facility (SNF), hospice, and home health agencies, and will cover the US primarily among those 65 years of age and older. Medicare FFS claims data are comprised of six different types of data files, with a unique identifier for each beneficiary, allowing linkage across all data files. Below is a summary of the different datasets:

Master Beneficiary Summary File (MBSF): This dataset contains information on beneficiary enrollment for each calendar month in Medicare Parts A, B, and D. Eligibility for sample selection, including original and current enrollment reason, and baseline characteristics, specifically demographic information, will be obtained from these data files.

Inpatient Claim File: FFS claims submitted by providers for cost reimbursement for services received during hospitalizations and ED visits are included in this dataset. Up to 25 diagnosis fields, including the admission diagnosis as well as a principal diagnosis, are available on each claim.

Outpatient Claim File: FFS claims that institutional, OP providers submit for reimbursement are available in this dataset. These include OP departments, rural health clinics, renal dialysis facilities, OP rehabilitation facilities, comprehensive OP rehabilitation facilities, Federally Qualified Health Centers, and community mental health centers. Up to 25 diagnosis fields as well as CPT codes are available for each OP claim.

Carrier File: Carrier datasets contain FFS claims submitted by professional providers, including physicians, physician assistants, clinical social workers, and nurse practitioners. Claims from freestanding facilities (eg, independent clinical laboratories) are also present in the Carrier files. These files contain up to 12 diagnosis fields as well as CPT codes.

SNF Claim File: This dataset contains FFS claims for paid services that are submitted by SNF institutional facility providers. Up to 25 diagnosis fields, including the admission diagnosis as well as a principal diagnosis, are available on each claim.

Prescription Drug Event (PDE) File: All medications dispensed at OP pharmacies that are submitted for reimbursement are available in this dataset. The NDC variable will be used in this study to identify all medications dispensed, and will also include some vaccinations, including ABRYSVO.

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 18 years of age and older without a prior history of atrial fibrillation as assessed during a 2-year baseline period. Analysis will be conducted separately among individuals at least 60 years of age and among individuals 18-59 years of age.

Of the nine million VHA enrollees,[20] it is estimated that 56% are at least 60 years of age[59] and one million VHA enrollees have a prior history of atrial fibrillation.[60] 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.[61] This results in approximately 3.8 million VHA enrollees at least 60 years of age estimated as eligible for inclusion in the study. Separately, approximately 11% of adults aged 18 to 49 and 29% of those aged 50 to 64 are immunocompromised or have a chronic condition that puts them at risk for severe RSV disease.[62] As such, an estimated 330,000 to 868,000 VHA enrollees aged 18 to 59 may be 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 for individuals at least 60 years of age and for individuals 18-59 years of age, separately. For individuals at least 60 years of age, 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,[9] assuming controls (vaccinated or unvaccinated) will be matched to ABRYSVO vaccinated individuals on a 4:1 ratio, a sample size of 37,444 and 116,493 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 a one-sided alpha level of 0.05, respectively.[63] For individuals 18-59 years of age, based on an expected

background rate of 4.4 per 1,000 person-years for incident atrial fibrillation reported for males 45-54 years of age[64] (which is assumed to comprise the majority of the 18-59 years age group as the VHA population is generally older) and assuming the same matching rate of controls to ABRYSVO vaccinated individuals (ie, 4:1 ratio), a sample size of 286,730 and 892,049 individuals vaccinated with ABRYSVO is needed to detect a 2-fold and 1.5-fold increase in the IRR, respectively, with a power of 80% and a one-sided alpha level of 0.05.[63] Power of ≥ 80% is typically desirable in drug safety research and the FDA views a risk ratio (RR) of >3 as meaningful, so these have also been used for the power calculations.[65] 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)	IRR	Number of controls needed in each comparator cohort (N)	Number of ABRYSVO vaccinated individuals needed (N)
Individuals at least 60 years of age			
4:1	1.2	2,413,066	603,267
	1.5	465,972	116,493
	2.0	149,777	37,444
	3.0	54,086	13,522
2:1	1.2	1,414,556	707,278
	1.5	266,270	133,135
	2.0	83,210	41,605
	3.0	29,124	14,562
Individuals 18-59 years of age			
4:1	1.2	18,478,144	4,619,536
	1.5	3,568,194	892,049
	2.0	1,146,920	286,730
	3.0	414,166	103,542
2:1	1.2	10,832,015	5,416,008
	1.5	2,038,968	1,019,484
	2.0	637,178	318,589
	3.0	223,013	111,507

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

Matching ratio (controls: ABRYSVO vaccinated)	IRR	Number of controls needed in each comparator cohort (N)	Number of ABRYSVO vaccinated individuals needed (N)

Abbreviations: IRR, incidence rate ratio.
Notes:
The power calculations are based on assuming one-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 for individuals at least 60 years of age, and a background rate of 4.4 incident atrial fibrillation events per 1,000 person years as observed among male 45-54 years of age was used for individuals 18-59 years of age.

Table 3 illustrates the estimated sample size required for the conditional Poisson regression using the SCRI design for individuals at least 60 years of age and for individuals 18-59 years of age, separately. For individuals at least 60 years of age, based on the 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 and a 4-day risk window (ie, days 0-3), a sample size of size of 38,453 and 129,204 individuals vaccinated with ABRYSVO is needed to detect a RR of 2 and 1.5, respectively, with 80% power and a one-sided alpha level of 0.05.[66] For individuals 18-59 years of age, based on an expected background rate of 4.4 per 1,000 person-years for incident atrial fibrillation reported for male 45-54 years of age[64] (which is assumed to comprise the majority of the 18-59 years age group) and a 4-day risk window (ie, days 0-3), a sample size of size of 294,458 and 989,381 individuals vaccinated with ABRYSVO is needed to detect a RR of 2 and 1.5, respectively, with 80% power and a one-sided alpha level of 0.05.[66]

Table 3. Sample size calculations for the conditional Poisson regression using the SCRI design

RR	Total number of events needed	Number of events expected in control interval	Number of *ABRYSVO* vaccinated individuals needed (N)
Individuals at least 60 years of age			
Days 0-3 risk interval			
1.2	787	467	718,310
1.5	156	84	129,204
2.0	53	25	38,453
3.0	22	9	13,843
Days 0-1 risk interval			
1.2	1,025	764	1,175,137
1.5	197	138	212,263

