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

CBER Surveillance Program Biologics Effectiveness and Safety Initiative (BEST)

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VERSION CONTROL

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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 following coronavirus disease 2019 (COVID-19) vaccination in near real-time surveillance following authorization or licensure. The addendum will describe the methodology for monitoring potential safety outcomes following COVID-19 bivalent dose vaccination.

1. Objectives

The primary objective of the protocol addendum is to expand monitoring of the rates of adverse events following COVID-19 vaccination to include surveillance after exposure to the Pfizer-BioNTech COVID-19 bivalent (BNT162b2 Bivalent (WT/OMI BA.4/BA.5))[1] and the Moderna COVID-19 bivalent (mRNA-1273.222)[2] vaccines. The CBER BEST Workgroup will use the observed incidence rates of various outcomes, as data accrue, to identify potential increases in the incidence rate of given adverse events following vaccination compared to a control baseline estimated from the incidence rates from a historical comparator group. The active safety monitoring in the 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 rate of the adverse event in the population exposed to the vaccine; such a result must be further investigated and verified. The protocol currently focuses on the population age groups in which COVID-19 bivalent vaccines have been authorized (ages ≥6 months for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and mRNA-1273.222). The scope of surveillance will be expanded to include additional age groups based on updates to vaccine authorization guidelines.

2. Overview

COVID-19 primary series vaccines have been authorized since December 11, 2020 to protect against COVID-19 infection, and to mitigate severe outcomes, including hospitalization and death. As of June, 2022, primary series COVID-19 vaccines have been recommended for individuals ages six months and older in the United States (U.S.). Initial primary series and booster vaccinations offered strong protection against symptomatic illness from the original COVID-19 strain.[3] On August 31, 2022, the U.S. Food and Drug Administration (FDA) released an emergency use authorization (EUA) for BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and mRNA-1273.222 vaccines with bivalent formulations for individuals aged 12 and 18 years and older respectively, given at least two months have passed since receiving either the primary series or monovalent booster dose.[4] On October 12, 2022, the FDA expanded the EUA to include individuals aged five through 11 years old for the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) vaccine and individuals aged six through 17 years old for the mRNA-1273.222 vaccine.[5] FDA expanded the EUA for both vaccine brands again on December 8, 2022 to include individuals aged 6 months and older.

The FDA has currently provided emergency use authorization for the following two COVID-19 bivalent dose vaccines:

- Pfizer-BioNTech COVID-19 Vaccine, Bivalent (BNT162b2 Bivalent (WT/OMI BA.4/BA.5)): authorized for individuals ages five years of and older as a single booster dose;[4,5] and individuals ages six months through four years as their third primary series vaccination dose, assuming their primary series has not yet been completed[6]

- Moderna COVID-19 Vaccine, Bivalent (mRNA-1273.222): authorized for individuals six months of age and older as a single booster dose[4-6]

The bivalent vaccine doses contain an mRNA component of the original strain of SARS-CoV-2 as well as an additional component of the SARS-CoV-2 virus that is shared between the BA.4 and BA.5 omicron subvariants to ensure increased protection against more recently circulating strains of the virus.[2]

BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and mRNA-1273.222 vaccines are the only currently authorized bivalent COVID-19 vaccines for use in any population. As of September 1, 2022, the Advisory Committee on Immunization Practices and the Centers for Disease Control and Prevention (CDC) recommended the COVID-19 bivalent vaccine formulations be used in the respective populations they are authorized in alignment with the FDA EUA for COVID-19 bivalent vaccines. This recommendation was re-issued on October 12, 2022 and again on December 9, 2022 to align with the expanded EUA for COVID-19 bivalent vaccines in younger age groups.[7-9] With the EUA for bivalent vaccine doses, FDA revoked authorization of the monovalent mRNA vaccines in situations where bivalent vaccines have been authorized as a replacement (for use as a booster or primary series dose, depending on age).[4-6]

