Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance

CBER Surveillance Program

Master Protocol

Assessment of Stroke Following COVID-19 mRNA, Bivalent Booster Vaccination

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Version Control

Name	Date	Version	Description
Acumen, LLC	January 24, 2023	0.1	Drafting
Acumen, LLC	February 7, 2023	0.2	Addition of a possible influenza vaccine analysis, refinement of study objectives, updated outcome definitions to include adjustments and exclusions, adjusted the prior COVID-19 definition
Acumen, LLC	February 9, 2023	0.3	Cleaned up language, restricted NH population to long term care residents only
Acumen, LLC	February 13, 2023	0.4	Moved NH analysis to follow-up, edited study population exclusions, elaborated on analysis purposes, reformatted
Acumen, LLC	February 22, 2023	0.5	Removed prior COVID-19 subgroup and clarified exclusion/censoring criteria. Made 508 compliance edits.

List of Abbreviations

AESI	Adverse event of special interest
AR	Attributable risk
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FFS	Fee for Service
HCPCS	Healthcare Common Procedure Coding System
HS	Hemorrhagic stroke
IP	Inpatient
IRR	Incidence rate ratio
MDS	Minimum Data Set
NRS	Near real-time surveillance
NHC	Nursing Home Compare
NHS	Non-hemorrhagic stroke
NHS/TIA	Non-hemorrhagic stroke or transient ischemic attack
OBPV	Office of Biostatics and Pharmacovigilance
OP-ED	Outpatient emergency department
OP/PB	Outpatient or Professional
POS	Place of Service
PPV	Positive predictive value
RCA	Rapid cycle analysis
SCCS	Self-controlled case series
SE	Standard error

SSD	Shared Systems Data
TIA	Transient ischemic attack
VSD	Vaccine Safety Datalink

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1 Background

On August 31, 2022 the U.S. Food and Drug Administration (FDA) authorized bivalent formulations of both the Moderna and Pfizer COVID-19 vaccines for use as a booster through emergency use authorization (EUA). The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (mRNA-1273.222) boosters include an mRNA component of the original COVID-19 strain as well as an mRNA component from the BA.4 and BA.5 Omicron variants. Pfizer-BioNTech COVID-19 Vaccine, Bivalent is currently recommended for those 5 years of age and older, and the Moderna COVID-19 Vaccine, Bivalent is currently recommended for those 6 months of age and older.

On January 13, 2023 the U.S. FDA and the Centers for Disease Control and Prevention (CDC) issued a public communication concerning the identification of a preliminary safety signal for ischemic stroke among persons aged 65 years who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in the CDC's Vaccine Safety Datalink (VSD) near real-time surveillance (NRS) system. The risk of stroke was identified in the 1-21 days following vaccination compared to 22-44 days following vaccination. As the communication indicates: "Following the availability and use of the updated (bivalent) COVID-19 vaccines, CDC's Vaccine Safety Datalink (VSD), a near real-time surveillance system, met the statistical criteria to prompt additional investigation into whether there was a safety concern for ischemic stroke in elderly persons who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Rapid-response investigation of the signal in the VSD raised a question of whether people 65 and older who have received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent were more likely to have an ischemic stroke in the 21 days following vaccination compared with days 22-44 following vaccination."[1] The signal was not identified with Moderna COVID-19 Vaccine, Bivalent. No other safety surveillance systems, notably FDA's Medicare Near Real-Time Surveillance, have identified a risk of stroke following the bivalent boosters among any age group.

On January 26, 2023 CDC presented these findings at a Vaccines and Related Biologic Products Advisory Committee meeting. At this meeting CDC noted that the risk of stroke in the population who had received a concomitant vaccination (receiving both a Pfizer-BioNTech COVID-19 Vaccine, Bivalent and a high-dose or adjuvanted influenza vaccines on the same day) was higher than the risk of stroke following receipt of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent alone.[2]

The NRS methods used by FDA and CDC have limitations and produce only a crude measure of association between an exposure and an outcome. A statistically significant result in these systems should be cautiously interpreted as it does not necessarily indicate an increased risk of adverse events of special interest (AESI) in the vaccinated population. Although the NRS systems adjusted for factors such as nursing home residency status, age, sex, and race, they did not adjust for any other potential confounding. In depth analyses which adjust for confounding are necessary to evaluate the signal.

The CBER Surveillance program has developed this protocol for use in conducting a more rigorous follow-up study of the results on the stroke outcomes identified in CDC VSD to determine whether there is an elevated risk using a more fully-controlled study design. This study will use a self-controlled case

series (SCCS) analysis to evaluate the preliminary stroke signal and the potential association between Pfizer-BioNTech COVID-19 Vaccine, Bivalent and stroke, including non-hemorrhagic stroke, hemorrhagic stroke, and transient ischemic attacks. The study will evaluate the Moderna COVID-19 Vaccine, Bivalent using the same methods. The study will also evaluate the risk of stroke outcomes following concomitant vaccination with a high-dose or adjuvanted influenza vaccine during the same study period. If a higher risk is identified post concomitant vaccination, this study will additionally evaluate the independent risk of stroke outcomes following high-dose or adjuvanted influenza vaccination.

