Protocol:

Evaluation of Multiple Safety Outcomes following Respiratory Syncytial Virus (RSV) Vaccination in Adults 60 Years and Older

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Biologics Effectiveness and Safety (BEST) Initiative

Center for Biologics Evaluation and Research

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List of Abbreviations

ADEM	Acute Disseminated Encephalomyelitis
ADI	Area Deprivation Index
Afib	Atrial Fibrillation
AHRQ	Agency for Health Research and Quality
AIDS	Acquired Immunodeficiency Syndrome
AMI	Acute Myocardial Infarction
AR	Attributable Risk
BEST	Biologics Effectiveness and Safety Initiative
CBER	Center for Biologics Evaluation and Research
CBSA	Core-Based Statistical Area
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CFR	Case Fatality Rate
CI	Confidence Interval
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CME	Common Medicare Environment
CMS	Centers for Medicare & Medicaid Services
COVID-19	Coronavirus Diseases 2019
CPT	Current Procedural Terminology
CVX	Vaccine Administered
EDB	Enrollment Database
EDS	Encounter Data System
EHR	Electronic Health Records
FDA	Food and Drug Administration
FFS	Fee-for-Service
FISMA	Federal Information Security Management Act
GBS	Guillain-Barré syndrome
HCPCS	Healthcare Common Procedure Coding System

HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IIS	Immunization Information System
IP	Inpatient
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
LRTD	Lower Respiratory Tract Disease
MA	Medicare Advantage
MDS	Minimum Data Set
MRR	Medical Record Review
MSP	Medicare Savings Program
NDC	National Drug Codes
NHS	Non-Hemorrhagic Stroke
NPV	Negative Predictive Value
OBPV	Office of Biostatistics and Pharmacovigilance
OASH	Office of the Assistant Secretary of Health
OHRO	Office of Regional Health Operations
OP-ED	Outpatient Emergency Department
OP/PB	Outpatient and Professional
PCV 13	13-valent Pneumococcal Conjugate Vaccine
PCV15	15-valent Pneumococcal Conjugate Vaccine
PCV20	20-valent Pneumococcal Conjugate Vaccine
PE	Pulmonary Embolism
POS	Place of Service
PPSV23	Pneumococcal Polysaccharide Vaccine
PPV	Positive predictive value
QBA	Quantitative Bias Analysis
QDWI	Qualified Disabled Working Individual

QI	Qualified Individual
QMB	Qualified Medicare Beneficiary
REV	Revenue Codes
RSV	Respiratory Syncytial Virus
SCCS	Self-Controlled Case Series
SE	Standard Error
SLMB	Specified Low-Income Medicare Beneficiary
SSD	Shared Systems Data
TIA	Transient Ischemic Attack
U.S.	United States

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1. Background

Respiratory syncytial virus (RSV) infection in older adults can result in Lower Respiratory Tract Disease (LRTD), which can lead to serious, life-threatening pneumonia and bronchiolitis.[1, 2] According to the Centers for Disease Control and Prevention (CDC), RSV infection causes approximately 60,000 – 120,000 hospitalizations and 6,000 – 10,000 deaths annually among adults ages 65 years of age and older.[1] The United States (U.S.) Food and Drug Administration (FDA) approved two RSV vaccines for the prevention of LRTD caused by RSV infection in individuals 60 years of age and older.[1, 3] The RSVPreF3 + AS01 (AREXVY) RSV vaccine was approved on May 3, 2023 and RSVPreF (ABRYSVO) RSV vaccine was approved on May 31, 2023 in individuals 60 years of age and older and on August 21, 2023 in pregnant individuals at 32 through 36 weeks gestational age.[1, 3]

This vaccine safety surveillance activity will identify and characterize potential elevations in the risk of several health outcomes being evaluated. The Center for Biologics Evaluation and Research (CBER) at the FDA regulates biologic products including vaccines and is responsible for monitoring the safety of approved RSV vaccines via active and passive surveillance systems.[4] The active surveillance program at CBER will conduct this work under the FDA-CMS (Center for Medicare & Medicaid Services) partnership for persons 65 years of age and older utilizing Medicare Fee-for-Service (FFS) claims data and the FDA-Biologics Effectiveness and Safety (BEST) Initiative for persons 60-64 years of age utilizing commercial insurance databases. Both systems are comprised of large number of large-scale administrative claims, to monitor rare health outcomes.[5]

Imbalances in three health outcomes were identified in clinical trials supporting the licensure of RSVPreF3 + AS01 and RSVPreF in individuals 60 years of age and older – atrial fibrillation (Afib), Guillain-Barré syndrome (GBS), and acute disseminated encephalomyelitis (ADEM).[6, 7] However, there may be limitations in safety data accrued during the pre-licensure clinical studies of RSV vaccines. First, if the clinical trial populations are not representative of the general population, results may not be generalizable. Second, the sample size of clinical trials may be too small to assess rare outcomes. Therefore, additional outcomes will be assessed in the surveillance of the approved RSV vaccines among individuals 60 years of age and older. Post-market vaccine surveillance and reporting of RSV vaccine-related outcomes enables better capture of a statistically significant association between an exposure and an outcome as well as provides timely information to support regulatory decision-making.

This protocol outlines the surveillance method to monitor RSV vaccine safety. Section 2 of the protocol describes the study objectives for RSV vaccine monitoring in the population aged 60 years and older. Section 3 through Section 7 describe the specifications for RSV vaccine monitoring in claims databases, including the data sources, study population, study period, exposures, outcomes, and covariates. Section 8 describes the Self-Controlled Case Series (SCCS) study design and its specifications as an inferential analysis method to evaluate the risk of various outcomes following exposure to each of the RSV vaccine products. Section 9 through Section 12 describe additional specifications including but not limited to statistical analyses, medical record review (MRR), and data quality assurance and control measures.

2. Study Objectives

The objectives of the study are:

(i) to descriptively monitor the vaccination uptake of the two RSV vaccines – RSVPreF3 + AS01 and RSVPreF, as well as the observed counts and rates of outcomes for each RSV vaccine among population enrolled in commercial health insurance databases (aged 60–64 years) and the CMS Medicare database (aged 65 years and older)

(ii) to assess the risk of outcomes following administration of each RSV vaccine product among the population aged 60 – 64 years enrolled in commercial health insurance databases and the population aged 65 years and older enrolled in CMS Medicare databases, using a SCCS study design

3. Overview of Study Approach

We will perform safety surveillance in each of the three commercial insurance databases and the Medicare claims database. The study will include descriptive monitoring to characterize vaccination uptake and inferential analyses assessing the risk of outcomes following RSV vaccination.

Using an observational cohort design, descriptive reports will be generated on a monthly basis to summarize the vaccination uptake post-licensure for each RSV vaccine as well as observed outcome counts and rates within pre-defined risk and control intervals. Further details on descriptive analysis are discussed in Section 9.1.

For outcomes with sufficient sample size estimated by a power analysis described in Section 9.6, inferential analyses will be conducted to assess the association between each RSV vaccine and specified outcomes using an SCCS study design. The inferential analyses will consist of two phases: (i) an early SCCS analysis using persons vaccinated relatively early post-licensure will provide rapid detection of highly elevated risk, and (ii) an end-of-surveillance SCCS analysis will provide the most precise estimate of risk on a larger population of vaccinated individuals. Further details on the SCCS methodology are provided in Section 8. Separate SCCS analyses will be conducted for each exposure and outcome within each database included in the study.

Additional analyses may be considered on an as-needed basis for each outcome based on the appropriateness of design assumptions and method of outcome evaluation.

4. Data Sources

The study will include claims data from the three commercial insurance databases – CVS Health, Carelon Research, and Optum pre-adjudicated claims – and Medicare FFS and Part D data from the CMS Medicare Shared Systems Data (SSD). Medicare Advantage (MA) data (also referred to as Medicare Part C) will be utilized to descriptively monitor RSV vaccination uptake. Additionally, MA data may be included in the end-of-surveillance SCCS analysis if sufficient RSV vaccination uptake is observed in Medicare Part C.

The commercial databases provide enrollment, pharmacy or prescription, inpatient (IP), outpatient (OP), and physician health insurance claims for privately insured enrollees. The CVS Health database includes adjudicated claims for enrollees in the Aetna commercial health plan. Optum's pre-adjudicated claims database includes claims that undergo initial processing on a daily basis from providers across the U.S.

who accept patients with health insurance. The Carelon Research Healthcare Integrated Research Database includes adjudicated claims from Elevance Health commercial health plan enrollees.

Immunization Information System (IIS) vaccination data from participating jurisdictions will be used to supplement commercial health claims data in improving RSV vaccination capture. The FDA BEST Initiative, via their data sharing network, facilitated the linkage of claims data with IIS to enhance the capture of RSV vaccinations in insured populations for RSV vaccine surveillance. IIS jurisdictions were solicited to link RSV vaccination data to member-level claims records within reach of the commercial data partners using personally identifiable information and IIS-specific linkage algorithms.

