**U.S. FOOD & DRUG ADMINISTRATION**

# Center for Biologics Evaluation and Research
# Office of Biostatistics and Epidemiology

# CBER Surveillance Program

## Master Protocol

## Assessment of Risk of Safety Outcomes Following COVID-19 Vaccination

May 28, 2021

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## ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AESI | Adverse event(s) of special interest |
| ATT | Average effect of the treatment on the treated |
| BEST | Biologics Effectiveness and Safety |
| CDC | Centers for Disease Control and Prevention |
| CMS | Centers for Medicare and Medicaid Services |
| CPT | Current Procedural Terminology |
| DIC | Disseminated Intravascular Coagulation |
| DVT | Deep Vein Thrombosis |
| FDA | US Food and Drug Administration |
| GBS | Guillain-Barré Syndrome |
| HCPCS | Healthcare Common Procedure Coding System |
| ICD-10-CM | International Classification of Diseases, Tenth Revision, Clinical Modification |
| IP | Inpatient |
| IPTW | Inverse probability treatment weighting |
| ITP | Immune Thrombocytopenia |
| MIS-C | Multisystem Inflammatory Syndrome in Children |
| MRR | Medical Record Review |
| NDC | National Drug Code |
| OP/PB | Outpatient and Professional |
| OP-ED | Outpatient Emergency Department |
| PE | Pulmonary Embolism |
| POS | Place of Service |
| PPV | Positive Predictive Value |
| PS | Propensity Score |
| SCCS | Self-controlled case series |
| SCRI | Self-controlled risk interval |
| SMD | Standardized mean differences |
| VAERS | Vaccine Adverse Event Reporting System |
| VSD | Vaccine Safety Datalink |

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# EXECUTIVE SUMMARY

**Background**

The US Food and Drug Administration (FDA) aims to assess the safety of COVID-19 vaccines authorized or approved for use in the United States. There are multiple COVID-19 vaccines that are either in prelicensure clinical trials or that have been authorized by emergency use authorization. The FDA, in collaboration with other federal partners, has instituted monitoring and surveillance programs to assess the real-world safety of COVID-19 vaccines. These include passive monitoring frameworks such as the Vaccine Adverse Event Reporting System (VAERS) as well as active surveillance through the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink (VSD) and FDA's vaccine surveillance efforts through the Biologics Effectiveness and Safety (BEST) Initiative. Potential safety signals identified during surveillance will be evaluated using inferential studies to estimate the risk of adverse events of special interest (AESI) following vaccination.

**Objective**

The objective of this study is to assess the risk of AESI within specified time periods after vaccination with COVID-19 vaccines**.** This master protocol outlines an overarching approach for potential inferential studies should safety signals be identified or studies be deemed necessary by FDA. The study team will develop protocols specific to each inferential analysis using this master protocol as a guide.

**Data Sources**

This study will use administrative claims data. This includes, but is not limited to, those within the BEST Initiative and CMS Medicare.

**Exposure and Outcomes**

Exposure is defined as receipt of any COVID-19 vaccination dose, as identified within the medical plan of interest by appropriate product codes. Pre-specified potential AESI will be considered as the study outcomes.

**Methods**

Either a self-controlled case series (SCCS), self-controlled risk interval (SCRI), or cohort study design will be considered for the inferential analyses. The primary study design will be selected separately for each AESI based on the appropriateness of design assumptions and method of outcome evaluation. The SCCS will compare the incidence of the AESI within pre-specified periods of hypothesized excess risk following COVID-19 vaccination with incidence during all other times after COVID-19 vaccination within the same individual. The cohort study design will compare incidence of AESI between a COVID-19-vaccinated cohort with either an unvaccinated or an alternative COVID-19-vaccinated cohort. The SCRI design is a special case of SCCS that defines a fixed control window relative to vaccination date, and will be considered for certain AESI with short, well-defined risk windows if advantageous.

If the inferential study involves collaboration across several data partners, steps will be taken to ensure consistent understanding and implementation of the protocol across data sources.

# 1. BACKGROUND

Coronavirus disease 2019 (COVID-19) is a contagious respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While a number of COVID-19 symptoms are similar to those of influenza, COVID-19 spreads more aggressively and presents more severely in some patients.[1] The first COVID-19 case was reported in China in December 2019,[2] and the first non-travel-related United States case was confirmed in February 2020, in a California resident.[3] As of March 23, 2021, a total of 123 million cases and 2.7 million deaths had been reported worldwide.[4] The highest number of cases and deaths has been reported from the United States (>29.8 million cases and >543,000 deaths).[5]

Multiple COVID-19 vaccines are under study in pre-licensure clinical trials; some have been authorized under emergency use authorization. As with all licensed or authorized vaccines, there can be limitations in the safety data accrued from the pre-licensure or pre-authorization COVID-19 vaccine clinical studies. Clinical trials may not adequately represent special populations, such as pregnant women, and may not be large enough to capture all potential safety outcome risks, particularly for rare outcomes such as Guillain-Barré syndrome (GBS).[6] Post-authorization safety monitoring during the COVID-19 pandemic vaccination program aims to continuously monitor the safety of COVID-19 vaccines to rapidly detect potential safety concerns. Inferential studies evaluate signals from monitoring programs such as the FDA and CDC's Vaccine Adverse Event Reporting System (VAERS), and the FDA active surveillance systems including the BEST Initiative. Inferential studies provide the analytical framework to assess the risk of adverse events of special interest (AESI) following immunization. An AESI is an untoward medical occurrence of scientific or medical concern which follows immunization, but does not necessarily have a causal relationship with the usage of the vaccine.[7]

This master protocol outlines the proposed methodologies for assessing the safety of COVID-19 vaccines post-licensure or post-authorization. Section 2 of the protocol describes the main objectives for the analyses, and Section 3 summarizes the data sources that will be included. Section 4 lists exposures and outcomes of interest and describes how they will be identified. Section 5 summarizes details of the proposed self-controlled and cohort study designs, and describes the advantages and disadvantages of each. The final section, Section 6, provides an overview of the medical record review process to be used to validate observed AESI cases.

**ETHICAL CONSIDERATIONS**

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

# 2. OBJECTIVES

The primary objective of this study is to assess the risk for AESI within pre-specified time windows after vaccination with each authorized or approved COVID-19 vaccine.

This objective will be achieved primarily through the implementation of inferential studies of self-controlled case series (SCCS) or cohort design. Inferential safety studies are planned to refine and evaluate safety signals or concerns based on sources of information such as passive reports, rapid cycle or sequential analysis, and published reports. The choice of the study design will be determined based on the outcome of interest. Self-controlled risk interval (SCRI) analyses may be selected under specific conditions. This master protocol outlines an overarching approach for inferential studies using these study designs. The study team will develop protocols specific to each inferential analysis using this master protocol as a guide.

