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COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol

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1. Objectives

The primary objective of this protocol is to monitor the rates of various adverse events of special interest (AESIs) following COVID-19 vaccination in near real-time following authorization or licensure. For this document, we also equate AESIs with adverse events or health conditions identified as having the potential to be associated with vaccination [1, 2]. The Workgroup will use the observed rates of these outcomes, as data accrue, to identify whether there is potential increased risk of AESIs following vaccination compared to a control baseline. Active monitoring is essential because it allows us to assess potential associations between vaccine exposure and adverse events in near-real time, determine if more comprehensive analyses should be conducted, and provide timely information to support regulatory decision-making processes. Our active safety monitoring detailed in this protocol is a method for signal detection and not signal evaluation. In other words, this method allows for faster detection of a statistically significant association between an exposure and an adverse event, but a statistically significant result does not necessarily indicate an increased risk of the adverse event in the population of interest exposed to the vaccine; such a result must be further investigated and verified.

2. Overview

The 2019 coronavirus (COVID-19) is a contagious respiratory illness caused by the SARS-CoV-2 virus. While a number of COVID-19 symptoms seem to be similar to those of influenza, COVID spreads more aggressively and presents more severely in some patients [3]. The first COVID-19 case was reported in China in December 2019 [4], and the first non-travel-related United States case was confirmed in February 2020, in a California resident [5]. As of December 15, 2020, a total of 73.2 million cases and 1.6 million deaths have been reported worldwide [6]. The highest number of cases and deaths has been reported from the United States (>16.6 million cases and >300,000 deaths) [7].

Multiple COVID-19 vaccines are under study in pre-licensure clinical trials. As with all licensed vaccines, there can be limitations in the safety data accrued during the pre-licensure clinical studies of a COVID-19 vaccine. Potential safety outcome risks of COVID-19 vaccines may not be captured in clinical trials, particularly for rare outcomes like Guillain-Barré syndrome (GBS) [8]. Post-market active monitoring and reporting of COVID-19 vaccine-related AESIs enables better capture of rare safety outcome risks and provides timely information to support regulatory decision-making processes.

To monitor COVID-19 vaccine safety risks, we will conduct active monitoring in large healthcare databases including insurance claims databases. The terminology for active monitoring also corresponds to near real-time surveillance, sequential analysis and rapid cycle analysis (RCA) and some terms will be used interchangeably in this protocol. We will regularly generate descriptive statistics of vaccination and outcome counts for the AESIs to describe rates post-COVID-19 vaccination in claims databases. We will conduct rapid safety surveillance of COVID-19 vaccines via sequential testing to assess the rate of each safety outcome compared to a control baseline rate (i.e., relative risk). If a potential signal for increased risk is identified by the active monitoring, we will conduct more extensive analyses to determine if there is a plausible relationship between COVID-19 vaccination and the AESI in question.

There are several challenges generally associated with active safety monitoring of vaccines. Vaccines that are widely administered, such as the COVID-19 and influenza vaccines, may be administered

outside of traditional health care settings (e.g., school, work, or mass vaccination campaigns) and may not be captured in standard insurance claim databases. Additionally, active monitoring requires frequent data updates to track vaccine uptake and potential adverse events [9]. Unlike retrospective observational studies, data in real-time observational studies are impacted by observation delay, which may bias estimates of risk [10, 11]. Another challenge lies in the types of vaccines currently in development. A number of the COVID-19 vaccines undergoing pre-licensure trials are mRNA vaccines [12, 13], which uses a novel vaccine platform and may be associated with a different array of AESIs or levels of risk compared to historical vaccines.

This protocol details the active monitoring method specifications that will be used, and proposes flexible solutions to address these contextual and technical challenges. In Section 3, we describe the claims databases that are under consideration for inclusion in the analysis. In Sections 4.1 – 4.6, we describe the specifications for safety monitoring in claims databases, including the study population, event definitions, planned descriptive statistics, and sequential methods. In Section 4.7, we describe the steps we will take to evaluate any signals triggered by our monitoring, including data quality assurance, temporal clustering assessment, inferential safety analyses, and medical record review.

3. Data Sources

The current study may include, but is not limited to, the following claims data sources: Blue Health Intelligence® (BHI®)[1] commercial claims, Centers for Medicare & Medicaid Services (CMS) Medicare claims, IBM MarketScan Commercial claims, and OptumServe commercial and Medicare Advantage claims. Table 1 briefly outlines currently available data sources and displays how often each data source is updated. Note that the data lag summarized in this table, as well as the time to data completeness referenced in subsequent paragraphs, refers to the amount of time between the date of service and the date of availability for use by research teams.

Table 1. Update frequency for each data source

Data Source		Update frequency	Data Lag*	Population
Claim data sources	Blue Health Intelligence (BHI)	Monthly	4 months for >80% coverage of inpatient claims	National; >17 million beneficiaries annually
	CMS Medicare Shared Systems Data (SSD)	Daily	30-70 days for >80% coverage of inpatient claims	National; >34 million beneficiaries annually

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[1] Blue Health Intelligence® (BHI®) is a trade name of Health Intelligence Company, LLC, an independent licensee of the Blue Cross Blue Shield Association.

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Data Source		Update frequency	Data Lag*	Population
Claim data sources (cont.)	MarketScan	Monthly	4 months for approximately 80% coverage of inpatient professional claims	National; 25 million Commercial enrollees annually
	OptumServe Clinformatics Data Mart	Monthly	1.5 months for pharmacy claims, 3 months for outpatient claims, and 6 months for inpatient claims	National; 66 million patients and ~14 million patients annually

* Data lag can vary by outcome; we will produce outcome- and setting-specific delay profiles.

BHI data provide HIPAA compliant, deidentified enrollment, demographic, and claims information from Blue Cross and Blue Shield commercial health insurance plans in the United States for the last ten years. Detailed data are available for a cohort of all enrollees who received a biologic product, were pregnant, or were born after October 1, 2015. Pregnant women are identified via codes for prenatal care, gestational age, or pregnancy outcomes. Currently, the BHI cohort population for this study contains over 34 million individuals in total and about 17 million enrollees annually, on average. Approximately 350,000 pregnancy outcomes are observed annually. BHI data are updated monthly and are over 80% complete within 4 months of the service date.

