ADDENDUM
COVID-19 Vaccine Safety Surveillance: Active Monitoring Protocol Addendum

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This document is intended to serve as an addendum to the COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol for monitoring the rates of various adverse events of special interest (AESIs) following coronavirus disease 2019 (COVID-19) vaccination in near real-time following authorization or licensure. The addendum will describe the methodology for monitoring potential safety outcomes of interest in the pediatric population under 18 years of age who have been authorized for COVID-19 vaccine use.

1. Objectives

The primary objective of the protocol addendum is to expand monitoring of the rates of AESIs following COVID-19 vaccination among the pediatric population between the ages of 5 and 17 years. The CBER BEST Workgroup will use the observed rates of the pediatric outcomes, as data accrue, to identify whether there is a potential increased risk of AESIs following vaccination compared to a control baseline. Similar to the master protocol, the active safety monitoring in the pediatric population detailed in this protocol addendum is a method for signal detection and not signal evaluation. A statistically significant result does not necessarily indicate an increased risk of the adverse event in the pediatric population exposed to the vaccine; such a result must be further investigated and verified.

2. Overview

COVID-19 vaccinations are currently recommended for everyone aged 5 years and older in the United States (U.S.). The U.S. Food and Drug Administration (FDA) has authorized three COVID-19 vaccine brands through Emergency Use Authorization (EUA) or full FDA approval for different age groups, including:

- Pfizer-BioNTech (BNT162b2) COVID-19 Vaccine authorized in ages 5-15 years and approved in ages 16 years and older
- Moderna (mRNA-1273) COVID-19 Vaccine approved in ages 18 years and older
- Janssen (Ad26.COV2.S) COVID-19 Vaccine authorized in ages 18 years and older [1].

The BNT162b2 vaccine is the only currently authorized COVID-19 vaccine for the pediatric population ages 5-17 years. EUA authorization for the BNT162b2 for ages 16 and older was issued on December 11, 2020, and FDA approval was granted on August 23, 2021. FDA expanded the EUA to include adolescents 12 through 15 years of age on May 10, 2021, and issued an EUA for a lower dose BNT162b2 vaccine series for children aged 5 through 11 years old on October 29, 2021.[2] [3] The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices' (ACIP) recommended that children 5 to 11 years old be vaccinated against COVID-19 with the BNT162b2 pediatric vaccine, expanding their recommendation to about 28 million children in the U.S. in this age group. [3]

For all ages, the vaccine is administered intramuscularly as a two-dose primary series, three weeks (21 days) apart. Ages 12+ are given a 30-microgram dose, and ages 5-11 years are given a lower dose of 10 micrograms. [2] [3] FDA amended the EUA for the BNT162b2 COVID-19 vaccine to allow for a third primary series dose at least 28 days following the second dose of the two-dose for certain moderately to severely immunocompromised persons aged 5-17. Additionally, the use of a single booster dose has been authorized in individuals aged 12+, given at least 5 months after completion of the primary vaccination series [4] [5].

Vaccine safety surveillance in the pediatric population will initially focus on the BNT162b2 COVID-19 vaccine, but it will be extended to any additional COVID-19 vaccines that may be available in the future for pediatric population. This post-market active monitoring and reporting is needed to address limitations with safety data from pre-licensure clinical studies, including small sample size and short follow-up for rare adverse events.

3. Data Sources

The current study will include the following commercial insurance databases: CVS Health, Optum pre-adjudicated claims, and HealthCore (HCI). The insurance databases may include both administrative claims data as well as immunization information system (IIS) vaccination data. The FDA BEST Initiative, through their data sharing network, facilitated linkage of claims data with IIS to enhance capture of vaccinations in insured populations for vaccine surveillance studies. IIS jurisdictions were solicited to link COVID-19 vaccination data to member-level claims records within each of the data partners using personally identifiable information and IIS-specific linkage algorithms. Table 1 below briefly outlines currently available administrative claims data sources and displays how often each data source is updated.