## 3. DATA SOURCES

This master protocol is for administrative claims data with access to medical records for outcome adjudication. This includes, but is not limited to, those within the BEST Initiative and CMS Medicare.

## 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 or professional (OP/PB) settings used in this study are defined.

**Table 1. Care setting definitions to be used across data partners**

| Care Setting | Definition |
|---|---|
| **Inpatient (IP)** | 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 or Professional (OP/PB)[1]** | Outpatient facility claims (UB-04)<br>-OR-<br>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 inpatient acute facility claims. 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 receipt of any COVID-19 vaccination dose, 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. 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.

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. We will investigate dose spacing patterns for two-dose COVID-19 vaccines in the data, and may institute a standard minimum time gap between doses. In this situation, if sequential doses for the same brand are observed in close proximity (e.g., within a few days of each other), then we may exclude the subsequent dose. We will conduct additional vaccination pattern investigations to determine how to group or deduplicate observed vaccination doses for a single dose vaccine (e.g., Johnson & Johnson's Janssen COVID-19 Vaccine).

## 4.3   SAFETY OUTCOMES (AESI)

To exclude prevalent cases of the safety outcome of interest, the subjects in the study population must not have had the safety outcome in the prespecified time period prior to COVID-19 vaccination (i.e., "clean window"). Incident outcomes will be defined as AESI occurring during outcome-specific, post-vaccination risk windows, with a clean window being applied pre-vaccination. Considerations in the selection of these potential AESI include serious events that have followed other immunizations, events that are potentially related to novel platforms or adjuvants, events that are related to COVID-19 severity that may potentially relate to vaccine failure/immunogenicity (i.e., enhanced disease), or events that are potentially specific to particular populations of interest. Table 2 describes the settings in which each outcome will be evaluated, as well as the clean and risk windows for each AESI. If safety signals of unanticipated potential AESI are identified during the course of surveillance, they will be added to the list and included in the analyses. Pediatric outcomes are defined in Appendix A in the event COVID-19 vaccines become available for the pediatric subpopulation. The diagnosis of AESI will be identified with International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes and the code list is provided as a supplemental document.

Note that the clean windows may be subject to change following further assessment of accumulated data and specific study questions. The post-vaccination risk windows to be used will vary by outcome based on existing literature and clinical input. Day 0 in the risk windows corresponds to the day of vaccination.

**Table 2. Potential AESI, settings, clean windows, and risk windows**

| AESI | Care Setting | Clean Window | Risk Window |
|---|---|---|---|
| Guillain-Barré Syndrome (GBS) | IP- primary position only | 365 days* | 1-42 days [8,9] |
| Bell's Palsy | IP, OP, PB | 183 days* | 1-42 days [10] |
| Anaphylaxis | IP, OP-ED | 30 days* | 0-1 days [11,12] |
| Encephalomyelitis/Encephalitis | IP | 183 days* | 1-42 days [13] |
| Narcolepsy | IP, OP, PB | 365 days* | 1-42 days† [14-16] |
| Appendicitis | IP, OP-ED | 365 days* | 1-42 days [17,18] |
| Non-hemorrhagic Stroke | IP | 365 days* | 1-28 days [19,20] |

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| AESI | Care Setting | Clean Window | Risk Window |
|---|---|---|---|
| Hemorrhagic Stroke | IP | 365 days* | 1-28 days [19,20] |
| Acute Myocardial Infarction | IP | 365 days* | 1-28 days [19,20] |
| Myocarditis/Pericarditis | IP, OP, PB | 365 days* | 1-42 days [21] |
| Deep Vein Thrombosis (DVT) | IP, OP, PB | 365 days* | 1-28 days [22-24] |
| Pulmonary Embolism# (PE) | IP, OP, PB | 365 days* | 1-28 days [22-24] |
| Disseminated Intravascular Coagulation (DIC) | IP, OP-ED | 365 days* | 1-28 days [25] |
| Immune Thrombocytopenia (ITP) | IP, OP, PB | 365 days* | 1-42 days [26,27] |
| Transverse Myelitis | IP, OP-ED | 365 days* | 1-42 days [28] |
| Multisystem Inflammatory Syndrome | IP, OP-ED | 365 days* | 1-42 days [29] |

*Definitions: Clean window is an interval used to define incident outcomes where an individual enters the study only if the AESI of interest did not occur during that pre-vaccination interval. Risk window is defined as an interval post-vaccination during which occurrence of the AESI of interest may be associated with the vaccine exposure. Day 0 of the risk window corresponds to the day of vaccination.*

*\* References for these windows could not be located in the literature and are instead based on input from clinicians*

*† Literature typically uses a longer window, but we propose a shorter risk window for the purposes of rapid signal detection, assuming that risk should either be constant or more concentrated in a shorter window nearer to vaccination.*

*# If an individual has both DVT and PE (i.e., the DVT progressed to PE), the case will be de-duplicated in analyses stage and assigned only PE. The PE onset date is determined by the date the PE code is reported in the database.*

## 5. METHODS

### 5.1 OVERVIEW OF STUDY DESIGNS

The three study designs described in this protocol, including the SCCS, SCRI, and cohort designs, will be considered. This section will provide a brief description of each method and its relative advantages and disadvantages. Table 3 below provides an overview of key features of each design.

**Table 3. Overview of key features of SCCS, SCRI and cohort designs**

| Feature | Self-Controlled Case Series (SCCS) | Self-Controlled Risk Interval (SCRI) | Cohort |
|---|---|---|---|
| Implicit Control for Time-Invariant Confounding | Yes | Yes | No* |
| Implicit Control for Time-Variant Confounding† | No | No | No |
| Requires Defining a Population that Did Not Receive a COVID-19 Vaccine | In some cases | No | In some cases |
| Requires the Outcome to be Recurrent and Independent or Non-Recurrent and Rare | Yes | Yes | No |

| Feature | Self-Controlled Case Series (SCCS) | Self-Controlled Risk Interval (SCRI) | Cohort |
|---|---|---|---|
| Can Handle Multi-dose Exposure | Yes | In some cases | Yes |

*Control for measured time-invariant confounding can be accomplished explicitly (e.g., through including covariates in the statistical model).

[†] Control for measured time-variant confounding for all three study designs, can be accomplished explicitly (e.g., through addition of covariates to the models).