2 Study Objectives

The objective of this study is to use a SCCS analysis to evaluate the risk of stroke outcomes after exposure to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent booster doses (bivalent boosters) among Medicare beneficiaries age 65 years and older who do not reside in a nursing home facility.

2.1 Primary Objectives

The primary objectives of this study are to evaluate:

I. The risk of stroke outcomes (as defined in Section 4.3) following exposure to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent booster doses (by brand) among Medicare beneficiaries age 65+.
II. The risk of stroke outcomes following exposure to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent booster doses (by brand) among age groups, those with a prior COVID-19 infection, and those who received a concomitant (same day administration) high-dose or adjuvanted influenza vaccine (see Section 5.5.3 for subgroup definitions).

The analysis for the primary objectives compares the risk of each outcome in a time interval after vaccination (risk window) to that in time intervals post-vaccination after completion of the risk window (control window) within the observation period.

2.2 Secondary Objectives

The secondary objectives of this study are to:

I. Conduct a temporal scan to identify clusters of stroke outcomes after exposure to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent COVID-19 mRNA bivalent booster doses (by brand) among Medicare beneficiaries age 65+.
II. Evaluate the independent risk of stroke outcomes (as defined in Section 4.3) following exposure to a high-dose or adjuvanted influenza vaccine (without concomitant administration of a bivalent booster) among Medicare beneficiaries age 65+, if power allows. This analysis will only be conducted on outcomes for which an increased risk of any stroke outcome following concomitant bivalent booster and influenza vaccination is identified.

SCCS analyses can be sensitive to the specification of intervals (risk and control). The temporal scan analysis will identify clusters of stroke outcomes for further consideration and evaluation. We will use the temporal scan analysis to validate our risk interval choices during the observation period.

2.3 Follow-Up Analysis

We have specified two follow-up analyses to occur at a later point in time. The objectives of these analyses are to evaluate:

I. The risk of stroke outcomes (as defined in Section 4.3) following exposure to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent booster doses among Medicare long-term stay nursing home residents age 65+.

II. The risk of hemorrhagic stroke (HS), non-hemorrhagic stroke (NHS), and the combined outcome of non-hemorrhagic stroke or transient ischemic attacks (NHS/TIA) following exposure to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent booster doses (by brand) among Medicare beneficiaries 65+ using an alternate definition of care setting (including the outpatient emergency department (OP-ED) setting in addition to the originally specified inpatient (IP) setting (see Section 4.3 for primary setting definitions).

3 Data Sources

The data source for this study is the US Medicare claims and enrollment databases in the Centers for Medicare & Medicaid Services (CMS) Shared Systems Data (SSD), for elderly persons aged 65 years and older in the US, with continuous Medicare Fee-for-Service (FFS) coverage only. Demographics and information on death is derived from the enrollment databases. Information on vaccinations, health covariates, preventive services, and outcomes are derived from Medicare Part A (inpatient) and Part B (outpatient settings and providers). Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. CMS Medicare SSD, which consists of claims sourced after enumeration, will be used in this study. SSD is updated daily and is over 80% complete within 30-70 days depending on the care setting and outcome. Information on nursing home residency status is derived from clinical assessment of residents in the Minimum Data Set (MDS). Additionally, we will capture nursing home characteristics through the Nursing Home Compare (NHC) dataset and COVID-19 Nursing Home COVID-19 public file reported to the CDC and provided by CMS.[3] For each person in the study, administrative claims from all care settings will be linked to create a longitudinal record of their health encounters, diagnoses, and drug prescriptions.

4 Exposure and Outcomes

4.1 Care Settings

Exposures and stroke outcomes will be identified within relevant care settings of interest, as specified based on clinical guidance. Table 1 defines the inpatient (IP), outpatient and professional (OP/PB), and outpatient emergency department (OP-ED) settings used in this study.

Table 1. Care setting definitions

Care Setting	Definition
Inpatient (IP)	Inpatient acute facility claims (e.g., UB-04 with type of bill = 11x)

Care Setting	Definition
Outpatient Emergency Department (OP-ED)	Outpatient facility claims (e.g., UB-04) in ED
Outpatient or Professional (OP/PB)[1]	Outpatient facility claims UB-04) -OR- Professional claims (CMS-1500) that contain at least one non-lab place of service[2]

[1] Including all sources of professional claims (e.g., urgent care etc.)

[2] Independent laboratory place of service code = 81

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 Emergency Department (OP-ED), identified through place of service (POS) and revenue (REV) codes, in PB and OP settings, respectively.

4.2 Exposures

Exposures for the primary analysis are defined as the receipt of any bivalent booster dose, as identified by Current Procedural Terminology (CPT®)/Healthcare Common Procedure Coding System (HCPCS) codes in any care setting (Table 2).

Table 2. Healthcare Common Procedure Coding System (HCPCS)/ Current Procedural Terminology (CPT) for COVID-19 Bivalent Booster Doses as of February 23, 2023

HCPCS/CPT Code	Manufacturer	Name	Vaccine Administration Code	Age Group
91312	Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	0124A	12+ years
91313	Moderna	Moderna COVID-19 Vaccine, Bivalent	0134A	18+ years

Exposures for secondary analysis II - influenza vaccines will be receipt of any high dose or adjuvanted flu vaccines, as identified by Current Procedural Terminology (CPT®)/Healthcare Common Procedure Coding System (HCPCS) codes in any care setting (Table 3).