Table 1. Description of Administrative Claims Data Sources

Data Source	Claims Type	Update frequency	Data Lag*	Population Enrolled Ages 5-17 years **
CVS Health	Fully Adjudicated	Monthly	Approximately 80% data completeness in 3-4 months for inpatient claims, 2-3 months for outpatient claims, and 1-2 months for professional claims	5-11 years: > 1.5 million 12-15 years: > 991k 16-17 years: > 558k
Optum pre-adjudicated claims	Pre-Adjudicated	Bi-Weekly	Approximately 80% data completeness in 1-2 months for inpatient, outpatient, and professional claims	5-11 years: > 1.3 million 12-15 years: > 840k 16-17 years: > 429k
HealthCore (HCI)	Fully adjudicated	Monthly	Approximately 80% data completeness in 2-3 months for inpatient claims and 1-2 months for outpatient and professional claims	5-11 years: > 1.8 million 12-15 years: > 1.2 million 16-17 years: > 647k

** Data lag based on 2020 claims delay distribution*

*** Average number of annual enrollees in a given age category between 2018-20*

4. Safety Monitoring in Commercial Insurance Databases

To provide a comprehensive characterization of the patterns of vaccine utilization and the rate of AESIs following vaccination in the pediatric population, we will conduct active monitoring in available commercial insurance databases.

As described in the primary protocol, claims databases have several advantages for use in 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 also have disadvantages. The use of administrative codes, to some extent, limits the ability to accurately and reliably identify AESIs. Moreover, the observation delay associated with claims data processing introduces bias in estimated risk. Further, some vaccinations for the pediatric population may not be billed to commercial insurance databases used in this study; therefore, the data may not be generalizable to the overall vaccinated pediatric population. The claims-based monitoring approaches outlined in this section are designed with these advantages and limitations in mind.

4.1 Study Population

The study population will include the pediatric population between the ages of 5 and 17 years. To be included in the AESI-specific analyses, beneficiaries must have been continuously enrolled in a medical health insurance plan from the start of the AESI-specific clean window to the date of COVID-19 vaccination. Beneficiaries are censored at death, disenrollment, end of risk window, end of study period, or a following vaccine dose, whichever comes first. The AESIs as well as associated clean and risk windows for the pediatric population are described in section 4.4.

4.2 Study Period

The study start date will be the earliest EUA date for the BNT162b2 vaccination for each age group:

- Age 5-11: October 29th, 2021
- Age 12-15: May 10th, 2021
- Age 16-17: December 11th, 2020

Surveillance will continue through a pre-specified surveillance length, set for each AESI and age group to the number of events expected to be observed in the 6-month period from initiation of surveillance 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 this time period. The study period may be adjusted if additional vaccines for the pediatric population are approved.

4.3 Exposure

The exposure will be defined as receipt of any dose(s), including the primary series doses (Dose 1+ Dose 2) and the third/booster dose, of the BNT162b2 COVID-19 pediatric vaccine or other future COVID-19 vaccines available for the pediatric population in US. Vaccinations will be identified in administrative claims data through product codes such as Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes or National Drug Codes (NDCs) in the professional, outpatient institutional, inpatient, or prescription drug care settings, and will be identified through product codes

such as CVX (vaccine administered) codes in IIS data. The list of valid codes will be continuously reviewed. The primary analysis will test for an increased risk of each AESI for Dose 1 and Dose 2 together, and the secondary analysis will focus on increased risk of AESIs following specific doses (e.g., Dose 1, Dose 2, and boosters/third doses separately)[1].

