

Center for Biologics Evaluation and Research
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CBER Surveillance Program

Assessment of Acute Myocardial Infarction, Pulmonary Embolism, Disseminated Intravascular Coagulation and Immune Thrombocytopenia Following COVID-19 Vaccination

Protocol

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Draft 2.0	06/15/2021	Added DIC and ITP
Draft 2.1	06/21/2021	Updated study design to include primary analysis using post-vaccination control interval, secondary analysis using both pre- and post-vaccination control intervals, and exploratory analysis using pre-vaccination control interval
Draft 2.2	7/9/2021	Incorporated additional workgroup comments and finalized the protocol
Final	7/30/2021	Removed death from exclusion criteria for the primary analysis

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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
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
DIC	Disseminated Intravascular Coagulation
ED	Emergency Department
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IP	Inpatient
IRR	Incidence Risk Ratio
ITP	Immune Thrombocytopenia
MDS	Minimum Data Set
MRR	Medical Record Review
NDC	National Drug Codes
NHS	Non-hemorrhagic Stroke
OP-ED	Outpatient Emergency Department
OP/PB	Outpatient and Professional
PE	Pulmonary Embolism
PHI	Protected Health Information
PII	Personal Identifying Information
PMaxSPRT	Poisson Maximized Sequential Probability Ratio Test

POS	Place of Service
PPV	Positive Predictive Value
RCA	Rapid Cycle Analysis
RR	Risk Ratio
SCCS	Self-Controlled Case Series
SCRI	Self-Controlled Risk Interval
SE	Standard Error
SSD	Shared Systems Data
STEMI	ST-elevation Myocardial Infarction
VAERS	Vaccine Adverse Events Reporting System

Protocol Synopsis / Executive Summary

Background

As of June 30, 2021, three coronavirus disease 2019 (COVID-19) vaccines (BNT162b2, Pfizer-BioNTech; mRNA-1273, Moderna; and Ad26.COV2.S, Johnson & Johnson/Janssen) have been granted emergency use authorization (EUA) by the United States (US) Food and Drug Administration (FDA). The FDA Center for Biologics Evaluation and Research (CBER), in partnership with the Centers for Medicare & Medicaid Services (CMS), conducted surveillance of these three vaccines using the Medicare database, which includes patients who were 65 years of age and older. The surveillance activity used the rapid cycle analysis (RCA) method also known as the near real-time surveillance. The RCA detected a statistical association between the Pfizer-BioNTech COVID-19 vaccine and four adverse events of special interest (AESI). As the next step, the CBER Biologics Effectiveness and Safety (BEST) program has developed this protocol to conduct an in-depth epidemiological study to evaluate the signals detected in the RCA study. This study will evaluate the potential association between the Pfizer-BioNTech COVID-19 vaccine and the four AESI that signaled in the RCA including acute myocardial infarction (AMI), pulmonary embolism (PE), disseminated intravascular coagulation (DIC), and immune thrombocytopenia (ITP). The study will also evaluate the Moderna and Janssen COVID-19 vaccines and the four AESI using the same methods. It should be noted that the RCA is a surveillance method and produces a crude measure of association between an exposure and an outcome. In the COVID-19 vaccines RCA, the crude relative risk reflected the comparison of the observed rate of AESI following COVID-19 vaccination with the historical incidence rates prior to the authorization of COVID-19 vaccines. Although the RCA adjusted for nursing home residency status, age, sex, and race, it did not adjust for other potential confounding by other factors. The current study aims to conduct a self-controlled design that will better adjust for confounding.

Objective

The primary objective of this study is to evaluate the risk of AMI, PE, DIC, and ITP following vaccination with Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccine using a self-controlled case series (SCCS) design.

Data Source

This study will use the CMS Medicare administrative claims data for elderly persons aged 65 years and older in the US.

Exposure and Outcomes

The exposure is defined as any dose of each of the three Pfizer-BioNTech, Moderna, and Johnson & Johnson/Janssen COVID-19 vaccines, as identified in the medical plan of interest by appropriate product codes. The outcomes include incident AMI, PE, DIC, and ITP identified by the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD10-CM) codes.

Methods

This study will use the SCCS design with post-vaccination control interval as the primary analysis. As the secondary analysis, the study will use control intervals defined within the observation period, including both pre- and post-vaccination time periods. As the exploratory analysis, the study will use the self-

controlled risk interval (SCRI) design with a pre-vaccination control interval only. A sample of charts for each AESI will be obtained and adjudicated for case confirmation. Quantitative bias analyses will be considered to evaluate the robustness of the risk estimates.

1 Background/ Introduction

COVID-19 is a contagious respiratory illness caused by the SARS-CoV-2 virus. Three COVID-19 vaccines (BNT162b2, Pfizer-BioNTech; mRNA-1273, Moderna; and Johnson & Johnson/Janssen, Ad26.COV2.S) are available in the US under an EUA granted by the FDA. CBER is monitoring the safety of these vaccines through both passive and active surveillance methods.¹ The passive surveillance relies on reporting of adverse events and deaths by manufacturers, health care providers, patients, and others using the Vaccine Adverse Events Reporting System (VAERS), and the active surveillance uses the BEST Initiative infrastructure along with collaboration with CMS. The active surveillance utilizes health care data from tens of millions of individuals along with different study designs and statistical methods.

The RCA study evaluated the risk of 14 AESI after exposure to one of the three COVID-19 vaccines. The evidence for the selection of these AESI originated from serious events that have followed other vaccinations, that are potentially related to novel platforms or adjuvants, that are related to COVID-19 severity and may potentially relate to vaccine failure/immunogenicity (enhanced disease), or events that are potentially specific to particular populations of interest. These AESI are not known to be associated with COVID-19 vaccines based on available pre-authorization or pre-licensure evidence.²

The RCA study was conducted in the Medicare Shared Systems database including patients aged 65 years and older at the time of COVID-19 vaccination. No statistical signals were identified for the Moderna or Janssen vaccines nor for 10 of 14 AESI after vaccination. The RCA detected statistical signals for four AESI, including pulmonary embolism (PE), acute myocardial infarction (AMI), disseminated intravascular coagulation (DIC), and immune thrombocytopenia (ITP), following receipt of any dose of the Pfizer-BioNTech vaccine (manuscript in preparation). As of June 25, 2021 (data through June 12, 2021), the observed number of deep vein thrombosis (DVT) and non-hemorrhagic stroke (NHS) events following Pfizer-BioNTech and Moderna vaccination exceeded the pre-specified number of expected events; The RCA completed for DVT and NHS with no evidence of a statistically significant increase in the risk. No other AESI have reached the pre-specified statistical threshold at this time, but the monitoring for the rest of the events continues.

Given the limitations of the RCA study design, this study plans to further evaluate the statistical association of the four aforementioned AESI with all three authorized vaccines.

2 Study Objectives

The primary objective of this study is to evaluate the risk of AMI, PE, DIC, and ITP following vaccination with Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccine using a self-controlled case series (SCCS) design.

2.1 Primary Analysis

Evaluate the risk of AMI, PE, DIC, and ITP after exposure to each COVID-19 vaccine using the self-controlled case series (SCCS) design. The primary analysis compares the risk of each event 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 study period.