In SCCS, only cases (i.e., individuals with an AESI) are sampled, with estimation of risk occurring during pre-defined risk intervals within cases rather than between cases. Created to assess the risk of acute events in clearly defined risk windows, this design implicitly controls for both measured and unmeasured time-invariant confounding by using individual observations as their own control. AESI-specific risk windows are defined post-vaccination. The observation period is usually independent of the vaccination date, with all time outside of the risk window counting as control time, but modifications will be made to the standard method to account for study-specific constraints. First, to address the concern of the occurrence of an AESI potentially affecting subsequent vaccine exposure, we will limit the window of control time to postvaccination only. Second, while the SCCS design traditionally includes both vaccinated and unvaccinated cases, to address the concern of exposure misclassification, we will restrict to cases with an exposure (i.e., COVID-19 vaccination).

The SCRI design is a special case of SCCS. In the SCRI approach, a person's risk of experiencing the outcome after exposure (i.e., during the risk window) is compared to the same person's risk of experiencing the outcome during a later, discretely defined period of time (control window). Unlike the standard SCCS design, the SCRI method requires defining a specific time interval within the observation period as the control window. Compared to SCCS, SCRI may be less affected by time-varying confounding due to the shorter control window; however, the shorter control window included in the analysis may reduce statistical power. Both the SCCS and the SCRI analyses are reliant on several assumptions, including an assumption that outcomes are recurrent and independent, or non-recurrent and rare, which may not be met for all AESI. These assumptions are described in more detail in section 5.2.2.

The cohort design compares incidence of AESI between a COVID-19 vaccine recipient cohort and a comparator cohort. The selection of the comparator group is dependent on the underlying question of interest. For example, an unvaccinated comparator cohort would generate estimates of the relative risk of AESI occurrence in vaccinated versus unvaccinated populations, whereas comparator groups receiving an alternative COVID-19 vaccine brand would generate estimates of relative risk between different COVID-19 vaccine brands. The cohort design is not limited by the assumptions required for the SCCS and SCRI designs, and can typically be completed more rapidly due to not requiring a post-vaccination control window. However, the cohort design does not provide implicit control for time-invariant confounding, which is particularly a concern when unknown or unmeasurable confounders exist. Additionally, in order to generate estimates of the relative risk between vaccinated and unvaccinated populations, the cohort design requires the definition of an unvaccinated cohort. It may be particularly challenging to properly identify a concurrent unvaccinated control cohort for the COVID-19 vaccine, given that vaccinations may be administered outside of typical reimbursement channels during the mass vaccination campaign currently underway and may not be comprehensively captured in claims data.

## 5.2   SELF-CONTROLLED DESIGNS

Self-controlled study design will be used to estimate the relative risk of the AESI by comparing the incidence of the AESI in the pre-defined risk window following COVID-19 vaccination with the incidence in a control window after COVID-19 vaccination. The SCCS design will be considered as the primary self-controlled study design for select outcomes.

### 5.2.1   Selection of SCCS versus SCRI

The standard SCCS design is more adaptable and is thus preferred when risk or control windows may be less well-defined, when there is a need to increase statistical power, or when time-varying confounding is a lesser concern. The SCCS design can also be more easily used to assess multiple occurrences of independent events within an individual.[30] The SCRI design is preferred when it is feasible to have strictly defined risk and control windows for outcomes of interest, or when time varying confounding is a concern. Given that the first two authorized COVID-19 vaccines in the US require two doses administered in close proximity, which may necessitate a flexible control window definition, and given that several of the outcomes are rare and would benefit from increased statistical power, SCCS will be the preferred self-controlled method, compared to SCRI.

While in the standard SCCS design the study population includes all cases within the study period, with or without an exposure, our study will restrict to individuals with the AESI of interest (i.e., cases) and a COVID-19 vaccination exposure.[31] We will use a post-vaccination time period to define control windows.

### 5.2.2   Assumptions of Self-Controlled Designs

As originally developed, the SCCS design, and by extension SCRI, rests on several key assumptions. They are listed below along with any relevant accommodations we will make in our study where they may not be met.

(i)   *Events must be independently recurrent, or non-recurrent and rare*

The original SCCS model was developed to assess the risk of independent recurrent events.[32] However, this requirement can be safely omitted if events meet the rare events assumption; that is, if events are non-recurrent and have a cumulative incidence <0.1 per individual over the total observation period.[33,34]

(ii)   *Occurrence of an event should not affect subsequent exposures or mortality*

The standard implementation of SCCS requires that the exposure must be exogenous. Given concerns that some AESI may reduce the chance of subsequent exposure, we will not be including any control time from before the first dose. This will ensure that any cases recorded within our study will have occurred subsequent to initial exposure. To accommodate this concern for the second dose, we can again rely on the rare event assumption described above in assumption (i). In other words, given a rare event, the amount of observation time post-event as well as the number of exposures that may be affected by the event following dose 1 will be small relative to the total amount of included observation time and included number of exposures. The SCCS design may be applied to unique, non-recurrent outcomes only when the event is rare.[33,35]

(iii)   *Events cannot happen at exact same time or age.*

Available evidence for the possible concerns for this assumption will be provided. Where no information is available, that will be stated.

*(iv) Event rates are constant within intervals*

Available evidence of constant risk and the possible impact to the results will be provided. Where no information is available, that will be stated.

*(v) Exposure is transient or intermittent*

Available evidence and the possible impact on the results will be provided. Where no information is available, that will be stated.

### 5.2.3 Study Population

For all analyses, the study population will be split into two age groups: the adult population (ages 18-64 years) and the elderly population (≥ 65 years of age). A third group, the pediatric population (<18 years of age), may also be considered if vaccines are authorized or approved for use among children (Pfizer-BioNTech vaccine is currently authorized for use in ages 12 and older). Subpopulations defined by specific age strata may be considered for a specific AESI.

The observation period for each individual is defined from the date of their first COVID-19 vaccine dose through 183 days following that first dose. The exposure risk window is defined as the time during which excess risk is hypothesized following each COVID-19 vaccine dose for each AESI based on biological plausibility and clinical input (see Table 2). The control windows are defined as time during the observation period that does not fall within the exposure risk window(s). The end of the study period is defined by the date through which complete data (defined as data that are at least 95% complete) are available for each data source at the time of study initiation.

For the primary self-controlled analysis (i.e., SCCS), the study population will consist of COVID-19-vaccinated individuals with an incident AESI. AESI will be defined as an incident event for a subject if there are no claims for the same AESI in the preceding clean window. Clean windows are AESI-specific and are listed in Table 3. The study population will consist of individuals

(i)   With enrollment in a medical plan during the observation period, as well as during the clean window prior to the start of the observation period.
- Continuous enrollment will be required from the start of an AESI's clean window relative to the first vaccine dose through day 183 post-vaccination, the end of the study period, disenrollment, or death whichever comes first.

