Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance

CBER Surveillance Program Biologics Effectiveness and Safety (BEST) Initiative

Master Protocol

Safety Assessment of 3rd Dose/Booster of COVID-19 mRNA Vaccines

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1.0	• Final Protocol	August 31, 2022
1.1	• Added post-hoc analysis (Section 5.5.5) • Revised power calculation description and table (Section 5.6)	October 21, 2022

List of Abbreviations

ADI	Area Deprivation Index
AESI	Adverse Events of Special Interest
AMI	Acute Myocardial Infarction
AR	Attributable Risk
BEST	Biologics Effectiveness and Safety
BP	Bell's Palsy
CBER	Center for Biologics Evaluation and Research
CFR	Case Fatality Rate
CI	Confidence Interval
CMS	Centers for Medicare & Medicaid Services
COVID-19	Coronavirus Disease-19
CPT	Current Procedural Terminology
ED	Emergency Department
EHR	Electronic Health Records
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FFS	Fee-for-Service
FISMA	Federal Information Security Management Act
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ITP	Immune Thrombocytopenia
IP	Inpatient
IRR	Rate Ratio
MRR	Medical Record Review
Myo/Peri	Myocarditis/Pericarditis
NDC	National Drug Codes
OP-ED	Outpatient Emergency Department

OP/PB	Outpatient and Professional
OBPV	Office of Biostatistics and Pharmacovigilance
PE	Pulmonary Embolism
POS	Place of Service
PPV	Positive Predictive Value
RCA	Rapid Cycle Analysis
RR	Risk Ratio
SCCS	Self-Controlled Case Series
SE	Standard Error
SSD	Shared Systems Data

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Protocol Synopsis / Executive Summary

Background

As of July 12, 2022, three COVID-19 (coronavirus disease 2019) vaccines, Comirnaty (BNT162b2 Pfizer-BioNTech COVID-19 Vaccine), Spikevax (mRNA-1273 Moderna COVID-19 Vaccine), and Janssen (Ad26.COV2.S COVID-19 Vaccine) have been granted emergency use authorization (EUA) or approved by the U.S Food and Drug Administration (FDA). The FDA also authorized third dose/first booster doses for all the three COVID-19 vaccines brands stated above. The U.S. FDA Center for Biologics Evaluation and Research (CBER) has been utilizing its Biologics Effectiveness and Safety (BEST) program to monitor these three vaccines. The surveillance approach uses the Rapid Cycle Analysis (RCA) to detect statistical association between the vaccines and adverse events of special interest (AESI) among patients who are 65 years and older.

Objective

The objective of the study is to evaluate the risk of Acute Myocardial Infarction (AMI), Pulmonary Embolism (PE), Immune Thrombocytopenia (ITP), Bell's Palsy (BP), and Myocarditis/Pericarditis (Myo/Peri) following exposure to COVID-19 third dose/first booster dose vaccinations (BNT162b2 and mRNA-1273) in the U.S elderly population aged 65 and older using a self-controlled study (SCCS) design.

Data Source

The data source for this study is the US Medicare Fee-for-Service (FFS) administrative claims and enrollment databases in the Centers for Medicare & Medicaid Services (CMS) Medicare Shared Systems Data (SSD) for persons aged 65 years and older in the US.

Exposure and Outcomes

The exposures of interest are defined as third dose/first booster doses of BNT162b2 and mRNA-1273 COVID-19 vaccines, as identified within the Medicare Fee-for-Service (FFS) claims data by appropriate product codes such as Current Procedural Terminology (CPT®)/Healthcare Common Procedure Coding System (HCPCS) codes or National Drug Codes (NDCs) in any care setting. The study excludes the Ad26.COV2.S booster from the exposure definition given the relatively modest uptake of this vaccine. The outcomes include Myo/Peri, BP, PE, ITP, and AMI identified by the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD10-CM) codes.

Methods

This study utilizes the SCCS design with a post-vaccination control interval, using adjustment for event-dependent observation periods. The study also considers a secondary analysis using the pre-vaccination and post-vaccination control intervals, and subgroup analyses by age group and sex, where case counts permit. The study considers different types of adjustments to the primary and secondary analyses to assess the robustness of the risk estimates in these analyses.