Table 3. Sample size calculations for the conditional Poisson regression using the SCRI design

RR	Total number of events needed	Number of events expected in control interval	Number of *ABRYSVO* vaccinated individuals needed (N)
2.0	64	41	63,064
3.0	24	13	19,996
Days 0-30 risk interval			
1.2	747	340	118,089
1.5	153	62	21,534
2.0	54	18	6,252
3.0	23	6	2,084
Individuals 18-59 years of age			
Days 0-3 risk interval			
1.2	787	467	5,500,485
1.5	156	84	989,381
2.0	53	25	294,458
3.0	22	9	106,005
Days 0-1 risk interval			
1.2	1,025	764	8,998,651
1.5	197	138	1,625,411
2.0	64	41	482,912
3.0	24	13	153,118
Days 0-30 risk interval			
1.2	747	340	904,273
1.5	153	62	164,897
2.0	54	18	47,873
3.0	23	6	15,958

Abbreviations: RR, risk ratio.
Notes:
Sample size calculations for the SCRI design were performed according to the method by Musonda et al.[67] The calculations are based on assuming one-sided α=0.05, a power of 80%, and the following scenarios: (1) a risk interval of 3 days and a control interval of 7 days (primary), (2) a risk interval of 2 days and a control interval of 7 days (secondary), (3) a risk interval of 31 days and a control interval of 31 days (secondary).

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 (CRF)

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, Statistical Analysis System (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.

All analyses will be conducted separately among individuals at least 60 years of age and among individuals 18-59 years of age. Pooled analyses among adults 18 years of age and older may be conducted using combined individual-level data from both age groups. Baseline characteristics will be descriptively compared and heterogeneity in the estimated incidence rates of atrial fibrillation among the 18-59 years old and 60 years and older age groups will be assessed using a two-population test (eg, Fisher’s exact test or Z-test). If significant heterogeneity is observed with respect to patient characteristics (other than age) and incidence rate estimates, then no pooled analyses will be conducted. Otherwise, if heterogeneity is not observed and characteristics are considered to be sufficiently similar, then individual-level data from both age groups will be combined, and the descriptive analyses of characteristics and outcomes will be conducted using the combined dataset. If sample size is sufficient to allow comparative cohort analyses to be performed separately among individuals 18-59 years of age and individuals 60 years and older, then comparative analyses will also be performed in the pooled population. Further details will be provided in the SAP.

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, standard deviation (SD), median, and interquartile range [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 (eg, OP clinic, pharmacy, IP 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

Average treatment effect among the treated (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.[68] Specifically, ATT weights will be calculated to allow for estimation of the average treatment effect among individuals receiving ABRYSVO.[69] 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 propensity score (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 (ie, 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 (ie, individuals vaccinated with ABRYSVO who experience safety events following vaccination) who have at least 41 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.[70] Further details will be described in the SAP.

Positive predictive value (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.[71] 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 (eg, 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 (ie, influenza vaccine, COVID-19 vaccine, or other pre-specified vaccines [eg, shingles, hepatitis B] listed in Section 9.3.3) on the same day.[18]

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 as applicable to each age group. 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 (ie, atrial fibrillation) but cannot plausibly be related to the exposure of interest (ie, vaccination with ABRYSVO).[72] 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.[73,74]

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.[75-77]

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 IP and OP diagnosis codes are captured. Referenced variables exist and are of appropriate length and type

Data retrieval will be coordinated by an experienced programmer/analyst. The analyst will write programming for retrieval of each data element from the electronic databases. Double programming will be performed for the first iteration of the analyses; results/datasets will be compared, and if any discrepancies are identified, both programmers will determine a resolution, bringing in a third programmer if needed. Subsequent iterations of analyses (ie, re-runs of the analyses) will be audited by a senior programmer. All tables will be reviewed by the project manager and the principal investigator to evaluate 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 (ie, the increased risk of experiencing a specific safety event due to ABRYSVO). The potential for selection bias (ie, 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.[78] 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.[79] 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 arrhythmia 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.[80] 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.[81] 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 for adults 60 years and older 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. Additionally, subgroup analysis will be conducted among priority group 1 Veterans who are most likely to receive all of their care from a VA facility to ensure data completeness among individuals aged 18-59 years old.

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 (CEP) 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 VA Informatics and Computing Infrastructure (VINCI). VHA data will not be provided to Pfizer or Analysis Group. Rather, only VA employees, including those with research service without compensation (WOC) employee status, who have completed necessary VA training and have proper clearance will access and analyze data on secure VA servers and behind necessary firewalls, under the direction and supervision of Dr. 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 (eg, 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 Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology,[82] the FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting, Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data[83] and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).[84]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

The requirements for reporting safety events on the NIS Adverse Event Monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the data collection tool (eg, 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 (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (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 YRR 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 (ie, Heads of Medicines Agencies [HMA]-European Medicines Agency [EMA] Catalogues of Real-world Data [RWD] studies) 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 (eg, 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.
	0069-0651-01	Pfizer, Inc.
	0069-1265-10	Pfizer, Inc.
	0069-1265-20	Pfizer, Inc.
	0069-2465-19	Pfizer, Inc.
	0069-2465-01	Pfizer, Inc.
	0069-2465-10	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; Categorical variable: • 60-64 • 65–69 • 70-74 • 75-79 • 80-84 • 85-89 • ≥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: • Male • Female • Unknown	
Race/ethnicity	Categorical variable: • White, non-Hispanic • Black • Hispanic ethnicity, any race • Asian • Native Hawaiian or Pacific Islander • American Indian or Alaskan native • Two or more races • Unknown	
VHA Service area (ie, US region)	Geographic regions in the US; Categorical variable:	Region associated with the most recent healthcare encounter prior to index date

Variable	Description	Operational definition
	• South • Midwest • West • Northeast • Other • Unknown	
Marital status	Categorical variable: • Currently married • Not currently married	
ABRYSVO Characteristics		
Month and year of vaccination	Calendar year and month of vaccination; Categorical variable: Year: • 2023 • 2024 • 2025 • 2026 Month: • January • February • March • April • May • June • July • August • September	