CMS Medicare data contain enrollment, demographic, and claims information for all individuals enrolled in Parts A/B (since 1991), Part C (since 2012), and Part D (since 2006). Medicare data currently contains over 100 million beneficiaries in total, and about 34 million beneficiaries annually, on average. Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. Medicare Shared Systems Data (SSD), which consists of claims sourced after enumeration, will be used in this study. SSD is updated on a daily basis and is over 80% complete within 30-70 days depending on setting and outcome. Personal identifying information is also available in Medicare data, enabling the possibility of conducting medical record reviews (MRRs) to validate AESIs using these data.

The MarketScan Research Databases capture person-level clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services since 1998. The MarketScan Commercial Database contains 25 million annual enrollees in each of the last 5 years, on average, and data from over 200 million active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continues, and dependents insured by employer-sponsored plans in total. MarketScan data are updated quarterly for production releases, and monthly for early-view releases, and is approximately 80% complete after 4 months.

The OptumServe Clinformatics Data Mart contains longitudinal health information for commercially insured and Medicare Advantage enrollees, and it includes more than 66 million lives since 2007. The

commercial portion of the Clinformatics Data Mart includes approximately 14.5 million people on an annual basis and the median dwell time in the database for enrollees is approximately 2.5 years. The OptumServe Clinformatics Data Mart contains claims for physician, hospital, and prescription drug services. The OptumServe Clinformatics Data Mart is updated monthly and is 90% complete within 1.5 months for pharmacy claims, 3 months for outpatient claims, and 6 months for inpatient claims.

The OptumServe pre-adjudicated claims database contains claims that are processed daily. The pre-adjudicated claims database includes data from January 2018.

4. Safety Monitoring in Claims Databases

To provide a comprehensive characterization of the patterns of vaccine utilization and the rate of AESIs following vaccination, we will conduct active monitoring in available insurance claims data sources, including Medicare Parts A & B Fee-for-Service (FFS) and private insurance claims databases.

Insurance claims databases have several advantages that make them useful for vaccine surveillance. Claims databases constitute well-defined, large populations of millions of enrollees, whose healthcare service utilization is captured longitudinally across nearly all care settings. Claims databases do have some disadvantages. They do not provide information about patient care that is as detailed or granular as medical records, thereby potentially limiting the ability to accurately and reliably identify AESIs. Furthermore, claims data processing (i.e., payment and adjudication) induces observation delay between the event of interest (i.e., vaccine exposure and disease incidence) and the final claim; without adjustment, this observation delay induces bias in estimated risk. The claims-based monitoring approaches outlined in this section are designed with these advantages and disadvantages in mind.

4.1 Study Population

The study population will contain all individuals who receive any COVID-19 vaccine dose. The study objectives will be assessed for each COVID-19 vaccine brand. To identify post-vaccination AESI incident cases, post-vaccination risk windows and pre-vaccination clean windows are pre-specified to define incident events per outcome. Risk and clean windows are specified for each outcome (Table 2). Given that analyses will be conducted in near real-time using partially accrued data, the entirety of a risk window and any AESIs that occur within it may not have elapsed by the time a vaccination claim is observed. Therefore, enrollment requirements for study inclusion will be anchored on the vaccination date rather than on the outcome date. For inclusion in the AESI-specific analysis population, continuous enrollment in a medical insurance plan is required from the start date of the clean window (vaccination date minus the length of the clean window) through the date of vaccination. We will assume that patients who meet this requirement will remain enrolled through the end of the risk window. Subjects who had experienced the AESI during the pre-vaccination clean window will be excluded from the AESI-specific analysis population. A historical comparator population will be defined from a time period prior to COVID-19 vaccine availability; see Section 4.6.3 for details.

To capture a study population with age, sex, and regional variation representative of the national population, both Medicare FFS and private insurance claims databases will be used. Patients in Medicare FFS will only be included if they are age 65 or above at the time of vaccination. Private insurance claims

databases will be restricted to patients under age 65 to reduce the chance that individuals are double-counted across databases. All patients in the study population are required to have birth year information.

The study populations will be individuals between 18-64 years old and individuals above 65 years old. If any vaccine(s) are approved or authorized for the pediatric population or any inadvertent exposure in the pediatric population is anticipated, the study population will include the pediatric population between the ages of 0 and 17. The potential safety outcomes of interest for the pediatric population are listed in the Appendix.

4.2 Study Period

The study period will be from the earliest date a vaccine is approved or authorized in the United States, either through Emergency Use Authorization or standard approval, through 1 year after vaccine authorization or approval or until such a time as it is deemed no longer necessary by the FDA.

4.3 Exposure

Exposure is defined as receipt of any COVID-19 vaccination dose for the primary analysis, as identified by product codes such as CPT/HCPCS codes or National Drug Codes (NDCs) in the professional, outpatient institutional, inpatient, or prescription drug care settings. The list of valid codes will be continuously reviewed and updated if new codes are added. If multiple vaccines are approved or authorized, analyses will be stratified by brand. COVID-19 vaccination will be identified using both product and administration codes. A secondary analysis that focuses on risk following a specific dose number will be considered.

4.4 Outcomes

A list of pre-specified potential AESIs following COVID-19 vaccine administration (Table 2) will be used for active monitoring. These AESIs have not been associated with COVID-19 vaccines based on available pre-licensure evidence. Considerations in the selection of these potential AESIs 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 (enhanced disease), or events that are potentially specific to particular populations of interest. Development of the claims-based AESI algorithms is based on literature reviews and consultations with clinical experts. Pediatric outcomes are defined in the Appendix in the event COVID-19 vaccines become available for the pediatric subpopulation. The list of AESIs may be updated based on observed adverse events in pre-licensure trials, adverse reporting from other surveillance sources or other sources including international regulators.

For each AESI observed within the risk window of interest, a clean window restriction defined prior to the COVID-19 vaccination will be implemented to more plausibly identify incident cases, as opposed to follow-up care to an initial diagnosis that occurred earlier. An event observed within the risk window will be counted as an incident case only if there are no historical events found within the clean window. The length of the clean window varies by outcome: acute conditions have a shorter clean window whereas chronic conditions have a longer clean window.

Claims from inpatient facilities (IP), outpatient facilities in the emergency department (OP-ED), and all outpatient facilities and individual providers or professionals (OP/PB) will be used to capture AESIs. A more detailed description of these settings is provided in Appendix 7.3, Table A2. Claim settings, age group of interest, length of risk window, and length of clean window (if applicable) specific to each AESI are specified in Table 2 below.

Table 2. Potential AESIs, age groups, settings, clean windows, and risk windows. These AESIs have not been associated with COVID-19 vaccines based on available pre-licensure evidence.