2.2 Secondary Analysis

Evaluate the risk of AMI, PE, DIC, and ITP after exposure to each COVID-19 vaccine using the self-controlled case series (SCCS) design. The secondary analysis compares the risk of each event in a time interval after vaccination (risk window) to that in time intervals other than the risk window within the observation period, including both pre- and post-vaccination time (control window).

2.3 Exploratory Analysis

Evaluate the risk of AMI, PE, DIC, and ITP after exposure to each COVID-19 vaccine using the self-controlled risk interval (SCRI) design. The exploratory analysis compares the risk of each event in a time interval after vaccination (risk window) to that in a time interval pre-vaccination (control window).

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). Medicare provides health insurance coverage to approximately 61 million persons aged ≥ 65 years in the US as well as nearly 9 million persons aged < 65 years with end-stage kidney disease (ESRD) or with certain disabilities in 2018.³ Only persons who were 65 years of age or older at the time of COVID-19 vaccination are included in the analysis. 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 and community settings) and Part D (prescription) claims. 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. Personal identifying information (PII) and protected health information (PHI) is also available in Medicare data, enabling the possibility of conducting medical record reviews (MRR) to validate AESI using these data. However, FDA does not have access to PII or PHI, and it only receives aggregate results without any PII or PHI attached. Information on nursing home residency status is derived from clinical assessment of residents in the Minimum Data Set (MDS). In addition, health-seeking attitudes and frailty conditions from the Medicare Current Beneficiary Survey may be considered for confounding adjustment. 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

Identification of exposures and AESI will occur within specific care settings of interest. Table 1 summarizes how the inpatient (IP), outpatient emergency department (OP-ED), and outpatient and professional (OP/PB) settings used in this study are defined.

Table 1. Care setting definitions

Care Setting	Definition
Inpatient (IP)	Hospital inpatient acute facility claims (e.g., UB-04 with type of bill = 11x)
Outpatient Emergency Department (OP-ED)	Outpatient facility claims (e.g., UB-04) in ED
Outpatient & 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 is defined by hospital inpatient acute facility claims. Hospital inpatient facility claims encompass the entire episode of inpatient care, and generally have more accurate diagnosis coding compared to professional claims given that diagnosis coding is linked to payment for facility claims. Additionally, if medical record requests are initiated, facilities are more responsive to those requests.

The OP-ED setting is defined using outpatient facility claims with services provided in the Emergency Department (ED), as defined by place of service (POS) and revenue codes. The OP-ED setting is a subset of the OP/PB setting.

The OP/PB setting, which includes both ED and non-ED services, is defined by all outpatient facility claims and all professional claims with non-laboratory places of service. This setting captures the broad spectrum of outpatient care regardless of care setting and provider type. Claims with laboratory places of service will be excluded since they often include “rule-out diagnoses” that may not represent true current or underlying conditions.

4.2 Exposure (COVID-19 Vaccination)

Exposure is defined as the receipt of any dose of Pfizer-BioNTech, Moderna, and Johnson & Johnson/Janssen COVID-19 vaccine, as identified within the medical plan of interest 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 (Table 2). The list of valid codes will be reviewed periodically and updated if new codes are added. Patients with a claim containing a relevant code or codes 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 and dose occurring on the same day, the codes will be de-duplicated so that the individual contributes only one exposure for that brand’s dose to the study. If an individual has codes representing multiple doses (e.g., 1st dose and 2nd dose) of the same brand on the same day, only the code representing the earliest administration will be kept (e.g., first dose). If no administration code is observed for an individual, and thus dose order is unknown, then dose number assignment will be based on the presence of prior doses of the same brand. If multiple brands are observed on the same day, that person will be excluded from the study. Dose spacing patterns for two-dose COVID-19 vaccines will be investigated in the data and a standard minimum time gap between doses may be instituted. In this situation, if sequential doses for the same brand are observed in close proximity

(e.g., within a few days of each other), the study may exclude the subsequent dose. Additional vaccination pattern investigation will be conducted to determine how to group or de-duplicate observed vaccination doses for a single dose vaccine (e.g., Janssen COVID-19 Vaccine).

Table 2. Healthcare Common Procedure Coding System (HCPCS)/ Current Procedural Terminology (CPT) and National Drug Codes (NDC) for COVID-19 vaccines as of June 15, 2021

HCPCS/CPT Code	Manufacturer	Name	Vaccine Administration Code	NDC 10/NDC 11 Labeler Product ID (Vial)	Dosing Interval
91300	Pfizer	Pfizer-BioNTech COVID-19 Vaccine	0001A (1 st dose) 0002A (2 nd dose)	59267-1000-01 59267-1000-02 59267-1000-03	21 Days
91301	Moderna	Moderna COVID-19 Vaccine	0011A (1 st dose) 0012A (2 nd dose)	80777-0273-10 80777-0273-99 80777-0273-15 80777-0273-98	28 Days
91303	Janssen Biotech Inc.	Janssen COVID-19 Vaccine	0031A	59676-0580-05 59676-0580-15	N/A

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

Each of the AESI including AMI, PE, DIC, ITP will be assessed separately in the analysis by vaccine brand. The diagnosis of AESI will be identified with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes (Appendix Table 1). The settings in which each outcome will be evaluated, as well as the clean (washout) and risk windows for each AESI are described in Table 3. The first occurrence of the event is defined as an incident AESI only if no event was recorded during the preceding pre-defined interval or the clean window. The risk window is defined as an interval post-vaccination during which occurrence of the AESI may be associated with the vaccine exposure. Both clean and risk windows are selected based on the literature and consultation with subject matter experts.

Table 3. AESI, settings, clean windows, and risk windows

AESI	Care Setting	Clean Window	Risk Window
Acute Myocardial Infarction (AMI)	IP	365 days*	1-28 days ^{4,5}
Pulmonary Embolism [#] (PE)	IP, OP/PB	365 days*	1-28 days ⁶⁻⁸
Disseminated Intravascular Coagulation (DIC)	IP, OP-ED	365 days*	1-28 days ⁹
Immune Thrombocytopenia (ITP)	IP, OP/PB	365 days*	1-42 days ^{10,11}

* Selection of clean 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 Self-Controlled Methods

The SCCS design^{12,13} compares the incidence of adverse events within periods of hypothesized excess risk due to exposure (risk interval) with incidence during all other times (control interval). In SCCS, only cases

(i.e., individuals with an incident AESI) occurring during the study observation period are sampled, with estimation of risk occurring within individuals rather than between individuals. Created to assess the risk of acute events in clearly defined risk intervals, this design implicitly controls for measured and unmeasured time-invariant confounding as each case serves as his/her own control. To address the concern that the occurrence of the AESI may possibly affect the likelihood of subsequent vaccination, we will limit the control intervals for the primary analysis to post-vaccination only. To minimize exposure misclassification, we will restrict the study population to cases receiving COVID-19 vaccines.

The SCRI design is a special case of SCCS. In SCRI, a person's risk of experiencing the outcome immediately after exposure (risk interval) is compared to the same person's risk of experiencing the outcome in a discretely defined period (control interval), during which the occurrence of AESI is deemed to be unrelated to the exposure. Unlike the standard SCCS design, the SCRI method requires defining a specific time interval within the observation period as the control interval. Compared to SCCS, SCRI may be less affected by time-varying confounding due to the shorter control interval, while the shorter control interval may reduce statistical power.