Table 3. Healthcare Common Procedure Coding System (HCPCS)/ Current Procedural Terminology (CPT) for High Dose/Adjuvanted Influenza Vaccines as of February 23, 2023

HCPCS/CPT Code	Manufacturer	Name	Age Group
90662	Sanofi Pasteur	Fluzone High-Dose Quadrivalent (2022/2023)	65+ years
90694	Seqirus	Fluad Quadrivalent (Adjuvanted) (2022/2023)	65+ years

The list of valid codes will be reviewed periodically and updated if new codes are added. Patients with a claim containing a relevant code will be classified as vaccinated. In the CMS Medicare claims data, COVID-19 vaccination has been primarily billed through Part B using CPT/HCPCS codes.

If an individual has more than one vaccination code for the same brand occurring on the same day, the codes will be de-duplicated so that the individual contributes only one exposure for that brand to the study. If multiple brands are observed on the same day or multiple vaccinations (same/different brand) are observed within 3 days of each other, the given person will be excluded from the study (see Section 5.3). Prior COVID-19 vaccination is not required for inclusion in the analysis.

4.3 Outcomes

The stroke outcomes included in the study are hemorrhagic stroke (HS), non-hemorrhagic/ischemic stroke (NHS), transient ischemic attack (TIA), and a combined outcome which includes persons who have been diagnosed with non-hemorrhagic stroke and/or TIA (NHS/TIA). Risk following bivalent booster vaccination will be assessed separately for each of these stroke outcomes by vaccine brand. Stroke outcomes will be identified with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes in either primary or secondary diagnosis positions.

The ICD-10 codes used to identify each stroke outcome, the care settings in which each outcome will be evaluated, as well as the clean and risk windows for each are described in Table 4. The first qualifying occurrence of the outcome in the observation period is defined as an incident stroke outcome only if no outcome of the same type was recorded during the preceding pre-defined clean window. The clean window is defined as a period prior to vaccination in which beneficiaries with an occurrence of an event during the pre-specified window are excluded because outcomes captured post-vaccination may be attributed to previous rather than incident risk. The risk window is defined as an interval post-vaccination during which occurrence of the stroke outcomes may be associated with the vaccine exposure and thus considered a qualifying outcome. Both clean and risk windows are selected based on literature review, consultation with subject matter experts, and to align with CDC definitions. Risk windows are further detailed in Section 5.4.2.

Table 4. Stroke outcomes and their respective care settings, clean and risk windows

Stroke outcomes	ICD-10 Codes	Care Setting (Primary and Secondary Analysis)	Clean Window	Risk Window
Hemorrhagic stroke (HS)	I61*, I62*	IP	365 days	1-21 days; 22-42 days
Non-hemorrhagic stroke (NHS)	I63*	IP	365 days	1-21 days; 22-42 days
Transient ischemic attack (TIA)	G45.8, G45.9	IP; OP-ED	365 days	1-21 days; 22-42 days
Non-hemorrhagic stroke *or* transient ischemic attack (NHS/TIA)	I63*, G45.8, G45.9	IP (NHS & TIA); OP-ED (TIA)	365 days	1-21 days; 22-42 days

Definitions: Clean Window is defined as an interval relative to stroke outcomes date used to define incident stroke outcomes where an individual enters the study cohort only if the stroke outcomes of interest did not occur during that interval. Risk Window is defined as an interval relative to exposure date during which occurrence of the stroke outcomes of interest will be included in the analyses

Follow-Up Analysis II – Care Settings will include the OP-ED setting for all outcomes.

If certain related outcome codes are observed in the one day prior to the stroke outcome of interest, we will adjust the onset date of the stroke outcome to start at the date of the related outcome. If certain outcome codes which may be associated with the onset of the stroke outcome are observed prior to or on the day of the stroke outcome, these cases will be excluded. These exclusions are implemented to clean the outcome cohort by eliminating stroke cases which are likely caused by factors other than vaccination. These exclusions are implemented in the CDC VSD Rapid Cycle Analysis (RCA).[4] The Appendix details these adjustments/exclusions (See Appendix Table A).

5 Methods

5.1 Study Design

The SCCS design compares the incidence of adverse outcomes during periods of hypothesized excess risk due to the exposure (risk interval) to that of the control interval. Only cases (i.e., individuals with an incident stroke outcome) occurring during the study observation period contribute to risk estimation in an SCCS design, with estimation occurring within, rather than between, individuals.[5] 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
    b. The SCCS method is typically considered valid when the risk of occurrence is 10% or less[5]

Given the fatal nature of some of the stroke outcomes included in the study (discussed below), the occurrence of an outcome can affect both subsequent exposures and reduce the observation length, thus violating both the first and the second assumptions referenced above.

A violation of the first assumption could bias the relative incidence in either direction, thus causing reverse causation bias that would affect subsequent exposures. To address this concern, the primary

analysis will be restricted to a post vaccination control interval which will avoid a bias of reverse causation but require additional data accrual after the post-vaccination risk window.