AESI	Age Group of Interest	Setting	Clean Window	Risk Window
Primary Outcomes				
General Population Outcomes				
Guillain-Barré Syndrome	All	IP- primary position only	365 days*	1-42 days [14, 15]
Bell's Palsy	All	IP, OP/PB	183 days*	1-42 days [16]
Anaphylaxis	All	IP, OP-ED	30 days*	0-1 day [17, 18]
Encephalomyelitis/Encephalitis	All	IP	183 days*	1-42 days [19]
Narcolepsy	All	IP, OP/PB	365 days*	1-42 days† [20-22]
Appendicitis	All	IP, OP-ED	365 days*	1-42 days [23, 24]
Non-hemorrhagic Stroke	All	IP	365 days*	1-28 days [25, 26]
Hemorrhagic Stroke	All	IP	365 days*	1-28 days [25, 26]
Acute Myocardial Infarction	All	IP	365 days*	1-28 days [25, 26]
Myocarditis/Pericarditis	All	IP, OP/PB	365 days*	1-42 days [27]
Deep Vein Thrombosis (DVT)	All	IP, OP/PB	365 days*	1-28 days [28-30]
Pulmonary Embolism# (PE)	All	IP, OP/PB	365 days*	1-28 days [28-30]
Disseminated Intravascular Coagulation (DIC)	All	IP, OP-ED	365 days*	1-28 days [31]
Immune Thrombocytopenia (ITP)	All	IP, OP/PB	365 days*	1-42 days [32, 33]
Transverse Myelitis	All	IP, OP-ED	365 days*	1-42 days [34]
Multisystem Inflammatory Syndrome	All	IP, OP-ED	365 days*	1-42 days [35]

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

Setting Definitions: IP refers to inpatient facility claims. OP-ED refers to a subset of outpatient facility claims occurring in the emergency department. OP/PB refers to all outpatient facility claims, and professional/provider claims except those professional/provider claims with a laboratory place of service.

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

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

4.5 Descriptive Analyses

We will use descriptive statistics to summarize the observed rates of AESIs in the study population. These statistics will also serve as inputs for the sequential monitoring analyses. We will present the following statistics:

- The number of observed COVID-19 vaccinations;
- The number of observed incident AESIs in the risk window for all patients vaccinated;
- The observed proportion of incident AESIs, calculated as the number of incidents per patients vaccinated;
- The observed rate of incident AESIs, calculated as the number of incidents per 100 person-years, where person-time is defined as the time during the risk window post COVID-19 vaccination; and
- The expected rates of incident AESIs, calculated using historical background rates.

These statistics will be stratified by age, sex, race (when available), region, and data source. Descriptive statistics will be updated continuously, synchronized with the sequential testing, on a weekly (Medicare SSD claims) or monthly (BHI, MarketScan, and OptumServe claims) basis, as allowed by the individual data source. The update frequency of each data source can be found in Section 3, Table 1. An example table representing the proposed descriptive statistics can be found below in Table 3.

Table 3. Example table of descriptive statistics

Patient Characteristic	# of COVID-19 Vaccinations	Observed Outcomes – [Outcome 1]	
		#	Rate (per 100 person-years)
Total			
Sex			
Female			
Male			
Race/Ethnicity			
Asian			
Black			
Hispanic			
White			

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Patient Characteristic	All Doses*		
	# of COVID-19 Vaccinations	Observed Outcomes – [Outcome 1]	
		#	Rate (per 100 person-years)
Other			
Age			
0-17			
18-25			
26-35			
36-45			
46-55			
56-64			
65-74			
75-84			
85+			
Region			
[Region 1]			
[Region 2]			
…			
[Region N]			

Additional statistics can be provided for first dose only and second dose only.

Note: Separate tables will be provided for each Data Partner.

4.6 Sequential Analyses for Safety Monitoring

To monitor for potentially increased risk of AESIs following COVID-19 vaccination, we will use the Poisson Maximized Sequential Probability Ratio Test (PMaxSPRT) and Binomial Maximized Sequential Probability Ratio Test (BMaxSPRT) to conduct sequential hypothesis tests. For all AESIs except anaphylaxis, PMaxSPRT will be the only analysis performed. Due to the short post-vaccination risk window for anaphylaxis, BMaxSPRT will be used as its primary analysis and PMaxSPRT will be used as its secondary analysis.

The PMaxSPRT will be used to detect increased risk following vaccination compared to a historical baseline, while adjusting for repeated looks at the data. The methodology was originally developed in response to direct vaccine safety surveillance needs in the Centers for Disease Control and Prevention (CDC)-sponsored Vaccine Safety Datalink (VSD) [36]. PMaxSPRT has been documented numerous times in the published medical literature [37, 38] and has been a common methodology used for other government-sponsored vaccine safety surveillance programs, such as the FDA Post-Licensure Rapid Immunization Safety Monitoring Program.

PMaxSPRT offers several advantages including the use of a composite alternative, making the method robust against varying levels of potentially increased risk; the use of a critical limit, providing a clear and statistically robust signal evaluation process; and the ability to define a surveillance stopping point based

on a pre-specified number of adverse events rather than calendar time, enabling continuous monitoring that is not constrained by the rate of vaccine uptake.

A self-controlled comparator window will be used for the BMaxSPRT sequential analysis for anaphylaxis. This approach will adjust for time invariant confounding in addition to the advantages offered by the PMaxSPRT.

4.6.1 Poisson MaxSPRT Statistical Model

The PMaxSPRT is a sequential testing methodology where hypothesis tests are continuously conducted until either a statistical signal occurs or until a maximum length of surveillance is reached, defined in terms of observed events.

The relative risk (RR) of the AESI is the target parameter and is defined as the ratio of AESI rates between the exposed (COVID-19 vaccinated) cohort and the historical comparator. Denote by θ_e the AESI rate in the exposed cohort and by θ_c the corresponding rate from the historical comparator; thus RR = θ_e / θ_c. At time t, under the null hypothesis, the expected number of patients from the population at risk to have the AESI, based on historical rates, is given by μ_t, and under the alternative hypothesis, the corresponding expected number of patients to have the AESI is given by RR x μ_t. As a result, the number of exposed patients at time t who experience the AESI is given by:

$$Y_t \sim Poisson(RR \times \mu_t)$$

Under the Poisson model, the log-likelihood ratio (LLR) comparing two hypotheses is calculated as the log of the ratio between the likelihood under an alternative hypothesis (chosen as a set of RR values, e.g., RR > 1) and the likelihood under the null (e.g., RR = 1). To calculate the PMaxSPRT test statistic, this LLR will be maximized over possible values of the relative risk under the alternative hypothesis, for example, if the null hypothesis is RR = 1 and the alternative hypothesis is RR > 1, then the LLR statistic at time t is given by:

$$LLR_t = max_{RR>1}[(1 - RR)\mu_t + y_t ln(RR)]$$

$$= \begin{cases} (\mu_t - y_t) + y_t ln(y_t/\mu_t) & \text{if } y_t \geq \mu_t \\ 0 & \text{if } y_t < \mu_t \end{cases}$$

where t is the week, y_t is cumulative count of outcomes in the risk window up to week t, and μ_t is the expected number of events based on the historical comparator up to week t.