The Medicare claims database includes well-defined longitudinal data that captures healthcare service utilization for millions of enrollees across multiple care settings including inpatient, outpatient-emergency department and outpatient non-emergency department, professional services non-laboratory and laboratory, and pharmacy settings (Medicare Part D). Claims data for the inpatient and outpatient settings will be accessed via the CMS Medicare Shared Systems Data (SSD) for FFS enrollees and the Encounter Data System (EDS) for Medicare Advantage enrollees. Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. CMS Medicare SSD will be used which consists of claims sourced after enumeration to reduce data lag. The CMS Medicare Enrollment Database (EDB) will be used to capture demographic characteristics and information on death. Information on nursing home residency status will be captured from the Minimum Data Set (MDS) 3.0, a mandatory clinical assessment administered to all residents in Medicare and Medicaid certified nursing homes.[8]

Table 1 below outlines administrative claims data sources included in surveillance and summarizes claims data characteristics by data source. IIS data characteristics are not presented, given the variability in data characteristics by IIS jurisdictions and differences in data partner access to IIS registry data.

Table 1. Description and Characteristics of Administrative Claims Data Sources

Data Source	Claims Type	Update Frequency	Data Lag*	Population Enrolled
CVS Health **	Fully Adjudicated	Monthly	Approximately 80% data completeness in 3-4 months for inpatient (IP) claims, 2-3 months for outpatient (OP) claims, and 1-2 months for professional (PB) claims	18-64 years: > 14.5 million
Carelon Research **	Fully Adjudicated	Monthly	Approximately 80% data completeness in 2-3 months for IP claims, and 1-2 months for OP and PB claims	18-64 years: >16.9 million
Optum **	Pre-Adjudicated	Bi-weekly	Approximately 80% data completeness in 1-2 months for IP, OP, and PB claims	18-64 years: >11.5 million
CMS Medicare Shared Systems Fee-for-Service (FFS) Data (SSD) ł	Pre-Adjudicated	Daily	Approximately >80% data completeness in 1-2 months for IP claims	>29 million beneficiaries annually
CMS Medicare Advantage (MA) from Encounter Data System (EDS) ł	Pre-Adjudicated	Weekly	Approximately 80% data completeness in ~80 days	>30 million beneficiaries annually

**Data lag is based on 2020 claims delay distribution*

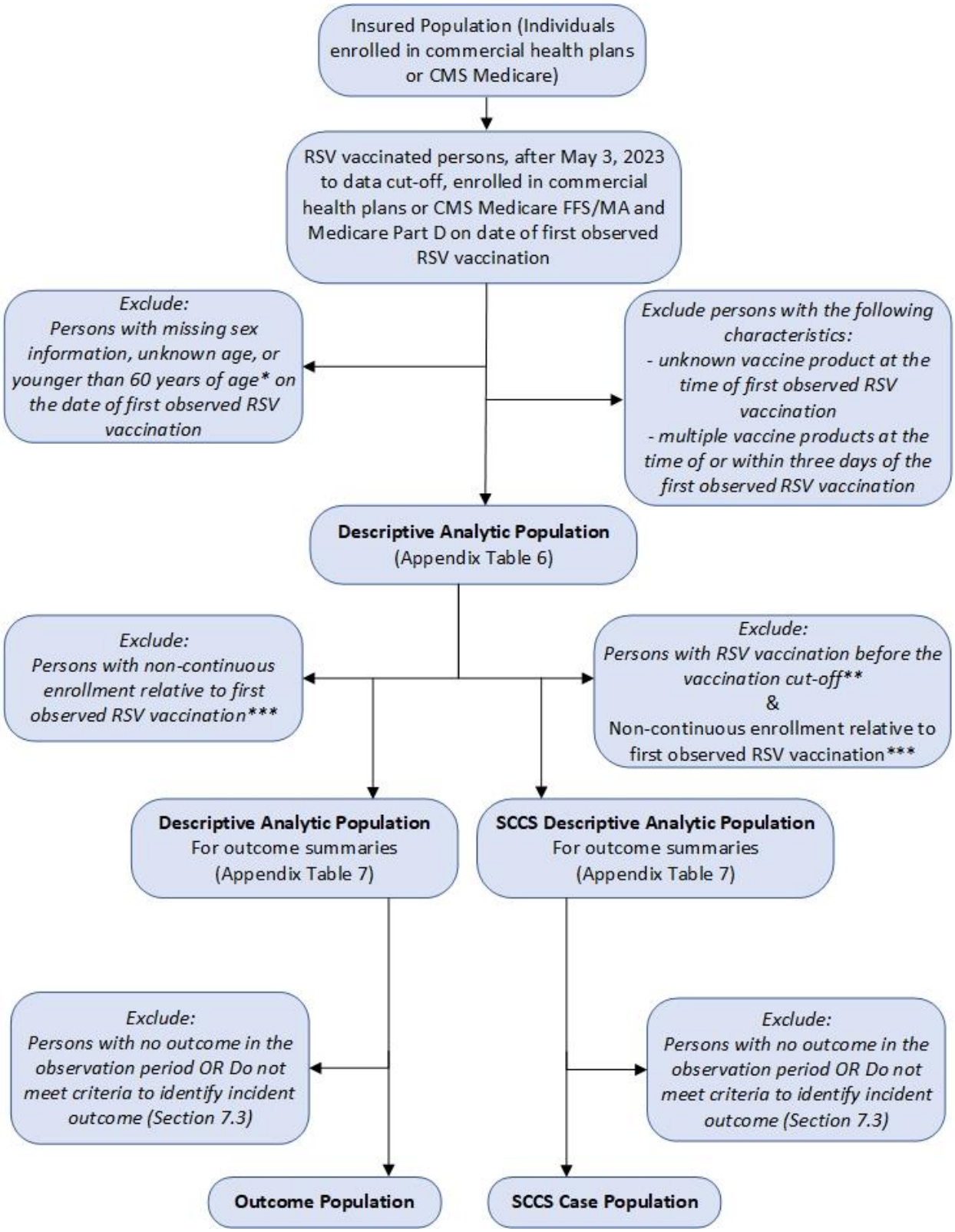
*** Average number of annual enrollees in a given age category between 2018-2021*

ł Number of enrollees in 2023, but only those aged 65 years and older will be included in the study

5. Study Population

The general study population will include eligible vaccinees who received one dose of either of the RSV vaccines, RSVPreF3 + AS01 or RSVPreF, during the study period and meet the eligibility criteria for the respective descriptive and inferential analyses outlined below (Figure 1).

Figure 1: Population Eligibility Criteria for Descriptive and Inferential Analyses



**Commercial health plan beneficiaries must be aged 60-64 years on the date of vaccination for study inclusion, and CMS Medicare beneficiaries must be aged 65 years and older on the data of vaccination for study inclusion.*

*** Cases eligible for SCCS analysis will be determined by identifying the number of vaccine exposures whose expected observation period meet a 90% data-completeness threshold. This threshold is met if the last calendar day of the planned observation period is expected to have 90% or greater data-completeness based on the outcome-specific claims-delay distribution estimated from historical data.*

**** Commercial health plan beneficiaries will be required to have continuous enrollment in their respective commercial health plans from the later of 60 days following their birthdate or 365 days prior to RSV vaccination. CMS Medicare beneficiaries will be required to have continuous enrollment in Medicare Parts A and B from 365 days prior to RSV vaccination.*

Note: Persons enrolled in commercial health plans and beneficiaries enrolled in CMS Medicare FFS will also require enrollment in a health plan with available prescription or pharmacy health plan data on vaccination date in the secondary analysis only, to ensure comprehensive capture of relevant concomitant vaccines.

6. Study Period

The study period will begin from the earliest date that RSV vaccines were approved, i.e., RSVPreF3 + AS01 – May 3, 2023, and RSVPreF – May 31, 2023, through 1 year after the vaccines' approval or until such a time as surveillance is deemed no longer necessary by the FDA.

7. Study Variables

7.1 Care Settings Definitions

Exposures and outcomes will be identified within relevant care settings of interest, as specified based on clinical guidance. These care settings are specific to administrative claims data only.

Table 2 defines the inpatient (IP), outpatient and professional (OP/PB), and outpatient emergency department (OP-ED) settings used in this study.

Table 2. Care Setting Definitions

Care Settings	Definition
Inpatient (IP)	Hospital inpatient acute facility claims
Outpatient and Professional (OP/PB)*	Outpatient facility claims [Non-ED] OR Professional claims (CMS 1500) that contain at least one non-laboratory place of service (POS)**
(A subset of OP/PB setting): Outpatient Emergency Department (OP-ED)	Outpatient facility claims in ED

** Including all sources of professional claims (e.g., urgent care etc.)*

*** Independent laboratory place of service code = 81*

Note: Admitting diagnosis will be excluded in all care settings

The IP setting represents hospital inpatient acute facility claims. Hospital inpatient facility claims provide information on the care and services received by patients during the entire duration of inpatient care. These tend to have more accurate diagnosis coding compared to professional claims, given that provider

facilities are reimbursed based on the types of diagnosis coded, which reflect the level of treatment required. Facilities are also generally more responsive to medical record requests initiated.