The control intervals in both designs can be defined as pre- and post-vaccination, and both have strengths and limitations. A pre-vaccination control interval can facilitate timely analyses. However, the pre-vaccination control interval is subject to bias if the occurrence of the AESI affects the probability of subsequent vaccination, biasing the relative incidence in either direction. If the event only temporarily delays vaccination or increases the probability of vaccination, a pre-exposure period can be excluded to reduce the healthy vaccinee effect. Post-vaccination control intervals will avoid such a bias of reverse causation but require additional data accrual after the post-vaccination risk window, resulting in an analysis delay; the delay of the analysis is greater for AESI with longer risk intervals.

5.2 Overview of Study Design

This protocol will use the SCCS design with post-vaccination control intervals as the primary analysis. This design is not subject to the bias from depletion or enrichment of AESI cases in the pre-vaccination control interval. However, it relies on an accurate definition of the risk window, which remains unknown following COVID-19 vaccination for each AESI. Inaccurate attribution of cases to the risk or control intervals may bias the risk estimate in either direction based on the shape of the underlying risk function of the AESI following vaccination. For example, for events with a late onset, attributing cases to the control intervals that should have been attributed to the risk interval may underestimate the relative risk. Sensitivity analyses, such as temporal scan, are proposed in Sections 5.7.2.1 and 5.7.3.1 to assess the robustness of risk intervals. Also, using post-vaccination control intervals will require additional data accrual following the post-vaccination risk interval, and this will delay the analysis.

The secondary analysis will use the SCCS design with control intervals around vaccination, including pre- and post-vaccination time other than the pre-specified risk interval (Table 3), during the observation period. This design has greater statistical power, compared with the primary analysis, by including more AESI cases. However, it is subject to the reverse causation bias from depletion or enrichment of AESI cases in the pre-vaccination control interval because the occurrence of an AESI during the observation period may affect the likelihood of subsequent vaccination. For example, if an AESI reduces the probability of subsequent vaccination, the relative incidence associated with vaccination will be biased upwards. It is

also subject to the same bias as the primary analysis from inaccurate definition of the risk window in the post-vaccination period.

The exploratory analysis will use the SCRI design with only a pre-vaccination control interval. This design can provide more timely results, compared with the primary analysis. However, it is subject to the same reverse causation bias described above from depletion or enrichment of AESI cases in the pre-vaccination control interval. This analysis is performed for comparison purposes to understand the magnitude and direction of the potential bias this study design may create in the measure of association.

This study will be implemented for each pre-defined AESI by vaccine brand (i.e., Pfizer-BioNTech, Moderna, and Janssen). A sample of medical charts for each AESI will be obtained and adjudicated to confirm the diagnosis of the outcome of interest.

5.3 Study Period

The study period will start on the date of the emergency use authorization for the first COVID-19 vaccine in the U.S. (December 11, 2020 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 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 RR is 1, the 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.

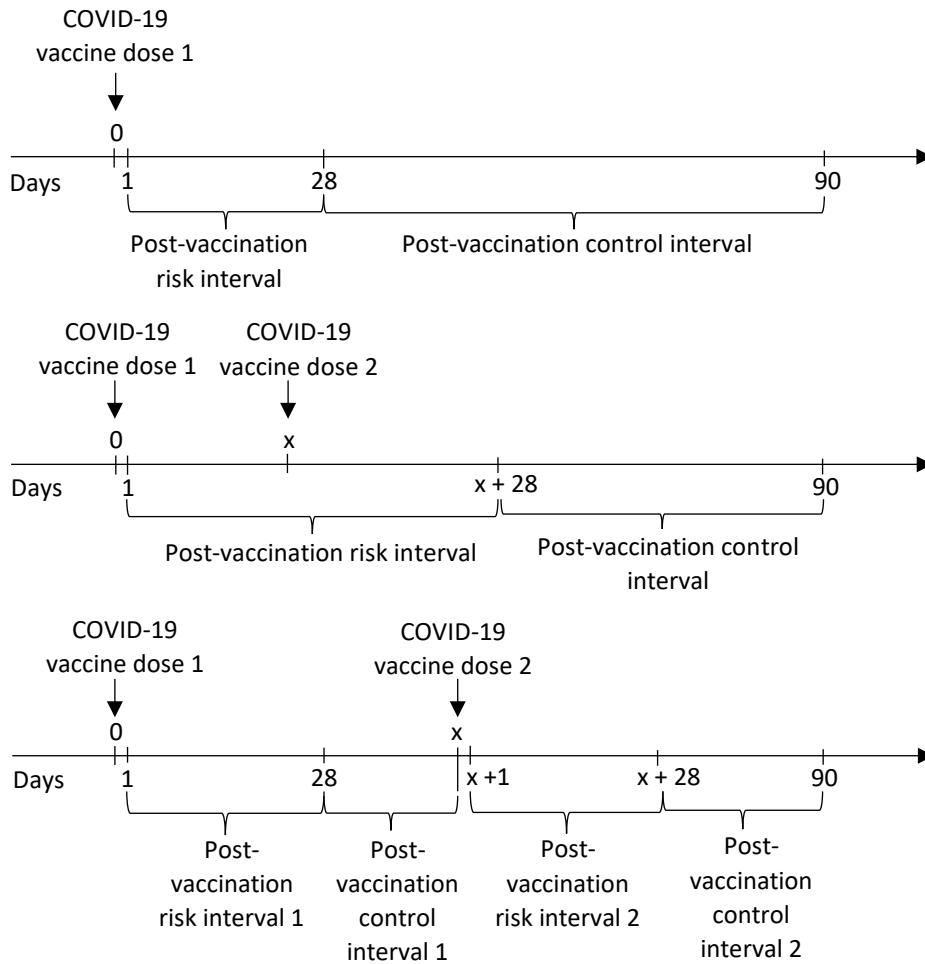
5.4 Definition of Risk and Control Intervals

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-first dose risk intervals will run until the end of the interval, or until the person receives his/her second dose (if within the risk interval). Post-second dose risk intervals will run until the end of the risk interval.

5.4.1 Primary Analysis: SCCS with Post-vaccination Control Intervals

The observation period will start from the vaccination date (day 0) of the first dose, if there are two doses, and extend to day 90. The post-vaccination control interval is defined as all follow-up time during the observation period following either the first or second COVID-19 vaccine dose (for two-dose COVID-19 vaccines) that is outside of the risk interval(s) until day 90 post-vaccination, end of study period, disenrollment, or death, whichever occurs first; while likely uncommon, this includes any time between the end of the first dose risk window and the receipt of a second dose. Figure 1 presents some hypothetical examples in design. Individuals who only accrued data during the risk intervals will be ineligible to be included in the analysis (Section 5.5.1).