Given concerns that stroke may have a high mortality rate, we calculated the 30-day Case Fatality Rate (CFR) for each outcome by utilizing SSD data from October 31, 2021-October 31, 2022 for beneficiaries 65 years and older with a 365-day prior clean window relative to the stroke outcomes and Medicare A/B enrollment from 365 days prior to vaccination date. Table 5 displays the case fatality rates within the 30-day observation period after the outcomes.

Table 5. 30 Day Case Fatality Rate by Outcome

Stroke outcomes	Hemorrhagic stroke (**HS)**	Non-hemorrhagic stroke (**NHS)**	Transient ischemic attack (**TIA)**
Case Fatality Rate	34.3%	17.0%	2.1%

The combined NHS/TIA outcome is expected to have a similar CFR to the NHS only outcome.

Given the high mortality rate, the observation time for these beneficiaries is truncated due to death which would violate the assumption that "occurrence of the outcome doesn't affect the observation length." To mitigate the violation of the second assumption that the observation time is independent of the outcome (e.g. death post-stroke outcomes censors follow-up time), a modified SCCS analysis will be conducted that will utilize a "Farrington adjustment" to adjust for censored, perturbed, or curtailed post-outcome exposures.[6]

5.2 Study Period

The study period will start on the date of the emergency use authorization for bivalent boosters in the U.S. (August 31, 2022) and will end on the date through which complete claims data (defined as at least 90% complete) and adequate power to assess risk estimation are available for the data source at the time of study initiation.

The completeness threshold was selected to balance the potential bias due to partially accrued observation of post-vaccination control intervals versus risk intervals, and a reasonable delay of the analysis. The 90% completeness is likely to overestimate relative risk by 10% or less. 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 RR is 1, the maximum bias due to observation delay is (100%/90%)-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.

5.3 Study Population

Eligible vaccinated individuals for the primary analysis are persons who received a bivalent booster and met the following inclusion/exclusion criteria regardless of the occurrence of the stroke outcomes. All eligible vaccinated individuals will be used for the attributable risk (AR) calculation

The case population will consist of bivalent booster vaccinated individuals with a stroke outcome. Incident stroke outcomes will be defined as the first recorded outcome for an individual during the study observation period if there are no claims for the same stroke outcomes in the preceding pre-defined clean window. The clean window will be anchored on the date of the stroke outcomes and will begin a pre-defined number of days prior to the stroke outcomes as specified in Section 4.3.

Eligible vaccinated individuals should meet the following inclusion/exclusion criteria.

5.3.1 Primary Analysis: Beneficiaries 65 years and older

Inclusion Criteria

I. Medicare beneficiaries enrolled in Part A (hospital insurance) and Part B (medical insurance) during the study observation period
II. Continuous enrollment will be required from 365 days prior to vaccination date until the earlier of 90 days post-vaccination, disenrollment, administration of a subsequent mRNA COVID-19 vaccine, death or study period end.
III. Received a bivalent booster in the observation period but not before the bivalent booster EUA, August 31, 2022.
IV. <u>For case population only</u>, had a record of a stroke outcome diagnosis during the study observation period.

Exclusion Criteria

I. Individuals less than 65 years of age at the time of bivalent booster vaccination.
II. Individuals vaccinated with multiple brands on the same day or multiple vaccinations (same/different brand) within 3 days of each other
III. Individuals who had a dialysis claim (identified as a type of bill code 72x) in the 90 days prior to event; excluded as we expect these patients to have a greater mortality risk than the typical Medicare beneficiary
IV. Individuals on hospice care on vaccination date; excluded because high fatality rate amongst this group may violate SCCS methods assumptions.
V. Individuals who reside in a nursing home at any point between August 31, 2022 and vaccination date.
VI. <u>For case population only:</u>
    a. Individuals that do not contribute follow-up time to both risk and control intervals. If individuals disenroll or reach the end of the study period during the risk window prior to accumulating any time for post-vaccination control intervals, they will be excluded.

b. Individuals who had a diagnosis of a stroke outcome during the outcome-specific clean window.
c. Individuals who had a diagnosis of COVID-19 in the 30 days prior to the stroke outcome.
d. Individuals who reside in a nursing home at any point between vaccination date and outcome date.

5.3.2 Secondary Analysis II: Influenza Vaccines

Eligible vaccinated individuals for the secondary analysis – influenza vaccination are persons who received a high-dose or adjuvanted influenza vaccine, and who did not receive a same day concomitant bivalent booster. All eligible vaccinated individuals will be used for the attributable risk (AR) calculation.

Inclusion Criteria

I. Medicare beneficiaries enrolled in Part A (hospital insurance) and Part B (medical insurance) during the study observation period
II. Continuous enrollment will be required from 365 days prior to vaccination date until the earlier of 90 days post-vaccination, disenrollment, administration of any subsequent influenza vaccine, administration of any mRNA COVID-19 vaccine, death or study period end.
III. Received a high-dose or adjuvanted influenza vaccine in the observation period but not before the study start date, August 31, 2022.
IV. <u>For case population only</u>, had a record of a stroke outcome diagnosis during the study observation period.