For all ages and manufacturers the vaccine is administered intramuscularly. For the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) vaccine, individuals aged 5 years and older may receive a single booster dose at least 2 months after completion of the primary series or receipt of the latest monovalent booster dose. Individuals aged 6 months through 4 years will receive the bivalent vaccine as the third dose of the BNT162b2 primary series.[4-6] For the mRNA-1273.222 vaccine, individuals aged 6 years and older may receive a single booster dose at least 2 months after completion of the primary series or receipt of the latest monovalent booster dose. Individuals aged 6 months through 5 years who received the mRNA-1273 primary series may receive a single booster dose at least two months after completing the primary series[4-6]. Dosing for the bivalent vaccinations are as follows:

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5)
    - Ages 12 years and older: 30 mcg/0.30 mL[10]
    - Ages five years through 11 years: 10 mcg/0.20 mL[10]
    - Ages six months through four years: 3mcg/0.20mL[10]
- mRNA-1273.222
    - Ages 12 years and older: 50 mcg/0.5mL[11]
    - Ages six years through 11 years: 25 mcg/0.25 mL[11]
    - Ages six months through five years: 10mcg/0.20mL[11]

Post-market active monitoring will build on pre-licensure trial research by providing access to robust safety data specific to COVID-19 bivalent vaccines including components of the omicron BA.4 and BA.5 variants.[7] Further, it will increase the generalizability of the vaccines' safety profiles to the general U.S. population through access to a larger, more diverse study population exposed to these bivalent vaccine formulations.

3. Data Sources

The current study will include the following claims data sources: CVS Health, Optum pre-adjudicated claims, HealthCore, and Centers for Medicare & Medicaid Services (CMS) Medicare claims. Immunization Information System (IIS) vaccination data from participating jurisdictions will also be used to supplement claims data in improving the capture of COVID-19 vaccine dose information. The FDA BEST Initiative, through its data sharing network, facilitated linkage of claims data with IIS data to enhance capture of vaccinations in insured populations for vaccine surveillance studies. IIS jurisdictions were solicited to share COVID-19 vaccination data that was then linked to member-level claims records by individual commercial insurer data partners using personally identifiable information and IIS-specific linkage algorithms. Table 1 outlines the administrative claims data sources included in surveillance, and summarizes claims data characteristics by data source. IIS data characteristics are not presented in Table 1, given the variability in data characteristics by IIS jurisdiction and differences in data partner access to IIS registry data.

Table 1. Description of Administrative Claims Data Sources

Data Source	Claims Type	Update frequency	Data Lag*	Population Enrolled
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: > 1.1 million 5-11 years: > 1.5 million 12-17 years: > 1.5 million 18-64 years: > 14.5 million
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: > 0.9 million 5-11 years: > 1.3 million 12-17 years: > 1.2 million 18-64 years: > 11.5 million
HealthCore†	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: > 1.3 million 5-11 years: > 1.8 million 12-17 years: > 1.8 million 18-64 years: > 16.9 million

Data Source	Claims Type	Update frequency	Data Lag*	Population Enrolled
CMS Medicare Shared Systems Fee-for-Service Data (SSD)	Pre-Adjudicated	Daily	>80% data completeness in 30-70 days for inpatient claims	>34 million beneficiaries annually

**Data lag is based on 2020 claims delay distribution*

†Average number of annual enrollees in a given age category between 2018-2021

4. Safety Monitoring in Public and Commercial Insurance Databases

To characterize the patterns of vaccine utilization and the rate of adverse events following COVID-19 bivalent dose vaccination, we will conduct active monitoring in three commercial insurance databases as well as the CMS Medicare database. Unless explicitly noted, methods will remain consistent with prior monitoring conducted for primary series vaccination, as specified in the Active Monitoring Master Protocol specific to the population aged 18 years and over, and the Active Monitoring Protocol Addendum for the population under 18 years.[12,13]

4.1 Study Population

The study population will include individuals aged six months and above in alignment with the latest EUA released for COVID-19 bivalent vaccines. The vaccine brand-specific study populations that will be used for surveillance will be consistent with authorization guidelines as specified in Section 2. This may be expanded to include further populations based on changes in vaccine authorization policies. Individuals aged 64 years and under will be captured in the commercial insurance databases. Individuals aged 65 years and over will be captured in the CMS Medicare database. To be included in the adverse event-specific analyses, beneficiaries must have been continuously enrolled in a medical health insurance plan from the start of the adverse event-specific clean window to the date of COVID-19 vaccination to allow for the sufficient washout/look back period to ensure the capture of incident outcomes. Beneficiaries are censored at death, disenrollment, end of risk window, end of study period, or a following vaccine dose, whichever comes first. The adverse events included in surveillance, and their associated clean and risk windows are specified in Section 4.4.