Variable	Description	Operational definition
	• October • November • December	
Care setting of vaccination	Categorical variable: • Outpatient clinic • Pharmacy Inpatient ward	
Clinical Characteristics		
Smoking Status	Dichotomous variable	ICD-10-CM codes: • F17.200, Nicotine dependence, unspecified, uncomplicated • Z7.20, Tobacco use • Z87.891, Personal history of nicotine dependence
BMI	Continuous variable; Categorical variable: • Underweight (<18.5) • Normal weight (18.5–<25) • Overweight (25–<30) • Obese (30–<40) • Severe obesity (≥40) • Unknown	Calculated from height and weight data (kg/m^2)
History of anaphylaxis/ allergic reactions	Dichotomous variable	ICD-10-CM code: • Z87.892 Personal history of anaphylaxis

Variable	Description	Operational definition
		• Z88.0–Z88.6, Z88.8, Z88.9, Allergy status to drugs, medications and biological substances, excluding serum and vaccine • T78.00xx–T78.09xx, Anaphylactic reaction due to food, initial encounter, subsequent encounter and sequela • T78.2xxx, Anaphylactic shock, initial encounter, subsequent encounter and sequela • T78.3xxx, Angioneurotic edema, initial encounter, subsequent encounter and sequela • T78.41xx, Arthus phenomenon • T80.51xx, Anaphylactic reaction due to administration of blood and blood products, initial encounter, subsequent encounter and sequela • T80.59xx, Anaphylactic reaction due to other serum, initial encounter, subsequent encounter and sequela • T88.6xxx, Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter, subsequent encounter and sequela
Previous anaphylaxis of vaccine component	Dichotomous variable	ICD-10-CM codes:

Variable	Description	Operational definition
		• T80.52xx, Anaphylactic reaction due to vaccination, initial encounter, subsequent encounter and sequela • Z28.04, Immunization not carried out because of patient allergy to vaccine or component • Z88.7, Allergy status to serum and vaccine
History of hospitalizations	Dichotomous variable; Continuous variable	Defined by having any hospitalizations (dichotomous) and number of hospitalizations (continuous)
Frailty index[85]	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.
CCI[86]	Continuous variable	ICD-10-CM codes: • I21.x, I21.xx, I22.x, I25.2, Myocardial infarction • I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I43.x, I50.x, I50.xx, CHF • 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

Variable	Description	Operational definition
		• G45, G45.x, G46.x, H34.0, I60.x–I63.x, I60.xx–I63.xx, I60.xxx–I63.xxx, I65.x–I69.x, I65.xx–I69.xx, I65.xxx–I69.xxx, Cerebrovascular disease • F00.x–F03.x, F00.xx–F03.xx, F05, F05.1, G30.x, G31.1, Dementia • I27.8, I27.9, J40.x–J47.x, J40.xx–J47.xx, J40.xxx–J47.xxx, J60.x–J67.x, J68.4, J70.1, J70.3, Chronic pulmonary disease • M05, M05.x, M05.xx, M05.xxx, M06, M06.x, M06.xx, M06.xxx, M31.5, M32.x–M34.x, M32.xx–M34.xx, M35.1, M35.3, M36.0, Rheumatic disease • K25.x–K28.x, Peptic ulcer disease • B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K74.xx, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4, Mild liver disease • E10.0, E10.1x, E10.6x, E10.6xx, E10.8, E10.9, E11.0x, E11.1x, E11.6x, E11.6xx, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0x, E13.1x, E13.6x, E13.6xx, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9, Diabetes without chronic complication

Variable	Description	Operational definition
		• E10.2x–E10.5x, E10.2xx–E10.5xx, E10.7, E11.2x–E11.5x, E11.2xx–E11.5xx, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5x, E13.7, E14.2–E14.5, E14.7, Diabetes with chronic complication • G04.1, G11.4, G80.1, G80.2, G81.x, G81.xx, G82.x, G82.xx, G83.0, G83.1–G83.3, G83.1x–G83.3x, G83.4, G83.9, Hemiplegia or paraplegia • I12.0, I13.1x, N03.2–N03.7, N05.2–N05.7, N18.x, N19, N25.0, Z49.0x–Z49.3x, Z94.0, Z99.2, Renal disease • C00–C75, C00.x–C75.x, C00.xx–C75.xx (excluding C44, C44.x and C44.xx), C7A., C7A.x, C7A.xx, C7B., C7B.x, C7B.xx, C76–C80, C76.x–C80.x, C76.xx–C80.xx, C81–C96, C81.x–C96.x, C81.xx–C96.xx, Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin • I85.0, I85.9, I86.4, I98.2, K70.4x, K71.1x, K72.1x, K72.9x, K76.5, K76.6, K76.7, Moderate or severe liver disease • C77.x–C80.x, C77.xx–C80.xx, Metastatic solid tumor • B20, B97.35, AIDS/HIV

Variable	Description	Operational definition
Alcohol abuse	Categorical variable	ICD-10-CM codes • F10, Alcohol related disorders
Alcohol dependence (excluding alcohol abuse)	Categorical variable	ICD-10-CM codes: F10.2x, F10.2xx, Alcohol dependence
Prior infections within 90 days of the index date[51,52]	Categorical variable for specified prior infections	ICD-10-CM codes: • A04.5, Campylobacter enteritis • B25.x, B27.1x, P35.1, CMV • U07.1, COVID-19 • B27.0x, D82.3, EBV • B17.2, HEV • J09.xx – J11.xx, Influenza virus • B96.0, J15.7, J20.0, Mycoplasma pneumonia • B97.4, J12.1, J20.5, J21.0, Respiratory syncytial virus • A02.1, A22.7, A26.7, A32.7, A40.x, A41.x, A41.xx, A42.7, A54.86, B37.7, O03.37, O03.87, O04.87, O07.37, O08.82, O85, O86.04, R65.2x, T81.44xx, Sepsis • A92.5, P35.4, Zika virus
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 • I48.0, Paroxysmal atrial fibrillation • I48.19, Other persistent atrial fibrillation

