ADDENDUM

COVID-19 Vaccine Safety Surveillance: Active Monitoring Protocol

CBER Surveillance Program Biologics Effectiveness and Safety Initiative (BEST)

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This addendum updates 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 authorization or licensure. The addendum will describe the methodology for evaluating potential safety outcomes of interest following third or booster dose administration among a commercially insured population aged 18-64 years and the Medicare population aged 65 years and older.

1. Objectives

The primary objective of this protocol addendum is to detail the approaches used to calculate the rates of AESIs following COVID-19 third primary series dose or first booster dose vaccination among both the commercially insured and Medicare populations and to compare the observed rates to the database-specific rates in historical controls (expected rates) to determine whether there is an increased rate in the vaccinated population. Rate ratios relative to an expected rate and corresponding 95% confidence interval (CI) will be calculated. A statistically significant rate ratio in the direction of increased risk of AESI post-vaccination in this screening analysis will not necessarily indicate an increased risk of the adverse event; such a result must be further investigated and verified.

2. Overview

COVID-19 third primary series doses are currently recommended for persons with immunocompromising conditions; a first booster dose (outside of the primary series) is recommended for everyone aged 12 years and older in the United States (U.S.). As of March 29, 2022, a second booster dose of COVID-19 has been authorized for those 50 years of age and older and for those 12 years and older with certain immunocompromising conditions.[1] The U.S. Food and Drug Administration (FDA) has authorized third or booster doses for three COVID-19 vaccine brands through Emergency Use Authorization (EUA). All authorized COVID-19 vaccines (including primary series doses), authorization dates, and dosing intervals are described in Table 1.

Table 1. COVID Vaccine EUAs and Dose Interval Recommendations

Manufacturer	Name	Vaccine Authorization Dates[2]		Dosing Interval[1,3-5]
Pfizer-BioNTech	BNT162b2 Pfizer-BioNTech COVID-19 Vaccine	1st Dose	12/11/2020	- 21 days between doses 1, 2
		2nd Dose	12/11/2020	- 28 days between doses 2, 3
		3rd Dose	8/12/2021	- 5 months between primary series and booster dose
		1st Booster Dose	9/22/2021	- 4 months between first and second booster doses
		2nd Booster Dose	3/29/2022	
Moderna	mRNA-1273 COVID-19 Vaccine	1st Dose	12/18/2020	- 28 days between doses 1, 2
		2nd Dose	12/18/2020	- 28 days between doses 2, 3
		3rd Dose	8/12/2021	- 5 months between primary series and booster dose
		1st Booster Dose	10/20/2021	- 4 months between first and second booster doses
		2nd Booster Dose	3/29/2022	
Janssen	Ad26.COV2.S COVID-19 Vaccine	1st Dose	2/27/2021	- 2 months between primary series and booster dose
		Booster Dose	10/20/2022	

3. Data Sources

The current study will include administrative claims data from the Centers for Medicare & Medicaid Services (CMS) Medicare database and the following private insurance databases: CVS Health, Optum pre-adjudicated claims, and HealthCore (HCI). Table 2 below outlines currently available administrative claims data sources and displays how often each data source is updated. All listed data sources were included in the COVID-19 Vaccine Safety Surveillance Rapid Cycle Analysis (RCA), including CVS Health and HCI which were added to the analysis after the original posting of the Active Monitoring Master Protocol.[6]

The commercial sources will additionally include available immunization information system (IIS) vaccination data.[7] The FDA BEST Initiative facilitated IIS data linkage for active health plan membership

within each of the commercial data partners. To enhance capture of vaccinations, IIS jurisdictions were solicited to share COVID-19 vaccination data. Linkage between IIS data and data partner claims was performed using personally identifiable information and IIS-specific linkage algorithms.