4.2 Study Period

The study start date will correspond to the respective EUA date for the given vaccine brand and age group. Study start dates by vaccine and age group for populations licensed to use COVID-19 bivalent vaccines are outlined below.[1]

- BNT162b2 Bivalent (WT/OMI BA.4/BA.5), authorized starting
    - August 31, 2022: Ages 12 years and older[4]

[1]The study period will similarly be determined if COVID-19 bivalent vaccines are authorized in additional age groups.

    - October 12, 2022: Ages five years through 11 years[5]
    - December 8, 2022: Ages six months through four years[6]
- mRNA-1273.222, authorized starting
    - August 31, 2022: Ages 18 years and older[4]
    - October 12, 2022: Ages six years through 17 years[5]
    - December 8, 2022: Ages six months through five years[6]

Surveillance in populations licensed to use COVID-19 bivalent vaccines will extend from the age-group specific start date until the pre-specified surveillance length is reached or until May 31, 2023, whichever is earlier. May 31, 2023 was selected to align with the end of influenza season when most uptake of bivalent vaccines is expected to have occurred. The specific approach that will be used to estimate surveillance length is specified in Section 4.6.1.

4.3 Exposure

The study exposure of interest will be defined as receipt of the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and mRNA-1273.222 vaccines. Vaccinations will be identified in administrative claims data through product codes specific to COVID-19 bivalent vaccines defined using Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes or National Drug Codes (NDCs) in all available claims settings. CVX codes will be used to identify COVID-19 bivalent vaccine exposures in IIS data. The list of valid codes is specified in Supplementary Table 1, and will be continuously reviewed and updated in conjunction with ongoing surveillance. An assessment of code usage patterns for COVID-19 bivalent vaccines will be conducted to ensure appropriate code usage. The final exposure definition may be revised to improve capture of the COVID-19 bivalent vaccine.

4.4 Outcomes

A list of pre-specified adverse events that will be included in surveillance following COVID-19 vaccine administration in the COVID-19 bivalent population is included in Table 2. For each adverse event, Table 2 outlines the settings of interest, risk windows, clean windows, age groups of interest and the analysis approach that will be used in surveillance of these outcomes. Certain adverse events are age-specific, and thus will be monitored in specific population subsets. Adverse events will be selected for either descriptive monitoring and/or sequential testing based on the availability of estimable incidence rates for the historical comparator group. Table 2 specifies analyses that will be implemented by adverse event and age group. This list of adverse events may be further updated based on additional evidence from pre-licensure trials and other surveillance systems indicating additional outcomes of particular safety concern.

The settings used to identify pulmonary embolism and immune thrombocytopenia events have been modified for COVID-19 bivalent vaccine surveillance compared to previous settings used in COVID-19

active monitoring surveillance, based on results from medical record review in the CMS population.[2] The following changes to outcomes are implemented:

- Pulmonary embolism—Events identified in IP claims setting only (previously IP/OP/PB)
- Immune thrombocytopenia—Events identified in IP claims setting (primary diagnosis) only (previously IP/OP/PB)
- Common thromboses with thrombocytopenia—Composite outcome including thrombotic event (consisting of pulmonary embolism, and other events) and thrombocytopenia event (defined in IP, OP/PB setting). The modified pulmonary embolism definition is used in identifying relevant thrombotic events. [3]

Table 2. Adverse Events, Settings, Clean Windows, Risk Windows, Age Groups, and Analysis Type for the Bivalent Dose Vaccinated Population

Adverse Event	Setting	Clean Window	Risk Window	Age Group of Interest	Analysis Type
Acute myocardial infarction	IP	365 days*	1-28 days[14,15]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive Only
				5-17/6-17 yrs.	
				18-64 yrs.	Descriptive + Sequential Testing
				65+ yrs.	
Anaphylaxis	IP, OP-ED	30 days*	0-1 day[16,17]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Appendicitis	IP, OP-ED	365 days*	1-42 days[18,19]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Bell's palsy	IP, OP/PB	183 days*	1-42 days[20,21]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Common thromboses with thrombocytopenia	[Definition below]**	365 days*	1-28 days[22]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing

[2] Background rates for the sequential testing historical comparator will be recalculated for modified outcomes as specified in Section 4.6.2.