Exclusion Criteria

I. Individuals less than 65 years of age at the time of influenza vaccination.
II. Individuals vaccinated with multiple brands of an influenza vaccine on the same day or multiple vaccinations (same/different brand) within 3 days of each other
III. Individuals who receive a concomitant bivalent booster vaccination
IV. Individuals who had a dialysis claim (identified as a type of bill code 72x) in the 90 days prior to vaccination; excluded as we expect these patients to have a greater mortality risk than the typical Medicare beneficiary
V. Individuals on hospice care on vaccination date; excluded because high fatality rate amongst this group may violate SCCS methods assumptions.
VI. Individuals who reside in a nursing home at any point between August 31, 2022 and vaccination date.
VII. <u>For case population only:</u>
    a. Individuals that do not contribute follow-up time to both risk and control intervals. If individuals disenroll or reach the end of the study period during the risk window prior to accumulating any time for post-vaccination control intervals, they will be excluded.

b. Individuals who had a diagnosis of a stroke outcome during the outcome-specific clean window.
c. Individuals who had a diagnosis of COVID-19 in the 30 days prior to the stroke outcome.
d. Individuals who reside in a nursing home at any point between vaccination date and outcome date.

5.3.3 Follow-Up Analysis II: Nursing Home Residents

Nursing home residents are studied separately from the 65+ year old population because they are considered a higher risk population for the outcomes.

Inclusion Criteria

I. Medicare beneficiaries enrolled in Part A (hospital insurance) and Part B (medical insurance) during the study observation period
II. Continuous enrollment will be required from 365 days prior to vaccination date until the earlier of 90 days post-vaccination, disenrollment, administration of a subsequent mRNA COVID-19 vaccine, death or study period end.
III. The resident must have been residing in a nursing home since August 31, 2022 and until vaccination date. (Gaps in NH stay are permitted unless they are discharged back to the community or death).
IV. The resident must have an MDS assessment in the 183 days prior to outcome date with no assessment records suggesting official discharge within the 100 days prior to study start date, and reside in a nursing home with available data in NHC.
V. Received a bivalent booster in the observation period but not before the bivalent booster EUA, August 31, 2022.
VI. <u>For case population only</u>, had a record of a stroke outcome diagnosis during the study observation period.

Exclusion Criteria

I. Individuals less than 65 years of age at the time of bivalent booster vaccination.
II. Individuals vaccinated with multiple brands on the same day or multiple vaccinations (same/different brand) within 3 days of each other
III. <u>For case population only:</u>
    a. Individuals that do not contribute follow-up time to both risk and control intervals. If individuals disenroll or reach the end of the study period during the risk window prior to accumulating any time for post-vaccination control intervals, they will be excluded.
    b. Individuals who had a diagnosis of a stroke outcome during the stroke outcome-specific clean window.
    c. Individuals who had a diagnosis of COVID-19 in the 30 days prior to the stroke outcome.

5.4 Risk and Control Intervals

The definitions for observation period, risk, and control windows are provided below.

5.4.1 Observation Period/Follow-Up

For each individual, the observation period will start from the day following bivalent booster vaccination date, i.e., day 1 after vaccination and until the earlier of 90 days post-vaccination, disenrollment, administration of a subsequent mRNA COVID-19 vaccine, death or study period end. Day 0 (date of vaccination) is not included in the observation period since we would not be able to attribute stroke outcomes on this day to the exposure.

5.4.1.1 Secondary Analysis II: Influenza Vaccines

For each individual, the observation period will start from the day following high-dose or adjuvanted influenza vaccination date, i.e., day 1 after vaccination and until the earlier of 90 days post-vaccination, disenrollment, administration of a subsequent influenza vaccine, administration of any mRNA COVID-19 vaccine, death or study period end. Day 0 (date of vaccination) is not included in the observation period since we would not be able to attribute stroke outcomes on this day to the exposure.

5.4.2 Risk Window

The risk interval is defined as the time during which risk of a stroke outcome is hypothesized to be related to vaccination based on biological plausibility and clinical input (Table 2). The selected risk intervals for all stroke outcomes are days 1-21 and days 22-42. The 1-21 day risk interval was selected to align with the definition of stroke as used by the CDC in their RCA.[2] The 22-42 day risk interval is selected to assess any difference in risk during this period, and to avoid any biases in risk estimates that may arise from a carryover effect from the vaccine exposure into the control interval. Implementing a split window addresses concerns that risk of the outcomes may not be constant throughout the risk period. Risk intervals will not be split further in an effort to preserve statistical power.

5.4.3 Control Window

The post-vaccination control interval is defined as all follow-up time during the observation period following a vaccination that is outside of the risk interval(s) until the earlier of 90 days post-vaccination, disenrollment, subsequent mRNA COVID-19 vaccination, death, or study period end. Individuals who only accrued data during the risk intervals will be excluded from the analysis.

5.5 Statistical Analysis

5.5.1 Descriptive Analysis

A descriptive analysis will be conducted to demonstrate the counts and percentages of each stroke outcomes by the covariates of interest. Counts and percentages will further be stratified by risk and control intervals. We will also summarize case fatality rate for each stroke outcome.