At each testing point, if the LLR exceeds a pre-specified critical value, the null hypothesis will be rejected and a potential safety signal will be declared. The null hypothesis will not be rejected if the total number of observed cases surpasses the stopping boundary without the LLR ever exceeding the critical value. Proposed hypotheses, historical comparators, and testing specifications for this study will be discussed in subsequent sections.

4.6.2 Primary Analysis using PMaxSPRT

Sequential analyses using the PMaxSPRT will be conducted separately for each AESI, data partner, and for each vaccine brand. For pediatric-only outcomes, only the analysis in that population will be

conducted if vaccine exposure in pediatrics is anticipated, e.g., approved or authorized pediatric indications of use. For the purpose of the sequential analysis, we will test for an increased risk for each AESI after any dose of vaccine as the primary analysis, and an increased risk for each AESI following each dose as the secondary analysis will be considered. Other key parameters are described as follows:

Testing Frequency: Testing using the PMaxSPRT will occur weekly for the Medicare SSD database, and monthly for BHI, OptumServe, and MarketScan claims data. Sequential testing on any additional databases that are included in the analysis will occur as frequently as those databases are updated. Sequential testing using the PMaxSPRT will begin when at least three events per AESI are observed.

Statistical Hypotheses: We will conduct one sided tests where the null hypothesis is that the observed rate of AESIs in the vaccinated cohort is no greater than the historical comparator beyond a prespecified test margin m ($m \geq 0$; expressed as a fraction of the comparator rate), and the alternative hypothesis is that the observed rate in the vaccinated cohort is greater than that in the comparator beyond the margin:

$$H_0: RR \leq (1 + m)$$

$$H_a: RR > (1 + m)$$

The test margin will be selected for each outcome based on expert guidance to ensure that large increases of risk will be detected while avoiding minimal increases that are unlikely to be clinically relevant, similarly to past applications[39].

Age Group Adjustment: As COVID-19 vaccination is initially expected to be targeted toward age groups with higher risk, the population of vaccinated beneficiaries may be older than the historical comparator population early in the surveillance period. As background rates of AESIs may vary by age, this difference may be a source of bias in the PMaxSPRT. Therefore, the comparator rate may be adjusted based on the observed age distribution of vaccinated persons. Further detail is provided in Section 4.6.3.

Significance Level and Number of Events to Signal: The significance level (alpha) of each sequential analysis will be set to 0.01. A stringent alpha level was specified to reduce the possibility of a large number of signals due to testing of multiple outcomes in a manner similar to previous applications of the PMaxSPRT [40]. To avoid spurious signals from a few early events, a least three events must be observed to declare a statistical signal.

Length of Surveillance: The upper limit of surveillance will be set for each AESI to the number of events expected to be observed during the course of the vaccination campaign, based on the incidence of the event estimated from historical data as well as the anticipated number of vaccine doses administered in the study population in a 1-year time period, a level similar to previous applications of the PMaxSPRT [41-43].

Critical Bound: The critical bound used for testing will be calculated for each AESI and data partner. The critical bound is comprised of the series of critical values that are calculated for each testing point; an observed AESI rate that exceeds the critical value for a given test is defined as a signal. Calculation of the critical values is based on several pre-specified parameters: the upper limit of expected events (the

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testing stopping boundary), the total alpha for the sequential analysis, the alpha spending plan, and the minimum number of events needed to signal. The critical bound will be calculated using numerical procedures implemented in the R package 'Sequential' [44].

Other: Since the sequential testing analysis requires adjustment for partially-accrued data, we will restrict the analysis to data sources that have a well-characterized pattern of observation delay.

4.6.3 Comparator Group Selection for PMaxSPRT

The expected rates of AESIs in the vaccinated population, assuming no adverse effects, is calculated as the background rate in a historical comparator group. The selection of the comparator group is influenced by several factors reflecting potential sources of confounding bias. One possible comparator group is the general population in each database. Another possible comparator group is defined by healthcare-seeking behavior, including non-COVID-19 vaccines that include influenza vaccines. A separate protocol is being developed to estimate background rates of AESIs and evaluate possible comparator groups.

In brief, a pre-COVID (i.e., historical) comparator population will be defined for study period January 1, 2017 through December 31, 2019. A separate peri-COVID population will be defined for study period March 1, 2020 through summer 2020, the exact end date being dictated by data availability in each data source and will be updated upon data availability. Within each population, AESI rates per person-time will be calculated for all enrollees in a given time period.

Another comparator group for consideration is the subset of enrollees who received influenza vaccines as a proxy for healthcare-seeking behavior. Individuals who typically receive vaccines tend to display different health-seeking behaviors and can have different underlying medical profiles compared to the general population. Although the distribution pattern of COVID-19 vaccinations will likely be different from that of the influenza vaccination, there still may be more similarities between previous influenza vaccine recipients and COVID-19 vaccine recipients than between the general population and those who receive the COVID-19 vaccine.

AESI rates within each population will be calculated and reported to describe the potential impact of the COVID-19 pandemic on the AESI incidence, which may have occurred for a number of reasons. For example, the allocation of resources intended to prevent the spread of COVID-19 may have affected the level of utilization of preventative care and medical treatment for other diseases; the implementation of population-wise social distancing measures may have led to an increase in the utilization of remote medical care such as telehealth services. These potential changes could also affect the observability of AESI diagnoses. Additionally, the exposure to or contraction of COVID-19 may have affected the AESI rates.

The following guidelines will be used to select the comparator population:

- If AESI rates are observed to be similar between pre-COVID and peri-COVID time periods, pre-COVID background rates will be selected as the comparator population, given that these rates are calculated over a larger time period and are thus more stable.

- If AESI rates in peri-COVID time are observed to be dramatically different, then the peri-COVID population will be selected as the comparator.
- The use of an all enrollee versus a previously influenza vaccinated population will be dictated by the characteristics of the initial population selected to receive the COVID-19 vaccination.