[3] Composite outcome defined using multiple qualifying events including pulmonary embolism. The modified pulmonary embolism (IP) definition will be used to identify relevant outcomes, previously identified using pulmonary embolism in IP/OP/PB. No other changes will be made to these outcomes.

Adverse Event	Setting	Clean Window	Risk Window	Age Group of Interest	Analysis Type
Common thromboses with thrombocytopenia (cont.)	[Definition below]**	365 days*	1-28 days[22]	5-17/6-17 yrs.	Descriptive + Sequential Testing
				18-64 yrs.	
				65+ yrs.	
Deep vein thrombosis	IP, OP/PB	365 days*	1-28 days[23-25]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Disseminated intravascular coagulation	IP, OP-ED	365 days*	1-28 days[26]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Encephalitis / encephalomyelitis	IP	183 days*	1-42 days[27]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Febrile Seizures	IP, OP-ED	42 days*	0-7 days[28]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive Only
				5-17/6-17 yrs.	
Guillain-Barré syndrome	IP- primary position only	365 days*	1-42 days[29,30]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	Descriptive Only
				18-64 yrs.	Descriptive + Sequential Testing
				65+ yrs.	
Hemorrhagic stroke	IP	365 days*	1-28 days [14,15]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	Descriptive Only
				18-64 yrs.	Descriptive + Sequential Testing
				65+ yrs.	
Immune thrombocytopenia	IP (primary diagnosis only)	365 days*	1-42 days[31,32]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	

Adverse Event	Setting	Clean Window	Risk Window	Age Group of Interest	Analysis Type
Kawasaki disease	IP, OP/PB	365 days*	1-28 days[33,34]	6 mos.-4 yrs. / 6 mos.-5 yrs..	Descriptive Only
				5-17/6-17 yrs.	
Multisystem Inflammatory Syndrome	IP, OP-ED	365 days*	1-42 days[35]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive Only
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Myocarditis/Pericarditis	IP, OP/PB IP, OP-ED	365 days*	1-7 days[36,37] 1-21 days[38]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-34 yrs.	
				18-64 yrs.	
				35-64 yrs.	
				65+ yrs.	
Narcolepsy	IP, OP/PB	365 days*	1-42 days[39-41]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive Only
				5-17/6-17 yrs.	Descriptive + Sequential Testing
				18-64 yrs.	
				65+ yrs.	
Non-hemorrhagic stroke	IP	365 days*	1-28 days[14,15]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Pulmonary embolism	IP	365 days*	1-28 days[23-25]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
				18-64 yrs.	
				65+ yrs.	
Seizures/Convulsions	IP, OP-ED	42 days*	0-7 days[28]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive + Sequential Testing
				5-17/6-17 yrs.	
Transverse myelitis	IP, OP-ED	365 days*	1-42 days[42]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive Only
				5-17/6-17 yrs.	
				18-64 yrs.	Descriptive + Sequential Testing
				65+ yrs.	
Unusual site thrombosis (broad) with thrombocytopenia	[Definition below]**	365 days*	1-28 days[43]	6 mos.-4 yrs. / 6 mos.-5 yrs.	Descriptive Only
				5-17/6-17 yrs.	

Adverse Event	Setting	Clean Window	Risk Window	Age Group of Interest	Analysis Type
Unusual site thrombosis (broad) with thrombocytopenia (cont.)	[Definition below]**	365 days*	1-28 days[41]	18-64 yrs. 65+ yrs.	Descriptive + Sequential Testing

Definitions: Clean Window is defined as an interval used to define incident outcomes where an individual enters the study cohort only if the adverse event of interest did not occur during that interval. Risk Window is defined as an interval during which occurrence of the adverse event 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 clean window could not be located in the literature and are instead based on clinician input*
***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*.

