ADDENDUM
COVID-19 Vaccine Safety Surveillance: Protocol Addendum for Near Real-Time Surveillance of COVID-19 Vaccines in the Pediatric Population

CBER Surveillance Program
Biologics Effectiveness and Safety Initiative (BEST)

Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)

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STUDY TEAM

FDA/CBER/OBE	
Hui-Lee Wong, PhD Patricia Lloyd, PhD, ScM Yun Lu, PhD Joyce Obidi, PhD	Richard Forshee, PhD Azadeh Shoaibi, PhD, MHS Steven A. Anderson, PhD Joann Gruber, PhD
Acumen, LLC	
John Hornberger, MD, MS, FACP Michael Wernecke, BS Yoganand Chillarige, MPA Mao Hu, BS Mahasweta Mitra, MPH Elizabeth Smith, BS Carla Gomez Victor, BA Yuhui Feng, MS Rowan McEvoy, BA Jing Wang, BA Sandia Akhtar, BS	Gyanada Acharya, MS Emily Lassman, MS Michelle Ondari, MSPH Kathryn Matuska, BA Yixin Jiao, MPP Shruti Parulekar, MPH Rose Do, MD Marna Bogan, BS, RN, CPC Laurie Feinberg, MD, MPH, MS Thomas MaCurdy, PhD
CVS Health	
Djeneba Audrey Djibo, PhD Cheryl N McMahill-Walraven, MSW, PhD Charlalynn Harris, PhD Smita Bhatia, MCA	Annemarie Kline, MS Nancy Sheffield, BS Harpreet Dhillon, MS Aparna Srikanti, MS
Optum	
Kandace Amend, PhD, MPH Jennifer Song, MA, MURP	C. Robin Clifford, MS John Seeger, DrPH, PharmD
HealthCore/IQVIA	
Alex Secora, PhD (IQVIA) Michael Goodman, PhD (IQVIA)	Christian Reich, MD, PhD (IQVIA) Daniel Beachler, PhD, MHS (HealthCore)

VERSION CONTROL

Version	Description	Date
v1.0	Addendum describing monitoring of BNT162b2 among ages 5-17 years	4/12/2022
v2.0	Methods expanded to include authorization of BNT162b2 to ages 6 months - 4 years, mRNA1273 to ages 6 months – 17 years, and NVX-CoV2373 to ages 12 years – 17 years.	12/01/2022

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 (AESI) following coronavirus disease 2019 (COVID-19) vaccination in near real-time following authorization or licensure. The addendum describes 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 AESI following COVID-19 vaccination among the pediatric population between the ages of 6 months 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 AESI 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 ages 6 months and older in the United States (US). The U.S. Food and Drug Administration (FDA) has authorized four 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 6 months-15 years and approved in ages 16 years and older
- Moderna (mRNA-1273) COVID-19 Vaccine authorized in ages 6 months-17 years and approved in ages 18 years and older
- Janssen (Ad26.COV2.S) COVID-19 Vaccine authorized in ages 18 years and older
- Novavax (NVX-CoV2373) COVID-19 Vaccine authorized in ages 12 years and older

The authorized vaccinations in the pediatric population are summarized below by age group:

Table 1. Dosing Administration Schedule for EUA Authorizations

Brand	Age Group	Authorization	Date of Authorization
BNT162b2	6 months – 4 years	Three-dose primary series (3 micrograms)	EUA: 06/17/2022[1]
	5-11 years	Two-dose primary series (10 micrograms) Third primary series dose for immunocompromised individuals (10 micrograms) Single booster at least 5 months after completion of primary series (10 micrograms)	EUA (primary series): 10/29/2021[2] EUA (third dose): 01/03/2022[2] EUA (single booster): 05/17/2022 [3]
	12-15 years	Two-dose primary series (30 micrograms) Third primary series dose for immunocompromised individuals (30 micrograms) First booster at least 5 months after completion of primary series (30 micrograms) Second booster at least 4 months after receipt of first booster for immunocompromised individuals (30 micrograms)	EUA (primary series): 05/10/2021[4] EUA (third dose): 08/12/2021[5] EUA (first booster): 01/03/2022[6] EUA (second booster): 03/29/2022[6] EUA (bivalent booster): 08/31/2022[7]
	16-17 years	Two-dose primary series (30 micrograms) Third primary series dose for immunocompromised individuals (30 micrograms) First booster at least 5 months after completion of primary series (micrograms) Second booster at least 4 months after receipt of first booster for immunocompromised individuals (micrograms)	Approval (primary series): 08/23/2021[8] EUA (primary series): 12/11/2020 [8] EUA (third dose): 08/12/2021[5] EUA (first booster): 12/9/2021[6] EUA (second booster): 03/29/2022[6] EUA (bivalent booster): 08/31/2022[7]