The OP/PB setting represents all outpatient and professional services claims with non-laboratory places of service and captures the broad spectrum of outpatient care regardless of care setting or provider type. Claims with laboratory places of service are excluded, given that these claims often include "rule-out-diagnoses" that may not reflect true existing or underlying conditions present in patients.

The OP-ED setting is a subset of the OP/PB setting and represents outpatient facility claims with services specifically provided in the ED, identified through revenue (REV) codes.

7.2 RSV Vaccine Exposures

The exposure will be defined as receipt of the single dose of the RSVPreF3 + AS01 RSV vaccine occurring after May 3, 2023, or a single dose of the RSVPreF RSV vaccine occurring after May 31, 2023. Vaccinations will be identified through product codes such as Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDCs) in administrative claims data and will be identified through product codes such as CVX (vaccine administered) codes in IIS data.

Table 1 in the Appendix describes product descriptions, dosage forms, product compositions, dose strengths, authorization dates, and relevant product codes (CPT/HCPCS, NDC, and CVX codes) for the two approved RSV vaccines.[6, 7, 9]

To deduplicate exposures identified via multiple sources such as claims and IIS data, the following cleaning rules will be applied:

i. multiple vaccination records containing the same RSV vaccine product, occurring on the same day or within three days will be deduplicated.
ii. persons with multiple vaccination records containing multiple RSV vaccine products, occurring on the same day or within three days will be excluded from the study

The list of valid RSV vaccine codes specified in Table 1 in the Appendix will be continuously reviewed and updated during the course of surveillance.

7.3 Outcomes

Table 3 presents a list of pre-specified outcomes that will be monitored following RSV vaccine administration, including specifications for the respective care settings, clean windows, risk intervals, and control intervals for the statistical analyses (Section 9), Outcomes in the observation period will be identified by a two-step process:

i. outcomes that are considered 'incident' after implementing the outcome-specific cleaning window will be included, and
ii. only first incident outcome in the observation period will be retained

Unless otherwise indicated, each outcome will be monitored in all age groups. If there is a lack of sufficient power to perform a SCCS analysis for a given RSV vaccine brand and outcome, some outcomes may only be descriptively monitored.

The list of these outcomes may be updated based on observed outcomes in pre-licensure trials, outcomes reporting from other surveillance sources, or other sources including international regulators.

Table 3. Outcomes, Care Settings, Clean Windows, Risk Intervals, and Control Intervals for Surveillance

Health Outcome	Care Settings	Clean Window*	Risk Interval**	Control Interval***
Acute Disseminated Encephalomyelitis (ADEM)	IP	183 days	1-42 days [10]	43-90 days
Acute Myocardial Infarction (AMI)	IP	365 days	1-28 days [11, 12]	29-90 days
Anaphylaxis	IP, OP-ED	30 days	0-1 day [13, 14]	3-16 days
Atrial Fibrillation (Afib)	IP, OP-ED	365 days	1-42 days [15]	43-90 days
Deep Vein Thrombosis	IP, OP/PB	365 days	1-28 days [16-18]	29-90 days
Encephalitis or Encephalomyelitis (excluding ADEM)	IP	183 days	1-42 days [10]	43-90 days
Guillain-Barré Syndrome (GBS)	IP – Primary Position only	365 days	1-42 days [19]	43-90 days
Myocarditis / Pericarditis	IP, OP-ED	365 days	1-7 days [20]	8-90 days
Non-Hemorrhagic Stroke (NHS)	IP ♦	Complex♦	1-21 days; 22-42 days [21, 22]	43-90 days
Non-Hemorrhagic Stroke / Transient Ischemic Attack (TIA)	IP (NHS & TIA), OP-ED (TIA) ♦	Complex♦	1-21 days; 22-42 days [21, 22]	43-90 days
Pulmonary Embolism (PE)	IP	365 days	1-28 days [16-18]	29-90 days
Transverse Myelitis	IP, OP-ED ♦	365 days	1-42 days [23]	43-90 days
Chronic inflammatory demyelinating polyneuropathy (CIDP)ŧ	IP, OP/PB	365 days	1-98 days	-

** Clean Window is defined as an interval relative to outcome date used to define an incident outcome where an individual enters the study cohort only if the outcome did not occur during that interval. References for the duration of the clean window could not be located in the literature and are instead based on clinician input.*
***Risk Interval is defined as an interval during which excess risk is hypothesized following RSV vaccination. Risk intervals are determined based on clinical guidance and literature review.*
**** Control interval is defined as all follow-up time during the observation period that is not in the risk interval or in a washout period.*
ǂ The descriptive monitoring period for CIDP will be 1-98 days.
♦ The algorithm used to identify incident outcomes are more complex and are referenced in the Appendix (Section 14.4).

7.4 Covariates

The covariates listed below will be assessed to characterize the persons receiving RSV vaccination as well as persons with outcomes following vaccination. Characteristics such as demographic, geographic and socioeconomic status will be identified using information from commercial insurance and Medicare enrollment databases. Immunocompromising conditions, other medical conditions, and concomitant vaccinations will be identified using diagnosis or procedure codes identified in medical claims. A detailed description of all covariates and their assessment are described in the Appendix. Covariates will be summarized as follows:

(i) Socio-demographic characteristics:
- Sex
- Age
- Race/Ethnicity (CMS Medicare only)
- Rural /Urban Residency Status
- Health and Human Services (HHS) Region [24]
- Facility/Provider type
- Nursing Home Residency Status (CMS Medicare only) [25]
- Reason for Medicare Eligibility (CMS Medicare only) [26, 27]
- Medicare-Medicaid Dual Eligibility Status (CMS Medicare only) [28]
- Area Deprivation Index (ADI) rank (CMS Medicare only) [29]

(ii) Medical conditions or baseline health characteristics (CMS Medicare only; commercial health plan population, where feasible):
- Prior hospitalization
- Asthma
- Blood disorders
- Chronic lung disease
- Diabetes
- Heart disease
- Kidney disorders
- Liver disorders
- Neurological or neurodevelopmental conditions
- Malignant neoplasms
- Immunocompromised status (A binary variable that will be defined as the presence of any of the listed conditions in the Appendix) [30]
- Charlson Comorbidity Index (CCI) [31]

(iii) Concomitant vaccinations:
- Coronavirus Disease 2019 (COVID-19) vaccine – 2023-2024 Formula
- Seasonal influenza vaccine – 2023- 2024 Formula
- 15-valent- and 20-valent- Pneumococcal Conjugate Vaccine (PCV 15/20) or Pneumococcal Polysaccharide Vaccine (PPSV23)*
- Shingles vaccine

**Note: FDA may monitor the concomitant vaccination of 13-valent Pneumococcal Conjugate Vaccine (PCV13) for descriptive monitoring if the sufficient uptake is observed*

8. Study Design and Approach

8.1 Self-Controlled Methods

The SCCS design compares the incidence of an outcome during periods of hypothesized excess risk due to the exposure (risk interval) to the incidence of an outcome during all other parts of the observation period as well as not in the washout window (control interval). The method assumes that the cases will be distributed roughly uniformly over the risk and control intervals if there is no association between the exposure and outcome of interest. If cases are concentrated in the risk interval(s), there is evidence of an association but not necessarily a causal association. Only cases (i.e., persons with an incident outcome) occurring during the observation period (case population) are sampled in SCCS, with estimation of risk occurring within, rather than between, individuals.[32] However, the SCCS design has a number of assumptions that have to be met in order to ensure valid unbiased risk estimates. These assumptions are outlined below:

(i) Occurrence of an outcome does not substantially affect subsequent exposures
(ii) Occurrence of an outcome does not affect the observation length
(iii) Outcome rates are constant within risk intervals
    a. Outcomes must be independently recurrent or rare
(iv) Risk and control intervals are correctly specified

Certain modifications to the SCCS design will be performed to reduce bias from potential violations of these assumptions. Study analyses will be restricted to the post-vaccination control interval to reduce bias from reverse causation, where early occurrences of an outcome affect the likelihood of subsequent exposure (i.e., RSV vaccination).

Some outcomes may have high case fatality rate (CFR) causing censoring of observation time, which would be a violation of the assumption that outcome occurrence does not affect the observation length. For example, in past studies the 30-day case-fatality rate for AMI and PE in the Medicare population 65 years and older was assessed to be 22% and 19% respectively.[33] To mitigate the violation of the second assumption that the observation time is independent of the outcome (e.g. death post-outcome censors follow-up time), the primary analysis may utilize the "Farrington adjustment" to adjust for outcome- or event-dependent observation times. [34] The Farrington adjustment will be applied to outcomes that meet a pre-specified 30-day CFR threshold for the CMS Medicare population. The Farrington adjustment may not be applied to outcomes for the commercially insured population due to lack of availability of CFR for outcomes in this population.