4.5 Descriptive Analyses

As in the master protocol, we will use similar descriptive statistics to summarize the observed rates of adverse events in the bivalent vaccine study population. Descriptive summaries will be produced by data source. Table 2 specifies the adverse events that will be undergoing descriptive surveillance. Descriptive statistics will be stratified by age group, sex, region, urban/rural status, and care setting. The prevalence of concomitant use of the influenza vaccine within the COVID-19 bivalent vaccine population will be summarized on the same date and within 42 days prior to and after the index vaccination date (in alignment with the broadest adverse event-specific risk interval). Descriptive statistics will be updated continuously on a monthly basis, synchronized with sequential testing. Table 3 represents the descriptive statistics that will be produced as part of COVID-19 bivalent vaccine surveillance.

Table 3. Sample Descriptive Statistics Table for COVID-19 Bivalent Vaccine Surveillance

Patient Characteristic	Bivalent Vaccine Doses			
	# of COVID-19 Vaccinations	Observed Outcomes		
		Rate		
		#	Per million vaccinations	Per 100,000 Person-Years
Total				
Sex				
Female				
Male				
Age				
6 mos.-4 yrs/6 mos.-5 yrs*				
5-11/6-11 yrs*				
12-17 yrs.				
18-25 yrs.				

Patient Characteristic	Bivalent Vaccine Doses			
	# of COVID-19 Vaccinations	Observed Outcomes		
		Rate		
		#	Per million vaccinations	Per 100,000 Person-Years
26-35 yrs.				
36-45 yrs.				
46-55 yrs.				
56-64 yrs.				
65-74 yrs.				
75-84 yrs.				
85+ yrs.				
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				
Concomitant Vaccination				
Influenza (+/- 42 days)***				
Influenza (same day)				

**Descriptive statistics will be provided for the 6 months-4 years and 5-11 years age groups for BNT162b2 Bivalent, and the 6 months-5 years and 6-11 years age groups for mRNA-1273.222 based on brand-specific authorization guidelines*

***Health and Human Service (HHS) regions are administrative regions consisting of multiple U.S. states, established by the Office of Regional Health Operations (OHRO) within the Office of Assistant Secretary Health (OASH) in alignment with its regional offices (HHS region reference)*

****Relative to bivalent dose vaccination date to align with the broadest adverse event-specific risk interval*

4.6 Sequential Analyses for Safety Monitoring

For safety monitoring in the COVID-19 bivalent dose vaccinated population, we will use the Poisson Maximized Sequential Probability Ratio Test (PMaxSPRT) to conduct sequential hypothesis testing for adverse events indicated as undergoing sequential testing in Table 2.

The sequential analysis will test for an increased rate of each adverse event following the BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and mRNA-1273.222 vaccines relative to expected rates estimated from a historical comparator group that will be used as a control baseline. Vaccine brands included in sequential testing may be expanded based on future vaccine authorizations. Independent testing will occur by data partner, vaccine brand, and adverse event-specific age groups. The PMaxSPRT sequential testing methodology will remain the same as in previous sequential testing for the COVID-19 primary series and monovalent booster vaccines, where hypothesis tests will be continuously conducted until the earlier of a statistical signal or the maximum pre-specified length of surveillance is reached which is defined in terms of observed events. If length of surveillance hasn't been reached by May, testing will end on May 31, 2023.

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 will be conducted separately for each adverse event (as listed in Table 2), data partner, vaccine brand, and adverse event-specific age group. Stratification adjustment by sex, age and potentially other covariates (e.g., nursing home status in CMS) will be conducted where background rates permit. We will test for an increased rate of each adverse event after the COVID-19 bivalent dose. If additional COVID-19 bivalent vaccines are authorized in the future, the analyses will be expanded to include these vaccine brands of interest. Other key parameters are described as follows:

Age Group Stratification: Analyses will be stratified by the relevant adverse event-specific age groups. In the CMS database, analyses will be conducted in the full population aged 65+ years. Among commercial data partners, testing will be conducted separately in the 6 months-4 years (BNT162b2 Bivalent)/6 months-5 years (mRNA-1273.222), 5-17 years (BNT162b2 Bivalent)/6-17 years (mRNA-1273.222), and 18-64 years (BNT162b2 Bivalent/mRNA-1273.222) populations. For myocarditis/pericarditis specifically, testing will be additionally conducted in the 18-34 and 35-64 years age groups.