1 Background/ Introduction

COVID-19 (coronavirus disease 2019) is a disease caused by the virus SARS-CoV-2 which was discovered in December 2019 in Wuhan, China. As of July 11, 2022 there have been a total of 88,424,802 cases and a total of 1,016,293 deaths due to COVID-19 in the United States (U.S.).[1] The U.S. FDA has authorized/approved COVID-19 vaccines that are effective at preventing severe illness, hospitalizations, and death due to COVID-19.[2] These vaccines are BNT162b2, mRNA-1273, Ad26.COV2.S, and NVX-CoV2373 (Novavax) COVID-19 vaccines.[2]

The U.S. FDA has authorized third dose/first booster doses for the BNT162b2, mRNA-1273, and Ad26.COV2.S COVID-19 vaccine brands through EUA. COVID-19 third primary series doses are currently recommended for immunocompromised individuals only; a first booster dose (outside of the primary series) is recommended for ages 12 and older in the U.S.[3] As of March 29, 2022, a second booster dose of COVID-19 has also been authorized for those 50 years of age and older and for those 12 years and older with certain immunocompromising conditions. All three COVID-19 vaccines (including primary series doses), authorization dates, and dosing intervals are described in Table A1 in the Appendix.[3]

CBER at the FDA regulates biologic products including vaccines and is responsible for monitoring the safety of authorized COVID-19 vaccines via active and passive surveillance systems.[4] The active surveillance program at CBER is called the BEST Initiative, comprising a large number of large-scale administrative claims, electronic health records (EHR), and linked claims-EHR data.[4]

The third dose/first booster dose addendum detailed the approaches used to calculate rates of AESI following COVID-19 third primary series dose or first booster dose vaccinations, and compared the observed rates to the database specific rates in historical controls (expected rates).[5] The primary objective of this study was to determine whether there was an increased rate of AESI in the vaccinated population compared to the baseline.[5] Since this was a method for signal detection and not signal evaluation, a statistically significant result should be cautiously interpreted as it does not necessarily indicate an increased risk of AESI in the vaccinated population.[5] Another limitation of this analysis was that it used a historical comparator that did not adjust for secular trends and had limited adjustment for age and sex based on estimable background rates.[5] This dictated our motivation to use a self-controlled analysis approach in our current study. This study aims to evaluate the risk of AESI following third dose/first booster dose vaccinations with BNT162b2 and mRNA-1273 among the Medicare population aged 65 years and older. This study excludes Ad26.COV2.S boosters from the exposure definition given the relatively modest uptake of this vaccine in the U.S.

The five AESI in scope for this study are Myocarditis/Pericarditis (Myo/Peri), Bell's Palsy (BP), Pulmonary Embolism (PE), Immune Thrombocytopenia (ITP), and Acute Myocardial Infarction (AMI). The AESI for this study were selected based on the following evidence. In an RCA study evaluating the safety of the primary series of the two mRNA vaccines in the Medicare population, we found a signal for PE and AMI. In a cohort study of the third dose/first booster dose safety in the Medicare population where historical controls were used, we detected a statistically significant risk for ITP (IRR=1.66, CI=[1.17, 2.29]) and AMI (IRR=1.15, CI=[1.02,1.29]) among individuals with prior COVID-19 diagnosis as well as an increased risk of BP (IRR=1.11, CI=[1.03,1.19]) and PE (IRR=1.05, CI=[1.0001,1.100]) in general. In addition, a number of

studies have reported an increased risk of Myo/Peri after exposure to both COVID-19 mRNA vaccines, particularly after the second dose.[6]

This master protocol outlines the proposed methodology to evaluate the potential risk of AESI following the third dose/first booster doses of COVID-19 vaccines. This study will initially focus on the above-mentioned AESI following BNT162b2 and mRNA-1273 third dose/first booster doses, but as more data becomes available due to additional vaccinations getting authorized in the population, the study may be extended to include additional booster doses, AESI, and vaccines as relevant.

2 Study Objectives

The primary objective of the study is to evaluate the risk of AMI, PE, ITP, Myo/Peri, and BP following exposure to COVID-19 third dose/first booster dose vaccinations (BNT162b2 and mRNA-1273) in the U.S. Medicare population ages 65 years and older, using a self-controlled case series (SCCS) design.

The primary analysis compares the risk of each outcome in a time interval after vaccination (risk window) to that in another time interval post-vaccination after completion of the risk window (control window) within the study period. To assess the robustness of the analysis, a modified SCCS analysis will be conducted which adjusts for censored, perturbed or curtailed post-event exposures. This study will specifically utilize a Farrington Adjustment to account for the curtailed observation time.[7] Further details on the SCCS methodology are provided in Section 5.5.2

Additional adjustments to primary analyses will also be conducted to assess the robustness of the risk estimations from the primary analysis. To evaluate potential time-varying confounding, the study will assess the association of time-varying risk factors with the AESI such as seasonality, prior COVID-19 diagnosis exclusion, and a combination of both seasonality and prior COVID-19 diagnosis exclusion. Additionally, because certain claims-identified outcome cases may not be true cases during the observation period due to misclassification, a PPV-adjusted risk estimate will also be calculated using the PPVs from the medical record review process (see Section 6). Other types of adjustments will also be considered for beneficiaries receiving concomitant flu/pneumococcal vaccines, and beneficiaries with a booster dose administration code who were not captured in Medicare data as having received a primary vaccination series. Further details are provided in Section 5.5.3.