8.2 Definition of Observation Period, Risk and Control Intervals

The definitions for observation period, risk and control intervals are outcome-specific, and are provided below.

8.2.1 Observation Period

For all outcomes except anaphylaxis, the observation period will start from the day after vaccination, i.e. day 1, as an outcome occurring on the day of vaccination may or may not be attributable to the vaccine. For anaphylaxis, the observation period starts at day 0 to capture outcomes occurring immediately after vaccination. The observation period for all outcomes except for anaphylaxis will extend to day 90. The observation period for anaphylaxis will extend to day 16 due to its shorter risk interval length.

Individuals may not be followed through the full length of their observation period if the following censorship criteria occur: death, disenrollment, or the end of the study period.

8.2.2 Risk Interval

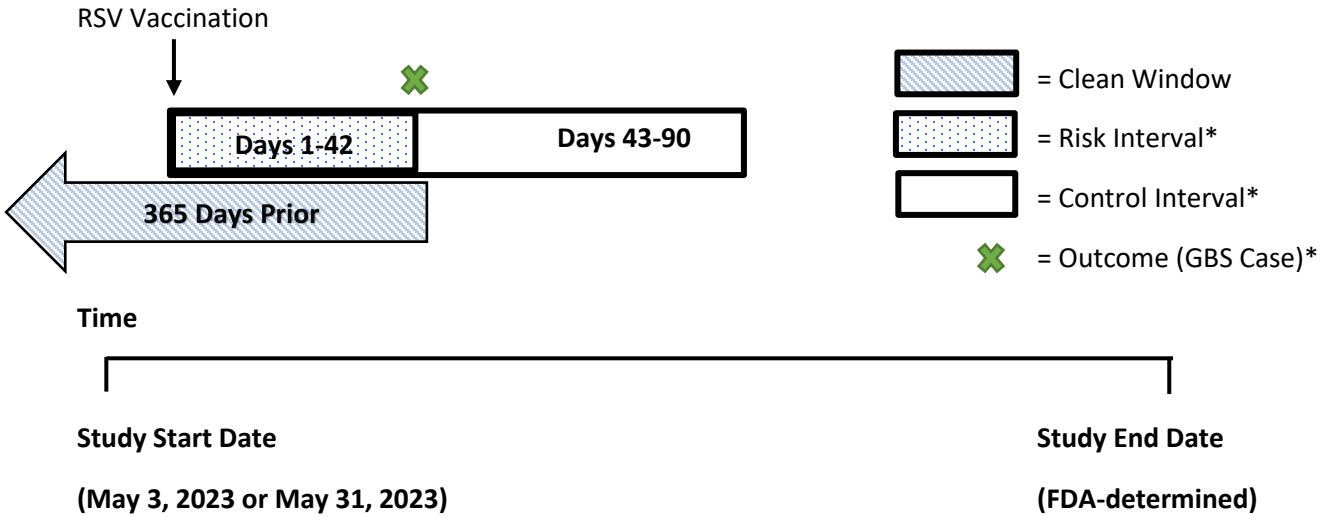
The risk interval is defined as the time during which excess risk is hypothesized following a single dose of RSV vaccine for the outcome based on biological plausibility and clinical input (Table 3). The selected risk intervals are outcome-specific and are determined based on review of literature and consultation with subject matter experts.

8.2.3 Control Interval

The post-vaccination control interval is defined as all follow-up time during the observation period following one dose of either of the RSV vaccines that is outside of the risk interval(s) or washout intervals until the earlier of the end of the observation period, disenrollment, death, or the study period end.

Figure 2 represents a sample schematic for the risk and control interval definition for a person receiving a single dose of either of the RSV vaccine that experiences a qualifying GBS outcome following vaccination. The observation period for this person will begin the day after vaccination and extend to 90 days following vaccination, including a risk interval from days 1-42 and a control interval from days 43-90.

Figure 2. Hypothetical Example of Observation Period, Risk and Control Interval for Individual with a Qualifying GBS Outcome Following Vaccination



**Note: The length of the risk and control intervals will vary depending on the outcome*

The clean window is relative to the outcome date; risk and control intervals are relative to the vaccination date

9. Statistical Analyses

9.1 Descriptive Analyses

Within each of the commercial health insurance and Medicare databases, descriptive analyses will be conducted to summarize RSV vaccination uptake trends and characteristics of vaccine recipients as well as the case population following RSVPreF3 + AS01 or RSVPreF RSV vaccines. The vaccination uptake summary will provide the counts and percentages of vaccinees and case population by various socio-demographic characteristics as well as medical conditions and concomitant vaccinations for both RSV vaccine products (Covariates are discussed in detail in Section 7.4). In addition to these statistics, the descriptive analyses will also summarize covariate and interval-stratified observed rates of each outcome (per 100,000 person-years) for all vaccinees and case populations for both RSV vaccine products. All descriptive statistics will be produced on a monthly basis.

Table 5 and Table 6 in the Appendix present a sample table containing the above-mentioned proposed descriptive statistics.

9.2 Primary Inferential Analyses

If sufficiently powered, an early SCCS analysis may be conducted in each commercial health plan and CMS Medicare database to detect potential large associations between an exposure, i.e., RSV vaccination and pre-specified outcomes during initial stages of vaccination roll-out. The analysis will be conducted (i) if sufficient sample size is accumulated to detect an Incidence Rate Ratio (IRR) of 3 to 10 with 80% power and a two-sided alpha of 0.01, or (ii) if scientific evidence for regulatory decision-making is needed. Conducting the SCCS analysis at an earlier stage can help rapidly identify any unusual patterns in terms of safety signals that warrant further investigations.

The end-of-surveillance SCCS analysis may be conducted at the end of the surveillance period as determined by FDA. This analysis would allow for a more comprehensive assessment of the association between an exposure and an outcome by containing additional data that would potentially contain a wider range of individuals who have received either of the RSV vaccines. Estimates derived from the end-of-surveillance analysis would provide more precision compared to the early season analysis by capturing more cases. To guide the selection of the end-of-surveillance analysis date, a power analysis will assess whether there is sufficient sample size to detect a minimum detectable IRR of 1.2 to 3 at 80% power with a two-sided alpha of 0.01 following either RSV vaccine administration. [35] However, if the outcome counts are limited or the vaccination uptake is low, the end-of-surveillance analysis may be conducted even if the target detectable IRR is not achieved.

IRR and Attributable Risk (AR) estimates will be estimated for both early and end-of-surveillance SCCS analyses (Section 9.2.1). Additional adjustments to these SCCS analyses will also be conducted to assess the robustness of the IRR and AR estimates. These adjustments are further described in Section 9.4

9.2.1 IRR Estimation and AR Estimation

For both early and end-of-surveillance SCCS analysis, the rates of the outcomes following the single dose of either of the RSV vaccines will be evaluated. This analysis will compare the rates of outcome in the risk and control intervals using a conditional Poisson regression model. The primary inferential analysis may use a Farrington-adjusted SCCS model that will adjust for outcome- or event-dependent observation time. [34] The non-Farrington-adjusted SCCS model is presented below:

$$\log\left(E(Y \mid X) = \beta_1(risk\_interval) + \log(t) + strata(patient\_id)\right.$$

$Y = Outcome$

$risk_{interval} = binary\ term\ indicating\ outcome\ occurrence\ in\ risk\ interval$

$t = number\ of\ days\ in\ the\ interval$

$\log(t)$ indicates non-Farrington-adjusted model; $\log\big(w(t)\big)$ indicates Farrington-adjusted model

$patient_{id} = term\ identifying\ the\ patient$

Under this model, the null and alternative hypotheses are written as, respectively:

$H_0 : e^{\beta 1} = 1 \qquad H_a : e^{\beta 1} \neq 1$

where $e^{\beta 1}$ will be interpreted as the IRR for an outcome in the risk interval compared to the control intervals. Thus, statistical significance of the coefficient on the risk interval variable at a pre-specified level will indicate a statistically significant association between RSV vaccination and an outcome. Statistical significance will be determined using a two-sided hypothesis test of increase using a significance level of 0.01. [35] The significance level was selected in order to reduce the probability of false positive results given the large number of outcomes being assessed. Corresponding 95% and 99% confidence intervals (CI) for the IRR will be estimated to assess the precision of the estimated risk.

For both early and end-of-surveillance SCCS analysis, the study will also estimate an AR per 100,000 vaccinations and 100,000 person-years, which will represent the excess number of outcome cases associated with vaccination per 100,000 doses and per 100,00 person-years, respectively. [36] The excess

number of outcomes within the study population will be calculated by the difference between the expected number of outcomes based on the model and the expected number of outcomes assuming no exposure. [37]

$$Excess\ Outcomes\ associated\ with\ Vaccination =$$

$$E(Y) - E(Y|No\ exposure) = \sum_{i=1}^{m} \left(E(Y_i|X_i) - E(Y_i|X_i = 0)\right)$$

$Y = number\ of\ outcomes$
$m = total\ number\ of\ persons\ in\ the\ study\ population$
$Y_i = outcome\ status\ of\ the\ ith\ person\ in\ the\ study\ population$
$X_i = exposure\ status\ of\ the\ ith\ person, where\ X_i$
$= 0\ denotes\ the\ hypothetical\ absense\ of\ exposure$

The AR per 100,000 vaccine doses (and per 100,000 person-years) will then be calculated by dividing the excess number of outcomes associated with vaccination by the number of eligible doses (or eligible person-years) and multiplying by 100,000.