Variable	Description	Operational definition
		• I48.20, Chronic atrial fibrillation, unspecified • I48.91, Unspecified atrial fibrillation
Comorbidities	Categorical variable *Cardiovascular* • Cardiomyopathy • CAD§ • CHF • Cardiac valvular disease • Conduction disorder • Heart failure§ • Congenital heart disease§ • Hypertension • Myopericarditis • Pericarditis • Stroke/Transient ischemic attack *Hematological* • Bleeding diathesis or condition associated with prolonged bleeding • Hematologic malignancy§ • Sickle cell disease§ • Thalassemia§ • VTE *Hepatic* • HBV • HCV • Liver disease§	*Cardiovascular* Cardiomyopathy: ▪ ICD-10-CM codes: ▪ I42.x, Cardiomyopathy CAD: ▪ ICD-10-CM codes: ▪ 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 Cardiac valvular disease: ▪ ICD-10-CM codes: ▪ I05.x, I06.x, I07.x, I08.x, I09.x, I09.xx, I34.x, I34.xx, I35.x, I36.x, I37.x, I38.x, I39, Q22.x, Q23.x, Z95.3, Z95.4, Valve diseases

Variable	Description	Operational definition

	Immunological
	• Autoimmune disease
	• Immunocompromising conditions§
	  ○ Islet transplant§
	  ○ Solid organ transplant§
	  ○ HSCT§
	  ○ Hematologic or solid malignancy§
	  ○ HIV/AIDS§
	  ○ Moderate or severe primary immunodeficiency (ie common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)*§
	  ○ Rheumatologic/inflammatory conditions*
	  ○ Other immune deficiencies
	Neurological/neuromuscular
	• Dementia (ie, Alzheimer's disease and related disorders, senile dementia)
	• Neurological disease
	  ○ Neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness (ie, poststroke dysphagia, amyotrophic lateral sclerosis, or muscular dystrophy)*§
	  ○ Other neurologic diseases
	Respiratory
	• Asthma§
	• Chronic bronchiectasis
	• COPD/interstitial lung disease/ emphysema*§
		CHF:
		▪ ICD-10-CM codes:
		  ▪ I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I43.x, I50.x, I50.xx, CHF
		Conduction disorder:
		▪ ICD-10-CM codes:
		▪ I44.x, I44.xx, Atrioventricular and left bundle-branch block
		▪ I45.x, I45.xx, Other conduction disorder
		Congenital heart disease (excluding isolated hypertension):
		▪ ICD-10-CM codes:
		▪ Q20.x, Q21.x, Q21.xx, Q22.x, Q23.x, Q24.x, Q25.x, Q25.xx, Congenital heart disease
		Heart failure:
		▪ ICD-10-CM codes:
		  ▪ 150.x, 150.xx, Heart failure
		Hypertension:
		▪ ICD-10-CM codes:
		  ▪ H35.03x, Hypertensive retinopathy
		  ▪ I10, I11.x–I16.x, I13.xx, Hypertensive diseases
		  ▪ I67.4, Hypertensive encephalopathy diseases
		Myocarditis:

Variable	Description	Operational definition
	• Cystic fibrosis*§ • Obstructive sleep apnea • Pneumonia *Other* • Cancer • Chronic kidney disease/dialysis§ • Diabetes mellitus without complications • Diabetes mellitus with complications*§ • Down syndrome • End-stage renal disease*§ • Gout • Hyperlipidemia • Hyperthyroidism (excluding autoimmune thyroiditis) • Illicit drug use (eg, cocaine) • Metabolic syndrome • Panic disorders • Stimulant use (eg, amphetamines, caffeine) • Severe obesity (BMI ≥40 kg/m^2)§ • Reaction to stress * ICD-10-CM diagnosis codes, ICD-10-PCS codes, CPT, or HCPCS procedure codes will be provided in the SAP. § Conditions that increase the risk of RSV as defined according to CDC.[19]	▪ ICD-10-CM codes: ▪ I40.x, Acute myocarditis ▪ I41, Myocarditis in diseases classified elsewhere ▪ I51.4, Myocarditis, unspecified ▪ B33.22, Viral myocarditis Pericarditis: ▪ ICD-10-CM codes: ▪ I30.x, Acute pericarditis ▪ I32, Pericarditis in diseases classified elsewhere ▪ B33.23, Viral pericarditis Stroke/transient ischemic attack: ▪ ICD-10-CM codes: ▪ 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,

Variable	Description	Operational definition
		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 ▪ G45, Transient ischemic attack *Hematological* Bleeding diathesis or condition associated with prolonged bleeding: ▪ ICD-10-CM codes: ▪ D65, Disseminated intravascular coagulation ▪ D66, Hereditary factor VIII deficiency ▪ D67, Hereditary factor IX deficiency ▪ D68, D68.x, D68.xx, Other coagulation defects ▪ D69, D69.x, D69.xx, Purpura and other hemorrhagic conditions Hematologic malignancy: ▪ ICD-10-CM codes: ▪ C81, C82, C83, C88, C89, C90, C91, C92, C93, C94, C95, C96, Hematologic malignancy

Variable	Description	Operational definition
		Sickle cell disease: ▪ ICD-10-CM codes: ▪ D57, D57.x, D57.xx, D57.xxx, Sickle-cell disorders Thalassemia: ▪ ICD-10-CM codes: ▪ D56.x, Thalassemia VTE: ▪ ICD-10-CM codes: ▪ I26, I26.x, I26.xx, Pulmonary embolism ▪ I80, I80.x, I80.xx, I80.xxx, Phlebitis and thrombophlebitis ▪ I81, Portal vein thrombosis ▪ I82, I82.x, I82.xx, I82.xxx Other venous embolism and thrombosis *Hepatic* HBV: ▪ ICD-10-CM codes: ▪ B18.0, B18.1, Chronic viral hepatitis B ▪ B19.1, B19.1x, Unspecified viral hepatitis B HCV: ▪ ICD-10-CM codes:

Variable	Description	Operational definition
		▪ B18.2, Chronic viral hepatitis C ▪ B19.2x, Unspecified viral hepatitis C Liver disease: ▪ ICD-10-CM codes: ▪ K70.x, K70.xx, Alcoholic fatty liver ▪ K71.x, K71.xx, Toxic liver disease ▪ K72.xx, Hepatic failure, not elsewhere classified ▪ K73.x, Chronic hepatitis, not elsewhere specified ▪ K74.x, K74.xx, Fibrosis and cirrhosis of liver ▪ K75.x, K75.xx, Other inflammatory liver diseases ▪ K76.x, K76.xx, Other diseases of liver ▪ K77, Liver disorders in diseases classified elsewhere *Immunological* Autoimmune disease: ▪ ICD-10-CM codes: ▪ D69.3, Immune thrombocytopenic purpura ▪ E06.3, Autoimmune thyroiditis

Variable	Description	Operational definition
		▪ G35, Multiple sclerosis ▪ G61.0 and G65.0, GBS and sequelae of GBS ▪ L40.x, L40.5x, Psoriasis ▪ L93.x, Lupus erythematosus ▪ M05.x, M05.xx, M05.xxx, Rheumatoid arthritis with rheumatoid factor ▪ M06.x, M06.xx, M06.xxx, Other rheumatoid arthritis ▪ M31.5, M31.6, Giant cell arteritis ▪ M35.0x, Sicca (Sjogren's) syndrome ▪ N05.9, Glomerulonephritis ▪ D84.9, Immunodeficiency, unspecified Immunocompromising conditions: ▪ Solid organ transplant ▪ CPT codes: ▪ 32850–32856, Transplantation of lung ▪ 33930–33945, Transplantation of heart ▪ 44132, 44133, 47133, 47135, 47136, 47140–

Variable	Description	Operational definition
		47147, Transplantation of liver ▪ 44135–44137, 44715, 44720, 44721, Transplantation of intestine ▪ 48160, 48550–48552, 48554, 48556, Transplantation of pancreas ▪ 50300, 50320, 50323, 50325, 50327, 50328, 50329, 50340, 50360, 50365, 50370, 50380, Renal transplantation ▪ ICD-10-PCS codes: ▪ 02YA0Z0, 02YA0Z1, Transplantation of heart ▪ 0BYC0Z0, 0BYC0Z1, 0BYD0Z0, 0BYD0Z1,

Variable	Description	Operational definition
		0BYF0Z0, 0BYF0Z1, 0BYG0Z0, 0BYG0Z1, 0BYH0Z0, 0BYH0Z1, 0BYJ0Z0, 0BYJ0Z1, 0BYK0Z0, 0BYK0Z1, 0BYL0Z0, 0BYL0Z1, 0BYM0Z0, 0BYM0Z1, Transplantation of lung ▪ 0DY60Z0, 0DY60Z1, Transplantation of stomach ▪ 0DY80Z0, 0DY80Z1, Transplantation of small intestine ▪ 0DYE0Z0, 0DYE0Z1, Transplantation of large intestine ▪ 0FY00Z0, 0FY00Z1,

Variable	Description	Operational definition
		Transplantation of liver ▪ 0FYG0Z0, 0FYG0Z1, Transplantation of pancreas ▪ 0TY00Z0, 0TY00Z1, 0TY10Z0, 0TY10Z1, Transplantation of kidney ▪ Islet transplant: ▪ CPT codes: ▪ 0584T, 0585T, 0586T, 48160, Islet cell transplant ▪ HCPCS: ▪ S2102, Islet cell tissue transplant from pancreas; allogeneic ▪ HSCT: ▪ CPT codes: ▪ 38240, 38241, 38242, 38243 ▪ HCPCS: ▪ S2150, S2142 ▪ ICD-10-PCS:

Variable	Description	Operational definition
		▪ 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,

Variable	Description	Operational definition
		30260Y0, 30260Y1, 30263X0, 30263X1, 30263Y0, 30263Y1, 30230AZ, 30230G1, 30230G2, 30230G3, 30230G4, 30230X1, 30230X2, 30230X3, 30230X4, 30233AZ, 30233G1, 30233G2, 30233G3, 30233G4, 30233X1, 30233X2, 30233X3, 30233X4, 30240AZ, 30240G1, 30240G2, 30240G3, 30240G4, 30240X1,

Variable	Description	Operational definition
		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,

Variable	Description	Operational definition
		30240U4, 30240X0, 30243G0, 30243U2, 30243U3, 30243U4, 30243X0 ▪ Hematologic or solid malignancy: ▪ ICD-10-CM codes: ▪ C81, C82, C83, C88, C89, C90, C91, C92, C93, C94, C95, C96, Hematologic malignancy ▪ 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, C40, C41, C42, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52,

Variable	Description	Operational definition
		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 ▪ HIV/AIDs:

Variable	Description	Operational definition
		▪ ICD-10-CM codes: ▪ B20, HIV disease ▪ B97.35, HIV type 2 as the cause of diseases classified elsewhere ▪ B21, B22, B23, B24, HIV/AIDs disease ▪ Receipt of HCT: ▪ ICD-10-PCS codes: ▪ 30250Y0, 30253Y0, 30260Y0, 30263Y0, Transfusion of Autologous Hematopoietic Stem Cells ▪ 30250Y1, 30253Y1, 30260Y1, 30263Y1, Transfusion of Nonautologous Hematopoietic Stem Cells ▪ Moderate or severe primary immunodeficiency: ▪ DiGeorge syndrome:

Variable	Description	Operational definition
		▪ ICD-10-CM codes: • D82.1, DiGeorge syndrome ▪ Wiskott-Aldrich syndrome: ▪ ICD-10-CM codes: • D82.0, Wiskott-Aldrich syndrome ▪ Rheumatologic/inflammatory conditions ▪ ICD-10-CM codes: ▪ M35.9, Systemic involvement of connective tissue, unspecified ▪ M32.9, Systemic lupus erythematosus, unspecified ▪ M06.9, Rheumatoid arthritis, unspecified ▪ M30.0, Polyarteritis nodosa ▪ M31.3, Wegener's granulomatosis