Figure 1. Hypothetical examples of SCCS design with post-vaccination control intervals for one-dose and two-dose vaccines

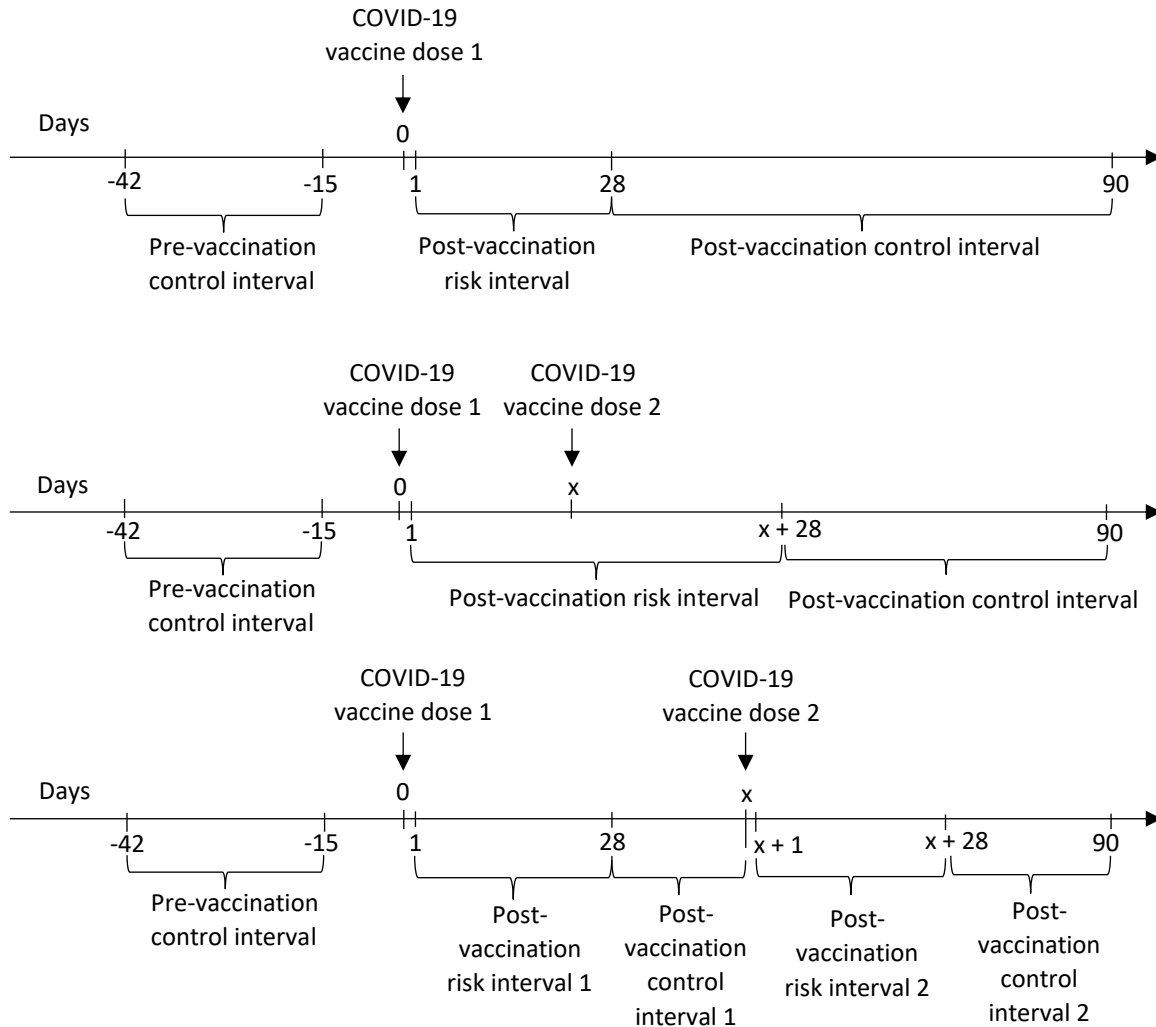


Note: The hypothetical risk interval following one dose is up to 28 days. However, the length of the risk and control intervals will vary for each AESI.

5.4.2 Secondary Analysis: SCCS with Pre- and Post-vaccination Control Intervals

The observation period will start on the first day of the pre-vaccination control interval and extend to day 90 after vaccination (day 0). The pre-vaccination control interval in the SCCS design will be defined as the interval with the same length as the risk interval (Table 3) ending 15 days prior to the date of the first (or, only) 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.¹⁴ Sensitivity analyses will be conducted by using longer pre-exposure intervals, e.g., 28 days, and plotting incidence rates of the AESI by day prior to vaccination (Section 5.7.3.1). The post-vaccination control intervals will be defined the same as in the primary analysis (Section 5.4.1). Control intervals will be analyzed regardless of whether they are pre- or post-vaccination. Figure 2 presents some hypothetical cases in this design.

Figure 2. Hypothetical examples of SCCS design with pre- and post-vaccination control intervals for one-dose and two-dose vaccines

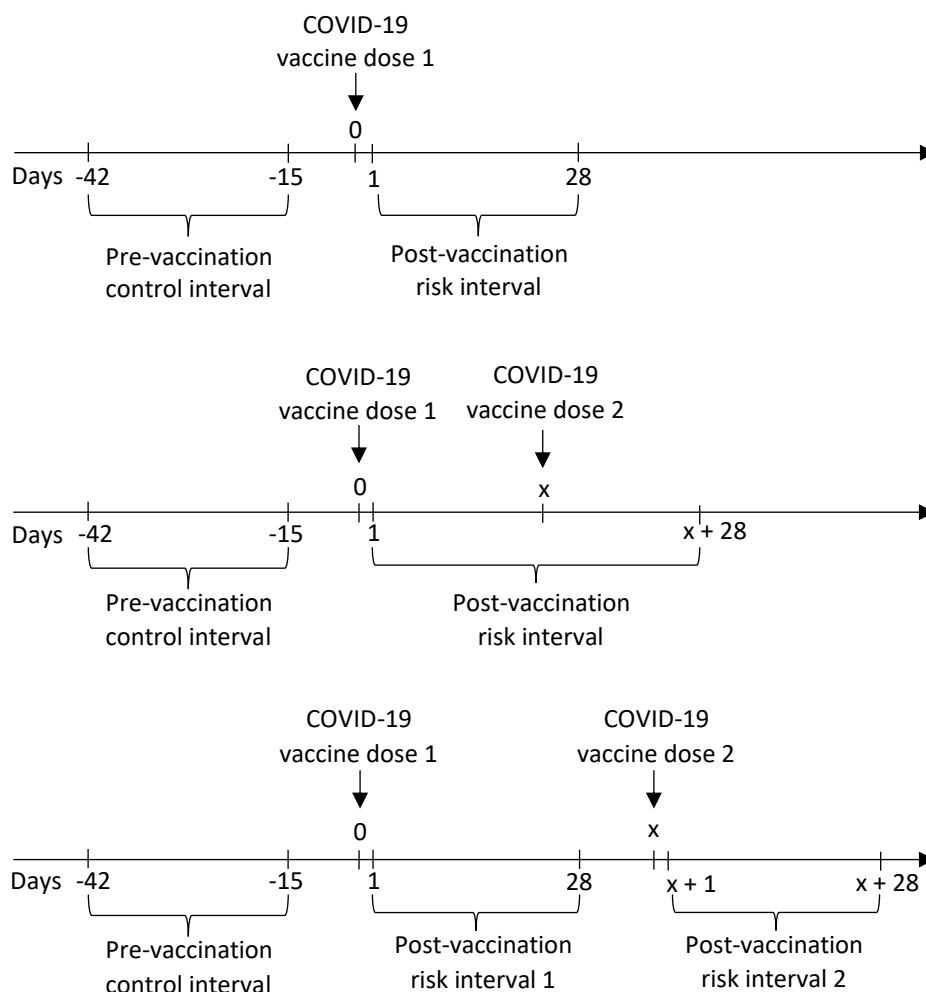


Note: The hypothetical risk interval following one dose is up to 28 days. However, the length of the risk and control intervals will vary for each AESI. The length of pre-vaccination control interval will vary based on the risk interval for each AESI and different analyses.