We will exclude individuals

(i)   Who do not have both risk and control window time. If an individual disenrolls, dies, or reaches the end of the study period during the risk window prior to accumulating any control window time, they will be excluded;
(ii)  Who have COVID-19 vaccination patterns that do not conform to expectations for the analysis of interest. For the self-controlled primary analysis, this includes individuals who receive multiple brands or who receive more than the recommended number of vaccine administrations. For a potential brand-specific analysis, individuals who have received at least one dose of the brand of interest and have the required follow-up time will be considered. More inclusion/exclusion criteria will be considered on an analysis-specific basis once more data on vaccination patterns are available;
(iii) With a diagnosis of the safety outcome of interest during the AESI-specific clean window (Table 2); or

(iv) Who received different COVID-19 vaccine brands for the first and second dose.[a]

### 5.2.4 Risk and Control Window Definition

The selected risk windows (listed in Table 2) are AESI-specific and were determined based on review of literature and consultation with subject matter experts. Post-first dose risk windows will run until the end of the pre-specified risk window, or until the subject receives their second dose. Post-second dose risk windows will run until the end of the pre-specified risk window. The control windows will include all non-risk window time after either the first or second dose, up until day 183 post-vaccination, the end of study period, disenrollment, or death; 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 displays a selection of example cases that may be encountered using this design.

In order to ensure that both risk and control window time is included for each subject, the SCCS design includes all follow up time during the observation period (i.e., no censoring on the first AESI onset day even though the person may not be "at risk" in the following time depending on the pre-specified clean window).[34]

**Figure 1. Example cases for SCCS design (Primary Analysis)**



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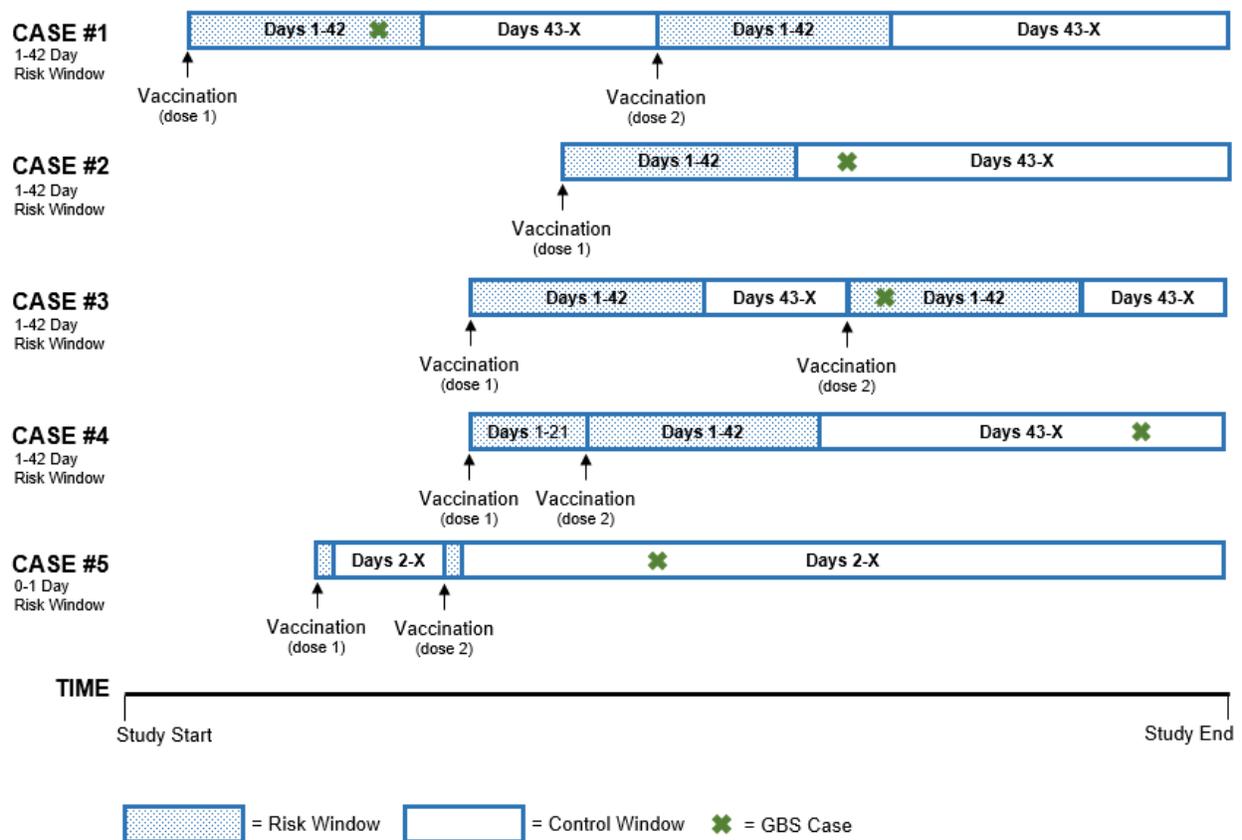
[a] This exclusion criteria will be reconsidered if a large proportion of patients receive multiple brands.

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### 5.2.5 Time-varying Confounders

While self-controlled designs implicitly control for time-invariant confounding, they are still susceptible to time-varying confounding. A number of the AESI may be affected by factors that change during the course of the study period. Some AESI (e.g., GBS and Bell's palsy) exhibit seasonal trends. COVID-19 can cause cardiovascular disorders,[36] and the risk of COVID-19 exposure varies throughout the study period and could affect risk of related AESI. Treatment decisions, such as steroid use, can vary throughout the study period and affect outcome risk. In the case of certain chronic diseases, such as thrombocythemia, the severity of the disease may change (e.g., platelet counts may normalize), which can also affect the risk of an AESI. Outcome-specific time-varying confounding will be considered based on their impact on the risk of developing individual AESI.

### 5.2.6 Statistical Analyses

In SCCS, subjects will serve as their own control. Person-time will be split into successive time intervals determined by changes in exposure status and by the end of observation. Only risk and control window information for vaccinated individuals with an AESI case will be included in the analysis. The entire observation period will be included for these individuals regardless of when the AESI diagnosis occurs, assuming cases are non-recurrent and rare, or independently recurrent. The analysis will be conducted by vaccine brand, where available.