Regardless of the comparator ultimately selected, calculated rates will be stratified, at a minimum, by the study population age groups specified in section 4.1. Rates within additional stratifications (e.g., sex, race) may also be calculated for descriptive analysis. Age distributions between the comparator population and the observed COVID-19 vaccinated population will be compared. If substantial differences are noted, the age group adjusted rates in the comparator population will be weighted based on the age group breakdown of the COVID-19 vaccinated population in order to create a representative expected rate. The age groups that will be used are per Table 3.

4.6.4 Calculation of PMaxSPRT Inputs

For each test within a database occurring at observation week s, the PMaxSPRT will compare an observed number of events to an expected number of events. The cumulative expected number of events μ_s will be based on the observed exposed person-time following any eligible dose occurring in each database and contain adjustments for observation delay due to partially accrued data and the implementation of the test margin in the statistical hypothesis, and will be calculated as follows:

$$\mu_s = \sum_{t=1}^{s} \sum_{i=1}^{n_t} \sum_{w=0}^{T_i} \sum_{a=1}^{A} l_{stiwa} \times \theta_a \times (1+m) \times P(s,t)$$

where:

- s represents the study time period (e.g. study week) at which sequential testing is planned (e.g. $s = 1, …, 52$).
- t in $1 … s$.
- n_t is the number of subjects vaccinated during time period t. Ineligible doses due to lack of enrollment or having an AESI in the cleaning period will be excluded.
- i in $1 … n_t$.
- T_i represents the exposed weeks at risk following a dose (i.e. within the AESI-specific risk window) for subject i.
- w in $0 … T_i$. Study weeks in which AESIs occur are represented by $t + w$, with $t + 0$ being the same study week as the vaccine dose, $t + 1$ the next week, etc.
- A is the number of age group adjustment strata
- a in $1 … A$.
- l_{stiwa} in $0 … 7$ is the number of exposed days following a vaccine dose in study week w post vaccine dose for a patient identified by i, t in age strata a based on data at observation week s.
    - If the dose is administered on day 5 of study week t, then the first 1-2 days of a 1-42 day post-vaccination risk window would occur in $w = 0$ post dose (with $l_{sti(w=0)a} = 2$). The next 3-9 days would occur in week $w = 1$ post dose (with $l_{sti(w=1)a} = 7$), etc.

- o The occurrence of a second dose may contribute additional exposed time but overlapping time will not be double-counted. For example, if the risk window length is 42 days, a second dose 22 days after the first dose will result in an overall risk period of 1 to (42 + 42 – 21 overlap) = 63 days. In the case when the gap between doses is larger than the risk interval post first dose, the follow-up after the first dose would be censored at the end of the planned risk window and restarted at the second dose.
- Θ_a is the per-day comparator incidence rate of the AESI within age group a. It is assumed that the AESI rate is constant across all time at risk.
- m is the test margin described above.
- $P(s,t)$ is the proportion of AESIs occurring in study week $t + w$ that would be observed by week s. This adjustment factor adjusts for the observation delay due to the use of partially accrued data.

The cumulative observed number of events will be calculated as follows:

$$y_s = \sum_{t=1}^{s} y_{st}$$

where y_{st} is the number of AESI incidents following any dose occurring in the exposed risk windows from patients vaccinated by time period s and whose dose is administered in service week t. When the risk window for an AESI is longer than the time between vaccine doses, expected and observed events from overlapping time at risk occurring will not be double counted (i.e. it is assumed that overlapping exposed time has the same risk as non-overlapping exposed time).

Similar analysis will be considered for dose-specific cumulative expected number of events μ_s. AESI incidents following a specific dose occurring in the exposed risk windows from patients vaccinated by time period s and whose corresponding dose was administered in service week t will be included. When an individual initiates dose 2 within the risk window of dose 1, the risk window of dose 1 will be truncated on the date of dose 2 vaccination.

To account for the sequential nature of the PMaxSPRT, each sequential test will be run on the cumulative data up to that test, but previous tests will be fixed. Additional observed or expected cases counted since the last sequential test ($y_s - y_{s-1}$ and $\mu_s - \mu_{s-1}$) will be added to the cumulative count for the current test only. In other words, the cumulative data used in the tests are ordered by week of observation s rather than the week of vaccination administration. Partially-accrued data is expected to have some degree of data flux; for example, claims may arrive which reclassify an incident outcome case as a prevalent case, or adjudicated versions of a claim may have updated information (e.g. dates). The most accurate count of cases available at the time of each test will be used. In the case of unadjudicated and adjudicated claims, only the first instance of claims will be included in the sequential testing.

Further details about the selection of the test margin m and the estimation of the observation delay adjustment $P(s, t)$ are described in Sections 4.6.7 and 4.6.5, respectively.

4.6.5 Adjustment for Observation Delay

AESIs in the claims data used for the PMaxSPRT analysis will be observed with a certain amount of observation delay, which may vary by outcome and database. Given the need to rapidly evaluate the safety of the vaccine, analyses will be performed using data that has only partially accrued. In order to accurately assess how observed AESI rates compare to expected rates, we need to adjust for the observation delay. If the delay is not accounted for, signals indicating elevated AESI risk may be missed since the expected number of events will be indicative of complete data accrual and therefore be greater than what would be expected under partial data accrual.

To adjust for observation delay, we will use an approach similar to those previously described in the literature for partially accrued data [10]. For each AESI within each database, we will calculate a processing delay distribution *P(s, t)* based on historical data, which represents the probability that an AESI event is observed *t* weeks after it occurs using data arriving in observation week *s*. We will assume that the processing delay distributions are identical among the current and historical time periods. Since this assumption is most plausible for consecutive time periods, we will use recent calendar time to estimate the delays. For the processing delay distribution, we will use the most recent year (2019) to reflect the most up-to-date processing speed. We will explore processing delay from March 2020 to June 2020 to assess potential differences in claims delay during the COVID-19 pandemic.

The observation delay distribution will be used to adjust the expected number of events in the Poisson MaxSPRT. For data arriving in observation week *s*, we will calculate the cumulative proportion of AESIs we would expect to be observed in the database from exposure weeks administered in week *t* | *t ≤ s* using the observation delay distribution:

$$P(s,t) = \sum_{i=0}^{s-t} p(i)$$

This 'percent data complete' reflects the fraction of outcomes that has been observed so far from week *t* by week *s* out of the total data that is expected to be observed once all data has accrued. As a result, earlier exposure weeks will be more complete than later weeks, and the completeness of a fixed exposure week will increase for later observation weeks.