A secondary analysis using pre-vaccination and post-vaccination control intervals will be conducted as well as an additional subgroup analysis stratified by age groups (65-74, 75-84, 85+), and sex if case counts permit detailed in Section 5.5.4. The same adjusted analyses conducted for the primary analysis will be conducted for the secondary analysis, to assess the robustness of risk estimates.

3 Data Sources

The data source for this study is the US Medicare claims and enrollment databases in the CMS Medicare Shared Systems Data (SSD), for elderly persons aged 65 years and older in the US, with continuous Medicare Fee-for-Service (FFS) coverage only.

4 Exposure and Outcomes

4.1 Care Settings

Exposures and AESI 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 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**
(A subset of OP/PB above): 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

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

4.2 Exposure (COVID-19 Vaccination)

The exposure of interest is the third dose/first booster dose of the BNT162b2 and the mRNA-1273 vaccines occurring after August 12, 2021. These exposures will be identified in the study population using COVID-19 product and administration codes, as specified by the Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDCs).

Table A1 in the Appendix summarizes the COVID-19 vaccine codes that will be used to identify the exposures of interest. The list of COVID-19 vaccine codes will be reviewed periodically and updated with any changes to previous coding or newly authorized vaccine codes.

Dose assignment is based on the vaccine administration codes and chronological dose ordering for defining third dose/first booster doses. If the administration code is missing, then only the third

chronological order (dose order = 3) will be used to define a third dose/first booster dose. The primary descriptive and inferential analyses will be restricted to persons who received the same vaccine product for all doses given that risk assessment will occur by vaccine brand. Beneficiaries who receive heterologous booster vaccines will be excluded from the primary analysis. Given that a substantial portion of the study population's primary series administrations were not captured in Medicare data,[8] we will also conduct adjustments to the primary and secondary analyses to assess the robustness of the results in this population. The assumption is that their third dose/first booster dose vaccine brand is consistent with their primary series doses.

Cleaning and de-duplication rules will be implemented to account for scenarios in which multiple vaccine doses of the same or different vaccine brands are observed on the same day, or vaccine doses are observed in closer proximity than indicated based on vaccine authorization guidelines. The following are the rules that will be applied to vaccine dose cleaning and de-duplication steps:

(i) If an individual has more than one vaccination code for the same brand and dose occurring on the same day, the codes will be de-duplicated prioritizing the dose with the earliest administration code. This will ensure that the individual contributes only one exposure for that brand's dose to the study.
(ii) If no administration code is observed for an individual, and thus dose order is unknown, then dose number assignment will solely be based on the presence of prior doses of the same brand.
(iii) If multiple brands are observed on the same day or multiple vaccinations (same/different brand) observed within 3 days of each other, the given person will be excluded from the study.

4.3 Safety outcomes: Adverse events of special interest (AESI)

The AESI included in the study are AMI, PE, ITP, Myo/Peri, and BP. AESI risk following third dose/first booster vaccination, will be assessed separately for each of these AESI by vaccine brand. AESI will be identified with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes.

The care settings in which each AESI will be evaluated, as well as the clean (washout) and risk windows for each are described in Table 2. The first qualifying occurrence of the event in the observation period is defined as an incident AESI only if no event of the same type was recorded during the preceding pre-defined clean window. Beneficiaries with an event in the clean window will be excluded because in this case, 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 AESI may be associated with the vaccine exposure and thus considered a qualifying outcome. Both clean and risk windows are selected based on literature review and consultation with subject matter experts.

Table 2. AESI and their respective care settings, clean and risk windows

AESI	Care Setting	Clean Window*	Risk Window*
Acute Myocardial Infarction (AMI)	IP	365 days	1-28 days[9,10]
Pulmonary Embolism(PE)**	IP	365 days	1-28 days[11,12,13]
Immune Thrombocytopenia (ITP)	IP (primary diagnosis)	365 days	1-42 days[14,15]
Bell's palsy (BP)	IP, OP/PB	183 days	1-42 days[16]
Myocarditis/pericarditis (Myo/Peri)	IP, OP/PB	365 days	1-21 days[17]

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

* Selection of clean and risk window duration is based on clinician input

** The PE onset date is determined by the date the PE code is reported in the database.

5 Study Design

5.1 Study Population

The general study population will include eligible vaccinees who received the third dose/first booster dose of one of COVID-19 mRNA vaccines and met the inclusion/exclusion criteria outlined below, regardless of AESI occurrence. All eligible vaccinees will be used for the attributable risk (AR) calculation. The AR calculation is explained further in Section 5.5.2.2.