Table 6. Descriptive Statistics

Covariates	Data Sources
Age (Categorical)	Medicare Enrollment Database

Covariates	Data Sources
Sex	Medicare Enrollment Database
CMS Medicare Race/Ethnicity	Medicare Enrollment Database
HHS Region	Medicare Enrollment Database
Urban/Rural Status	Medicare Enrollment Database
Dual Eligibility	Medicare Enrollment Database
Facility/Provider Type	Medicare Enrollment Database
Reason for Entering Medicare	Medicare Enrollment Database
Outcome Setting	
IP	Medicare Claims
OP-ED	Medicare Claims
Concomitant Influenza Vaccination – Same Day as Bivalent Booster Administration	
High-dose	Medicare Claims
Adjuvanted	Medicare Claims
Recombinant	Medicare Claims
Live-attenuated	Medicare Claims
Cell-cultured	Medicare Claims
Standard	Medicare Claims
Other Vaccinations – Administered During Risk/Control Intervals	
Pneumococcal	Medicare Claims
Prior COVID-19 diagnosis (relative to outcome date)	
COVID-19 diagnosis in the 30 days prior	Medicare Claims
COVID-19 diagnosis in the 31 to 365 days prior	Medicare Claims
Presence of Medical Conditions	
Hospitalization (prior 12 months)	Medicare Claims
Ischemic Heart Disease	Medicare Claims
Hypercholesterolemia	Medicare Claims
Hypothyroidism	Medicare Claims
Chronic Kidney Disease	Medicare Claims
Heart Failure	Medicare Claims
Chronic Obstructive Pulmonary Disease	Medicare Claims
Asthma	Medicare Claims
Gout	Medicare Claims
Obesity	Medicare Claims

Covariates	Data Sources
Nicotine Dependency	Medicare Claims
ITP	Medicare Claims
Impaired Mobility	Medicare Claims
Depression	Medicare Claims
Charlson Comorbidities Index	
Nursing Home Measures (For Nursing Home Residents Follow-Up Analysis)	
Health Inspection Five-Star Rating	
Health Inspection - 1 Star	Nursing Home Compare Dataset
Health Inspection - 2 Stars	Nursing Home Compare Dataset
Health Inspection - 3 Stars	Nursing Home Compare Dataset
Health Inspection - 4 Stars	Nursing Home Compare Dataset
Health Inspection - 5 Stars	Nursing Home Compare Dataset
Quality Measure Five-Star Rating	
Quality Measure - 1 Star	Nursing Home Compare Dataset
Quality Measure - 2 Stars	Nursing Home Compare Dataset
Quality Measure - 3 Stars	Nursing Home Compare Dataset
Quality Measure - 4 Stars	Nursing Home Compare Dataset
Quality Measure - 5 Stars	Nursing Home Compare Dataset
For-Profit Status	
For-Profit	Nursing Home Compare Dataset
Non-Profit	Nursing Home Compare Dataset
Government (Non-Veterans)	Nursing Home Compare Dataset
Veterans Homes	Nursing Home Compare Dataset
Nurse Aid Staffing Hours per Resident per Day	Nursing Home Compare Dataset
Licensed Practical Nurse Staffing Hours per Resident per-day	Nursing Home Compare Dataset
Registered Nurse Staffing Hours Per Resident per Day	Nursing Home Compare Dataset
Average Number of Residents per Day	Nursing Home Compare Dataset
Population Construction Statistics (Case Counts by Inclusion/Exclusion Criteria)	Medicare Claims

5.5.2 Primary Analysis: SCCS with Post-vaccination Control Intervals

5.5.2.1 Incidence Rate Ratio (IRR) Estimation

For the primary SCCS analysis, the rates of the stroke outcomes following the bivalent booster doses dose will be evaluated by brand. This analysis will compare the stroke outcomes rates in the risk and control intervals using a conditional Poisson regression model. A Farrington-adjusted SCCS model will be implemented that adjusts for the reduced observation time that can occur from the occurrence of an outcome.[6] We assume that only one incident event can occur in the observation period. Therefore, we only consider the first observed outcome.

$$log\big(E(Y|X)\big) = \beta_1(risk\ window_1) + \beta_2(risk\ window_2) + log(t) + strata(pateint\ id)$$

$$Y = Stroke\ Outcome$$

$$risk\ interval = indicator\ for\ exposure$$

$$t = interval$$

$$patient\ id = term\ identifying\ the\ patient$$

Under this model, the null and alternative hypotheses for each risk window can be written as, respectively:

$$H_0: e^{\beta_1} = 1 \quad H_a: e^{\beta_1} \neq 1$$

$$H_0: e^{\beta_2} = 1 \quad H_a: e^{\beta_2} \neq 1$$

Where, $e^{\beta 1}$ and $e^{\beta 2}$ will be interpreted as the IRR for the stroke outcomes in the risk intervals 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 COVID-19 vaccination and the stroke outcomes. Statistical significance will be determined using 95% CIs of IRRs and two-sided p-values ($p \leq 0.05$).