The standard error (SE) of the AR is estimated by bootstrap resampling 10,000 times. For each iteration, this study will sample the beneficiaries with outcomes with replacement and calculate the AR. The SE is calculated as the square root of the variance of the 10,000 AR values.

9.3 Secondary Inferential Analyses: Concomitant Vaccinations Subgroup Analysis

To account for the possibility of the outcome occurring due to other medical procedures performed such as administration of other vaccines on the same day as that of the either of the RSV vaccine, an additional subgroup analysis will be performed, with one subgroup containing individuals with concomitant vaccinations observed on the same date as the RSV vaccination, and another subgroup containing individuals without any concomitant vaccinations. The analyses will only be performed for outcomes where the primary analysis IRR is elevated and the one-sided p-value is less than 10%, a less stringent threshold than the statistical significance threshold of 0.01. [35] Concomitant vaccines of interest for the analysis will be age-specific and include:

- Coronavirus Disease (COVID-19) updated monovalent booster dose vaccine (season 2023-2024 formula)
- Influenza vaccine (season 2023-2024 formula)
- Pneumococcal vaccine*
    - Pneumococcal Polysaccharide Vaccine (PPSV23),
    - 15-valent Pneumococcal Vaccine (PCV15),
    - 20-valent Pneumococcal Vaccine (PCV20)
- Shingles vaccine

**Note: FDA may monitor the concomitant vaccination of PCV13 vaccine for secondary inferential analysis*

Table 2 in the Appendix describes the list of concomitant vaccinations and the relevant product codes (CPT/HCPCS, NDC, and CVX codes) for the concomitant vaccinations subgroup analysis

9.4 Adjustments to the Primary and Secondary Inferential Analyses

Adjustments to the early and end-of-surveillance SCCS analyses for both primary and secondary analyses will be conducted to assess the robustness of the risk estimations. To evaluate potential time-varying confounding given the length of observation period, the study will assess the association of time-varying risk factors with the outcome and adjust for the changing risk of the outcome associated with the major time-varying risk factors such as seasonality. Additionally, to account for potential outcome misclassification, a positive predictive value (PPV)-adjusted analysis will be conducted.

9.4.1 Seasonality Adjustment Analysis (Including Farrington Adjustment for Outcomes Meeting CFR Threshold)

Both the primary and secondary inferential analyses specified in Section 9.2 and Section 9.3, respectively, will include a seasonality adjustment. To evaluate potential time-varying confounding given the length of the observation period, the study will adjust for the changing risk of the outcome over calendar months. Some outcomes, including AMI, may exhibit seasonal trends. [34] In addition, given that RSV has been associated with LRTD, and the risk of exposure to RSV is likely to vary throughout the study period, the risk of related outcomes may vary during the study period as well. [38] Baseline outcome risk will be estimated from a similar population during the same calendar months in previous years and will be included as an offset term in the Poisson regression model (refer to the model below). For each outcome, comparator rates will be selected from contiguous months from 2021 to 2022, matching the calendar months of the study.

Defined below, is the Farrington and seasonality-adjusted SCCS model.

$$\log\big(E(Y|X)\big) = \beta_1 * risk_{interval} + \log\big(w(t)\big) + \log\ (seasonal_{risk}) + strata\ (patient_{id})$$

$Y = \ Outcome$

$risk_{interval} = binary\ term\ indicating\ AE\ occurrence\ in\ risk\ interval$

$w(t) = Farrington\ adjusted\ weight$

$$seasonal_{risk} = \frac{1}{IR_r * t}\sum_{m=1}^{12}(IR_M * t_m)$$

$IR_m = daily\ incident\ rate\ for\ month\ 'm'$

$IR_r = daily\ incident\ rate\ for\ reference\ month\ 'r'$

$$t_m = number\ of\ days\ in\ an\ interval\ in\ month\ 'm'\ or\ equivalently\ t = \sum_{m=1}^{12} t_m$$

$patient_{id} = term\ identifying\ the\ patient$

In this model, the null and alternative hypotheses can be written as, respectively:

$H_0 : e^{\beta 1} = 1 \qquad H_a : e^{\beta 1} \neq 1$

9.4.2 PPV-Adjusted Analysis (Including Farrington Adjustment for Outcomes Meeting CFR Threshold)

Both the primary and secondary inferential analyses specified in Section 9.2 and Section 9.3, respectively, will include a PPV-adjusted analysis. To reduce bias from outcome misclassification based on claims-based outcome definitions, a PPV-adjusted analysis will be performed using quantitative bias analysis (QBA) using PPVs available from prior MRR of outcomes following vaccine exposures. The PPV is calculated as the number of chart-confirmed cases over the total number of charts identified using the claims-based outcome definition and returned via abstraction process. Cases with "insufficient evidence" are not considered chart confirmed or used in estimating the PPV.

QBA will be conducted by creating multiple datasets where the status of claims-identified cases is imputed by assigning them the status of "chart-confirmed" with the probability equal to the PPV. Analyses conducted on each of the individual imputed datasets will be combined using a rule developed by Schenker and Rubin (1986). [39] Assuming normality of the coefficient estimates, the p-values for the imputed analyses are found by dividing the coefficient estimate by the model's standard error to arrive the z-statistic.

MRR and PPV-adjusted analyses may be performed for additional outcomes, with a statistically significant increased risk in outcome rates identified from primary and secondary inferential analyses. Section 10 provides further details on the planned MRR approach.

Table 4 presents the PPV estimates that will be used for the PPV-adjusted analysis based on prior MRR findings.

Table 4. PPV Estimates for Health Outcomes from MRR in CMS Medicare Population (Ages 65 and older) only

Health Outcomes (Care Settings)	PPVs (95% CI)
Acute Myocardial Infarction (IP)	80.0% (95% CI: 70.6%, 87.0%) [40]
Anaphylaxis (IP, OP-ED)	66.0% (95% CI: 56.00%, 76.00%) [41]
Guillain-Barré Syndrome (IP – Primary Diagnosis only)	71.0% (95% CI: 63.00%, 79.00%) [42]
Myocarditis / Pericarditis (IP, OP-ED)	40.0% (95% CI: 16.82%, 68.73%)
Pulmonary Embolism (IP)	83.3% (95% CI: 69.40%-91.68%) [40]

9.4.3 Seasonality, and PPV-Adjusted Analysis (Including Farrington Adjustment for Outcomes Meeting CFR Threshold)

For the primary and secondary inferential analysis, a Farrington, seasonality, and PPV-adjusted analysis will be performed for outcomes with available PPV estimates with the respective 95% CI. The results from this analysis will be considered the main results since they include the most adjustments for potential confounders that could bias outcome rate estimates. For outcomes without PPV estimates, the results from the seasonality-adjusted analysis will be considered the main results.

9.5 Sensitivity Analysis

9.5.1 Assessment of Washout Period between Risk and Control Intervals

In order to assess the sensitivity of results to the selection of the post-vaccination risk and control intervals, we will also re-run analyses with a washout period between the intervals.

9.5.2 Full Planned Observation Time

To assess the robustness of the Farrington adjustment, a sensitivity analysis will be conducted for outcomes that used Farrington adjustment in the primary analysis in which the full planned observation time is credited to each individual, regardless of death or disenrollment. No Farrington adjustment will be made as the observation time is not conditional on outcomes.

9.6 Statistical Power Calculations

A power analysis will be performed to help determine when the early and end-of-surveillance SCCS analyses can be conducted upon accumulation of sufficient sample size. For each outcome and RSV vaccine, the power for an SCCS analysis will be assessed at each data cut date. The power will be assessed by:

(i) identifying the number of cases eligible for an SCCS analysis under a 90% data-completeness threshold, and

(ii) calculating the power of an SCCS analysis to detect a minimum IRR of 3 to 10 (early SCCS analysis) or 1.2 to 3 (end-of-surveillance SCCS analysis).

Cases with outcomes eligible for an SCCS analysis will be determined by first identifying the number of vaccine exposures whose expected observation period meets a 90% data-completeness threshold. This threshold is met if the last calendar day of the planned observation period is expected to have 90% or greater data-completeness based on the outcome-specific claims-delay distribution estimated from historical data. Cases from this vaccinated population will be used in the analysis.