A case population who experienced one of the AESIs will also be defined that will be used for rate ratio (IRR) estimation in the primary SCCS analysis. This is explained further in Section 5.5.2.1.

The study inclusion and exclusion criteria for both the general and case populations are provided below.

Inclusion criteria:

(i) Medicare beneficiaries enrolled in Part A (hospital insurance) and Part B (medical insurance) during the study observation period.

(ii) Received a third dose or a booster COVID-19 vaccine during the vaccination period of interest. The end of the vaccination period is defined as the vaccination cut-off date.
- The vaccination cut-off date will be selected for each outcome to reduce the possibility of bias due to incomplete capture of events.

(iii) All beneficiaries will be required to have continuous enrollment in Medicare Parts A and B FFS from 365 days prior to vaccination through the 90-day observation period until death, disenrollment, subsequent booster, or end of the study period, whichever comes first.

(iv) For case population only, each case must have a record of the AESI diagnosis during the study observation period**.**

Exclusion criteria:

(i) Individuals less than 65 years of age at the time of COVID-19 vaccination.

(ii) 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.
(iii) Individuals vaccinated with multiple brands on the same day or multiple vaccinations (same/different brand) within 3 days of each other
(iv) Had a diagnosis of the AESI during the AESI-specific clean window.
(v) Received different COVID-19 vaccines for the booster dose compared to the primary series vaccine dose.

5.2 Self-Controlled Methods

The SCCS design compares the incidence of adverse events 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 AESI) occurring during the study observation period are sampled in SCCS, with estimation of risk occurring within, rather than between, individuals.[18] 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 event does not substantially affect subsequent exposures
(ii) Occurrence of an event does not affect the observation length
(iii) Event rates are constant within risk intervals
    a. Events must be independently recurrent or rare

Given the fatal nature of the AESI included in the study (discussed below), the occurrence of an event 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.

We calculated the 30-day Case Fatality Rate (CFR) for AMI and PE by utilizing SSD data from Jan 2021-Dec 2021 for beneficiaries 65 years and older with a 365-day prior clean window relative to the AESI and Medicare A/B enrollment on the date of occurrence of AESI. Our results found that the CFR for AMI and PE were 22% and 19% respectively, within the 30-day observation period after the vaccination. Given the high mortality rate observed for the AESI, the observation time for these beneficiaries (~20%) is truncated due to death which would violate the assumption that "occurrence of the event doesn't affect the observation length". To mitigate the violation of the second assumption that the observation time is independent of the event (e.g. death post-AESI censors follow-up time), a modified SCCS analysis will be conducted that will utilize the "Farrington adjustment" to adjust for censored, perturbed, or curtailed post-event exposures.[7]

5.3 Study Period

The study period will start on the date of the earliest emergency use authorization for first booster dose vaccines in the U.S. (August 12, 2021 for Pfizer-BioNTech vaccine) and will end on the date through which complete claims data (defined as at least 90% complete) 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 threshold is likely to overestimate relative risk by 10% or less. Assuming that event observation delays are accurately estimated from historical data, a 90% completeness threshold limits the difference in observation of events 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-(100%/90%) =11%. However, we expect the potential bias due to claims delay to be smaller in practice because risk and control interval completeness will likely fall between 100% and 90%.

5.4 Definition of Risk and Control Intervals

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

5.4.1 Observation Period

For each individual, the observation period will start from the vaccination date, i.e., day 1 of the third dose/first booster dose vaccination and extend to day 90. Day 0 is not included in the observation period since we wouldn't be able to attribute AESI on this day to the exposure.