#### 5.2.6.1 Descriptive Statistics

Descriptive statistics for AESI within strata of each of the following population categories will be reported:

    (i)      Demographics (e.g., age, sex, race/ethnicity [where available], region);

    (ii)     Where relevant, the number of cases with concomitant influenza vaccination or influenza vaccine administration in the risk or control windows for each dose; and

    (iii)    The number of cases that are affected by inclusion and exclusion criteria to be used to construct the study population

#### 5.2.6.2 Primary Analysis

For the primary self-controlled analysis, the risk of the select AESI will be evaluated following any dose, without distinguishing between dose numbers. This analysis will compare the AESI rates in the risk and control windows using a conditional Poisson regression model. The model assumes constant risk throughout each risk window, regardless of how close together the two doses may be given (i.e., no additive risk from overlapping risk windows). Under this assumption, the following model will be fitted:

$$\log\big(E(Y|X)\big) = \beta_1(risk\_window) + \log(t) + strata(patient\_id)$$
$$Y = AESI$$
$$risk\_window = binary\ term\ indicating\ AESI\ occurrence\ in\ risk\ window$$
$$t = interval$$
$$patient\_id = term\ identifying\ the\ patient$$

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

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

where $e^{\beta_1}$ will be interpreted as the rate ratio for AESI in the risk window compared to the control window. Thus, statistical significance of the coefficient on the risk window 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 ($p \leq 0.05$).

Attributable risk (per million vaccinations) will be calculated as well. The rate ratio obtained from the conditional Poisson regression model will be multiplied by the ratio of risk window in the observation period, then divide by the total number of vaccinated individuals.

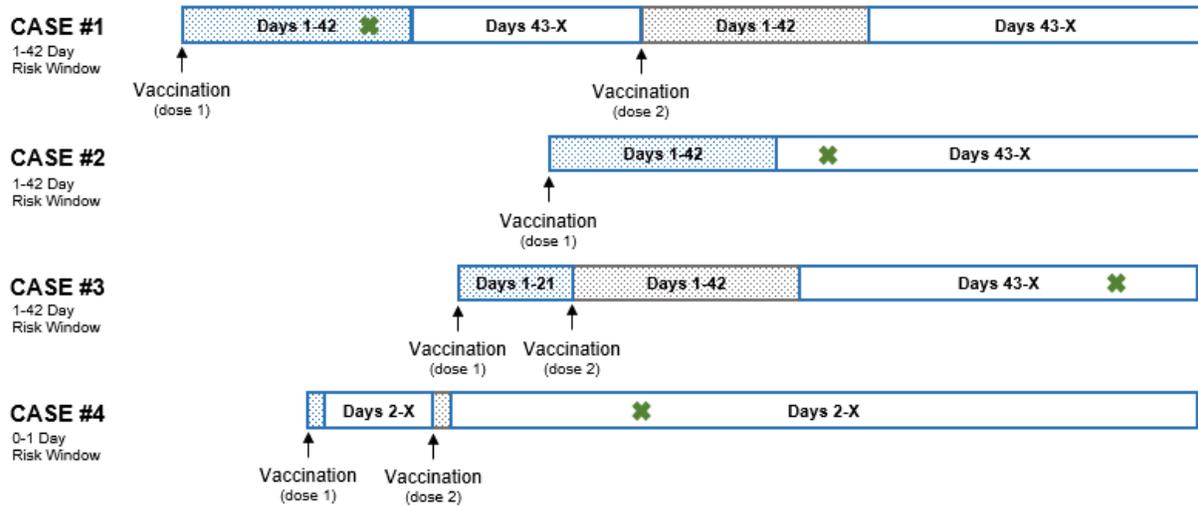### 5.2.6.3  Secondary Analyses

The secondary analyses will maintain a similar methodology to the primary analysis, but will investigate potential differences in risk stratified by vaccine dose. The observation period and the control period are defined as the same time periods utilized in the primary analysis.

For the first dose risk estimation, if a second dose is observed before the end of the first dose risk window, the risk window will be truncated at the time of second dose. Time during the risk window following the second dose will be excluded from this analysis. Control window time will then be defined as the time from the end of the second dose risk window through the end of the observation window.
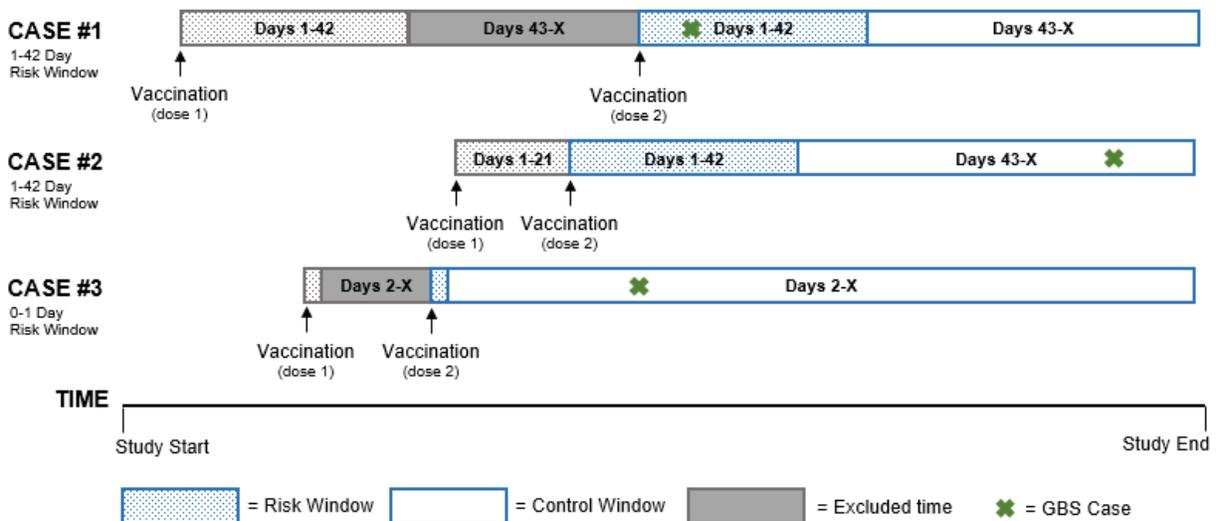
For the second dose risk estimation, the risk window will be initiated on the date of the second vaccine dose and extend for the risk window length as specified in Table 2, even if the second dose is administered during a first dose risk window. Cases included in the second dose-specific analysis will be limited to subjects who have received both doses. Control window time will again be defined as the time from the end of the second dose risk window through the end of the observation window. Time during the risk window following the first dose prior to the administration of dose 2 will be excluded from this analysis, assuming the risk is constant during periods of overlap between risk windows. See Figure 2 for example cases.