Table 2. Description of Administrative Claims Data Sources

Data Source		Update frequency	Claims Data Lag*	Enrollees
Centers for Medicare & Medicaid Services (CMS) data sources	Medicare Fee-For-Service	Weekly	Approximately 80% data completeness in 1-3 months for inpatient, outpatient, and professional claims	~48 million total from 2017-2021 ~33 million annually
Commercial claims data sources	CVS Health	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	~37 million total from 2018-2021 ~22 million annually
	Optum Pre-Adjudicated Claims	Bi-Weekly	Approximately 80% data completeness in 1-2 months for inpatient, outpatient, and professional claims	~29 million total from 2017-2021 ~15-16million annually
	HealthCore (HCI)	Monthly	Approximately 80% data completeness in 2-3 months for inpatient claims and 1-2 months for outpatient and professional claims	~46 million total from 2016-2021 ~24 million annually

** Data lag based on 2020 claims delay distribution; does not reflect data lag for IIS data*

4. Safety Monitoring in Administrative Claims Databases

The administrative claims-based monitoring approaches outlined in this section are designed with the advantages and limitations of claims data in mind. As described in the Active Monitoring Master Protocol, one disadvantage of administrative claims data sources is the lower accuracy of identifying health conditions or adverse events of interest by using specific coding systems designed for billing purposes and not clinical management. Moreover, the observation delay associated with claims data processing may introduce exposure or outcome misclassification leading to bias in estimated risk. Furthermore, some exposures such as vaccinations may be under-reported in these databases because the vaccine administration may not be billed to insurance databases and lead to exposure misclassification. While the inclusion of IIS data helps to address this limitation in the relevant states, the

data at large may not be generalizable to the overall vaccinated population. All of these limitations apply to the current study.

4.1 Study Population

The study population will include the Medicare population (aged 65 years and older) and a commercially insured population (aged 18-64 years). To be included in the AESI-specific analyses, persons must have been continuously enrolled in a medical health insurance plan from the start of the AESI-specific clean window (defined in Table 3) to the date of their third or booster COVID-19 vaccine dose.

The comparator group consists of historical controls that provide expected rates of AESI as described in the Active Monitoring Master Protocol. Within each database, AESI rates per person-time will be calculated for all enrollees in a given time period. The selection of the comparator group is identified from background rates analyses conducted on each database.[8] The study will use the same background rates selections as those used in the primary series RCA.

4.2 Study Period

The study start date will be the EUA date for the BNT162b2 vaccination of December 11th, 2020. The study end date is the last date of service or process date in each database at the time of the analysis. Third or booster doses will be included if they occur after August 12th, 2021, which is the date that the U.S. FDA authorized the additional vaccine dose for certain immunocompromised individuals.[9]

4.3 Exposure

The exposures of interest are third or booster doses of the BNT162b2 COVID-19 vaccine and the mRNA-1273 COVID-19 vaccine. Descriptive analyses for Ad26.COV2.S will also be produced, but outcome counts are not sufficient to conduct inferential analyses for this vaccine. The inferential analysis is restricted to persons who received the same product for all three doses although descriptive summaries of heterologous boosting or third dose are provided. Vaccinations will be identified by 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 they will be identified by product codes such as CVX (vaccine administered) codes in IIS data sources. The list of valid codes can be found in the Active Monitoring Master Protocol.

Dose assignment is based on the chronological order in which vaccinations are observed for each person. Third or booster doses are restricted to doses following a two-dose primary series of mRNA vaccines, and following a one-dose primary series for the Ad26.COV2.S vaccine. If greater than 3 doses of mRNA-1273 or BNT162b2 or greater than 2 doses of Ad26.COV2.S are observed, follow-up time is censored at the time of that dose administration. Because sequential vaccines observed in quick succession are likely data entry errors rather than truly distinct vaccinations, if multiple vaccinations for the same person are observed within 3 days of each other, only the first of these is included in the analysis.

4.4 Follow-Up Time

Follow-up time is censored at death (as available), disenrollment, end of risk window, end of study period, a subsequent vaccine dose, or at AESI occurrence, whichever comes first. The AESIs, as well as associated clean and risk windows, are outcome-specific as described in section 4.5.

4.5 Outcomes

A list of pre-specified potential AESIs following COVID-19 third or booster dose vaccinations in the commercially insured and Medicare populations is included in Table 3.

Table 3. AESIs, Settings, Clean Windows, and Risk Windows for the Medicare and Commercial Data Population.