4.4 Outcomes

A list of pre-specified potential AESIs following COVID-19 vaccine administration in the pediatric population is included in Table 2. AESIs pre-specified for descriptive and sequential testing are labeled as analysis type "Rapid Cycle Analysis (RCA) and Descriptive," and those pre-specified for descriptive monitoring only are noted "Descriptive Only". The classification of outcomes into those to be monitored descriptively and those monitored via sequential testing is based on the availability of estimable background rates for the outcomes and the expected frequency of events. This list of AESIs may be updated based on observed adverse events in pre-licensure trials, adverse events reporting from other surveillance sources or other sources including international regulators.

Table 2. AESIs, Age Groups, Settings, Clean Windows, Risk Windows, and Analysis Type for the Pediatric Population

AESI	Age Group of Interest	Setting	Clean Window	Risk Window	Analysis Type***
Pediatric Outcomes					
Myocarditis/ Pericarditis	Ages 5-17 years	IP, OP/PB	365 days*	1-7 days[6]	RCA and Descriptive
	Ages 5-17 years	IP, OP/PB	365 days*	1-21 days[38]	RCA and Descriptive
	Ages 5-17 years	IP, OP-ED	365 days*	1-7 days[6]	RCA and Descriptive
	Ages 5-17 years	IP, OP-ED	365 days*	1-21 days[38]	RCA and Descriptive
Guillain-Barré syndrome (GBS)	Ages 5-17 years	IP- primary position only	365 days*	1-42 days[7,8]	Descriptive Only
Multisystem inflammatory syndrome in children (MIS-C)	Ages 5-17 years	IP, OP-ED	365 days*	1-42 days[9]	Descriptive Only
Encephalitis / myelitis / encephalomyelitis	Ages 5-17 years	IP	183 days*	1-42 days[40]	RCA and Descriptive
Transverse myelitis	Ages 5-17 years	IP, OP-ED	365 days*	1-42 days[11]	Descriptive Only
Anaphylaxis	Ages 5-17 years	IP, OP-ED	30 days*	0-1 day[12,13]	RCA and Descriptive

[1] Dose assignment is based on the chronological order in which vaccinations are observed for the person, i.e., the first vaccination observed for a person is assigned a dose number of 1, the second vaccination observed a dose number of 2, and the third observed vaccination a dose number of 3. Further observed doses are not counted within analyses. Vaccine doses must occur at least 3 days apart to be considered distinct doses.

AESI	Age Group of Interest	Setting	Clean Window	Risk Window	Analysis Type***
Common thromboses with thrombocytopenia	Ages 5-17 years	[Definition below]**	365 days*	1-28 days[14]	RCA and Descriptive
Unusual site thrombosis (broad)with thrombocytopenia-cerebral and abdominal thrombosis	Ages 5-17 years	[Definition below]**	365 days*	1-28 days[15]	Descriptive Only
Seizures/Convulsions	Ages 5-17 years	IP, OP-ED	42 days*	0-7 days[16]	RCA and Descriptive
Bell's palsy	Ages 5-17 years	IP, OP/PB	183 days*	1-42 days[17]	RCA and Descriptive
Deep vein thrombosis (DVT)	Ages 5-17 years	IP, OP/PB	365 days*	1-28 days[18-20]	RCA and Descriptive
Pulmonary embolism (PE)	Ages 5-17 years	IP, OP/PB	365 days*	1-28 days[18-20]	RCA and Descriptive
Disseminated intravascular coagulation (DIC)	Ages 5-17 years	IP, OP-ED	365 days*	1-28 days[21]	RCA and Descriptive
Immune thrombocytopenia (ITP)	Ages 5-17 years	IP, OP/PB	365 days*	1-42 days[22,23]	RCA and Descriptive
Kawasaki disease	Ages 5-17 years	IP, OP/PB	365 days*	1-28 days[24,25]	Descriptive Only
Narcolepsy	Ages 5-17 years	IP, OP/PB	365 days*	1-42 days[26-28]	RCA and Descriptive
Appendicitis	Ages 5-17 years	IP, OP-ED	365 days*	1-42 days[29,30]	RCA and Descriptive
Non-hemorrhagic stroke	Ages 5-17 years	IP	365 days*	1-28 days[31,32]	RCA and Descriptive
Hemorrhagic stroke	Ages 5-17 years	IP	365 days*	1-28 days [31,32]	Descriptive Only
Acute myocardial infarction	Ages 5-17 years	IP	365 days*	1-28 days[31,32]	Descriptive Only