	Age Group	Authorization	Date of Authorization
mRNA-1273	6 months – 5 years	Two-dose primary series (25 micrograms) Third primary series dose for immunocompromised individuals (25 micrograms)	EUA (primary series): 06/17/2022[9] EUA (third dose): 06/17/2022[9]
	6-11 years	Two-dose primary series (50 micrograms) Third primary series dose for immunocompromised individuals (50 micrograms)	EUA (primary series): 06/17/2022[9] EUA (third dose): 06/17/2022[9]
	12-15 years	Two-dose primary series (100 micrograms) Third primary series dose for immunocompromised individuals (100 micrograms)	EUA (primary series): 06/17/2022[9] EUA (third dose): 06/17/2022[9]
	16-17 years	Two-dose primary series (100 micrograms) Third primary series dose for immunocompromised individuals (100 micrograms)	EUA (primary series): 06/17/2022[9] EUA (third dose): 06/17/2022[9]
NVX-CoV2373	12-17 years	Two dose primary series (5 micrograms)	EUA (primary series): 08/19/2022[10]

Vaccine safety surveillance in the pediatric population initially focused on the BNT162b2 COVID-19 vaccine among ages 5-17 years, and will be expanded to include the additional authorizations of mRNA-1273 in the 6 months to 17 years population, BNT162b2 in the 6 months to 4 years population, and NVX-CoV2373 in the 12-17 years 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 following commercial insurance databases are included in the study: 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.[11] Table 2 below briefly outlines currently available administrative claims data sources and displays how often each data source is updated.

Table 2. Description of Administrative Claims Data Sources

Data Source	Claims Type	Update frequency	Data Lag*	Population Enrolled Ages 0-17 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	0-4 years: 1.2 million 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	0-4 years: 1 million 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	0-4 years: 1.4 million 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 AESI 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 AESI. 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 6 months 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 AESI 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 vaccination for each age group:

- BNT162b2
  - Age 6 months-4 years: June 17th, 2022
  - Age 5-11 years: October 29th, 2021
  - Age 12-15 years: May 10th, 2021
  - Age 16-17 years: December 11th, 2020
- mRNA-1273:
  - Age 6 months-17 years: June 17th, 2022
- NVX-CoV2373:
  - Age 12-17 years: August 19th, 2022

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 and the third/monovalent booster dose,[1] of the BNT162b2 COVID-19, mRNA-1273, or NVX-CoV2373 pediatric vaccines or other future COVID-19 vaccines available for the pediatric population in US. Bivalent booster doses will be excluded from this analysis and will be evaluated in a separate analysis. 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 primary series, and the secondary analysis will focus on increased risk of AESI following specific doses (e.g., Dose 1, Dose 2, and boosters/third doses separately).[2]

4.4 Outcomes

A list of pre-specified potential AESI following COVID-19 vaccine administration in the pediatric population is included in Table 3 AESI 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 AESI 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 3. AESI, Age Groups, Settings, Clean Windows, Risk Windows, and Analysis Type for the Pediatric Population

AESI	Setting	Clean Window	Risk Window	Age Groups of Interest	Descriptive Monitoring	Sequential Testing
Pediatric Outcomes						
Acute Myocardial Infarction	IP	365 days*	1-28 days [40, 41]	6 m-4 y, 6 m-5 y	Yes	No
				5-17 y, 6-17 y	Yes	No

[1] For BNT162b2 in ages 5-17 and mRNA-1273, the primary series is defined as doses 1 and 2. For BNT162b2 ages 6 months – 4 years, the primary series is defined as doses 1, 2 and 3. For NVX-CoV2373, the primary series is defined as doses 1 and 2 in ages 12-17 years.