Variable	Description	Operational definition
		▪ M31.9, Necrotizing vasculopathy, unspecified ▪ Other immune deficiencies: ▪ ICD-10-CM codes: ▪ D80, D80.x, Immunodeficiency with predominantly antibody defects ▪ D81, D81.x, D81.xx, Combined immunodeficiencies ▪ D82, D82.x, Immunodeficiency associated with other major defects ▪ D83, D83.x, Common variable immunodeficiency ▪ D84, D84.x, D84.xx, Other immunodeficiencies ▪ D86, D86.x, D86.xx, Sarcoidosis ▪ D89, D89.x, D89.xx, Other disorders involving the immune mechanism, not elsewhere classified

Variable	Description	Operational definition
		Neurological/neuromuscular Dementia (ie, Alzheimer's disease and related disorders, senile dementia): ▪ ICD-10-CM codes: ▪ F00.x–F03.x, F00.xx–F03.xx, F05, F05.1, G30.x, G31.1, Dementia Neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness (ie, poststroke dysphagia, amyotrophic lateral sclerosis, or muscular dystrophy): ▪ Poststroke dysphagia: ▪ ICD-10-CM codes: ▪ I69.191, Dysphagia following nontraumatic intracerebral hemorrhage ▪ I69.291, Dysphagia following other nontraumatic intracranial hemorrhage ▪ I69.391, Dysphagia following cerebral infarction ▪ I69.891, Dysphagia following other

Variable	Description	Operational definition
		cerebrovascular disease ▪ I69.991, Dysphagia following unspecified cerebrovascular disease ▪ Amyotrophic lateral sclerosis: ▪ ICD-10-CM codes: ▪ G12.20, Motor neuron disease, unspecified ▪ G12.21, Amyotrophic lateral sclerosis ▪ Muscular dystrophy: ▪ ICD-10-CM codes: ▪ G71.0, Muscular dystrophy Other neurological disease: ▪ ICD-10-CM codes: ▪ R41, R41.x, R41.xx, Other symptoms and signs involving cognitive functions and awareness ▪ R42, Dizziness and giddiness ▪ R43, R43.x, Disturbances of smell and taste

Variable	Description	Operational definition
		▪ R44, R44.x, Other symptoms and signs involving general sensations and perceptions ▪ R45, R45.x, R45.xx, Symptoms and signs involving emotional state ▪ R46, R46.x, R46.xx, Symptoms and signs involving appearance and behavior *Respiratory* Asthma: ▪ ICD-10-CM codes: ▪ J45.2x–J45.3x, Mild intermittent asthma ▪ J45.4x, Moderate persistent asthma ▪ J45.5x, Severe persistent asthma ▪ J45.9x, Other and unspecified asthma Chronic bronchiectasis: ▪ ICD-10-CM codes: ▪ J47.0, J47.1, J47.9, Bronchiectasis COPD/interstitial lung disease/ emphysema: ▪ ICD-10-CM codes:

Variable	Description	Operational definition
		▪ J41.x Simple and mucopurulent chronic bronchitis ▪ J42, Unspecified chronic bronchitis ▪ J43.x, Emphysema ▪ J44.x, Other COPD ▪ J80, J81.x, J82.xx, J84.xx, J84.xxx, Other respiratory diseases principally affecting the interstitium ▪ M05.10, Rheumatoid lung disease with rheumatoid arthritis of unspecified site Cystic fibrosis: ▪ ICD-10-CM codes: ▪ E84.x, E84.xx, Cystic fibrosis Obstructive sleep apnea: ▪ ICD-10-CM codes: ▪ G47.33 Obstructive sleep apnea (adult) (pediatric) Pneumonia: ▪ ICD-10-CM codes: ▪ J12.x, J12.xx Viral pneumonia, not elsewhere classified ▪ J13 Pneumonia due to Streptococcus pneumoniae

Variable	Description	Operational definition
		▪ J14 Pneumonia due to Hemophilus influenzae ▪ J15.x, J15.xx, J15.xxx Bacterial pneumonia, not elsewhere classified ▪ J16.x Pneumonia due to other infectious organisms, not elsewhere classified ▪ J17 Pneumonia in diseases classified elsewhere ▪ J18.x Pneumonia, unspecified organism *Other* Cancer: ▪ ICD-10-CM codes: ▪ C00–C75, C00.x–C75.x, C00.xx–C75.xx, C7A., C7A.x, C7A.xx, C7B., C7B.x, C7B.xx, Malignant neoplasms, stated or presumed to be primary (of specified sites), and certain specified histologies, except neuroendocrine, and of lymphoid, hematopoietic and related tissue ▪ C76–C80, C76.x–C80.x, C76.xx–C80.xx, Malignant neoplasms of ill-defined,

Variable	Description	Operational definition
		other secondary and unspecified sites ▪ C81–-C96, C81.x–C96.x, C81.xx–C96.xx, Malignant neoplasms of lymphoid, hematopoietic and related tissue Chronic kidney disease/dialysis: ▪ ICD-10-CM codes: ▪ D59.3, Hemolytic-uremic syndrome ▪ I12.x, Hypertensive chronic kidney disease ▪ I13.x, I13.xx, Hypertensive heart and chronic kidney disease ▪ I70.1, Atherosclerosis of renal artery ▪ I72.2 Aneurysm of renal artery ▪ K76.7, Hepatorenal syndrome ▪ M10.30–M10.39, M10.30x–M10.37x, Gout due to renal impairment ▪ M32.14, Glomerular disease in systemic lupus erythematosus

Variable	Description	Operational definition
		▪ M32.15, Tubulo-interstitial nephropathy in systemic lupus erythematosus ▪ M35.04, Sicca syndrome with tubulo-interstitial nephropathy ▪ N00.x–N07.x, N08, Glomerular diseases ▪ N13.1, N13.2, N13.3x, Obstructive and reflux uropathy ▪ N14.x, Nephropathy ▪ N15.x, Other renal tubulo-interstitial diseases ▪ N16, Renal tubulo-interstitial disorders in diseases classified elsewhere ▪ N17.x, N18.x, N19, Acute kidney failure and chronic kidney disease ▪ N25.x, N26.x, N25.xx, Other disorders of kidney and ureter ▪ Q61.02, Q61.11x, Q61.2–Q61.9, Cystic kidney disease ▪ Q62.x, Q62.xx, Congenital obstructive defects of renal