5.4.3 Exploratory Analysis: SCRI with a Pre-vaccination Control Interval

The observation period will start from the first day of the pre-vaccination control interval and extend through the end of the available risk interval, date of death, disenrollment, or the end of the study period, whichever comes first. The pre-vaccination control interval and pre-exposure interval will be defined the same as in the secondary analysis (Section 5.4.2). Figure 3 presents some hypothetical cases in this design.

Figure 3. Hypothetical examples of SCRI design with a pre-vaccination control interval for one-dose and two-dose vaccines



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. The length of pre-vaccination control interval will vary based on the risk interval for each AESI and different analyses.

5.5 Study Population

Eligible vaccinees are persons who received at least one dose of the COVID-19 vaccine and met the following inclusion/exclusion criteria regardless of the occurrence of the AESI. All eligible vaccinees will be used for the attributable risk (AR) calculation.

The case population will consist of COVID-19-vaccinated individuals with the AESI. Incident AESI will be defined as the first recorded event for an individual during the study observation period if there are no claims for the same AESI in the preceding pre-defined clean window. The clean window will be anchored on the date of the AESI and will begin a pre-defined number of days prior to the AESI as specified in Table 3. Sensitivity analyses will be conducted with different lengths of clean windows to assess the robustness of the incident AESI definition (Sections 5.7.2.1 and 5.7.3.1).

5.5.1 Primary Analysis: SCCS with Post-vaccination Control Intervals

Eligible vaccinees should meet the following inclusion/exclusion criteria.

Inclusion criteria:

- (i) Medicare beneficiaries enrolled in Part A (hospital insurance) and Part B (medical insurance) during the study observation period, as well as during the clean window prior to the occurrence of the AESI.
 - Continuous enrollment will be required from the start of an AESI's clean window relative to the occurrence of the AESI through day 90 post-vaccination, the end of the study period, disenrollment, or death, whichever comes first.
- (ii) Received at least one dose of a 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) For case population only, had a record of the AESI diagnosis during the study observation period.

Exclusion criteria:

- (i) Less than 65 years of age at the start of observation period.
- (ii) Does 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) Had COVID-19 vaccination patterns that do not conform to expectations for the analysis of interest, e.g., doses that occur within a short time period following another dose or have a higher than expected dose number; more specific rules will be determined once more data on vaccination patterns are available.
- (iv) Had a diagnosis of the AESI during the AESI-specific clean window (Table 3) or during alternate clean windows assessed in sensitivity analyses.
- (v) Received different COVID-19 vaccines for the first and second dose. Based on the preliminary assessment, such a scenario only occurred in approximately 0.12% of cases with an AESI.

5.5.2 Secondary Analysis: SCCS with both Pre- and Post-vaccination Control Intervals

Eligible vaccinees should meet the following inclusion/exclusion criteria.

Inclusion criteria:

The same as the primary analysis (Section 5.5.1).

Exclusion criteria:

The same as the primary analysis (Section 5.5.1) with one additional criterion below.

- (vi) Had a diagnosis of the AESI during 14 days prior to COVID-19 vaccination or different pre-exposure intervals in sensitivity analyses.

5.5.3 Exploratory Analysis: SCRI with a Pre-vaccination Control Interval

Eligible vaccinees should meet the following inclusion/exclusion criteria:

Inclusion criteria:

The same as the primary analysis (Section 5.5.1).

Exclusion criteria:

The same as the secondary analysis (Section 5.5.2) except that the following criterion is not required.

- (ii) Does 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.

5.6 Time-varying Confounding

Time-varying confounding may be of concern in the SCCS design with longer control intervals during the study observation period. Some AESI, including AMI, exhibit seasonal trends. 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.^{15,16} Adjustment for time-varying confounding will be considered based on their association with the individual AESI and addressed using statistical models if strong time-varying confounding exists. The SCRI design is less susceptible to time-varying confounding given the discrete and relatively short risk and control intervals.

5.7 Statistical Analysis

5.7.1 Descriptive Statistics

Descriptive statistics will present counts and percentages of AESI overall and by risk/control interval for the following covariates, where available in the database:

- Demographics: age, sex, race/ethnicity, region, urban/rural, dual eligibility status, area deprivation index (ADI), nursing home residency status
- Cases that died in the observation period
- Cases that received an influenza vaccine at the same time as the COVID-19 vaccine
- Cases that received other vaccines (e.g., influenza and pneumococcal) in the risk or control intervals for each dose
- Cases with a history of a medically attended COVID-19 infection, defined by the ICD-10-CM codes U07.1 (COVID-19)
- Cases affected by the inclusion and exclusion criteria used to construct the study population
- Plot occurrence of AESIs by day and by vaccine brand during the observation period, e.g., stacked strip plots
- Risk factors for the AESI. Based on signal evaluation investigations in RCA, the following risk factors are considered, but not limited to:
 - Hospitalization (prior 6 months)
 - Prior hospitalization for other AESI (e.g. in AMI analysis, hospitalization for stroke)
 - Neurological/Neurodevelopmental Conditions

- Hypertension
- Diabetes
- COPD/Asthma
- Atrial Fibrillation
- Charlson Comorbidity Index

5.7.2 Primary Analysis: SCCS with Post-vaccination Control Intervals

For the primary self-controlled analysis, the risk of the AESI following any dose will be evaluated, without distinguishing between dose numbers. This analysis will compare the AESI rates in the risk and control intervals using a conditional Poisson regression model. For two-dose COVID-19 vaccines, the model assumes constant risk throughout each risk window, regardless of how close together the two doses may be administered (i.e., no additive risk from overlapping risk windows). Sensitivity analysis (Section 5.7.2.1) is planned to evaluate the robustness of this assumption. Under the assumption of constant risk, the following model will be fit:

$$\log(E(Y|X)) = \beta_1(\text{risk_interval}) + \log(t) + \text{strata}(\text{patient_id})$$

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:

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

where e^{β_1} will be interpreted as the rate ratio 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% confidence intervals of rate ratios and two-sided p-values ($p \leq 0.05$).

The study will 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 vaccination (i.e., all observed time is treated as control time). The unadjusted AR is the excess number of AESI cases divided by the number of eligible vaccinations (or eligible follow up dose-years). The standard error (SE) of the unadjusted AR is estimated by bootstrap resampling 10,000 times.¹⁷ 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. The AR following COVID-19 vaccination may be compared to the AR following other vaccinations and other AESI-triggering exposures. While the unadjusted ARs are directly obtained from the primary claims-based analysis and secondary chart-confirmed analysis, they might not be truly representative of the underlying AESI risk. Thus, a positive predictive value (PPV)-adjusted AR may be calculated following the completion of the medical record review (see Section 6 for the medical record review process).

When sample size permits, subgroup analyses by age group, sex, race/ethnicity, and nursing home residency status will be performed.