4.6.6 Alpha Spending Plan

The critical bound will be calculated by applying a constant alpha spending plan over the course of the sequential tests. Based on preliminary simulations using historical vaccine uptake data, alpha spending plans spending more alpha earlier in the testing process [45] did not provide meaningfully decreased time-to-signal (data not shown). The specific alpha spending plan may be revised on the basis of further simulations or additional information in a future protocol amendment.

4.6.7 Selection of Test Margin

A test margin will be specified for each AESI within each database in order to improve the operating characteristics of the PMaxSPRT and improve the quality of information for regulatory decision making. As COVID-19 vaccines are expected to be approved or authorized following a favorable benefit-risk

assessment based on data from Phase I-III studies, statistical signals generated by active monitoring are most effectively targeted to detect increases of risk that are large enough to prompt signal refinement.

We investigated the level of severity of the AESIs as a factor when defining the test margin, however since most AESI (except for DVT without PE and Bell's Palsy) have a level of seriousness in that they typically require care in the inpatient environment, severity (as defined by requiring hospitalization) was not one of the considerations in determining the test margins. Instead, the choice of test margin was guided by calculations based on historical AESI incidence rates.

In this study, the test margins *m* are defined based on comparator rates (from historical data) of the outcome θ adjusted for the length of the risk window and a target number of doses needed to harm (NNH). NNH can be interpreted as the number of vaccine doses needed to cause one additional case of AESI within the length of the AESI risk window as compared to a non-vaccinated historical comparator over the same length of time. As the NNH = 1/(θ x RR − θ) (where RR≠1), and RR = 1 + m, the test margin can be defined as:

$$m = \frac{1}{\theta \times NNH}$$

For example, in the scenario where the number needed to harm is set at 500,000 doses, for an outcome with a 42-day risk window with a background rate of 2 events per 100,000 person-years, the test margin would be calculated to be equal to 87% to result in one additional case per 500,000 doses; for a more common outcome with the same risk window and a background rate of 64 events per 100,000 person-years, the margin is instead 2.7%, i.e. rarer events require a higher degree of elevated risk to result in an equal increase in the number of attributable cases compared to more common outcomes.

We selected the threshold of "Number Needed to Harm" (NNH) at 500,000s for potential AESIs (Table 2) based on the relative risk of 2.5 derived in simulations conducted for the detection of GBS in updating sequential probability ratio test (USPRT) analyses during the 2017-18 influenza season[39]. We calculated the "Risk Ratio (1+m)" that achieves NNH of 500,000 for each AESI using historic incidence rates reported in an unpublished FDA/CDC literature review. References will be updated in this protocol upon publication of the literature review. We categorized the test margins for the AESIs into the following three categories:

- H_a: >1.25 – all AESIs except for the AESIs listed in other categories below
- H_a: >1.5 – Multisystem inflammatory syndrome (MIS), Multisystem inflammatory syndrome in children (MIS-C), anaphylaxis, transverse myelitis, myocarditis/pericarditis
- H_a: >2.5 – encephalomyelitis/encephalitis, narcolepsy, Guillain-Barré syndrome (GBS)

4.6.8 BMaxSPRT Analysis for Anaphylaxis

For the anaphylaxis outcome, we will conduct the primary sequential analysis using a self-controlled risk interval design and the Binomial MaxSPRT (BMaxSPRT), in addition to a secondary analysis using PMaxSPRT with a historical comparator. In both cases, analyses will be conducted separately for each data partner and for each vaccine brand. We will test for an increased risk after any dose of vaccine as

the primary analysis, and will consider testing for an increased risk for each AESI following each dose as the secondary analysis. Other key parameters are described as follows:

Testing Frequency: Testing using the BMaxSPRT will occur weekly for the Medicare SSD database, and monthly for BHI, OptumServe, and MarketScan claims data. Sequential testing on any additional databases that are included in the analysis will occur as frequently as those databases are updated. Sequential testing using the BMaxSPRT will begin when at least three events are observed.

Risk and Control Windows: The risk window for anaphylaxis will be 0-1 days as indicated in Table 2. A post-vaccination control window of 7-8 days will be used as in previous vaccine surveillance studies.[40, 46].

Statistical Hypotheses: We will conduct one sided tests where the null hypothesis is that the observed rate of anaphylaxis in the risk window is no greater than 1.5 times the control window, and the alternative hypothesis is that the observed rate in the risk window is greater than 1.5 times the control window: H_o: RR ≤ 1.5 and H_a > 1.5.

Significance Level and Number of Events to Signal: The significance level (alpha) of each sequential analysis will be set to 0.01. At least three events must be observed to declare a statistical signal.

Length of Surveillance: The upper limit of surveillance will be set to the number of events expected to be observed during the course of the vaccination campaign, based on the incidence of the event estimated from historical data as well as the anticipated number of vaccine doses administered in the study population in a 1-year time period.

Critical Bound: The critical bound used for testing will be calculated for each data partner. The critical bound is comprised of the series of critical values that are calculated for each testing point. Calculation of the critical values is based on several pre-specified parameters: the upper limit of events (the testing stopping boundary), the total alpha for the sequential analysis, the alpha spending plan, and the minimum number of events needed to signal. The critical bound will be calculated using numerical procedures implemented in the R package 'Sequential' [44].

Alpha Spending Plan: The critical bound will be calculated by applying a constant alpha spending plan over the course of the sequential tests.

Adjustment for Partially-Accrued Data: We will use previously-implemented adjustments for partially accrued data in the BMaxSPRT[10]. First, we will only include AESI from a given week within a window if the corresponding week in the matched risk or control window has also elapsed to ensure a comparable time exposed in each window under the null hypothesis. Second, we will include event data from a given week when the data from that week is expected to be 95% complete or greater.

4.6.9 Simulation Study to Determine Testing Parameters and Power

To evaluate the operating characteristics of the PMaxSPRT, we will conduct a simulation study to assess the statistical power, false positive rate, and time-to-signal of the method under hypothetical scenarios representing different vaccine uptake patterns and AESI rates post-vaccination. This simulation study will incorporate the comparator rates and observation delays estimated from historical data in order to

provide a robust assessment of the PMaxSPRT under realistic scenarios. The results of the simulation study conducted using Medicare data will be incorporated into an amendment to this protocol document.