A 90% threshold for data completeness is required at the specified data cutoff date to reduce differences in data accrual and the likelihood of observing outcomes during risk relative to control intervals. Assuming that outcome observation delays are accurately estimated from historical data; a 90% completeness threshold limits the difference in observation of outcomes in risk intervals (at most 100% complete) versus control intervals (at minimum 90% complete). If the true IRR is 1, the bias due to observation delay is (1/0.9)-1=11%. However, in practice, risk and control interval completeness will fall between 100% and 90% and we expect the potential bias due to claims delay to be smaller. The 90% completeness is likely to overestimate the IRR by 10% or less.

10. Medical Record Review

Medical record review may be performed for outcomes with a statistically significant elevation in risk identified from the primary inferential analysis. The purpose of MRR will be to evaluate the accuracy of the claims-based outcome definition(s) used, to ensure that true cases have been identified in the analysis. An outcome-specific PPV and 95% CIs will be estimated based on MRR to assess the probability of outcome misclassification based on the claims-based definition(s) used. Once PPVs are available from MRR for relevant outcomes, a PPV-adjusted analysis may be performed to adjust for bias from outcome misclassification.

The first step of the MRR process will be to identify the specific claims-identified outcome cases for which records should be requested. Depending on the number of outcomes, records for either all outcomes or a sample (simple random or representative) of outcomes can be requested. Second, a case review form based on the selected case definition must be developed. This form outlines the key questions that must be answered using the record in order to obtain the information necessary to assign case classifications.

Once records for the claims-identified cases are received, there are three different abstraction-adjudication workflows that can be followed:

1. *Abstraction followed by algorithmic adjudication:* In this option, trained abstractors will review the records to extract the information from the medical records (i.e., abstract the records) that is needed to adjudicate (i.e., assign case classifications). After that, if the case definition is clear and uniform, that abstracted information will be evaluated to automatically determine case classifications.

2. *Abstraction followed by expert clinician adjudication (with optional algorithmic adjudication):* In this option, trained abstractors will abstract the records, and that abstracted information will be provided to clinicians with expertise on the outcome of interest. The clinician will then review this information, in tandem with the record itself, to implement the selected case definition and assign case classifications. Generally, two clinicians will review each record.

3. *Immediate expert clinician adjudication:* In this option, records will be immediately provided to expert clinicians who will then review the record to implement the selected case definition and assign case classifications.

If abstraction-adjudication workflow #1 or #2 are selected, an abstraction tool, based on the case review form, will need to be developed. Abstractors will use this tool to extract the information from medical records needed to confirm a diagnosis (as well as limited descriptive information, if desired). As part of this process, we must:

1. test the abstraction tool using a small subset of pilot records to ensure that the tool functions as intended; and

2. develop a user guide for abstractors.

If abstraction-adjudication workflow #2 or #3 are selected, arbitration among the expert clinical reviewers must take place to ensure agreement in case classifications. If the two reviewers for each case agree with the classification, that will be set as the final classification. If the two reviewers disagree, we will facilitate discussions between the two reviewers to determine if a consensus can be reached. If after the discussions there is still disagreement, a third clinician will review the case to break the tie.

We will leverage any existing outcome case definitions, case review forms, and analysis infrastructure to complete MRR.

11. Ethical Evaluation

This surveillance activity is conducted as part of the FDA-CBER BEST Initiative under the FDA Amendments Act of 2007. This current study performs analysis using administrative commercial insurer data from three databases (CVS Health, Carelon Research, and Optum pre-adjudicated claims), and CMS Medicare claims data.

The study involves no direct intervention on study participants; data used in this study is de-identified and anonymized before its use; the analysis conducted in a Federal Information Security Management Act (FISMA) compliant environment; and the results were presented in aggregate.

Using commercial insurer and Medicare data for this surveillance activity is permitted under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule for public health practice without individual authorization. Furthermore, public health surveillance activities including this study are not subject to the Common Rule as verified in the Office of Human Research Protections correspondence.[43] Therefore, this study as a public health surveillance activity within the Sentinel Initiative was exempt from an Institutional Review Board (IRB) review and approval. In addition, our study practices were performed in accordance with the Declaration of Helsinki guidelines.[44]

12. Quality Assurance and Control

The analyses described in this protocol will be conducted using well-characterized databases, the commercial insurer and CMS Medicare databases, in which Office of Biostatistics and Pharmacovigilance's (OBPV) has previously conducted numerous epidemiologic studies. For the current study, the team has performed quality control measures in the database such as executing verification checks examining the validity of claims data variables, stability of enrollment and health outcome trends, and consistency with population selection criteria for the database, if any.

13. References

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14. Appendix

14.1 RSV Vaccine Product Code List

Appendix Table 1 presents 2023-2024 RSV vaccine product descriptions, dosage forms, product compositions, dose strengths, authorization dates, and relevant codes (HCPCS/CPT, NDC, and CVX codes) for the approved RSV vaccines. CVX codes are used in IIS data to identify immunization exposures and will supplement claims data in identifying RSV vaccine administrations in IIS data. This code list will undergo further review and revision during the surveillance process.

Appendix Table 1. Product Descriptions, Dosage Forms, Product Compositions, Dose Strengths, Authorization Dates, and Relevant Codes for Approved Respiratory Syncytial Virus (RSV) Vaccines. [6, 7, 9]

Scientific Name	Proprietary Name and Manufacturer	Description and Composition	Vaccine Authorization Date	CVX Code	NDC 11 Labeler Product ID	HCPCS / CPT Code
RSVPreF3 + AS01	AREXVY – GlaxoSmithKline Biologics	Respiratory syncytial virus (RSV), vaccine, recombinant, protein subunit RSV prefusion F, adjuvant reconstituted, 0.5 mL, preservative free; Composition: 120 µg RSV - RSVpreF3; adjuvant AS01E	May 3, 2023	303	58160072303 58160074403 58160084811	90679
RSVPreF	ABRYSVO – Pfizer Inc.	Respiratory syncytial virus (RSV), vaccine, bivalent, protein subunit RSV prefusion F, diluent reconstituted, 0.5 mL, preservative free; Composition: 60 µg RSVpreF from RSV-A 60 µg RSVpreF from RSV-B	May 31, 2023	305	00069020701 00069025001 00069034401 00069034405 00069034410	90678

Abbreviations: HCPCS: Healthcare Common Procedure Coding System; NDC: National Drug Code; CVX: Vaccine Administered Codes.

14.2 Concomitant Vaccination Code List

Concomitant vaccines will be captured using HCPCS/CPT and NDCs. Appendix Table 2 outlines the vaccine products and administration codes that will be used to identify persons with concomitant vaccinations.

Appendix Table 2. Concomitant Vaccine Products and Administration Code List

Concomitant Vaccination	CPT/HCPCS	CVX Code	Vaccine Administration Code	NDC
COVID-19 Vaccination (Updated Monovalent Booster – Season 2023-2024)	91304 91320 91322	309 312 313	N/A	80777-0102-01 80777-0102-04 80777-0102-93 80777-0102-95 80777-0102-96 80631-0105-01 80631-0105-02 00069-2362-01 00069-2362-10 00069-2392-01 00069-2392-10
Influenza Vaccination (Season 2023-2024)	90662 90672 90674 90682 90686 90687 90688 90694 90756	149 150 158 171 185 186 197 205	G0008	19515-0814-41 19515-0814-52 33332-0323-03 33332-0323-04 33332-0423-10 33332-0423-11 49281-0123-65 49281-0123-88 49281-0423-50 49281-0423-88 49281-0639-15 49281-0639-78 49281-0723-10 49281-0723-88 58160-0909-41 58160-0909-52 66019-0310-01 66019-0310-10 70461-0323-03 70461-0323-04 70461-0423-10 70461-0423-11 70461-0123-03 70461-0123-04

Concomitant Vaccination	CPT/HCPCS	CVX Code	Vaccine Administration Code	NDC
15-valent / 20-valent Pneumococcal Conjugate Vaccine (PCV 15/20), Pneumococcal Polysaccharide Vaccine (PPSV23)	90671 90677 90732	33 215 216	G0009	00005-2000-01 00005-2000-02 00005-2000-10 00006-4329-01 00006-4329-02 00006-4329-03 00006-4739-00 00006-4739-01 00006-4837-01 00006-4837-02 00006-4837-03 00006-4943-00 00006-4943-01 50090-6026-00 50090-6026-01 54868-3339-01 54868-3339-09 54868-4320-00 54868-4320-09
Shingles Vaccine	90396 90736 90750	36 121 187	N/A	00006-4963-00 00006-4963-01 00006-4963-41 50090-5147-00 58160-0819-12 58160-0823-11 58160-0828-01 58160-0828-03

14.3 Covariate Definitions

Appendix Table 3 outlines the description of covariates and their respective assessments.