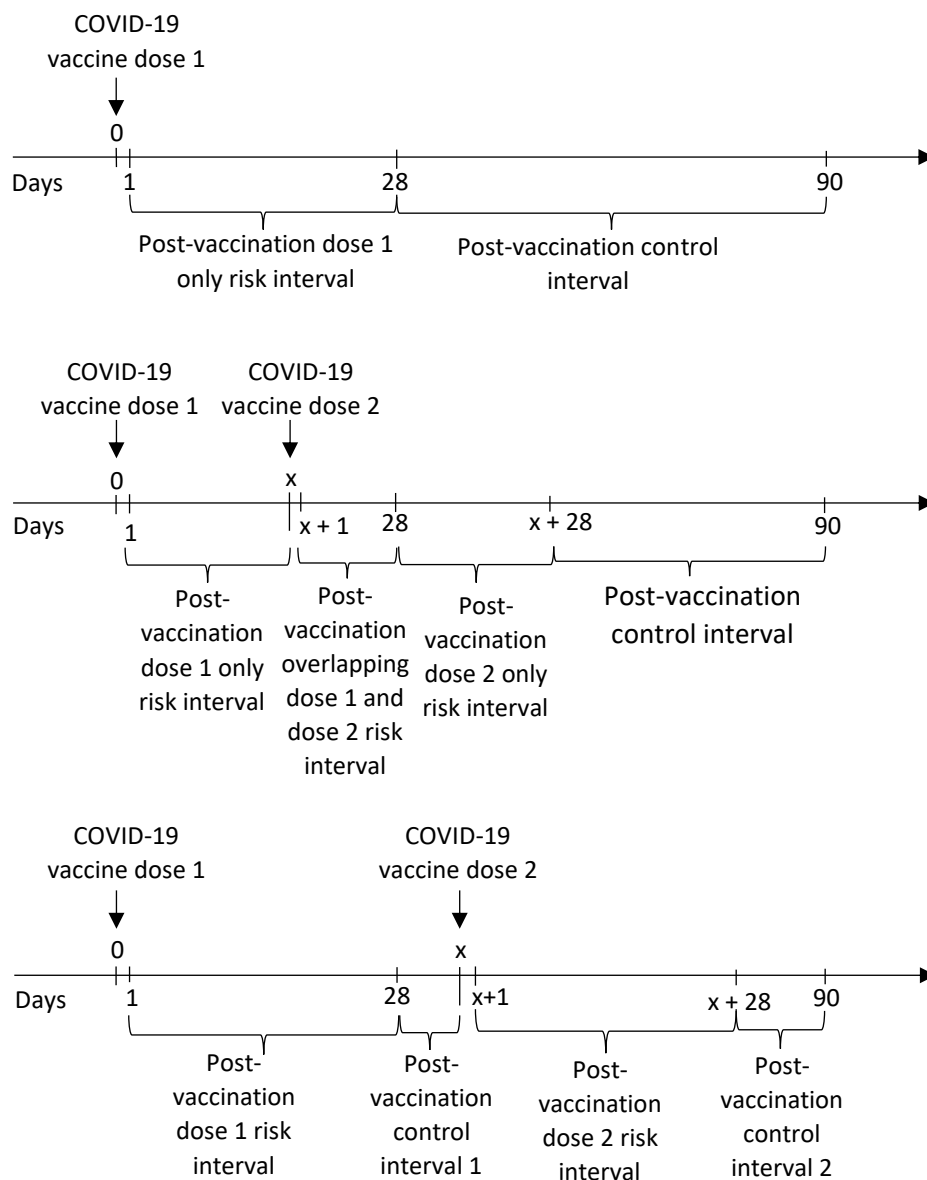
5.7.2.1 *Sensitivity Analyses for the Primary Analysis*

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. For example, historical incidence rates of AMI have exhibited seasonality. The following methods will be explored to estimate the baseline risk curve as an offset term to be included in the conditional Poisson regression model.

- From a similar population during the same calendar months in previous years. However, health care utilization was reported to be affected in the early pandemic¹⁸, and historical monthly rates may not be comparable.
- From post-vaccination control intervals if sample size permits.

To evaluate the assumption of constant risk throughout each risk interval for two-dose COVID-19 vaccines, potential differences in risk will be stratified by vaccine dose if sample size permits. Analyses will be restricted to vaccinations where the administration codes are concordant with the order of vaccination procedure codes. The overall risk interval will be categorized as 1) dose 1 only; 2) overlapping dose 1 and dose 2, where risk intervals of each dose overlap; and 3) dose 2 only. Risk of the AESI occurring in these three categories of the risk intervals will be compared separately with the post-vaccination control intervals. Figure 4 presents some hypothetical examples in SCCS design with varying risk during the risk intervals and post-vaccination control intervals.

Figure 4. Hypothetical examples of SCCS design with varying risk during the risk interval and post-vaccination control intervals for two-dose vaccines



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.

To assess the robustness of the case definition:

- Different clean window lengths will be explored.
 - Instead of using a fixed clean window length to define “incident AESI”, the study may consider clean windows that are longer than the length of the pre-defined clean windows (Table 3), constructed retrospectively from the anchoring date using all available data, for AMI, PE, DIC,

and ITP; however, extending the continuous enrollment to cover the full period of all available data is not required.

- In addition, a clean window shorter than the pre-defined clean window may be examined for AMI and PE as shown in Table 4 below.

Table 4. Alternative clean windows

AESI	Care Setting	Clean Window
Acute Myocardial Infarction (AMI)	IP	28 days ¹⁹
Pulmonary Embolism (PE)	IP, OP/ PB	183 days ²⁰

- To exclude chronic ITP among cases, all thrombocytopenia events in the pre-specified clean window (Table 3) will be excluded. Chronic ITP may be more common in the older adult population.²¹
- Alternative event definitions in Table 5 will be considered. Restriction to the inpatient setting is likely to increase the likelihood to capture acute events or relapse/exacerbation of the chronic events.

Table 5. Alternative AESI definitions

AESI	Care Setting
Acute Myocardial Infarction (AMI)	IP, primary diagnosis position
Type I AMI	IP
Type I AMI	IP, primary diagnosis position
Pulmonary Embolism (PE)	IP
Pulmonary Embolism (PE)	IP, primary diagnosis position
Disseminated Intravascular Coagulation (DIC)	IP
Disseminated Intravascular Coagulation (DIC)	IP, primary diagnosis position
Immune Thrombocytopenia (ITP)	IP
Immune Thrombocytopenia (ITP)	IP, primary diagnosis position

To assess the robustness of risk and control intervals, different lengths of the risk interval and the control interval will be explored with clinical input and consideration of empirical data from temporal clustering by plotting the distribution of incident AESI since vaccination and temporal scans to detect statistical clustering of events post vaccination. Given the potential carry-over effect, we will exclude a range of periods (e.g., 7, 14, and 21 days) after the end of the risk interval from contributing to the control intervals.

To assess the robustness of the analysis to potential violation of the assumption that exposures are independent of outcomes (e.g. AESI post first-dose may delay or preclude administration of the second-dose), a modified SCCS analysis will be conducted which adjusts for censored, perturbed or curtailed post-event exposures.²²

To assess the robustness of the analysis to the potential violation of the assumption that observation time is independent of outcomes (e.g. death post-AESI censors follow up time), a modified SCCS analysis will be conducted which removes the independence assumption.²³

To assess the robustness of the analysis to the potential under-capture of second doses administered by providers who do not submit insurance claims, a sensitivity analysis will be conducted removing projected second-dose exposed time potentially misclassified as control time among patients with only one observed dose. The empirical distribution of exposed time post-second dose will be assessed among patients with two doses, and the corresponding time will be excluded from the control time of patients with only one observed dose.