[2] 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 is assigned a dose number of 2, and the third observed vaccination is assigneda 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	Setting	Clean Window	Risk Window	Age Groups of Interest	Descriptive Monitoring	Sequential Testing
Anaphylaxis	IP, OP-ED	30 days*	0-1 day [19, 20]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Appendicitis	IP, OP-ED	365 days*	1-42 days [36,37]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Bell's Palsy / Facial Nerve Palsy	IP, OP, PB	183 days*	1-42 days [24]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Common Site Thromboses with Thrombocytopenia	[Defined in Footnote]**	365 days*	1-28 days [21]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Deep Vein Thrombosis	IP, OP, PB	365 days*	1-28 days [25, 27]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Disseminated Intravascular Coagulation	IP, OP-ED	365 days*	1-28 days [28]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Encephalomyelitis	IP	183 days*	1-42 days [17]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Febrile Seizures	IP, OP PB	42 days*	0-1 days	6 m-4 y, 6 m-5 y	Yes	No
				5-17y, 6-17 y	Yes	No
Guillain-Barre Syndrome	IP – Primary Position Only	365 days*	1-42 days [14,15]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	No
Hemorrhagic Stroke	IP	365 days*	1-28 days [40, 41]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	No
Immune Thrombocytopenia	IP, OP, PB	365 days*	1-42 days [29, 30]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Kawasaki Disease	IP, OP, PB	365 days*	1-28 days	6 m-4 y, 6 m-5 y	Yes	No
				5-17 y, 6-17 y	Yes	No

AESI	Setting	Clean Window	Risk Window	Age Groups of Interest	Descriptive Monitoring	Sequential Testing
Multisystem Inflammatory Syndrome in Children	IP, OP-ED	365 days*	1-42 days [16]	6 m-4 y, 6 m-5 y	Yes	No
				5-17 y, 6-17 y	Yes	No
Myocarditis / Pericarditis (All Settings) (1-7 day)	IP, OP, PB	365 days*	1-7 days [12]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Myocarditis / Pericarditis (All Settings) (1-21 day)	IP, OP, PB	365 days*	1-21 days [13]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Myocarditis / Pericarditis (IP/OP-ED) (1-7 day)	IP, OP-ED	365 days*	1-7 days [12]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Myocarditis / Pericarditis (IP/OP-ED) (1-21 day)	IP, OP-ED	365 days*	1-21 days [13]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Narcolepsy	IP, OP, PB	365 days*	1-42 days [33-35]	6 m-4 y, 6 m-5 y	Yes	No
				5-17 y, 6-17 y	Yes	Yes
Non-Hemorrhagic Stroke	IP	365 days*	1-28 days [40, 41]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Pulmonary Embolism	IP, OP, PB	365 days*	1-28 days [25-27]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Seizures / Convulsions	IP, OP-ED	42 days*	0-7 days [23]	6 m-4 y, 6 m-5 y	Yes	Yes
				5-17 y, 6-17 y	Yes	Yes
Transverse Myelitis	IP, OP-ED	365 days*	1-42 days [18]	6 m-4 y, 6 m-5 y	Yes	No
				5-17 y, 6-17 y	Yes	No
Unusual Site Thromboses (Broad) with Thrombocytopenia	[Defined in Footnote]**	365 days*	1-28 days [22]	6 m-4 y, 6 m-5 y	Yes	No
				5-17 y, 6-17 y	Yes	No

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 FDA and external clinical experts.*
*** 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*
Feasibility of sequential testing of certain outcomes in <5 age group may be further evaluated based on availability of background rates.

4.5 Descriptive Analyses

As in the master protocol, we will use similar descriptive statistics to summarize the observed rates of AESI in the pediatric population. Table 3 lists all the AESI for which we will be conducting descriptive monitoring only. These statistics will be stratified by age group[3], 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 4 represents the proposed (observed) descriptive statistics for the pediatric population.

Table 4. Example Table of Descriptive Statistics

Patient Characteristic	All Doses*		
	# of COVID-19 Vaccinations	Observed Outcomes – [Outcome]	
		#	Rate (per 100k person-years)
Total			
Sex	No data	No data	No data
Female			
Male			
Age (years)	No data	No data	No data
5-11			
12-15			
16-17			
Urban/Rural	No data	No data	No data
Urban			
Rural			

[3] For BNT162b2, the age groups will be: 6 months-4 years, 5-11 years, 12-15 years, and 16-17 years
For mRNA-1273, the age groups will be: 6 months-5 years, 6-11 years, 12-15 years, and 16-17 years. For NVX-CoV2373, the age groups will be: 12-15 years and 16-17 years. For the "all brand" descriptive statistics, the age stratifications for BNT162b2 will be used where applicable.