**Figure 2. Example cases for SCCS design (Secondary Analyses)**



**First Dose Risk Estimation**

CASE #1
1-42 Day Risk Window

CASE #2
1-42 Day Risk Window

CASE #3
1-42 Day Risk Window

CASE #4
0-1 Day Risk Window

**Second Dose Risk Estimation**

CASE #1
1-42 Day Risk Window

CASE #2
1-42 Day Risk Window

CASE #3
0-1 Day Risk Window

TIME
Study Start — Study End

Legend: = Risk Window   = Control Window   = Excluded time   ✖ = GBS Case

### 5.2.6.4 Sensitivity Analyses

A potential sensitivity analysis will assess varying risk of AESI following vaccination during dose risk window overlaps. While the primary analysis assumed constant risk regardless of multiple vaccine exposures, this sensitivity analysis will not assume that the risk of outcome is constant across all risk-window time, including any overlap in risk windows for the first and second dose. The varying risk model would assess the risk during: (i) the non-overlapping portion of the first dose risk window; (ii) any period of overlap between the risk windows of the first and second dose; and (iii) the non-overlapping portion of the second dose risk window.

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Another potential sensitivity analysis would vary the length of the risk window for the AESI of interest, allowing for an evaluation of the appropriateness of the pre-specified risk window. This may be particularly relevant for AESI where there is variation in the reports of risk windows in the literature. If sample size permits, a temporal scan will be considered to empirically identify the risk window for the specific AESI.

For AESI that exhibit seasonality, we will explore adjustment methods or assess other temporal patterns.

### 5.2.6.5  Power Calculations

To assess the power of the SCCS analysis, the following formula is applied from Whitaker et al.[37]

$$Power = P(x < Z_{1-\gamma}), \quad Z_{1-\gamma} = \frac{\sqrt{nA} - Z_{\alpha/2}}{\sqrt{B}}$$

$$n = number\ of\ cases$$
$$\alpha = 0.05$$
$$A = 2\left[\left(\frac{Rr}{Rr + 1 - r}\right)log(R) - log(Rr + 1 - r)\right]$$
$$B = \frac{[log(R)]^2}{A} \frac{Rr(1-r)}{(Rr + 1 - r)^2}$$
$$R = rate\ ratio\ to\ detect\ of\ 1.5, 2, 3, 4, \dots, 9, 10$$
$$r = \frac{person - days\ in\ risk\ window}{person - days\ in\ control\ window}$$

### 5.2.7  Limitations

Self-controlled designs must be adjusted for time-varying confounding; otherwise, they can bias results, particularly when outcomes are rare. This limitation is less prominent in the SCRI design because of the generally shorter observation time. Self-controlled designs are susceptible to exposure misclassification, particularly when the control window time from the unvaccinated population is included. This is controlled for in this study because our adapted SCCS design only includes cases with a recorded COVID-19 vaccination in the primary analysis.

## 5.3  COHORT DESIGN

### 5.3.1  Cohort Study

The cohort study design will be used to estimate relative risk by comparing the incidence of the AESI in the post-vaccination risk window for a given COVID-19 vaccination with the incidence in the same risk window for the comparator group. The exposure of interest is a pre-specified brand, where available. The comparator cohort of interest may be an unvaccinated cohort or a cohort receiving an alternative COVID-19 vaccine brand.

### 5.3.2  Study Population

For all analyses, the study population will be split into two age groups: the adult population (ages 18-64 years) and the elderly population (≥ 65 years of age). A third group, the pediatric population (<18 years of age), may also be considered if vaccines are authorized or approved for use among children (Pfizer BioNTech vaccine is currently authorized for use in ages 12 and older). Subpopulations defined by specific age strata may be considered for a specific AESI.

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Analysis populations and statistical analysis plans will be determined separately for each AESI. The study period will start on the date of the emergency use authorization for a COVID-19 vaccine in the United States (the earliest possible date is December 11, 2020 for Pfizer BioNTech vaccine) and will end on the date through which complete data (defined as 95% complete) are available for each data source at the time of study initiation. Study populations will consist of individuals

(i) With continuous enrollment in a medical insurance plan for 365 days prior to the index date for ascertainment of potential confounders (e.g., comorbidities, history of healthcare use). The index date is defined as the eligible COVID-19 vaccine dose administration(s) or the match day for the unvaccinated group. Each COVID-19 vaccine dose administration can be assigned as the index date if all inclusion and exclusion criteria are met.

The following individuals will be exlcuded:

(i) With a diagnosis of an AESI during the AESI-specific clean window pre-vaccination (Table 2); or
(ii) With timing patterns that do not conform to expectations (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).

Additional exclusion criteria that will be considered as the specific study question is developed. For example, to compare COVID-19 vaccine brands, individuals who have claims for multiple vaccine brands should be excluded.

If a second dose occurs during the post-vaccination risk window following the first dose, the risk window following the first dose will be truncated at the time of the second dose, and the second dose will be considered for cohort inclusion based on the above criteria. An individual's first observed dose being ineligible for cohort inclusion may not automatically exclude that individual's second dose. This will be determined on a study specific basis.

The primary treatment exposure will be comprised of individuals who received at least one dose of the COVID-19 vaccine within the study period of interest. The comparison cohort can be variably defined to compare different qualities of interest:

- **Unvaccinated population:** The comparison cohort can be defined as those individuals who have not been recorded to have received any COVID-19 vaccine at the time of sampling for the vaccinated group. Individuals who are sampled into the unvaccinated group on the match day can later receive the COVID-19 vaccine of interest and enter the vaccination group if all inclusion and exclusion criteria are met. The period within a certain number of days around the COVID-19 vaccination date will be considered to assign the match day depending on the specific AESI.

  This comparison group choice has the benefit of having an easily interpretable result (i.e., the potential increased risk of the AESI following COVID-19 vaccine is likely associated with the vaccination, compared with those who were not vaccinated), but is most likely to be impacted by selection effects where vaccine recipients are different from non-recipients according to prognostic variables (confounding by indication and/or healthy user bias). Carefully selecting unvaccinated individuals to account for their comparability to the vaccinated population on demographics, comorbidities, and healthcare utilization could allow for a more reliable estimation of vaccine risk.

  o To address possible selection bias due to health seeking behaviors, among the unvaccinated population, we will further restrict to those who have had preventive health

care encounters (e.g., vaccination, well care visits, and screening) in the past years prior to the match day. Comparability of vaccinated and unvaccinated in respect to baseline characteristics will be evaluated. An alternative schema of sampling and assigning an index date for the unvaccinated cohort will be considered for each AESI; the date of preventive health care encounters should fall within a specified number of days from the COVID-19 vaccination date.

COVID-19 vaccinations that do not require reimbursement may not be recorded in the claims data, rendering potential misclassification of this comparison group. The extent of misclassification will be evaluated using external data sources linked to the claims data (e.g., electronic health records or state immunization information systems, pharmacy benefits management data), where available, and the impact will be assessed by quantitative bias analysis.