5.7.3 Secondary Analysis: SCCS with Pre- and Post-vaccination Control Intervals

A similar conditional Poisson regression as the primary analysis (Section 5.7.2) will be conducted, except that control interval will include both pre- and post-vaccination time during the observation period.

When sample size permits, subgroup analyses by age group, sex, race/ethnicity, and nursing home residency status will be performed.

5.7.3.1 Sensitivity Analyses for the Secondary Analysis

To assess the healthy vaccinee effect, the incidence of the AESI prior to vaccination by day will be plotted to look for a potential drop in proximity to COVID-19 vaccination. If a reduction in the incidence of the AESI in the pre-vaccination period is detected, a different length of the pre-exposure window (e.g., 28 days) will be excluded based on empirical data.

To assess the robustness of risk and control intervals, the study will explore different lengths of the risk and control intervals with clinical input and consideration of empirical data from temporal clustering. For example, two times the length of the risk interval (Table 3) for the control interval is considered for greater statistical power although the likelihood of potential time-varying confounding is higher, given the longer observation period. To address the potential carry-over effect following the risk interval, a range of periods (e.g., 7, 14, and 21 days) after the end of the risk interval will be excluded from contributing to the control intervals.

5.7.4 Exploratory Analysis: SCRI with a Pre-vaccination Control Interval

The study will compare the rate of AESI in the risk intervals after the first dose and all doses combined with those in the pre-vaccination control interval in a conditional Poisson regression that estimates incidence rate ratio (IRR).

When sample size permits, subgroup analyses by age group, sex, race/ethnicity, and nursing home residency status will be performed.

5.7.4.1 Sensitivity Analyses for the Exploratory Analysis

To assess bias by factors that may affect the likelihood of subsequent vaccination, when the period prior to the vaccination is considered as the comparison or control interval, the following sensitivity analyses will be conducted to evaluate validity and robustness of the risk estimates:

- *Cases with comorbidities that are risk factors for the AESI and increase the likelihood of COVID-19 vaccination.* Using a pre-vaccination control interval is likely to overestimate the incidence risk ratio (IRR) because as more patients with the risk factors are vaccinated, more patients are likely to develop the AESI in the post-vaccination period (risk interval). Stratified analysis by major risk factors will be considered to assess the impact of such a bias.
- *Cases with comorbidities that are risk factors for the AESI and reduce the likelihood of COVID-19 vaccination (healthy vaccinee effect).* When there are pre-existing comorbidities which preclude

vaccination, using a pre-vaccination control interval is likely to underestimate the IRRs as there will be a deficit of patients who are at high risk of AESI in the risk interval. To address this issue, the incidence of the AESI prior to vaccination by day will be plotted to look for a potential drop in proximity to COVID-19 vaccination. A different length of the pre-exposure window will be excluded based on empirical data. Stratified analysis by major risk factors will be considered to assess the impact of such bias.

- *Cases have an increased probability of death pre-vaccination.* If the occurrence of AESI (e.g., PE, AMI, DIC, or ITP), existing comorbidities, or living in a nursing home increases the risk of mortality²⁴ in the pre-vaccination control interval, vaccinations that might have otherwise occurred after the event will never occur nor be known. These “cases” will not be included in the study due to lack of observation of the risk interval, and this scenario leads to an artificial deficit of the cases during the control interval, leading to an overestimated risk. The study will conduct SCCS with post-vaccination control intervals and the additional sensitivity analysis addressing curtailed observation time.

To assess the robustness of risk and control intervals, the study will explore different lengths of the risk and control intervals with clinical input and consideration of empirical data from temporal clustering. For example, two times the length of the risk interval (Table 3) for the control interval is considered for greater statistical power, although the likelihood of potential time-varying confounding is higher, given the longer observation period.

5.8 Statistical Power and Sample Size

Assuming the risk interval ranges from 28 to 56 days within the observation period of 90 days, Table 6 presents the minimum number of observed AESI required for an SCCS study design to detect the risk ratios (RR) detected in CMS Medicare RCA study at 80% power with two-sided alpha=0.05.^{25,26} The AESI-specific RRs following any-dose of Pfizer-BioNTech vaccination was used for power calculation in this study because they reached the statistical threshold in the CMS Medicare RCA study. We assume similar RR for Moderna and Janssen vaccines in this calculation. Given that delays in processing time of claims vary by AESI and that the primary SCCS analysis requires complete data (≥90%) for both post-vaccination risk intervals and post-vaccination control intervals, we plan to start the inferential study for each AESI when the minimum number of AESI is observed. Based on each AESI’s delay distribution of claims, the study anticipates implementing this protocol at the earliest in June 2021 for AMI, PE and ITP and in mid-July 2021 for DIC, when the primary analysis is estimated to be statistically powered for Pfizer-BioNTech and Moderna. For the Janssen vaccine, the analysis will start when a sufficient number of cases following vaccination is accrued.

Table 6. Sample size required to detect the risk ratios (RR) detected in CMS Medicare RCA at 80% power with two-sided alpha=0.05 for an SCCS study

AESI	Length of Risk Intervals (days)	RR*	Estimated Sample Size
Acute Myocardial Infarction (AMI)	28	1.42	281
Acute Myocardial Infarction (AMI)	56	1.42	286
Pulmonary Embolism (PE)	28	1.54	183
Pulmonary Embolism (PE)	56	1.54	191
Disseminated Intravascular Coagulation (DIC)	28	1.91	79

Disseminated Intravascular Coagulation (DIC)	56	1.91	89
Immune thrombocytopenia (ITP)	28	1.44	259
Immune thrombocytopenia (ITP)	56	1.44	265

* Unadjusted association detected in the CMS Medicare RCA study for any dose of Pfizer-BioNTech vaccine.

6 Medical Record Review

During the course of the study, a convenient sample of medical records for each AESI will be retrieved and undergo an adjudication process to assign potential cases identified in claims data as true cases and non-cases, and potentially indeterminate; a clinical case definition based on clinical input from subject matter experts will be used for each AESI. Brighton Case definitions are not available for these events at the time of this protocol development. The study will identify appropriate clinical reviewers to review the redacted medical records and abstracted data to recommend expert case designations.

A sample size of up to 100 adjudicated cases for each safety outcome will result in reasonable precision (10%) to estimate a positive predictive value (PPV) of 0.8. The PPV is defined as the likelihood that a person with the diagnosis code recorded in administrative claims data within a prespecified period actually has the disease (Table 7).

Table 7. Precision of PPVs based on the total sample size and the point estimate

Total Sample Size	PPV Confidence Intervals (CI)					
	True PPV = 0.4	True PPV = 0.5	True PPV = 0.6	True PPV = 0.7	True PPV = 0.8	True PPV = 0.9
50	(0.28, 0.54)	(0.37, 0.63)	(0.46, 0.72)	(0.56, 0.81)	(0.67, 0.89)	(0.79, 0.96)
100	(0.31, 0.50)	(0.40, 0.60)	(0.50, 0.69)	(0.60, 0.78)	(0.71, 0.87)	(0.83, 0.94)
150	(0.33, 0.48)	(0.42, 0.58)	(0.52, 0.67)	(0.62, 0.77)	(0.73, 0.86)	(0.84, 0.94)
200	(0.33, 0.47)	(0.43, 0.57)	(0.53, 0.67)	(0.63, 0.76)	(0.74, 0.85)	(0.85, 0.93)

The study will consider a Quantitative Bias Analysis based on an array of hypothetical parameters informed by PPVs estimated from the outcome validation.²⁷ This analysis will assess the direction, magnitude, and uncertainty associated with systematic errors influencing measures of associations. Details of the analysis will be developed later.