Variable	Description	Operational definition
		pelvis and congenital malformation of ureter Diabetes mellitus without complications: ▪ ICD-10-CM codes: ▪ E10.9, Type 1 diabetes mellitus without complications ▪ E11.9, Type 2 diabetes mellitus without complications Diabetes mellitus with complications: ▪ ICD-10-CM codes: ▪ E10.x (excluding E10.9), E10.xx, E10.xxx, Type 1 diabetes mellitus with complications ▪ E11.x (excluding E11.9), E11.xx, E11.xxx, Type 2 diabetes mellitus with complications Down syndrome: ▪ ICD-10-CM codes: ▪ Q90.x, Down syndrome End stage renal disease: ▪ ICD-10-CM codes: ▪ N18.6, End stage renal disease ▪ I12.0, Hypertensive chronic kidney disease with stage 5 chronic kidney

Variable	Description	Operational definition
		disease or end stage renal disease ▪ I13.1, Hypertensive heart and chronic kidney disease without heart failure ▪ I13.2, Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease Gout: ▪ ICD-10-CM codes: ▪ 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

Variable	Description	Operational definition
		Hyperlipidemia ▪ ICD-10-CM codes: ▪ E78.0–E78.5, E78.0x, E78.4x, Hyperlipidemia Hyperthyroidism (excluding autoimmune thyroiditis): ▪ ICD-10-CM codes: ▪ E05.x, E05.xx, Hyperthyroidism Illicit drug use: ▪ ICD-10-CM codes: ▪ F11.xx, F11.xxx, Opioid related disorders ▪ F12.xx, F12.xxx, Cannabis related disorders ▪ F14.xx, F14.xxx, Cocaine related disorders ▪ F16.xx, F16.xxx, Hallucinogen related disorders ▪ F18.xx, F18.xxx, Inhalent related disorders ▪ F19.xx, F19.xxx, Other psychoactive substance related disorders ▪ Z72.51, For counseling/surveillance of the drug abuser Stimulant use: ▪ ICD-10-CM codes:

Variable	Description	Operational definition
		▪ F14.xx, F14,xxx, Cocaine related disorders ▪ F15.xx, F15.xxx, Other stimulant related disorders Metabolic syndrome ▪ ICD-10-CM codes: ▪ E88.810, Metabolic syndrome Panic disorders ▪ ICD-10-CM codes: ▪ F40.01, Agoraphobia with panic disorder ▪ F41.0, Panic disorder [episodic paroxysmal anxiety] Reaction to stress ▪ ICD-10-CM codes: ▪ F43.0, Acute stress reaction ▪ F43.1x, Post-traumatic stress disorder ▪ F43.8x, Other reactions to severe stress ▪ F43.9, Reaction to severe stress, unspecified
Concomitant medications	Categorical variable: • Antineoplastic (ie, 7-con-o-methylnogaril, aclacinomycin a, cisplatin, doxorubicin,	Medications will be identified by string searching the specific medication names and using NDC codes that will be described in the SAP.

Variable	Description	Operational definition
	etaracizumab, ifosfamide, melphalan, mitoxantrone, trastuzumab) • Bisphosphonates (ie, alendronate) • Cardiovascular (ie, adenosine, dobutamine) • Central nervous system (ie, clozapine, morphine) ie	
Other medications/procedures (identified outside of the AHA criteria)	• NSAIDs • Respiratory (ie, theophylline) • Ivabradine • Digitalis • CAR T-cell therapy*§	Other medications/procedures will be identified by string searching the specific medication or procedure names and using NDC codes or HCPCS codes, CPT codes, and ICD-10-CM codes that will be described in the SAP. CAR T-cell therapy: ▪ CPT codes: ▪ 0537T, 0538T, 0539T, 0540T ▪ ICD-10-PCS codes: XW033C3, XW043C3, Q2041, Q2042
History of immunization	Categorical variable: • Seasonal influenza • COVID-19 • Tetanus diphtheria and pertussis (Tdap or Td) • Chickenpox (Varicella) • Shingles (Herpes Zoster recombinant and/or live)	See Annex 3 Table A-3 for vaccine codes

Variable	Description	Operational definition
	• HPV • Pneumococcal conjugate • Pneumococcal polysaccharide • Hepatitis A • Hepatitis B • MenACWY and MenB • Haemophilus influenzae type b	
Co-administered immunizations (same list as history of 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	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
		91318	Pfizer
		91319	Pfizer
		91320	Pfizer
		91315	Pfizer (bivalent)
		91317	Pfizer (bivalent)
		91312	Pfizer (bivalent)
		91301	Moderna
		91306	Moderna
		91309	Moderna
		91311	Moderna
		91321	Moderna
		91322	Moderna
		91314	Moderna (bivalent)
		91316	Moderna (bivalent)
		91313	Moderna (bivalent)
		91302	AstraZeneca
		91303	Janssen
		91304	Novavax
		90480	All
	HCPCS	0001A	Pfizer
		0002A	Pfizer
		0003A	Pfizer
		0004A	Pfizer
		0051A	Pfizer
		0052A	Pfizer
		0053A	Pfizer
		0054A	Pfizer
		0071A	Pfizer

Vaccine	Code Type	Code	Manufacturer/Description
		0072A	Pfizer
		0073A	Pfizer
		0074A	Pfizer
		0081A	Pfizer
		0082A	Pfizer
		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

Vaccine	Code Type	Code	Manufacturer/Description
		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	5926743151	Pfizer
		59267431501	Pfizer
		5926743152	Pfizer
		59267431502	Pfizer
		5926743311	Pfizer
		59267433101	Pfizer
		5926743312	Pfizer
		59267433102	Pfizer
		0069236201	Pfizer
		00069236201	Pfizer
		0069236210	Pfizer
		00069236210	Pfizer
		0069239201	Pfizer
		00069239201	Pfizer
		0069239210	Pfizer
		00069239210	Pfizer
		0069237701	Pfizer
		00069237701	Pfizer
		0069237710	Pfizer
		00069237710	Pfizer
		8077728707	Moderna
		80777028707	Moderna
		8077728792	Moderna
		80777028792	Moderna
		8077710204	Moderna
		80777010204	Moderna
		8077710295	Moderna