- **Alternate COVID-19 vaccines:** By defining the comparison cohort as including those individuals who have received a different brand or type of vaccine than the primary treated population, this approach would allow for the evaluation of the comparative safety of different COVID-19 vaccines used in the population. Exposure and alternate-exposure populations would be defined by vaccine brand or vaccine type.

### 5.3.3  Follow-up Time

Patients will be followed from the index date until occurrence of an AESI, death, the end of study period, a change in exposure cohorts, disenrollment, or the end of the risk window.

The index date is defined as the first eligible COVID-19 vaccination date or the eligible match day selected for the unvaccinated groups, when the unvaccinated cohort is considered.

The receipt of another vaccination dose will not censor the follow-up on the person level, but receipt of another vaccination dose will censor the follow-up for the previous dose and institute another index date if all inclusion and exclusion criteria are met.

### 5.3.4  Covariates and Cohort Balance

Potential confounders will be accounted for in the statistical analysis through covariate adjustment. Each AESI-specific cohort analysis will adjust for factors that may be related to the development of the AESI of interest. Covariates under consideration (when available) may include, but are not limited to:

- Age
- Sex (Male; Female)
- Race/Ethnicity (White; Black; Other)
- Census region (West; Midwest; South; Northeast; Other)
- Calendar year/ season
- Area Deprivation Index (ADI)
- Health care utilization
- Concomitant vaccines
- Comorbidities (e.g., chronic health conditions)
- Frailty conditions
- Other AESI-specific risk covariates

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- General and specific preventative services

To achieve a balance between cohorts, we will use inverse probability treatment weighting (IPTW). In IPTW, the propensity score (PS) is used to weight each subject, creating a "pseudo-population in which the covariates and the treatment assignment [e.g., exposure to COVID-19 vaccine] are independent of each other."[38] Propensity scores may be calculated on the individual level at the time of the first dose or index date. The second dose for the same individual would then also be assigned that propensity score. This method of calculation assumes that the factors influencing an individual's likelihood of receiving treatment (i.e., a COVID-19 vaccination) do not change between receipt of the first dose and receipt of the second dose. Alternatively, if time-dependent variables are thought to play a substantial role in the propensity to receive a vaccination, time-dependent propensity scores or marginal structural models may be considered.[39]

Weights will be calculated such that they can be used to estimate the average effect of the treatment on the treated (ATT). Additionally, weights will be stabilized to reduce variability and instabilities in estimation that can be created by extreme weights. Stabilized weights are defined by multiplying the reciprocal of the probability of receiving a given treatment by the marginal probability of receiving the given treatment. The formula for the calculation of the stabilized weight, w, for a subject $i$ with Z = treatment status and e = propensity score, is given by:[40]

$$w_{i,ATT} = \Pr(Z = 1)Z_i + \Pr(Z = 0)\frac{(1 - Z_i)e_i}{1 - e_i}$$

Diagnostic analyses will be considered: 1) the mean of the stabilized weight should equal to 1; and 2) extreme stabilized weights will be trimmed to avoid particular influential persons. The implementation of IPTW will be assessed by calculating pairwise standardized mean differences (SMD) between cohorts for variables included in the propensity score model, as well as their two-way interactions, before and after weighting. An SMD of 0.1 or less post-weighting will be taken as an indication of an acceptable balance between cohorts. The distribution of propensity scores, stabilized weights, and continuous variables included in the propensity score model (e.g., age) will also be assessed to ensure that no extreme values exist and that distributions appear similar across cohorts.

### 5.3.5   Statistical Analyses

#### 5.3.5.1   Descriptive Statistics

Descriptive statistics will be used to summarize the observed rates of AESI in the study population and guide inferential method selection, such as:

- The number of individuals that are affected by the various eligibility criteria used to construct the study population, including the number of individuals who switch exposure cohorts;
- The number of observed COVID-19 vaccinations;
- The number of observed incidents of AESI in the risk window for all patients included in the analysis (or for only the control population);
- The observed rate of incident AESI, calculated as the number of incidents per 100,000 person-years, where person-time is defined as the time during the risk window post-COVID-19 vaccination; and

These statistics will be stratified, when available, by age, sex, race, region, data source, and other clinical or sociodemographic features necessary for confounder control in the cohort study design.

### 5.3.5.2 Primary Analysis

For the primary analysis, the pooled AESI risk after any vaccine dose will be evaluated, without distinguishing between first and second dose. This analysis will compare the post-vaccination AESI rates between cohorts using a Cox regression model as the primary analysis. The model assumes constant risk throughout each risk window, regardless of how close together two doses may be given (i.e., no additive risk from overlapping risk windows). Under this assumption, the model can be specified by:

$$\lambda(t|X) = \lambda_0(t) \exp(\beta_1 X_1)$$
$$\lambda(t|X) = hazard\ at\ time\ t\ given\ covariates\ X$$
$$\lambda_0(t) = baseline\ hazard$$
$$X_1 = COVID-19\ vaccination\ status$$
$$t = exposure\ time$$

Given this model, $e^{\beta_1}$ will be interpreted as the hazard ratio for the COVID-19 vaccination of interest. Cluster-robust standard errors or bootstrap variance estimators will be calculated to adjust for correlation between individuals who received multiple doses of vaccines. Clusters will be defined at the patient level. Statistical significance will be determined using 95% confidence intervals of rate ratios and two-tailed p-values ($p \leq 0.05$).

### 5.3.5.3 Secondary and Sensitivity Analyses

The main secondary analysis will investigate potential differences in risk stratified by vaccine dose. For the first dose risk estimation, if a second dose is observed before the end of the first dose risk window, the window will be truncated at the time of second dose. If there is no overlap, the first dose risk window will extend for the full risk window length specified in Table 2. Time during the risk window following the second dose will be excluded from this analysis. Patients will be followed until the end of the risk window, the administration of the second dose, the occurrence of an AESI, death, disenrollment, or the end of the study period.

For the second dose risk estimation, the risk window will start on the date of the second vaccine dose and extend for the risk window length as specified in Table 2. Individuals included in the second dose-specific analysis will be limited to subjects who have received both doses. Time during the risk window following the first dose prior to the administration of dose 2 will be excluded from this analysis, assuming the risk is constant risk during periods of overlap between risk windows.

An additional potential secondary analysis will be considered for select AESI, where there is a reason to suspect varying risk across the risk window or during periods of overlap between the risk windows following the first and second vaccine doses. This analysis will use a single risk window starting from the first day of the risk window following the first dose and ending on the last day of the risk window following the second dose (in cases where there is overlap between windows). This analysis will classify person-times for three exposure categories: dose 1 only, overlapping dose 1 and dose 2, and dose 2 only, allowing for varying risk during each specific risk window.