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*

*** Both Common thromboses with thrombocytopenia and Unusual site thrombosis (broad) with thrombocytopenia are combined outcomes consisting of a thrombotic event (made up of other events such as acute myocardial infarction, deep vein thrombosis etc.,) and a thrombocytopenia event (defined in the IP, OP/PB setting). The overall setting definition for each outcome depends on individual setting definitions for each of these components*

****Analyses Type "RCA and Descriptive" refers to AESIs for which we will be conducting descriptive monitoring and sequential testing*

4.5 Descriptive Analyses

As in the master protocol, we will use similar descriptive statistics to summarize the observed rates of AESIs in the pediatric population. Table 2 lists all the AESI for which we will be conducting descriptive monitoring only. These statistics will be stratified by age group (5-11, 12-15, and 16-17 years), sex, region, urban/rural status, and data source. Descriptive statistics will be updated continuously, synchronized with the sequential testing, on a monthly basis, as allowed by the individual data source. Table 3 represents the proposed (observed) descriptive statistics for the pediatric population.

Table 3. Example Table of Descriptive Statistics

Patient Characteristic	All Doses*		
	# of COVID-19 Vaccinations	Observed Outcomes – [Outcome]	
		#	Rate (per 100k person-years)
Total			
Sex			
Female			
Male			
Age (years)			
5-11			
12-15			
16-17			
Urban/Rural			
Urban			
Rural			
HHS Region			
[Region 1]			
[Region 2]			
[Region 3]			
[Region 4]			
[Region 5]			
[Region 6]			
[Region 7]			
[Region 8]			
[Region 9]			
[Region 10]			
Facility/Provider Type			
Hospital			
Office			
Pharmacy			
Skilled Nursing Facility			
Home Health Agency			
Mass Immunization Center			
Others			

** Additional statistics will be provided by individual doses*

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

4.6 Sequential Analyses for Safety Monitoring

For safety monitoring in the pediatric population, we will be using the Poisson Maximized Sequential Probability Ratio Test (PMaxSPRT) to conduct sequential hypothesis tests for AESIs labeled as RCA in Table 2.

The sequential analysis will test for an increased risk for each pediatric AESI following BNT162b2 vaccine relative to expected rates. The PMaxSPRT sequential testing methodology will remain the same as in the Adult RCA where hypothesis tests will be continuously conducted until either a statistical signal occurs or until a maximum length of surveillance is reached which is defined in terms of observed events.

Proposed hypotheses, historical comparators, and testing specifications for this study will be discussed in subsequent sections.

4.6.1 PMaxSPRT Specifications

Sequential analyses using the PMaxSPRT for pediatric-only outcomes will be conducted separately for each AESI (as listed in Table 2), data partner, and age group (5-11, 12-15, and 16-17 years). Stratification adjustment by sex will be conducted where background rates permit. Similar to the adult RCA, for the purpose of the sequential analysis, we will test for an increased risk of each AESI after dose 1 and dose 2 together as the primary analysis, and an increased risk for each AESI following each dose (dose 1, dose 2, and boosters/third doses separately) as the secondary analysis will be considered. If additional COVID-19 vaccines are approved in the future for the pediatric population in U.S., the analysis will also be stratified by vaccine brand. Other key parameters are described as follows:

Age Group Stratification: Analyses will be stratified by age groups 5-11, 12-15, and 16-17 ages (i.e., separate analyses will be performed for each age group). [2]

Testing Frequency: Testing using the PMaxSPRT will occur on a monthly basis for OptumServe, CVS Health, and HCI. For individual AESIs, at least three events must be observed to initiate sequential testing.