5.5.2.2 Attributable Risk (AR) Estimate

The study will also estimate the AR (per 100,000 doses and person-years). The number of excess stroke cases due to the vaccine will be directly derived from the conditional Poisson regression model, defined as the difference between the sum of the model fitted values (i.e., model predicted number of cases), and the sum of the expected cases if there were no vaccinations (i.e., all observed time is treated as control time). The AR is the excess number of stroke outcomes cases divided by the number of eligible beneficiaries (or eligible follow up dose-years). The standard error (SE) of the AR is estimated by bootstrap resampling 10,000 times. For each iteration, the study will sample the beneficiaries with stroke outcomes with replacement and repeat the AR calculation. The SE is calculated as the square root of the variance of the 10,000 AR values.

5.5.3 Subgroup Analysis

For each stroke outcome, subgroup analyses will be conducted to assess the risk of stroke outcomes following bivalent booster vaccination by age group and concomitant influenza vaccination status. Prior to executing this analysis, a power analysis will be conducted to assess the feasibility of executing the subgroup analysis. For each stroke outcome, case counts by each subgroup will be determined, and used to estimate the minimum detectable IRR that will be observable in the subgroup analysis. These will be benchmarked against stroke outcomes risk estimates following either COVID-19 bivalent booster or third/monovalent booster doses available in the literature, to determine if there is sufficient power to detect previously referenced risk estimates.

5.5.3.1 Age Subgroup Analysis

To evaluate difference in risk by age, a subgroup analysis will be conducted to assess bivalent booster risk by age group (65-74, 75-84, 85+) within the study population.

5.5.3.2 Concomitant Influenza Vaccination Analysis

To account for the possibility that the stroke outcome is occurring due to influenza vaccination or due to a combined effect between influenza and bivalent booster vaccination, a subgroup analysis will be conducted to assess stroke risk among beneficiaries with:

I. Same day vaccination of a COVID-19 bivalent booster and a high dose or adjuvanted influenza vaccine
II. A COVID-19 bivalent booster without any concomitant influenza vaccination (high-dose, adjuvanted, recombinant, or standard-dose). Concomitant vaccination defined as the receipt of a bivalent booster and a high-dose or adjuvanted influenza vaccine on the same day.

5.5.4 Sensitivity Analysis

Adjustments to the primary analysis will be conducted to assess the robustness of the risk estimations from the primary analysis. 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 stroke outcomes and adjust for the changing risk of the stroke outcomes associated with seasonality. Additionally, to account for potential outcome misclassification, a positive predictive value (PPV) adjusted analysis will be calculated. These analyses will be conducted after the finalization of the primary analyses.

5.5.4.1 Seasonality Adjustment Analysis

To evaluate potential time-varying confounding given the length of the observation period, the study will assess the association of time-varying risk factors with the stroke outcomes and adjust for the changing risk of the stroke outcomes, namely that some of the stroke outcomes exhibit seasonal trends.[8] In addition, given that COVID-19 has been associated with stroke, and the risk of exposure to COVID-19 varies throughout the study period, the risk of related stroke may vary during the study period as well.[7] Baseline stroke 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. For each stroke outcome, rates between 2017-2021 will be evaluated to determine a reasonable comparator year. If rates vary across years, the selected comparator year will be the one with the minimum stroke outcomes rate, whereas if there is limited variation, the median year among 2017-2021 will be selected.

5.5.4.2 Positive Predictive Value (PPV) Adjusted Analysis

A PPV-adjusted risk estimate will also be calculated using the PPVs from the medical record review process (see Section 6). While the IRRs are directly obtained from the primary claims-based analysis, they might not be truly representative of the underlying stroke outcomes risk given certain claims-identified cases may not be true cases during the observation period. PPV adjusted results may be reported subsequent to primary analysis results.

5.5.5 Secondary Analysis I: Temporal Scan

To identify clusters of increased stroke risk within the 1-90-day period after bivalent booster vaccination, we will conduct a retrospective temporal scan. We will use SaTScan[9] to perform the analysis. The temporal scan will only be conducted for analyses of interest, to be determined after completion of the SCCS analyses.

In order to identify clusters of meaningful specificity and size, we will set the maximum cluster size to be 50% of the observation period (45 days) and the minimum window length to 3 days. The unit of time aggregation will also be 3 days.

5.5.6 Secondary Analysis II: Influenza Vaccines

If we observe a risk of any stroke outcome in the concomitant vaccinated subgroup, we will conduct a secondary SCCS analysis to evaluate the risk of that stroke outcome following high-dose or adjuvanted influenza vaccination (without concomitant bivalent booster vaccination). Similar to the primary analysis, this analysis will compare the stroke outcomes rates in the risk and control intervals using a conditional Poisson regression model. A Farrington-adjusted SCCS model will be implemented that adjusts for the reduced observation time that can occur from the occurrence of an outcome.[6]

5.5.7 Follow-Up Analysis I: Nursing Home Residents

The specifications for the statistical analysis portion of the secondary analysis on nursing home residents will be consistent with the primary analysis (Section 5.5.2).