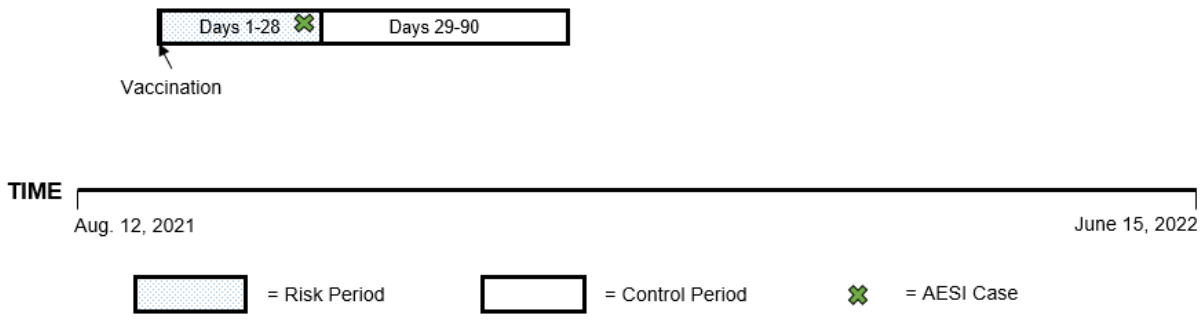
5.4.2 Risk Window

The risk interval is defined as the time during which excess risk is hypothesized following each COVID-19 vaccine dose for the AESI based on biological plausibility and clinical input (Table 3). The selected risk intervals are AESI-specific and are determined based on review of literature and consultation with subject matter experts. Post third dose/first booster dose risk intervals will run until the AESI-specific end of the interval.

5.4.3 Control Window

The post-vaccination control interval is defined as all follow-up time during the observation period following any third/first booster COVID-19 vaccine dose that is outside of the risk interval(s) until the earlier of 90 days post-vaccination, disenrollment, subsequent booster dose, death or study period end. Individuals who only accrued data during the risk intervals will be excluded from the analysis. Figure 1 represents a sample schematic for the risk and control interval definition.

Figure 1. The Risk and Control Window for the SCCS Design



Note: The hypothetical risk interval following one dose is up to 28 days. However, the length of the risk and control intervals will vary for each AESI.

5.5 Statistical Analysis

5.5.1 Descriptive Analysis

A descriptive analysis will be conducted to demonstrate the counts and percentages of each AESI by the covariates of interest. For the third dose/ first booster analysis, we will initially use the covariates outlined below, which may be expanded in the future when additional boosters get authorized. Counts and percentages will further be stratified by risk and control intervals.

(i) Demographics: stratifications by age, sex, race/ethnicity, region, urban/rural, dual eligibility status, area deprivation index (ADI)[19], nursing home residency status
(ii) Influenza vaccination at the time of COVID-19 vaccination, among the case population
(iii) Other vaccinations (i.e. pneumococcal vaccine) administered during both the risk and control intervals.
(iv) Calendar time, by periods distinguished by different dominant COVID-19 variants and other time periods of interest
(v) Prior COVID-19 diagnosis (defined by the ICD-10-CM code U07.1 (COVID-19)), among the case population
(vi) Case counts by the different inclusion and exclusion criteria for study population construction
(vii) Temporal clustering of cases during the observation period
(viii) The following baseline clinical conditions will be considered, but not limited to:
    - Hospitalization (prior 12 months)
    - Prior hospitalization for other AESI
    - Hypertension
    - Diabetes
    - COPD/Asthma
    - Atrial Fibrillation
    - Charlson Comorbidity Index
    - Bronchiectasis
    - Coronary Revascularization
    - Depression
    - Gout
    - Interstitial Lung Disease
    - Impaired Mobility
    - Obesity
    - Pneumonia
    - Stroke

5.5.2 Primary Analysis: SCCS with Post-vaccination Control Intervals

5.5.2.1 Rate Ratio (IRR) Estimation

For the primary SCCS analysis, the rates of the AESI following the third/first booster dose will be evaluated. This analysis will compare the AESI 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 event.[7]

$$\log\big(E(Y|X)\big) = \beta_1(risk\_interval) + \log(t) + strata(patient\_id)$$

$Y = AESI$

$risk\_interval = binary\ term\ indicating\ AESI\ occurrence\ in\ risk\ interval$

$t = interval$

$patient\_id = term\ identifying\ the\ patient$

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

$$\mathrm{H}_0: e^{\beta_1} = 1 \qquad \mathrm{H}_a: e^{\beta_1} \neq 1$$

Where, $e^{\beta 1}$ will be interpreted as the IRR for the AESI 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 COVID-19 vaccination and the AESI. 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 million vaccinations). The number of excess AESI 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 AESI 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 AESI 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 Adjustments to Primary Analysis

Adjustments to 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 AESI and adjust for the changing risk of the AESI associated with the major time-varying risk factors such as seasonality, prior COVID-19 risk exclusion, and both seasonality and prior COVID-19 risk exclusion. Additionally, to account for potential outcome misclassification, a PPV-adjusted analysis will be calculated. An analysis will also be conducted expanding the study population to including beneficiaries with a booster dose administration code, for whom we did not observe a primary series within the same vaccine brand. Lastly, an analysis that excludes individuals with concomitant vaccinations will be performed.