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 that in 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:

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

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

[2] Age groups selected to match ages included in EUA authorizations

Where 'RR' refers to the rate ratio comparing the post-vaccination rate with the expected rate. The test margin will be selected for each outcome similar to the adult RCA, 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. The specifications for test margins for all AESIs for sequential testing are specified in Table 4.

Table 4. List of AESIs and Corresponding Test Margins for RCA Analysis

AESIs for Sequential Testing	Test Margin
Bell's Palsy	1.25
Anaphylaxis	1.5
Encephalitis/myelitis/encephalomyelitis	2.5
Narcolepsy	2.5
Appendicitis	1.25
Non-hemorrhagic stroke	1.25
Myocarditis/ pericarditis*	1.5
Deep vein thrombosis (DVT)	1.25
Pulmonary embolism (PE)	1.25
Disseminated intravascular coagulation (DIC)	1.25
Immune thrombocytopenia (ITP)	1.25
Common thromboses with thrombocytopenia	1.25
Seizures/convulsions	1.5

** This includes all 4 myocarditis/pericarditis outcomes as specified in Table 2*

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 [33].

Length of Surveillance: The upper limit of surveillance will be set for each AESI to the number of events expected to be observed in the 6-month period from initiation of surveillance, 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 this time period [34-36]. For RCA of third/booster dose in age groups 12-15 and 16-17 years, we will set the surveillance length to the expected number of events within a 6-month period assuming 30% uptake of the booster dose among the subset of persons eligible based on timing of completion of the primary series [39]. In the 5-11 years age group, surveillance length will be calculated similarly as above assuming future authorization of booster doses in this age group.

Critical Bound: Similar to the Adult RCA, 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 maximum length of surveillance), 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' [37]

4.6.2 Comparator Group Selection for PMaxSPRT

Similar to the Adult RCA, 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. A separate background rates protocol has been developed to estimate background rates of AESIs and evaluate possible comparator groups.

In brief, a pre-COVID-19 (i.e., historical) comparator population will be defined for study period January 1, 2019 through December 31, 2019. A separate peri-COVID-19 population will be defined using 2020 data. Within each population, AESI rates per person-time will be calculated for all enrollees in a given time period.

The following guidelines will be used to select the comparator population by comparing pre-COVID-19 and peri-COVID-19 rates

- If 95% confidence intervals of pre-COVID-19 and peri-COVID-19 periods overlap, pre-COVID-19 background rates will be selected as the comparator population
- If the 95% confidence intervals do not overlap because of low outcome counts (<50 counts) or seasonal fluctuations, pre-COVID-19 background rates will be selected as the comparator population
- If the 95% confidence intervals do not overlap because of large fluctuations, more stable background rates will be selected
- Otherwise, if none of the above conditions are satisfied, the time period with lower rate will be selected

Regardless of the ultimate comparator selected, calculated rates will be stratified by age group (5-11, 12-15, and 16-17 years) and by sex if there are sufficient cases (5 or greater) in subgroups of the comparator population. The calculation of PMaxSPRT inputs will remain the same as the adult RCA wherein each test will compare an observed number of events to an expected number of events. The cumulative expected number of events 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.

4.6.3 Output Statistics

Example statistics produced by the PMaxSPRT are presented in Table 5. 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 month during the surveillance period.

Table 5. Example Active Monitoring Statistics Where True Rate Ratio=2*

Month	Observed # of Events	Risk Ratio vs. Comparator	LLR vs. Null Hypothesis.	Critical Bound	Signal Observed
1	2	1.89	0.33	-	No
2	5	2.30	1.34	2.27	No
3	11	2.65	3.87	2.94	Yes

Month	Observed # of Events	Risk Ratio vs. Comparator	LLR vs. Null Hypothesis.	Critical Bound	Signal Observed
4	14	2.15	3.24	-	Yes
5	20	2.09	4.31	-	Yes

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

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