For each AESI and population of interest, we will generate simulated observed data under 24 different hypothetical scenarios, each varying two scenario characteristics: (i) the pattern of vaccine uptake in the database and (ii) the risk ratio of the AESI rate relative to the comparator rate. Four uptake patterns will be generated: a single-dose pattern using the historical uptake of the 2019-2020 influenza vaccine (single-dose), a single-dose pattern where uptake is delayed so that the week when 50% of all doses are administered occurs one month later than observed (delayed single-dose), a two-dose pattern using the single-dose pattern where the second dose is administered approximately four weeks after the first dose (two-dose), and a two-dose pattern using the delayed single-dose pattern for the timing of the first dose. The delayed patterns reflect the possibility that COVID-19 vaccine uptake is slower than influenza vaccine uptake. The relative risk under the alternative hypothesis will include these values: 1, 1.1, 1.5, 2, 5, and 10 (i.e., the AESI rate in the vaccinated cohort is a multiple of the comparator rate, according to those relative risk values).

For each scenario, 1,000 sets of simulated observed surveillance data will be generated. To each simulated set of data, the PMaxSPRT method will be applied, and results across the simulated sets will be combined to obtain an overall assessment of the operating characteristics of the method.

Statistical power to detect high RRs (e.g., 5x, 10x) will be calculated by dividing the number of simulated observed seasons in which the sequential hypothesis testing declares a statistical signal by the total number of simulations (1,000) in scenarios generated using those high RRs. False positive rates for no increase in risk will be calculated in a similar way, except using simulations generated from scenarios generated using an RR of 1x. The distribution of the surveillance week when statistical signals occur will be used to estimate the mean time-to-signal.

Example tables for simulation statistics are presented in Tables 4, 5, and 6.

Table 4. Probability of Statistical Signal at Surveillance Week 10

Outcome	Uptake Scenario	Ha: = 1x	1.1x	1.5x	2x	5x	10x
Event A (H$_0$: RR ≤ 1.78x)	Single Dose	0.0%	0.0%	0.0%	0.6%	26.0%	85.3%
Event A (H$_0$: RR ≤ 1.78x)	Single Dose, Delayed	0.0%	0.0%	0.0%	0.0%	0.5%	3.4%
Event A (H$_0$: RR ≤ 1.78x)	Two Dose	0.0%	0.0%	0.0%	0.1%	19.9%	82.1%
Event A (H$_0$: RR ≤ 1.78x)	Two Dose, Delayed	0.0%	0.0%	0.0%	0.0%	0.8%	4.3%

Table 5. Probability of Statistical Signal at Surveillance Week 30

Outcome	Uptake Scenario	Ha: = 1x	1.1x	1.5x	2x	5x	10x
Event A (H$_0$: RR ≤ 1.78x)	Single Dose	0.0%	0.0%	0.3%	5.2%	100.0%	100.0%
Event A (H$_0$: RR ≤ 1.78x)	Single Dose, Delayed	0.2%	0.0%	0.4%	5.2%	100.0%	100.0%
Event A (H$_0$: RR ≤ 1.78x)	Two Dose	0.0%	0.0%	0.2%	4.5%	100.0%	100.0%
Event A (H$_0$: RR ≤ 1.78x)	Two Dose, Delayed	0.0%	0.0%	0.1%	4.9%	100.0%	100.0%

Table 6. Mean Time-to-Signal in Weeks*

Outcome	Uptake Scenario	Ha: = 1x	1.1x	1.5x	2x	5x	10x
Event A (H$_0$: RR ≤ 1.78x)	Single Dose	N/A	N/A	N/A	15.72	11.47	9.78
Event A (H$_0$: RR ≤ 1.78x)	Single Dose, Delayed	N/A	N/A	N/A	16.19	14.14	12.10
Event A (H$_0$: RR ≤ 1.78x)	Two Dose	N/A	N/A	N/A	13.69	11.44	9.77
Event A (H$_0$: RR ≤ 1.78x)	Two Dose, Delayed	N/A	N/A	N/A	19.19	14.04	12.05

*Time to signal not displayed for alternatives less than the null hypothesis

4.6.10 Output Statistics

Example statistics produced by the PMaxSPRT are presented in Table 7. The critical bound will be reported until the maximum length of surveillance or until a statistical signal occurs. All other statistics will be reported for every week in the surveillance period.

Table 7. Example Active Monitoring Statistics Where True RR=2*

Week	Observed # of Events	Risk Ratio vs. Comparator	LLR vs. Null Hyp.	Critical Bound	Signal Observed
10	2	1.89	0.33	-	No
11	5	2.30	1.34	2.27	No
12	11	2.65	3.87	2.94	Yes
13	14	2.15	3.24	-	Yes
14	20	2.09	4.31	-	Yes

* Minimum number of events to signal = 3, test margin set to zero (m = 0%)

Output statistics from the BMaxSPRT will be similar, with the exception that the observed number of events will be split by the risk and control windows.

4.6.11 Limitations of Poisson MaxSPRT and Binomial MaxSPRT

There are several important limitations to our active monitoring approach. The PMaxSPRT provides a comparison of the observed rate of outcomes to a historical comparator and is not expected to adjust for potential confounders (beyond covariates for stratification), such as differences in clinical conditions in the compared populations or changes in overall health care utilization. The test margin implemented for some AESIs may reduce our sensitivity to these sources of bias.

Although alternative sequential testing procedures such as the Binomial MaxSPRT may be less sensitive to time-invariant confounding due to the use of self-matched risk and control windows, we decided to use self-controlled methods for active monitoring only for short time lag, i.e., anaphylaxis. For the other AESIs, observation delay in claims databases is a strong source of time-varying bias which is difficult to adjust for appropriately. In addition, some long risk windows in self-controlled methods may be a challenge in timely safety monitoring. Self-controlled methods will instead be used in interim and final inferential analyses, which are less impacted by observation delay.

The specification of a test margin may reduce the power of the PMaxSPRT and BMaxSPRT to detect small or moderate increases of AESI risk, which may result in a delayed response to potential vaccine safety concerns. However, signal detection necessarily involves a tradeoff between sensitivity and

specificity of statistical signals. While the hypothesis testing could be specified to detect any increase in risk above the comparator, the large size of the database and resulting high statistical power may result in a signal detection procedure that would generate a large number of spurious results. As the objective of active monitoring is to detect highly elevated risk, we will implement a test margin in the testing to improve the quality of signals that are identified. Small increases in risk will be more effectively identified in the interim and final inferential analyses, which implement stronger control for confounding.