5.5.8 Follow-Up Analysis II: Alternate Setting Definitions

To evaluate the performance of our outcome setting definitions and to align algorithms to those of the CDC, we will conduct an exploratory SCCS analysis for the NHS, HS, and NHS/TIA outcomes. The specifications for the statistical analysis portion of the exploratory analysis will be consistent with the primary analysis (Section 5.5.2).

5.6 Statistical Power and Sample Size Calculations

To ensure sufficient sample size, a power analysis will be conducted to evaluate the minimum detectable IRR for each of the stroke outcomes following COVID-19 bivalent booster vaccination, at 80% power and a two-sided alpha of 0.05. A minimum detectable IRR will be calculated at various data cutoff dates for the study, and the study cutoff data date will be determined based on an assessment of minimum risk detection at varied timeframes. 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 events during risk relative to control intervals. Minimum detectable IRRs will be benchmarked against a comparable stroke outcomes risk estimate following either COVID-19 bivalent booster or third/monovalent booster doses present in the literature, to ensure sufficient sample size to detect the hypothesized IRR.

6 Medical Record Review

During the course of the study, a sample of medical records for each stroke outcome will be retrieved and undergo an adjudication process to assign cases identified in claims data as true cases, non-cases, and potentially indeterminate. We will sample to attain:

- 30 Cases of HS
- 30 Cases of NHS
- 30 Cases of TIA

A clinical case definition based on clinical input from subject matter experts will be used for each stroke outcome. The study will identify appropriate clinical reviewers to review the redacted medical records and abstracted data to recommend expert case designations.

If we conduct an influenza vaccine only analysis, a sample of medical records for the relevant stroke outcomes following influenza vaccination will also be retrieved and undergo a similar adjudication process.

7 Ethical Evaluation

This surveillance activity is conducted as part of the FDA CBER Initiative under the FDA Amendments Act of 2007. This current study performs analysis using Medicare administrative claims data. The study will not involve personal health Information; no intervention will be conducted on study participants; data used in this study will be de-identified and anonymized before its use.

Using Medicare data for this surveillance activity is permitted under the HIPAA Privacy Rule for public health practice without individual authorization.[10] 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. Therefore, this study as a public health surveillance activity is exempt from an IRB review and approval. In addition, our study practices will be performed in accordance with the Declaration of Helsinki guidelines.[11]

8 Quality Assurance and Control

The analyses described in this protocol will be conducted using a well-characterized database, the CMS Medicare database, in which OBPV has previously conducted numerous epidemiologic studies. For the current study, the team has performed quality control measures in the database such as executing 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. In addition, the team has validated codes for identifying individuals who received a COVID-19 vaccination and those who have been diagnosed with a stroke outcome.

Data quality is continuously monitored with every update from the study database to ensure insurance claims representing vaccinations and stroke outcomes are captured accurately. As an overall check, the total number of claims newly observed in each data cut will be counted, stratified by care setting and

HHS region. If substantial increases or decreases in the rate of claims accrual relative to previous cuts are observed, steps will be implemented to trace the potential causes of the discrepancy, such as by examining regions with accrual different from the national average, examining whether the data cut spans holidays that may reduce service utilization, or identifying providers whose claims submission patterns have changed. The study will also conduct more specific checks on the health care encounters occurring in care settings similar to COVID-19 vaccination or stroke outcomes, such as other vaccinations as negative control exposures or hospitalization for external injuries as negative control outcomes. Well-established and validated software such as SAS version 9.4, Stata version 17, R version 4.1.2, and SaTScan[9] will be used for statistical analyses.

9 References

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A Appendix

Table A. ICD-10 Codes Which Indicate Onset Date Adjustment or Exclusion for Outcomes of Interest[4]

Outcome	Adjust onset date if observed in the 1 day prior to outcome (in all settings)	Exclusions for Prevalence (in all settings)	Exclusions – other known causes (in all settings)
Hemorrhagic Stroke (HS)	I63.9, R51*, R47*, R29.810, R53.1, R42*, R41.82, R40.4, H53.13*, H53.9, G81.9*	If occurs in the 365 window prior to outcome I69*, Z86.73	If in last 30 days prior to outcome U07.1 If in last 1 day prior to outcome S06* If same day as outcome S06*, Physical Trauma Code
Non-Hemorrhagic Stroke (NHS)	Z92.82, R51*, R47*, R29.810, R53.1, R42, R41.82, R40.4, G81.9*, H53.9, H53.13*	If occurs in the 365 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*, 174* In same day as outcome S15*, I74*, Physical Trauma Code

Outcome	Adjust onset date if observed in the 1 day prior to outcome (in all settings)	Exclusions for Prevalence (in all settings)	Exclusions – other known causes (in all settings)
Non-hemorrhagic stroke or Transient Ischemic Attacks (NHS / TIA)	Z92.82, R51*, R47*, R29.810, R53.1, R42, R41.82, R40.4, G81.9*, H53.9, H53.13*	If occurs in the 365 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*, 174* In same day as outcome S15*, I74*, Physical Trauma Code
Transient Ischemic Attacks (TIA)	R51*, R47*, R29.810, R53.1, R42, R41.82, R40.4, G81.9*, H53.9, H53.13*	If occurs in the 365 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* In same day as outcome S15*, Physical Trauma Code