Appendix Table 3: Description of Covariates

Characteristics	Description
Sex	Sex is determined using most recent available sex data in the Medicare and commercial enrollment databases. Sex is self-declared at Medicare enrollment. It is a categorical variable that is stratified by male and female.
Race/Ethnicity (CMS Medicare Only)	Race/Ethnicity is determined using most recent data in the Medicare and commercial enrollment database. Race/Ethnicity is self-declared at Medicare enrollment. The variable is stratified by Asian, Black, Hispanic, American Indian/Alaskan Native, White, Other, and Missing/Unknown

Characteristics	Description
Urban/Rural	The core-based statistical area (CBSA), which categorizes areas as micropolitan or metropolitan, was assigned based on the beneficiary's most recently available residential address. • Metropolitan statistical areas are CBSAs associated with at least one urbanized area that has a population of at least 50,000 or more population, plus adjacent territory that has a high degree of social and economic integration with the core as measured by commuting ties. Persons falling within this category are classified as urban. • Micropolitan statistical areas are a new set of statistical areas that have at least one urban cluster of at least 10,000 but less than 50,000 population, plus adjacent territory that has a high degree of social and economic integration with the core as measured by commuting ties. Persons falling within this category are classified as rural.
Age	Age is defined as a person's age at the time of vaccination. The variable is categorized as persons aged 60-64 years in the commercial health plans. In CMS Medicare data, this variable is categorized as persons aged 65-69, 70-74, 75-79, 80-84, 85-89, and 90+ years.
Facility / Provider Type	Facility or provider type will be assessed at the time of first observed RSV vaccination. This variable will be stratified as: • Hospital • Office Visit • Pharmacy • Skilled Nursing Facility • Home Health Agency • Mass Immunization Center • Other • Missing or Unknown
Health and Human Services (HHS) Region [24]	The Health and Human Services (HHS) region is assigned based on persons' state of residence. The HHS regions divide up the country into 10 regions, each representing a regional office that directly serve state and local organizations. These regions include: • Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont) • Region 2 (New Jersey, New York, Puerto Rico, and the Virgin Islands) • Region 3 (Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia) • Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee) • Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) • Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, and Texas) • Region 7 (Iowa, Kansas, Missouri, and Nebraska) • Region 8 (Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming) • Region 9 (Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, and Republic of Palau) • Region 10 (Alaska, Idaho, Oregon, and Washington)

Characteristics	Description
Prior COVID-19 Diagnosis	Prior COVID-19 Diagnosis is assessed by identifying outcome cases with a preceding U07.1 code in any care setting in the 30 days prior to and including the outcome date.
Nursing Home Residency Status (CMS Medicare Only) [25]	Nursing home residency status will be captured from the Minimum Data Set (MDS) 3.0, a mandatory clinical assessment administered to all residents in Medicare & Medicaid certified nursing homes. Nursing home residency status is categorized by nursing home residents and non-nursing home residents.
Dual-Eligibility Status (CMS Medicare only) [28]	Medicare & Medicaid dually eligible beneficiaries are beneficiaries enrolled in both Medicare and Medicaid. The term includes beneficiaries enrolled in Medicare Part A, Part B, or both, and getting full Medicaid benefits or only help with Medicare premiums or cost-sharing through 1 of the Medicare Savings Programs (MSP) eligibility groups. These MSPs are: Qualified Medicare Beneficiary (QMB) program, Specified Low-Income Medicare Beneficiary (SLMB) program, Qualified Individual (QI) program, and Qualified Disabled Working Individual (QDWI) program.
Area Deprivation Index (ADI) Rank (CMS Medicare only) [29]	The ADI is an index of seventeen socioeconomic indicators which includes block group measures of education, employment, income, housing, household composition, and household resources. The ADI measure is constructed by ranking the ADI score from low to high for the nation and grouping the blocks into bins corresponding to each 1 percent range of the ADI score. The national ADI ranks block groups from 1 being the least disadvantaged, to 100 being the most disadvantaged in the U.S.
Original Reason for Medicare Eligibility (CMS Medicare only) [26, 27]	The original reason for Medicare entitlement, is classified as: • Aged without End-Stage Renal Disease (ESRD) • Aged with ESRD • Disabled without ESRD • Disabled with ESRD • ESRD only The Medicare Status of a beneficiary is identified using the variable 'MDCR_STATUS_CODE_01' commonly found in the CMS Common Medicare Environment (CME) database and is used to distinguish between aged, disabled, and ESRD populations.
Concomitant Vaccination	Concomitant Vaccinations will be defined as a receipt of: • Seasonal influenza vaccine (2023-2024 formula) • Updated COVID-19 vaccine (2023-2024 formula) • PCV 15/20 or PPSV23 vaccine, and Shingles vaccination that happened on the same day as that of the RSV vaccination index date. Concomitant vaccines will be captured using HCPCS/CPT, NDCs, and CVX codes.

Characteristics	Description
Medical Conditions (CMS Medicare only; commercial health plan population where feasible)	The following medical conditions or baseline health characteristics will be monitored for case populations only with a lookback window of 183 days prior to and including the RSV vaccination date. • Asthma • Blood Disorders • Chronic Lung Disease • Diabetes • Heart Disease • Kidney Disease • Liver Disorders • Neurological / Neurodevelopmental Conditions • Malignant Neoplasms These conditions will be identified using ICD-10-CM codes in IP/OP/PB settings
Immunocompromised Status (CMS Medicare only; commercial health plan population where feasible) [30]	Immunocompromised Status will be monitored for case population only and will be determined based on a CBER-adapted algorithm modified from a previously developed and validated algorithm by Greenberg et al. to identify immunocompromised persons. The modified version of the algorithm also includes eight mutually exclusive categories of immunosuppression. Relevant indicators included in the algorithm will be identified in the 183 days prior to RSV vaccination. The conditions will be identified using ICD-10-CM codes and additional codes from AHRQ criteria for identifying individuals at risk of immunosuppression. • HIV / AIDS • Hematological Malignancy and Related Conditions • Immune deficiencies (treatment-dependent and treatment-independent) • Solid Malignancy • Transplant and Related Conditions • Rheumatological / Inflammatory Conditions • Dialysis This variable will be stratified by the presence or absence of immunocompromised status.
Charlson comorbidity index (CMS Medicare only; commercial health plan population where feasible) [31]	The Charlson Comorbidity Index will be monitored for case population only and will be used to categorize comorbidities of case population only based on the ICD-10-CM diagnosis codes found in administrative claims data. Each comorbidity category has an associated weight (from 1 to 6) based on the adjusted risk of mortality or resource use. The original index was developed with 19 categories [45], but had been modified to 17 categories. [46] A score of zero indicates no comorbidities. The higher the score, the higher is the predicted mortality rate or the higher is the resource use.

Characteristics	Description
Prior hospitalization (CMS Medicare only; commercial health plan where possible)	The following medical conditions or baseline health characteristics will be monitored for case populations only with a lookback window of 183 days prior to and including the RSV vaccination date. Prior hospitalization will be identified by the presence of an IP stay in the claims data with any diagnoses. This baseline health characteristic will be summarized for Medicare and commercially enrolled population if feasible.

14.4 Adjustments and Exclusions for Complex Outcomes

Appendix Table 4 summarizes the adjustments and exclusions for Non-Hemorrhagic Stroke (NHS), and Non-Hemorrhagic Stroke or Transient Ischemic Attack (NHS/TIA).

Appendix Table 4. Adjustments and Exclusions for NHS and NHS/TIA

Outcome	Basic Exclusion	Adjust onset date if observed in the day 1 prior to outcome (in all settings)	Exclusions for Prevalence (in all settings)	Exclusions – other known causes (in all settings)
Non-Hemorrhagic Stroke (NHS)	If in last 365 days prior to outcome NHS in IP setting	Z92.82, R51*, R47*, R29.810, R53.1, R42*, R41.82, R40.4, G81.9*, H53.9, H53.13*	If occurs in the 365-day window prior to outcome I69*, Z86.73, I48*, D57*, D68.5*	If in last 30 days prior to outcome U07.1 If in last 28 days prior to outcome I21* If in last 1 day prior to outcome S15*, I74* In same day as outcome S15*, I74*, Physical Trauma Code
Non-Hemorrhagic Stroke or Transient Ischemic Attack (NHS/TIA)	If in last 365 days prior to outcome NHS in IP setting or TIA in IP/OP-ED setting	Z92.82, R51*, R47*, R29.810, R53.1, R42*, R41.82, R40.4, G81.9*, H53.9, H53.13*	If occurs in the 365-day window prior to outcome I69*, Z86.73, I48*, D57*, D68.5*	If in last 30 days prior to outcome U07.1 If in last 28 days prior to outcome I21* If in last 1 day prior to outcome S15*, I74* In same day as outcome S15*, I74*, Physical Trauma Code

Appendix Table 5 summarizes the exclusions for Transverse Myelitis.