The PMaxSPRT can rapidly identify increased risk of AESIs following vaccination but does not generate other information such as confidence intervals for the AESI risk or probabilities that the risk is elevated beyond a certain level. Furthermore, the sequential testing procedure will not be able to specifically identify risk in subgroups that are not pre-specified. To account for these limitations, in the event of a statistical signal we will supplement the statistics generated by the PMaxSPRT with additional statistics generated using alternative approaches as part of signal evaluation.

4.7 Quality Assurance

The study will be conducted using well-characterized databases, such as Medicare, in which the study team members have conducted numerous epidemiologic studies. The study team has assessed these databases for quality and suitability for epidemiologic studies by 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. Further databases added to the active monitoring study will undergo a similar detailed evaluation to assess data quality.

During the active monitoring, data quality will be continuously monitored with every update from the study databases in order to ensure that insurance claims representing vaccinations and AESIs 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, we will implement steps 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. We will also conduct more specific checks on the uptake of health care events occurring in settings similar to COVID-19 vaccination or AESIs, such as other vaccinations or hospitalization for external injuries.

Well-established and validated software such as SAS version 9.4, Stata, and R will be used for statistical analyses. Programs will be developed under version control and changes to programs or other specifications will be tracked (e.g. updates to code lists due to new diagnosis codes). Procedures such as regular code reviews by senior programmers or double programming will be used to ensure integrity of statistical analyses.

4.8 Signal Verification

Near real-time monitoring of AESIs after COVID-19 vaccination provides a useful tool for early signal detection. A signal is a pre-specified threshold.

However, a signal occurring during active monitoring does not necessarily indicate a conclusive, causal association and must be further evaluated. In the event that a signal arises, the following potential steps[2] can be taken by FDA to verify the validity of the signal, and further evaluate the magnitude of elevated risk that it represents.

4.8.1 Post-Signal Data Quality Assurance

As a first step in evaluating the validity of a signal, the quality of the data which produced the signal could be assessed through the following steps:

- Check for possible duplications of vaccinations, safety outcomes, or persons (e.g., if subsequent claims are counted as new episodes of vaccination or AESIs).
- Check for unusual variability in claim accrual by process date and by service date.
- Check for coding issues (e.g., unexpected codes for vaccinations).
- Check for changes in claims recording processes.

4.8.2 Signal Characterization

Signals can further be verified by monitoring them over time and assessing them for patterns like temporal or geographic clustering. Steps that may be taken include:

- Assess the patient's individual diagnoses or procedures surrounding the date of each case in order to identify other potential exposures or to provide additional context about health status.
- Evaluate geographical distribution of cases, checking for any obvious over or underrepresentation of states or regions. Geographical distribution may be relevant to lot distribution or diagnostic practices.
- Evaluate distribution of vaccinations/cases across sub-populations at time of signal and compare to distribution among the population used to calculate background rates. Certain sub-populations that could potentially receive vaccinations earlier on (e.g. nursing home residents) may also be at higher risk for safety outcomes.
- Assess clinical setting of cases (e.g., persons may be more likely to be diagnosed when vaccinated in a physician's office) and the specialty of diagnosing physicians.
- Assess changes in diagnostic criteria or behavior regarding AESIs over time, or changes in guidelines of detecting AESIs or COVID vaccinations
- Use temporal scan statistics to help determine whether any of the AESIs are temporally clustered in particular post-vaccination windows [47].
- Cross-check any potential signals with results from other government-wide sequential analyses findings to see if the signal is identified in other systems

4.8.3 Medical Record Review

To further evaluate potential signals, we may conduct a chart review of representative cases to confirm or rule out AESI outcomes, and evaluate onset date in relation to vaccination date.

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[2] Additionally, FDA specifies at which steps others outside of the Office of Biostatistics and Epidemiology (OBE) would be notified. CMS counterparts will be kept updated on all phases of the signal evaluation once basic data quality checks have been conducted.

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- Cases with an onset date prior to vaccination will be excluded. For those with onset after vaccination, we will assess the onset pattern by week/days instead of relying on admission date from the electronic data.
- For outcomes with a case definition algorithm, which classifies cases as having different levels of probability/plausibility, we will assess how many cases fall in each group. For outcomes without a case definition algorithm, we will consult with experts.

4.8.4 Inferential Safety Analyses

In the case where a signal is considered valid, and it indicates a significantly increased risk for any of the AESIs (as confirmed by the evaluation processes described earlier), we will accelerate the timeline for conducting inferential safety analyses. These analyses will use additional methods, such self-controlled or cohort designs, to evaluate and confirm risk levels using fully accrued data.

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7. Appendix

7.1 Pediatric Outcomes

In the event that the vaccine is approved or authorized for children, the following potential AESIs will be studied among the pediatric subpopulation. These AESIs have not been associated with COVID-19 vaccines based on available pre-licensure evidence.

Table A1. Potential AESIs, age groups, settings, clean windows, and risk windows for the pediatric population.

Pediatric Outcomes				
AESI	**Age Group of Interest**	**Setting**	**Clean Window**	**Risk Window**
Multisystem Inflammatory Syndrome [35]	Ages 0-17 years of age	IP, OP-ED	365 days*	1-42 days
Febrile Seizures [48]	Ages 6-60 months	IP, OP/PB	42 days	0-1 days
Kawasaki Disease [49, 50]	Ages 1-5	IP, OP/PB	365 days	1-28 days

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

Setting Definitions: IP refers to inpatient facility claims. OP-ED refers to a subset of outpatient facility claims occurring in the emergency department. OP/PB refers to all outpatient facility claims, and professional/provider claims except those professional/provider claims with a laboratory place of service.

* References for this window could not be located in the literature and are instead based on input from clinicians

7.2 Brighton Collaboration Case Definitions

Brighton Collaboration case definitions are available for the following AESIs:

- Guillain-Barré Syndrome (GBS)
- Bell's 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)

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Additionally, although a Brighton Collaboration case definition is not available for MIS-C, a CDC case definition is available and can be found here.

Case definitions are **not** available for the following AESIs:

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

7.3 Care Setting Definitions in Claims

The following table summarizes how each setting will be defined for AESI and vaccine exposure identification in claims data sources. Note that the OP-ED setting is a subset of the OP/PB setting.

Table A2. Care Setting Definitions in Claims

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 the ED
Outpatient & Professional (OP/PB)*	Outpatient facility claims (e.g. UB-04) OR Professional claims (e.g. CMS-1500) with at least one non-lab place of service[#]

*Including all sources of professional claims (e.g. urgent care etc.)
[#]Independent laboratory place of service code = 81