5.5.3.1 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 AESI and adjust for the changing risk of the AESI. Some AESI, including AMI, exhibit seasonal trends.[20] In addition, given that COVID-19 has been associated with cardiovascular disorders, and the risk of exposure to COVID-19 varies throughout the study period, the risk of related cardiovascular AESI may vary during the study period as well.[21] Baseline AESI 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 AESI, AESI rates between 2017-2019 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 AESI rate, whereas if there is limited variation, the median year among 2017-2019 will be selected.

5.5.3.2 Prior COVID-19 Exclusion Analysis

Previous studies indicated that some of the AESI hypothesized to be associated with COVID-19 vaccinations could also be associated with COVID-19 infection i.e. PE and Myo/Peri.[22,23] To assess the impact of potential confounding of risk estimates from COVID-19 infections, IRRs will also be calculated for a population excluding beneficiaries that had a COVID-19 diagnosis 365 days prior to their AESI diagnosis date.

5.5.3.3 Seasonality Adjustment Analyses and Prior Covid-19 Exclusion Analysis

A model will also be implemented that will incorporate a seasonality adjustment to account for the seasonality in AESI rates observed for certain events, and that will exclude beneficiaries with a prior COVID-19 diagnosis earlier than their AESI diagnosis date. This will allow for the evaluation of the robustness of the primary analysis risk estimates against the combined influence of the seasonality in AESI rates and prior COVID-19 status.

5.5.3.4 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 AESI risk given certain claims-identified cases may not be true cases during the observation period.

5.5.3.5 Expanded Study Population: Beneficiaries with Booster Dose Administration Codes and No Primary Series Doses

Since we expect a substantial proportion of the Medicare population to not have their primary series doses consistently captured,[8] we will conduct an additional analysis that includes such beneficiaries who have a booster dose administration code but no primary series vaccine doses observed.

5.5.3.6 Beneficiaries receiving concomitant flu/pneumococcal vaccines

To account for the possibility of the AESI occurring due to other medical procedures performed, an additional analysis will be performed to exclude beneficiaries with concomitant influenza or pneumococcal vaccinations observed on the same date as the COVID-19 vaccination; such cases will be censored if they appear in the risk/control window.

5.5.4 Secondary Analysis

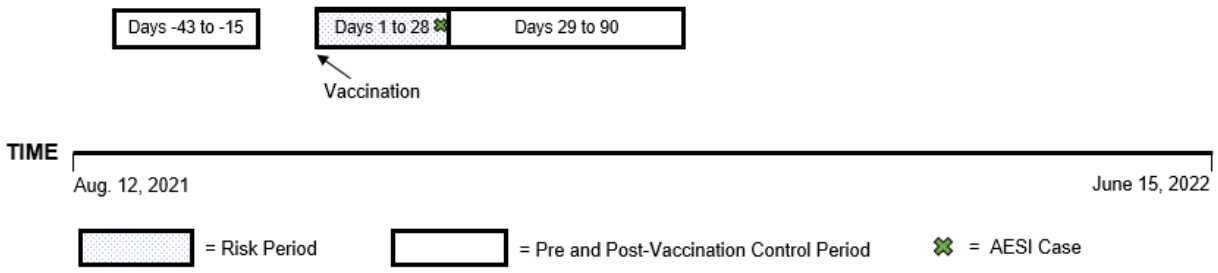
5.5.4.1 Subgroup Analysis by Age Group and Sex

For each AESI, a secondary subgroup analysis will be conducted to assess third dose/first booster dose risk by sex and age group (65-74, 75-84, 85+). Prior to executing this analysis, a power analysis will be conducted to assess the feasibility of executing the secondary analysis. For each AESI, case counts by age and sex will be determined, and used to estimate the minimum detectable IRR that will be observable in the secondary subgroup analysis. These will be benchmarked against AESI risk estimates following third dose/first booster doses available in the literature, to determine if there is sufficient power to detect previously referenced risk estimates.