Appendix Table 5. Exclusions for Transverse Myelitis

Outcome	Basic Exclusion	Exclusions – other known causes (in all settings)
Transverse Myelitis	If in last 365 days prior to outcome Transverse Myelitis in IP, OP/PB setting	If in last 365 days prior to outcome multiple sclerosis, neuromyelitis optica, other myelitis (infectious causes), spinal trauma, paraplegia and quadriplegia

14.5 Descriptive Analysis Table Shells

Appendix Table 6. Sample Table of Characteristics of Persons Receiving RSV Vaccines, Overall and by Vaccine Brand, Enrolled in [Commercial Health Plan / CMS Medicare] During the Study Period

Patient Characteristics	Total RSV Vaccinations		RSVPreF3 + AS01 (AREXVY)		RSVPreF (ABRYSVO)	
	Count	Percent	Count	Percent	Count	Percent
Total						
Age at Vaccine Administration (Years)						
[Commercial Health Database]						
60-64						
CMS Medicare						
65-69						
70-74						
75-79						
80-84						
85-89						
90+						
Sex						
Male						
Female						
Age and Sex						
[Commercial Health Database] Male						
60-64						
[Commercial Health Database] Female						
60-64						
(CMS Medicare) Male						
65-69						
70-74						
75-79						
80-84						

Patient Characteristics	Total RSV Vaccinations		RSVPreF3 + AS01 (AREXVY)		RSVPreF (ABRYSVO)	
	Count	Percent	Count	Percent	Count	Percent
85-89						
90+						
(CMS Medicare) Female						
65-69						
70-74						
75-79						
80-84						
85-89						
90+						
Race/Ethnicity (CMS Medicare Only)						
White						
Black						
Hispanic						
Asian						
American Indian/Alaskan Native						
Other/Unknown						
Urban/Rural Residency						
Urban						
Rural						
Missing/Unknown						
HHS Region [a]						
Region I (Boston)						
Region II (New York)						
Region III (Philadelphia)						
Region IV (Atlanta)						
Region V (Chicago)						
Region VI (Dallas)						
Region VII (Kansas City)						

Patient Characteristics	Total RSV Vaccinations		RSVPreF3 + AS01 (AREXVY)		RSVPreF (ABRYSVO)	
	Count	Percent	Count	Percent	Count	Percent
Region VIII (Denver)						
Region IX (San Francisco)						
Region X (Seattle)						
Missing/Unknown						
Nursing Home Residency Status (CMS Medicare only)						
Nursing Home Residents						
Non-Nursing Home Residents						
Medicare Status (CMS Medicare only)						
ESRD only						
Aged without ESRD						
Aged with ESRD						
Disabled without ESRD						
Disabled with ESRD						
Missing/Unknown						
Medicare & Medicaid Dual Eligibility (CMS Medicare only)						
Dual Eligible						
Non-Dual Eligible						
Area Deprivation Index (ADI) Rank (CMS Medicare only)						
1-10 (th)						
11-20						
21-30						
31-40						
41-50						
51-60						
61-70						
71-80						
81-90						
91-100						

Patient Characteristics	Total RSV Vaccinations		RSVPreF3 + AS01 (AREXVY)		RSVPreF (ABRYSVO)	
	Count	Percent	Count	Percent	Count	Percent
Missing/Unknown						
Facility/Provider Type						
Home Health Agency						
Hospital						
Mass Immunization Centers						
Office						
Pharmacy						
Prescription						
Other						
Missing/Unknown						
Concomitant Vaccinations [b]						
Influenza Vaccination						
COVID-19 Vaccination						
PCV 15/20 or PPSV23 Vaccination						
Shingles Vaccination						

[a] *Health and Human Services (HHS) regions are administrative regions consisting of multiple U.S. states, established by the Office of Regional Health Operations (OHRO) within the Office of Assistant Secretary Health (OASH) in alignment with its regional offices*

[b] *Concomitant vaccination will be defined as seasonal influenza, updated COVID-19, PCV 15/20 or PPSV23, and Shingles vaccination that happened on the same day as that of the RSV vaccination index date*

Appendix Table 7. Sample Table of Descriptive Statistics for [Outcome Cohort] Among Persons Receiving [Vaccine Brand] RSV Vaccine Product by Risk and Control Intervals

Patient Characteristics	Health Outcome									
	Number of Vaccine Doses [a]	Total Observed Outcomes			Outcomes during Risk Interval			Outcomes during Control Interval		
		Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]
Total										
Sex										
Male										
Female										
Age at Vaccine Administration (Years)										
[Commercial Health Database]										
60-64										
CMS Medicare										
65-69										
70-74										
75-79										
80-84										
85-89										
90+										
Race/Ethnicity (CMS Medicare only)										
White										
Black										
Hispanic										
Asian										
American Indian/ Alaskan Native										
Other/Unknown										

Patient Characteristics	Health Outcome									
	Number of Vaccine Doses [a]	Total Observed Outcomes			Outcomes during Risk Interval			Outcomes during Control Interval		
		Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]
Urban / Rural Residency										
Urban										
Rural										
Missing/Unknown										
HHS Region [d]										
Region I (Boston)										
Region II (New York)										
Region III (Philadelphia)										
Region IV (Atlanta)										
Region V (Chicago)										
Region VI (Dallas)										
Region VII (Kansas City)										
Region VIII (Denver)										
Region IX (San Francisco)										
Region X (Seattle)										
Missing / Unknown										
Nursing Home Residency Status (CMS Medicare only)										
Nursing Home Residents										
Non-Nursing Home Residents										
Medicare Status (CMS Medicare only)										

Patient Characteristics	Health Outcome									
	Number of Vaccine Doses [a]	Total Observed Outcomes			Outcomes during Risk Interval			Outcomes during Control Interval		
		Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]
ESRD only										
Aged without ESRD										
Aged with ESRD										
Disabled without ESRD										
Disabled with ESRD										
Missing/Unknown										
Medicare & Medicaid Dual-Eligibility Status (CMS Medicare only)										
Dual-Eligible										
Non-Dual-Eligible										
Area Deprivation Index (ADI) Rank (CMS Medicare only)										
1-10 (th)										
11-20										
21-30										
31-40										
41-50										
51-60										
61-70										
71-80										
81-90										
91-100										
Missing/Unknown										
Concomitant Vaccinations [e]										

Patient Characteristics	Health Outcome									
		Total Observed Outcomes			Outcomes during Risk Interval			Outcomes during Control Interval		
	Number of Vaccine Doses [a]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]
Influenza Vaccination										
COVID-19 Vaccination										
PCV 15/20 or PPSV23 Vaccination										
Shingles Vaccination										
Medical Conditions (Case Population Only)										
Prior hospitalization										
Asthma										
Blood disorders										
Chronic Lung Disease										
Diabetes										
Heart Disease										
Kidney Disorders										
Liver Disorders										
Neurological or Neurodevelopmental Disorders										
Malignant Neoplasms										
Immunocompromised Status (Case Population Only)										
Yes										
No										
Charlson comorbidity index (CCI) (Case Population Only)										

Patient Characteristics	Health Outcome									
	Number of Vaccine Doses [a]	Total Observed Outcomes			Outcomes during Risk Interval			Outcomes during Control Interval		
		Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]	Number of Outcomes [b]	Person-Years	Rate per 100,000 Person-Years [c]
0										
1										
2										
3										
4+										

[a] *The number of observed RSV vaccination exposure that are eligible for the follow up of a specific adverse event, i.e., clean for such outcome prior to the exposure date*

[b] *The number of observed outcomes overall or in the risk (comparison) interval*

[c] *The rate of outcomes in risk (comparison) interval, calculated by the # of outcomes in risk (comparison) interval divided by total risk (comparison) interval person time*

[d] *Health and Human Services (HHS) regions are administrative regions consisting of multiple U.S. states, established by the Office of Regional Health Operations (OHRO) within the Office of Assistant Secretary Health (OASH) in alignment with its regional offices*

[e] *Concomitant vaccination will be defined as seasonal influenza, updated COVID-19, PCV 15/20 or PPSV23, and Shingles vaccination that happened on the same day as that of the RSV vaccination index date*

14.6 Immunocompromised Algorithm

Individuals' immunocompromised status will be determined based on a CBER-adapted algorithm modified from a previously developed and validated algorithm by Greenberg et al. to identify immunocompromised persons.[30] The original algorithm was found to have a high accuracy of identifying immunocompromised persons with a PPV of 94.4% (95% CI 88.8–97.7), negative predictive value (NPV) of 94.3% (95% 91.0-96.6), sensitivity of 87.4% (95% CI 80.6–92.5%) and specificity of 97.6% (95% CI 95.0–99.9%).[30] The CBER-adapted algorithm was developed based on clinical consultation, and was modified to use ICD-10-CM codes and additional codes from the Agency for Healthcare Research and Quality (AHRQ) criteria for identifying individuals at risk of immunosuppression. The modified version of the algorithm also includes eight mutually exclusive (i.e. implemented one at a time) categories of immunosuppression. Relevant indicators included in the algorithm will be identified in the 183 days prior to RSV vaccination.

i. Human Immunodeficiency Virus (HIV) / Acquired Immunodeficiency Syndrome (AIDS)
ii. Hematological Malignancy and Related Conditions
iii. Immune Deficiencies (treatment-dependent)
iv. Immune Deficiencies (treatment-independent)
v. Solid Malignancy
vi. Transplant and Related Conditions
vii. Rheumatological / Inflammatory Conditions
viii. Dialysis