Marginal structural models will be considered to allow for transitional treatment (exposure) status and account for informative censoring.[41,42] These models may be more appropriate as the primary analysis for some AESI. In this model, all individuals would possibly enter the study on the earliest date of the emergency use authorization for a COVID-19 vaccine (earliest possible date is December 11, 2020 for Pfizer BioNTech vaccine), and would be able to change exposure status (i.e., move from an unvaccinated status to a vaccinated status) over time.

Finally certain sensitivity analyses, such as quantitative bias analysis for confounding and exposure misclassification or inclusion of negative control events, may be considered.

### 5.3.5.4  Power Calculations

Sample size and expected power will be assessed for a range of effect sizes (i.e., hazard ratio[43] or rate ratio[44]), using the same model as the primary analyses. The power calculation formula can be given by:

$$n_{jk} = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2}{p_j p_k \log\left(\gamma_{jk}\right)^2}$$

Where

$\alpha$ is the type I error,
$\beta$ is the type II error, $1-\beta$ is the power,
$\rho_j$ and $\rho_k$ are the proportions of beneficiaries in the study population that consists of group j and k,
$\gamma_{jk}$ is the hazard ratio to detect between treatment group j and k

### 5.3.5.5  Limitations

The main limitation of the cohort design for this study is the potential for unmeasured and residual confounding. For the COVID-19 vaccine, there may be concerns regarding the comparability of an unvaccinated cohort, because of socioeconomic status or access to health care even after explicit adjustments are made. Therefore, quantitative bias analysis for confounding or negative controls will be considered to evaluate the robustness of the results. Further, it is challenging to identify an unvaccinated comparator population using administrative claims data. Due to the mass vaccination campaign currently underway, it is likely that vaccinations will be given outside of typical reimbursement channels, and it will be difficult to confidently state that an individual is unvaccinated when a claim is not observed. Therefore, evaluation of potential misclassification of the exposure status and its impact on the results will be considered. Additionally, if vaccination coverage is high, few unvaccinated individuals will be available for comparison.

## 6.  MEDICAL RECORD REVIEW

During the course of the study, specific AESI identified through claims may go through the medical record review (MRR) process. This MRR process entails detailed review of the medical charts for patients who were diagnosed with select AESI to determine whether they met the accepted case definition for that particular AESI. Once the number of true cases and non-cases are identified, a chart-confirmed analysis may be completed using only the confirmed cases. Positive predictive values (PPV) and other metrics can also be calculated to better understand the rate and reliability of the outcome of interest.

When conducted, the complete MRR process entails: (i) developing an abstraction tool that isolates the information from medical records needed to confirm a diagnosis; (ii) testing the abstraction tool to ensure that it functions as intended; (iii) developing a user guide for abstractors; (iv) requesting records for claims-identified cases; (v) abstracting records using the tool; (vi) calculating Brighton Scores using abstraction results (if a Brighton algorithm is used); and (vii) reviewing inter-rater reliability and resolving discrepancies through an adjudication process. We will leverage any existing Brighton Collaboration case

definitions (Appendix B) and analysis infrastructure to assign case classifications and case certainty levels.

When implementing the selected adjudication methodology (e.g., Brighton Collaboration case definitions), three approaches will be considered. First, we could develop an automatic adjudication tool that uniformly applies the case definition algorithm to each case using the abstracted data. Second, we could identify expert clinical reviewers to review the redacted medical records and abstraction data and recommend case designations. Third, we could complete a combination of the two, where we first run an automatic adjudication process followed by expert review of the abstracted data and adjudication results, generally and/or a subset of case records of interest.

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# APPENDIX

## A. PEDIATRIC OUTCOMES

In the event that the vaccine is approved or authorized for children, the following potential AESI will be studied among the pediatric subpopulation. Considerations in the selection of these potential AESI include serious events that have followed other immunizations, events that are potentially related to novel platforms or adjuvants, events that are related to COVID-19 severity that may potentially relate to vaccine failure/immunogenicity (i.e., enhanced disease), or events that are potentially specific to particular populations of interest

**Table A1. Potential pediatric AESI, settings, clean windows, and risk windows.**

| AESI | Care Setting | Clean Window | Risk Window |
|---|---|---|---|
| Multisystem Inflammatory Syndrome in Children (MIS-C) | IP, OP-ED | 365 days* | 1-42 days [29] |
| Febrile Seizures | IP, OP/PB | 42 days | 0-1 days [45] |
| Kawasaki Disease | IP, OP/PB | 365 days* | 1-28 days [46,47] |

*Definitions: Clean window is an interval used to define incident outcomes where an individual enters the study cohort only if the AESI did not occur during that interval. Risk window is defined as an interval during which occurrence of the AESI may be associated with the exposure. Day 0 of the risk window corresponds to the day of vaccination.*

*\* References for these windows could not be located in the literature and are instead based on input from clinicians*

## B. MEDICAL RECORD REVIEW AND BRIGHTON COLLABORATION CASE DEFINITIONS

The Brighton Collaboration develops standardized case definitions and guidelines for data collection, analysis, and presentation via participation of more than 500 experts from 57 countries from public health, clinical care, academia, regulatory organizations, and industry. Brighton Collaboration case definitions are available for the following AESI:

- Guillain-Barré Syndrome (GBS)
- Facial Nerve Palsy
- Anaphylaxis
- Kawasaki Disease
- Febrile Seizures
    - A combination of the Generalized Convulsion case definition and Fever case definition can be used
- Encephalomyelitis/Encephalitis
- Narcolepsy
- Immune Thrombocytopenia (ITP)
- Transverse Myelitis (note: cases definitions are for myelitis that will be used for transverse myelitis)

Additionally, although a Brighton Collaboration case definition is not available for MIS-C, a CDC case definition is available and can be found on the following website: https://emergency.cdc.gov/han/2020/han00432.aspht.

Master Protocol: Assessment of Risk of Safety Outcomes Following COVID-19 Vaccination (May 28, 2021)

Brighton Case definitions are **not** available for the following AESI:

- Hemorrhagic Stroke
- Non-hemorrhagic Stroke
- Acute Myocardial Infarction
- Myocarditis/Pericarditis
- Pulmonary Embolism
- Deep Vein Thrombosis
- Disseminated Intravascular Coagulation (DIC)
- Appendicitis

Master Protocol: Assessment of Risk of Safety Outcomes Following COVID-19 Vaccination (May 28, 2021)