5.5.4.2 SCCS with Pre- and Post-vaccination Control Intervals

A similar conditional Poisson regression as the primary analysis (Section 5.5.2) will be conducted including both the pre- and post-vaccination time during the observation period, to account for the lack of evidence related to the period of increased risk following vaccination and the uncertainty of when risk returns to pre-exposure levels following vaccination. Moreover, including additional observation time with the pre- and post- vaccination control intervals would also improve the overall power for the analysis. The observation period will start on the first day of the pre-vaccination control interval and extend to day 90 after vaccination. The pre-vaccination control interval will be defined as the interval with the same length as the risk interval ending 15 days prior to the date of the third/first booster dose of the COVID-19 vaccination. The pre-exposure interval of 14 days will be excluded between the end of the control interval and exposure to vaccination to account for possible delay of vaccination following occurrence of an AESI.[24] The post-vaccination risk and control intervals will be defined the same as in the primary analysis (Section 5.4.2 and Section 5.4.3). The secondary analysis will also implement the same adjusted analyses implemented for the primary analysis (Section 5.5.3), to ensure adequate adjustment for known confounders that may bias risk estimates.

Figure 2. The Risk and Control Windows for the SCCS with Pre-and Post-Vaccination Control Windows



Note: The hypothetical risk interval following one dose is up to 28 days. However, the length of the risk and control intervals will vary for each AESI.

5.5.5 Post-Hoc Analyses

5.5.5.1 Seasonality Adjustment Analyses Using Post COVID-19 Pandemic Study Period

From an assessment of temporal trends in AESI incidence rates from 2018-2022, PE was observed to have large variation in incidence rates based on seasonality and comparing the pre-COVID-19 (2018-2019) and post-COVID-19 (2020-2021) pandemic periods. Given that the seasonality adjusted analyses pre-specified in the protocol use the pre-pandemic period to account for seasonal changes in AESI risk, post-hoc seasonality adjusted analyses will also be conducted for PE only, using incidence rates of PE during the study period. This will assess the robustness of risk estimates, accounting for differences in the baseline risk of PE during the pre and post-pandemic periods. This post-hoc analysis will be implemented for both primary and secondary seasonality-adjusted analyses, including the combined seasonality-adjusted and prior COVID-19 exclusion analyses, as specified in Section 5.5.3.1 and Section 5.5.3.3.

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 AESI following third/first booster administration, 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 AESI risk estimate following third/first booster dose COVID-19 vaccines present from prior studies, to ensure sufficient sample size to detect the hypothesized IRR. Table 3 presents the minimum IRR that can be detected for each of the AESI given varied sample sizes of first booster dose vaccines, at 80% power and a two-sided alpha of 0.05. For each vaccine brand, minimum detectable IRRs were compared against benchmark risk estimates, which represent the lowest significant AESI-specific IRRs among either Pfizer-BioNTech or Moderna-mRNA vaccines. Benchmark risk estimates are based on a previous signal detection study with minimal adjustment for confounders, which assessed AESI risk following third or first booster dose vaccines. The same AESI-specific benchmark risk estimates are used for both vaccine brands.

Table 3. Sample size required to detect the IRR observed in the post third/first booster dose AESI risk observed in prior studies, at 80% power with two-sided alpha=0.05 using data through 14th May 2022

AESI	Vaccine Brand	Data Through Date (90% Data Completeness Threshold)	Estimated Third/First Booster Vaccinations (N)	Minimum Detectable IRR (80% Power)	Benchmark IRR*
Acute Myocardial Infarction (AMI)	Pfizer	7/1/2022	3,043,411	1.065	1.15
		7/29/2022	3,101,411	1.065	
	Moderna	7/1/2022	3,142,543	1.064	
		7/29/2022	3,217,770	1.063	
Pulmonary Embolism (PE)	Pfizer	7/1/2022	3,043,411	1.124	1.05
		7/29/2022	3,101,411	1.123	
	Moderna	7/1/2022	3,142,543	1.122	
		7/29/2022	3,217,770	1.121	
Immune thrombocytopenia (ITP)	Pfizer	7/1/2022	3,043,411	2.177	1.66
		7/29/2022	3,101,411	2.145	
	Moderna	7/1/2022	3,142,543	2.145	
		7/29/2022	3,217,770	2.116	
Bell's Palsy	Pfizer	7/1/2022	3,079,845	1.151	1.11
		7/29/2022	3,115,065	1.15	
	Moderna	7/1/2022	3,189,969	1.148	
		7/29/2022	3,235,748	1.147	
Myocarditis/Pericarditis	Pfizer	7/1/2022	3,065,646	1.288	1.89
		7/29/2022	3,108,821	1.286	
	Moderna	7/1/2022	3,171,571	1.283	
		7/29/2022	3,227,347	1.28	

Note: Highlighted cells reflect data cutoff dates with sufficient sample size for AESI and first booster doses to detect the AESI IRRs observed in prior studies.