Vaccine	Code Type	Code	Manufacturer/Description
		80777010295	Moderna
		8077710201	Moderna
		80777010201	Moderna
		8077710293	Moderna
		80777010293	Moderna
		8077710296	Moderna
		80777010296	Moderna
		8063110502	Novavax
		80631010502	Novavax
		8063110501	Novavax
		80631010501	Novavax
		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

Vaccine	Code Type	Code	Manufacturer/Description
		00069202510	Pfizer
		00069202525	Pfizer
		5926700781	Pfizer
		59267007801	Pfizer
		5926700784	Pfizer
		59267007804	Pfizer
		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

Vaccine	Code Type	Code	Manufacturer/Description
		80631010210	Novavax
		8063110210	Novavax
		80631010201	Novavax
		8063110201	Novavax
		80631100001	Novavax
		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

Vaccine	Code Type	Code	Manufacturer/Description
		8077727310	Moderna
		8077727399	Moderna
		80777028302	Moderna (bivalent)
		8077728302	Moderna (bivalent)
		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

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

Vaccine	Code Type	Code	Manufacturer/Description
			dosage, quadrivalent, preservative free
	CPT	90687	Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent (pediatric use)
	CPT	90688	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent
	CPT	90694	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, inactivated, adjuvanted, preservative free
	CPT	90724	Immunization, active; influenza virus vaccine
	CPT	90756	Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free
	HCPCS	G0008	Administration of influenza virus vaccine
	HCPCS	G9141	Influenza a (H1N1) immunization administration (includes the physician counseling the patient/family)
	HCPCS	G9142	Influenza a (H1N1) vaccine, any route of administration
	HCPCS	Q2033	Influenza vaccine, recombinant hemagglutinin antigens, for intramuscular use (flublok)
	HCPCS	Q2034	Influenza virus vaccine, split virus, for intramuscular use (agriflu)
	HCPCS	Q2035	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (afluria)
	HCPCS	Q2036	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (flulaval)
	HCPCS	Q2037	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluvirin)

Vaccine	Code Type	Code	Manufacturer/Description
	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
	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

Vaccine	Code Type	Code	Manufacturer/Description
	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
	NDC	33332032001	Afluria Quadrivalent
	NDC	33332041610	AFLURIA QUADRIVALENT

Vaccine	Code Type	Code	Manufacturer/Description
	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
	NDC	58160088552	FLUARIX QUADRIVALENT
	NDC	58160089652	FLUARIX QUADRIVALENT

Vaccine	Code Type	Code	Manufacturer/Description
	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

Vaccine	Code Type	Code	Manufacturer/Description
	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	33332042310	Afluria Quadrivalent 2023-2024 Vial
	NDC	33332042311	Afluria Quadrivalent 2023-2024 Vial
	NDC	33332032303	Afluria Quadrivalent 2023-24 (3 Years and up)
	NDC	33332032304	Afluria Quadrivalent 2023-24 (3 Years and up)
	NDC	70461012303	Fluad Quadrivalent 2023-2024 Syringe
	NDC	70461012304	Fluad Quadrivalent 2023-2024 Syringe
	NDC	58160090941	Fluarix Quadrivalent 2023-2024 Syringe
	NDC	58160090952	Fluarix Quadrivalent 2023-2024 Syringe
	NDC	49281072310	Flublok Quadrivalent 2023-2024 Syringe
	NDC	49281072388	Flublok Quadrivalent 2023-2024 Syringe
	NDC	70461032303	Flucelvax Quadrivalent 2023-2024 Syringe
	NDC	70461032304	Flucelvax Quadrivalent 2023-2024 Syringe
	NDC	70461042310	Flucelvax Quadrivalent 2023-2024 Vial
	NDC	70461042311	Flucelvax Quadrivalent 2023-2024 Vial
	NDC	19515081441	Flulaval Quadrivalent 2023-2024 Syringe

Vaccine	Code Type	Code	Manufacturer/Description
	NDC	19515081452	Flulaval Quadrivalent 2023-2024 Syringe
	NDC	66019031001	Flumist Quadrivalent Nasal 2023-24
	NDC	66019031010	Flumist Quadrivalent Nasal 2023-24
	NDC	49281012365	Fluzone High-Dose Quadrivalent 2023-24
	NDC	49281012388	Fluzone High-Dose Quadrivalent 2023-24
	NDC	49281042350	Fluzone Quadrivalent 2023-2024 Syringe
	NDC	49281042388	Fluzone Quadrivalent 2023-2024 Syringe
	NDC	49281063915	Fluzone Quadrivalent 2023-2024 Vial
	NDC	49281063978	Fluzone Quadrivalent 2023-2024 Vial
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
HPV	CPT	90649	HPV vaccine, types 6, 11, 16, 18, quadrivalent (4vHPV), 3 dose schedule, for intramuscular use

Vaccine	Code Type	Code	Manufacturer/Description
	CPT	90650	HPV vaccine, types 16, 18, bivalent (2vHPV), 3 dose schedule, for intramuscular use
	CPT	90651	HPV 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
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

Vaccine	Code Type	Code	Manufacturer/Description
			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
MenACWY and MenB	CPT	90619	MenACWY, 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
	CPT	90733	Meningococcal polysaccharide vaccine, serogroups A, C, Y, W-135, quadrivalent (MPSV4), for subcutaneous use 90734, MenACWY, serogroups A, C, W, Y, quadrivalent, diphtheria toxoid carrier (MenACWY-D) or CRM197 carrier (MenACWY-CRM), for intramuscular use

Vaccine	Code Type	Code	Manufacturer/Description
	CPT	90734	MenACWY, 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.

Document Approval Record

Document Name:	C3671037_PROTOCOL- OLDER ADULT AFIB_V2.0_04DEC2024
Document Title:	C3671037_PROTOCOL- OLDER ADULT AFIB_V2.0_04DEC2024

Signed By:	Date(GMT)	Signing Capacity
Younus, Muhammad	05-Dec-2024 22:34:08	Final Approval
De Bernardi, Barbara	10-Dec-2024 10:17:17	EUQPPV Approval