7 Ethical Evaluation

This surveillance activity is conducted as part of the FDA public health surveillance mandate.

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 OBE 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 event 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 an AESI.

Data quality is continuously monitored with every update from the study database to ensure insurance claims representing vaccinations and AESI 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 AESI, 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, and R will be used for statistical analyses.

9 References

1. U.S. Food and Drug Administration. COVID-19 Vaccine Safety Surveillance. <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance>, last accessed on 5/7/2021. Published 2021. Accessed.
2. COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol. <https://www.bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-Protocol-2021.pdf>, last accessed on 5/7/2021 Published 2021. Accessed.
3. The 2019 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ReportsTrustFunds/Downloads/TR2019.pdf>, last accessed on 5/7/2021. Published 2019. Accessed.
4. Al Qudah Z, Abukwaik W, Souayah N. Stroke after Vaccination in United States. A Report from the CDC/FDA Vaccine Adverse Event Reporting System. [1990–2010] (P01.009). *Neurology*. 2012;78(1 Supplement):P01.009-P001.009.
5. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. *N Engl J Med*. 2004;351(25):2611-2618.
6. Kearon C. Natural History of Venous Thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I22-30.
7. Kearon C, Akl EA. Duration of Anticoagulant Therapy for Deep Vein Thrombosis and Pulmonary Embolism. *Blood*. 2014;123(12):1794-1801.
8. Vickers ER, McClure DL, Naleway AL, et al. Risk of Venous Thromboembolism Following Influenza Vaccination in Adults Aged 50 Years and Older in the Vaccine Safety Datalink. *Vaccine*. 2017;35(43):5872-5877.
9. Tang N, Li D, Wang X, Sun Z. Abnormal Coagulation Parameters are Associated with Poor Prognosis in Patients with Novel Coronavirus Pneumonia. *J Thromb Haemost*. 2020;18(4):844-847.
10. Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopenic purpura. *Br J Clin Pharmacol*. 2003;55(1):107-111.
11. D'Alò G L, Zorzoli E, Capanna A, et al. Frequently asked questions on seven rare adverse events following immunization. *J Prev Med Hyg*. 2017;58(1):E13-e26.
12. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ*. 2016;354:i4515.
13. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med*. 2006;25(10):1768-1797.
14. Virtanen M, Peltola H, Paunio M, Heinonen OP. Day-to-day Reactogenicity and the Healthy Vaccinee Effect of Measles-Mumps-Rubella Vaccination. *Pediatrics*. 2000;106(5):E62.
15. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. *JAMA Cardiol*. 2020;5(7):751-753.
16. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and Cardiovascular Disease: From Basic Mechanisms to Clinical Perspectives. *Nature Reviews Cardiology*. 2020;17(9):543-558.
17. Cox C, Li X. Model-based Estimation of the Attributable Risk: A Loglinear Approach. *Computational Statistics & Data Analysis*. 2012;56(12):4180-4189.
18. Cantor JH, Sood N, Bravata D, Pera M, Whaley CM. The Impact of the COVID-19 Pandemic and Policy Response on Health Care Utilization: Evidence from County-level Medical Claims and Cellphone data. <https://www.nber.org/papers/w28131>, last accessed on 6/22/2021. Published 2020. Accessed.
19. Mendis S, Thygesen K, Kuulasmaa K, et al. World Health Organization Definition of Myocardial Infarction: 2008-09 Revision. *Int J Epidemiol*. 2011;40(1):139-146.

20. Albertsen IE, Nielsen PB, Søgaard M, et al. Risk of Recurrent Venous Thromboembolism: A Danish Nationwide Cohort Study. *Am J Med.* 2018;131(9):1067-1074.e1064.
21. Fogarty PF, Segal JB. The epidemiology of immune thrombocytopenic purpura. *Current Opinion in Hematology.* 2007;14(5):515-519.
22. Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. *Biostatistics.* 2009;10(1):3-16.
23. Farrington CP, Anaya-Izquierdo K, Whitaker HJ, Hocine MN, Douglas I, Smeeth L. Self-Controlled Case Series Analysis With Event-Dependent Observation Periods. *Journal of the American Statistical Association.* 2011;106(494):417-426.
24. Mehta HB, Li S, Goodwin JS. Risk Factors Associated with SARS-CoV-2 Infections, Hospitalization, and Mortality Among US Nursing Home Residents. *JAMA Network Open.* 2021;4(3):e216315-e216315.
25. Musonda P, Paddy Farrington C, Whitaker HJ. Sample Sizes for Self-Controlled Case Series Studies. *Statistics in Medicine.* 2006;25(15):2618-2631.
26. Paddy Farrington, Heather Whitaker, Weldeselassie YG. *Self-Controlled Case Series Studies: A Modelling Guide with R.* Chapman and Hall/CRC; 2021.
27. Lash TL, Fox MP, Cooney D, Lu Y, Forshee RA. Quantitative Bias Analysis in Regulatory Settings. *Am J Public Health.* 2016;106(7):1227-1230.

10 Appendices

Appendix Table 1. ICD-10-CM for four AESIs

Outcome	Code	Description	Code Category	Code Type
Acute Myocardial Infarction	I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.29	ST elevation (STEMI) myocardial infarction involving other sites	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.3	ST elevation (STEMI) myocardial infarction of unspecified site	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.4	Non-ST elevation (NSTEMI) myocardial infarction	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.9	Acute myocardial infarction, unspecified	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.A1	Myocardial infarction type 2	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I21.A9	Other myocardial infarction type	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall	Diagnosis	ICD-10-CM

Outcome	Code	Description	Code Category	Code Type
Acute Myocardial Infarction	I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I22.2	Subsequent non-ST elevation (NSTEMI) myocardial infarction	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites	Diagnosis	ICD-10-CM
Acute Myocardial Infarction	I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site	Diagnosis	ICD-10-CM
Pulmonary Embolism (PE)	I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale	Diagnosis	ICD-10-CM
Pulmonary Embolism (PE)	I26.09	Other pulmonary embolism with acute cor pulmonale	Diagnosis	ICD-10-CM
Pulmonary Embolism (PE)	I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale	Diagnosis	ICD-10-CM
Pulmonary Embolism (PE)	I26.93	Single subsegmental pulmonary embolism without acute cor pulmonale	Diagnosis	ICD-10-CM
Pulmonary Embolism (PE)	I26.94	Multiple subsegmental pulmonary emboli without acute cor pulmonale	Diagnosis	ICD-10-CM
Pulmonary Embolism (PE)	I26.99	Other pulmonary embolism without acute cor pulmonale	Diagnosis	ICD-10-CM
Disseminated Intravascular Coagulation (DIC)	D65	Disseminated intravascular coagulation [defibrination syndrome]	Diagnosis	ICD-10-CM
Immune Thrombocytopenia (ITP)	D69.3	Immune thrombocytopenic purpura	Diagnosis	ICD-10-CM