* For each vaccine brand, minimum detectable IRRs were compared against benchmark risk estimates, which represent the lowest significant AESI-specific IRRs among either Pfizer-BioNTech or Moderna-mRNA vaccines. These estimates are based on a previous signal detection study which was minimally adjusted for confounders and assessed AESI risk following third or first booster dose vaccines. The same AESI-specific benchmark risk estimates are used for both vaccine brands.

6 Medical Record Review

For the current study, we will use existing positive predictive value (PPV) estimates from the Vascular Outcomes study for AMI and PE, provided in Table 4. Medical record review is ongoing for the Myo/Peri and BP outcomes among the elderly Medicare population using CMS FFS claims data; finalized PPV estimates from this review will be used in the current study for the PPV-adjusted model.

A separate MRR will need to be conducted for ITP given that this study uses a more restricted ITP definition from the Vascular Outcomes study.

The MRR process for the above mentioned AESI will have the same record abstraction, case-identification, and adjudication steps as the MRR conducted for the Vascular Outcomes study.

Table 4. Summary of the PPVs obtained from the MRR for the AESI's of interest

Category	Final PPV	
	AMI (IP) 65+ (CMS)	PE (IP) 65+ (CMS)
Confirmed cases only	38.0% (28.8, 48.3)	76.2% (61.5, 86.5)
Confirmed + probable	78.3% (68.8, 85.5)	83.3% (69.4, 91.7)
Confirmed + probable + possible	94.6% (87.9, 97.7)	92.9% (81.0, 97.5)

7 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 Medicare administrative claims data. The study involved no personal health Information; no intervention was conducted on study participants; data used in this study was de-identified and anonymized before its use; the analysis was conducted in a Federal Information Security Management Act (FISMA) compliant environment; and the results were presented in aggregate.

Using Medicare data for this surveillance activity is permitted under the HIPAA Privacy Rule for public health practice without individual authorization.[25] 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 within the Sentinel Initiative was exempt from an IRB review and approval. In addition, our study practices were performed in accordance with the Declaration of Helsinki guidelines.[26]

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 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 event trends, and consistency with population selection criteria for the database, if any.

9 References

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10 Appendix

10.1 COVID-19 Vaccine Exposure Codes

Table A1 presents COVID-19 vaccine product and administration codes available in the CPT, HCPCS and NDC diagnosis and medical service coding vocabularies, present as of August 5, 2022. These codes will be used to identify COVID-19 vaccine event exposures in the study population. The code list will undergo further review and revision, during analysis implementation.

Table A1. Healthcare Common Procedure Coding System (HCPCS)/ Current Procedural Terminology (CPT) and National Drug Codes (NDC) for COVID-19 Vaccines

HCPCS/CPT Code	Name	Vaccine Administration Code	Vaccine Authorization Dates	Age Groups	NDC 11 Labeler Product ID (Vial)	Dosing Interval
91300, 91305, 91307	Pfizer-BioNTech COVID-19 Vaccine	0001A, 0051A, 0071A (1st dose)	12/11/2020	16 years and older	59267-0078-01 59267-0078-02 59267-0078-04 59267-1000-01 59267-1000-02 59267-1000-03 59267-1025-01 59267-1025-02 59267-1025-03 59267-1025-04 59267-1055-01 59267-1055-02 59267-1055-04	21 days (dose 1 and 2) -28 days (doses 2 and 3) -5 months (primary series and booster dose)
		0002A, 0052A, 0072A (2nd dose)	12/11/2020	16 years and older		
		0003A, 0053A (3rd dose)	8/12/2021	12 years and older (Immunocompromised)		
		0004A, 0054A (1st and 2nd booster doses)	9/22/2021 and 3/29/2022, respectively	16 years and older; 50 years and older and 12 years and older (Immunocompromised)		

HCPCS/CPT Code	Name	Vaccine Administration Code	Vaccine Authorization Dates	Age Groups	NDC 11 Labeler Product ID (Vial)	Dosing Interval
91301, 91306	Moderna COVID-19 Vaccine	0011A (1st dose)	12/18/2020	18 years and older	80777-0273-10 80777-0273-99 80777-0273-15 80777-0273-98	-28 days (dose 1 and 2) -28 days (dose 2 and 3) -5 months (primary series and booster dose)
		0012A (2nd dose)	12/18/2020	18 years and older		
		0013A (3rd dose)	8/12/2021	18 years and older (Immunocompromised)		
		0064A (1st and 2nd booster doses)	10/20/2021 and 3/29/2022, respectively	18 and older (certain populations), and 50 years and older; and 18 years and older (Immunocompromised)		