Testing Frequency: Testing using the PMaxSPRT will occur on a monthly basis within all databases included in the study (Optum, CVS Health, HealthCore, and CMS). For each adverse event, at least three events must be observed after vaccination to initiate sequential testing.

Statistical Hypotheses: We will conduct one-sided tests as displayed in the formula where the null hypothesis is that the observed rate of adverse events in the vaccinated cohort is no greater than the rate in the historical comparator beyond a prespecified 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 test margin (1+m).

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

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

The rate ratio (IRR) as specified in the formula compares the post-vaccination rate with the expected rate. The test margin was selected for each outcome similar to the approach used for previous COVID-19 vaccine rapid cycle analysis (RCA), based on expert guidance to ensure that large meaningful increases in rates will be detected while avoiding minimal increases that may not be clinically relevant. The specifications for test margins for all adverse events for sequential testing are specified in Table 4 and are consistent with previously utilized test margins in COVID-19 active monitoring surveillance

Table 4. List of Adverse Events and Corresponding Test Margins for RCA

Adverse Events for RCA	Test Margin (6 months-4 years, BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and 6 months-5 years, (mRNA-1273.222)	Test Margin (5+ years, BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and 6+ years (mRNA-1273.222)
Acute Myocardial Infarction	N/A	1.25
Anaphylaxis	1.50	1.50
Appendicitis	1.09	1.25
Bell's Palsy	1.12	1.25
Common thromboses with thrombocytopenia	1.25	1.25
Deep vein thrombosis	1.25	1.25
Disseminated intravascular coagulation	1.25	1.25
Encephalitis/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*	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
Transverse Myelitis	N/A	1.50
Unusual Site thromboses (broad) with thrombocytopenia	N/A	1.50

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

***Sequential testing will be conducted in the 6 months-4 years and 5-17 years age groups for BNT162b2 Bivalent vaccine recipients, or. 6 months-5 years and 6-17 years age groups for mRNA-1273.222 vaccine recipients based on authorization guidelines*

Significance Level and Number of Events to Signal: The significance level (alpha) of each sequential analysis will be 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.[44]

Length of Surveillance: The upper limit of surveillance for each adverse event will be the earlier of (i) 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 and the anticipated number of vaccine doses administered in the study population in this time period or (ii) May 31, 2023 to align with the end of the influenza season.[45-47] The surveillance length will be estimated from the expected number of events within a 6-month period based on COVID-19 monovalent booster uptake.[48] A 100 percent market share will be assumed for both BNT162b2 Bivalent (WT/OMI BA.4/BA.5) and mRNA-1273.222 vaccines to ensure that the length of surveillance is not curtailed due to underestimation of uptake for either vaccine brand. An upper limit of expected events of 1,000 will be used for efficiency in the PMaxSPRT procedure. Surveillance length will similarly be calculated for expanded bivalent vaccine dose authorizations to additional age groups.

Critical Bound: Similar to the RCAs conducted for the COVID-19 primary series and monovalent boosters, the critical bound used for testing will be calculated for each adverse event and data partner. The critical bound is comprised of the series of critical values that are calculated for each testing point; an observed adverse event 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'.[49]

4.6.2 Comparator Group Selection for PMaxSPRT

For each adverse event, database-specific expected rates will be estimated based on a historical, unvaccinated comparator derived from pre-COVID-19 and peri-COVID-19 vaccine periods in 2017-2019 or 2020, respectively. The previously published background rates protocol details the approach used to estimate background rates of adverse events and evaluates possible comparator groups.[50]

Background rates will be consistent with prior analyses. For outcomes where background rate recalculation is required (i.e., pulmonary embolism, immune thrombocytopenia, common thromboses with thrombocytopenia), the following process will be followed: In brief, a pre-COVID-19 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 March-December or June-December 2020 data. Within each population, adverse event rates per person-time will be calculated for all enrollees in a given time period. The following guidelines will be used to select the historical comparator population by comparing pre-COVID-19 and peri-COVID-19 rates for each adverse event:

- If 95% confidence intervals of rates from pre-COVID-19 and peri-COVID-19 periods overlap, the pre-COVID-19 background rate will be selected as the comparator population.
- If the 95% confidence intervals of rates do not overlap because of low outcome counts (<50 counts) or seasonal fluctuations, the pre-COVID-19 background rate will be selected as the comparator population.
- If the 95% confidence intervals of rates from pre-COVID-19 and peri-COVID-19 periods do not overlap because of large fluctuations, the more stable background rate 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 the adverse event-specific 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 in the previous COVID-19 RCAs 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 (i.e., claims processing delay) due to partially accrued data and the implementation of the test margin in the statistical hypothesis.[51] Claims delay will be estimated using a delay distribution from 2019, 2020 or 2021.

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 is reached or until a statistical signal occurs. All other statistics will be reported monthly during the surveillance period.

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

Month	Observed # of Events	Rate Ratio (observed 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%)*

5. References

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6. Appendix

6.1 COVID-19 Bivalent Dose Vaccine Administration Code List

Supplementary Table 1 presents COVID-19 bivalent vaccine product and administration codes available in CPT, HCPCS, NDC diagnosis and medical service coding vocabularies, present as of October 3, 2022. These codes will be used to identify COVID-19 bivalent vaccine administration in the study population. CVX codes are a code set used in IIS data to identify immunization exposures and will be used to identify COVID-19 bivalent vaccine administrations in IIS data. This code list will undergo further review and revision during the surveillance process.

Supplementary Table 1. COVID-19 Bivalent Vaccine Administration Codes* in Claims and IIS data

Manufacturer	Name	Code Type	Code	Age Group
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	CVX Codes (IIS-Specific)	302	6 months-4 years
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	HCPCS/CPT Code	91315	5-11 years
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	HCPCS/CPT Code	0154A	5-11 years
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	CVX Codes (IIS-Specific)	301	5-11 years
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	HCPCS/CPT Code	91312	12+ years
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	HCPCS/CPT Code	0124A	12+ years
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	CVX Codes (IIS-Specific)	300	12+ years
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	NDC 11 Labeler Product ID (Vial)	59267030401	Non-Specific
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	NDC 11 Labeler Product ID (Vial)	59267140401	Non-Specific
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	NDC 11 Labeler Product ID (Vial)	59267140402	Non-Specific
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	NDC 11 Labeler Product ID (Vial)	59267056501	Non-Specific

Manufacturer	Name	Code Type	Code	Age Group
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	NDC 11 Labeler Product ID (Vial)	59267056502	Non-Specific
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	NDC 11 Labeler Product ID (Vial)	59267060901	Non-Specific
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	NDC 11 Labeler Product ID (Vial)	59267030402	Non-Specific
Pfizer-BioNTech	BNT162b2 Bivalent (WT/OMI BA.4/BA.5)	NDC 11 Labeler Product ID (Vial)	59267060902	Non-Specific
Moderna	mRNA-1273.222	CVX Codes (IIS-Specific)	230	6 months-5 years
Moderna	mRNA-1273.222	HCPCS/CPT Code	91314	6-11 years
Moderna	mRNA-1273.222	HCPCS/CPT Code	0144A	6-11 years
Moderna	mRNA-1273.222	HCPCS/CPT Code	91313	18+ years
Moderna	mRNA-1273.222	HCPCS/CPT Code	0134A	18+ years
Moderna	mRNA-1273.222	CVX Codes (IIS-Specific)	229	Non-Specific
Moderna	mRNA-1273.222	NDC 11 Labeler Product ID (Vial)	80777028205	Non-Specific
Moderna	mRNA-1273.222	NDC 11 Labeler Product ID (Vial)	80777028005	Non-Specific
Moderna	mRNA-1273.222	NDC 11 Labeler Product ID (Vial)	80777028299	Non-Specific
Moderna	mRNA-1273.222	NDC 11 Labeler Product ID (Vial)	80777028099	Non-Specific
Moderna	mRNA-1273.222	NDC 11 Labeler Product ID (Vial)	80777028399	Non-Specific
Moderna	mRNA-1273.222	NDC 11 Labeler Product ID (Vial)	80777028302	Non-Specific