Patient Characteristic	All Doses*		
	# of COVID-19 Vaccinations	Observed Outcomes – [Outcome]	
		#	Rate (per 100k person-years)
HHS Region	No data	No data	No data
[Region 1]			
[Region 2]			
[Region 3]			
[Region 4]			
[Region 5]			
[Region 6]			
[Region 7]			
[Region 8]			
[Region 9]			
[Region 10]			
Facility/Provider Type	No data	No data	No data
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 use the Poisson Maximized Sequential Probability Ratio Test (PMaxSPRT) to conduct sequential hypothesis tests for AESI labeled as RCA in Table 3.

The sequential analysis will test for an increased risk for each pediatric AESI following BNT162b2, mRNA-1273, or NVX-CoV2373 vaccination 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 3), data partner, and age group. 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 primary series as the primary analysis, [4] 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 (i.e., separate analyses will be performed for each age group):[5]

- BNT162b2: 6 months-4 years, 5-11 years, 12-15 years, and 16-17 years
- mRNA-1273: 6 months-5 years, 6-11 years, 12-15 years, 16-17 years
- NVX-CoV2373: 12-15 years and 16-17 years

Testing Frequency: Testing using the PMaxSPRT will occur on a monthly basis for OptumServe, CVS Health, and HCI. For individual AESI, 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 AESI 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:

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

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

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 AESI for sequential testing are specified in Table 5.

[4] For BNT162b2 in ages 5-17 years and mRNA-1273 all ages, the primary series is defined as doses 1 and 2. For BNT162b2 in ages 6 months to 4 years, the primary series is defined as doses 1, 2 and 3. For NVX-CoV2373, the primary series is defined as doses 1 and 2 in ages 12-17 years.

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

Table 5. List of AESI and Corresponding Test Margins for RCA Analysis

AESI for Sequential Testing	Test Margin (ages 6 months-4 years, BNT162b2, 6 months-5 years, mRNA-1273)	Test Margin (ages 5 years-17 years, BNT162b2, 6 years-17 years, mRNA-1273, NVX-CoV2373)
Anaphylaxis	1.50	1.50
Appendicitis	1.09	1.25
Bell's Palsy	1.12	1.25
Common Site Thromboses with Thrombocytopenia	1.25	1.25
Deep Vein Thrombosis	1.25	1.25
Disseminated Intravascular Coagulation	1.25	1.25
Encephalomyelitis	1.73	2.50
Guillain Barre Syndrome	2.38	2.50
Hemorrhagic Stroke	1.25	1.25
Immune Thrombocytopenia	1.10	1.25
Myocarditis/Pericarditis (All Settings)*	1.50	1.50
Myocarditis/Pericarditis (IP,OP/ED)*	1.50	1.50
Narcolepsy	N/A	2.50
Non-Hemorrhagic Stroke	1.25	1.25
Pulmonary Embolism	1.25	1.25
Seizures/Convulsions	1.00	1.50

** This includes all 4 myocarditis/pericarditis outcomes as specified in Table 3.*
If additional outcomes are added, test margins will be updated accordingly.

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. [42]

Length of Surveillance: The upper limit of surveillance is 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 [44-45]. When estimating the anticipated number of vaccine doses in the study population in this time period, the following considerations were used:

- For BNT162b2 primary series in ages 5-17 years, we used historical influenza vaccination rates to estimate total vaccine uptake. As BNT162b2 was authorized first for ages 5-17 years, we assumed 100% of market share being assigned to BNT162b2 at surveillance initiation.
    - For mRNA-1273 ages 6-11 years, 12-15 years, and 16-17 years and NVX-CoV2373 ages 12-15 years and 16-17 years, we will use the same vaccine uptake as was originally used for BNT162b2 ages 5-11 years, 12-15 years, and 16-17 years to ensure comparability of results.
- For BNT162b2 RCA of third/booster dose in age groups 5-11 years, 12-15 years and 16-17 years, we 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 [46].

- For BNT162b2 in ages 6 months-4 years and mRNA-1273 RCA in ages 6 months-5 years, we will use the COVID-19 primary series vaccine uptake rate in the 5-11 year age group in the 6 months following EUA to determine estimated total uptake. We assign each brand 100% of total estimated uptake.

Critical Bound: Similar to the Adult RCA, the critical bound used for testing is 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 is calculated using numerical procedures implemented in the R package 'Sequential' [47]

4.6.2 Comparator Group Selection for PMaxSPRT

Similar to the FDA 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 AESI and evaluate possible comparator groups.

In brief, a pre-COVID-19 (i.e., historical) comparator population is defined for study period January 1, 2019 through December 31, 2019. A separate peri-COVID-19 population is 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 are 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 are stratified by age group 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 6. 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 6. 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
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%). LLR = Likelihood Ratio*

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