AESI	Setting	Clean Window	Risk Window
Guillain-Barré syndrome (GBS)	IP- primary position only	365 days	1-42 days[10,11]
Bell's palsy	IP, OP/PB	183 days	1-42 days[12]
Anaphylaxis (positive control)	IP, OP-ED	30 days	0-1 days[13,14]
Encephalomyelitis	IP	183 days	1-42 days[15]
Narcolepsy	IP, OP/PB	365 days	1-42 days[16-18]
Appendicitis	IP, OP-ED	365 days	1-42 days[19,20]
Non-hemorrhagic stroke	IP	365 days	1-28 days[21,22]
Hemorrhagic stroke	IP	365 days	1-28 days[21,22]
Acute myocardial infarction	IP	365 days	1-28 days[21,22]
Myocarditis/pericarditis	IP, OP/PB	365 days	1-21 days[23]
	IP, OP-ED**	365 days	1-21 days[23]
Deep vein thrombosis (DVT)	IP, OP/PB	365 days	1-28 days[24,25]
Pulmonary embolism (PE)	IP, OP/PB	365 days	1-28 days[24,25]
Disseminated intravascular coagulation (DIC)	IP, OP-ED	365 days	1-28 days[26]
Immune thrombocytopenia (ITP)	IP, OP/PB	365 days	1-42 days[27,28]
Unusual site thrombosis (broad) with thrombocytopenia†	IP, OP-ED	365 days	1-28 days[29]
Common site thrombosis (broad) with thrombocytopenia†	IP, OP/PB	365 days	1-28 days[30]

AESI	Setting	Clean Window	Risk Window
Transverse myelitis	IP, OP-ED	365 days	1-42 days[31]

Definitions: Clean window is an interval used to define incident outcomes where an individual enters the study cohort only if the AESI did not occur during that interval. The anchor date of the clean window is the date of third or booster dose vaccination. Risk window is an interval during which occurrence of the AESI will be included in the analyses. All risk windows were selected based on input from clinicians and observations from the primary series RCA.

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

***Only to be used in the commercial claims analyses*

†Both common thromboses with thrombocytopenia and unusual site thrombosis (broad) with thrombocytopenia are combined outcomes consisting of a thrombotic event (composed 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.

4.6 Descriptive Analyses

The count of third or booster dose vaccines and outcomes following these vaccinations observed in the commercially insured (aged 18-64 years) and Medicare populations (aged 65 years and older) will be summarized. Statistics will be stratified by sex and age group (as defined in Table 4 below), as well as by prior history of COVID-19 diagnosis. Additionally, cohort construction statistics, counts of cases by outcome setting, and counts of homologous vs. heterologous booster doses will be produced. Length of hospital stay will be summarized for inpatient setting cases. Descriptive statistics will be produced for the three COVID-19 vaccine brands. Example tables representing the proposed descriptive statistics can be found below in Table 4.

Table 4a. Example Table of Descriptive Statistics- Vaccine Uptake

Age (years)	Vaccine Count by Brand			
	Overall	BNT162b2	mRNA-1273	Ad26.COV2.S
Overall Sex				
Overall				
18-25*				
26-35*				
36-45 *				
46-55*				

Age (years)	Vaccine Count by Brand			
	Overall	BNT162b2	mRNA-1273	Ad26.COV2.S
56-64*				
65-74**				
75-84**				
85+**				
Male				
Overall				
18-25*				
26-35*				
36-45*				
46-55*				
56-64*				
65-74**				
75-84**				
85+**				
Female				
Overall				
18-25*				
26-35*				
36-45*				
46-55*				
56-64*				
65-74**				
75-84**				
85+**				

Additional statistics will be provided by individual doses and AESIs.

**These age groups will be monitored in commercial claims population only*

***These age groups will be monitored in the Medicare population only*

Table 4b. Example Table of Descriptive Statistics- Homologous/Heterologous Boosting Summary

Brand	Count of Persons	Percent
Primary Series: BNT162b2		
Total third or booster doses among BNT162b2 primary series recipients		
Ad26.COV2.S booster		
BNT162b2 Third or booster		
mRNA-1273 Third or booster		
Primary Series: mRNA-1273		
Total third or booster doses among BNT162b2 primary series recipients		
Ad26.COV2.S booster		
BNT162b2 Third or booster		
mRNA-1273 Third or booster		
Primary Series: Ad26.COV2.S		
Total booster doses among Ad26.COV2.S primary series recipients		
Ad26.COV2.S booster		
BNT162b2 booster		
mRNA-1273 booster		

BNT162b2 or mRNA-1273 boosters will be excluded when the administration codes indicate third or booster dose while the chronology indicates either a first or second observed dose.

Ad26.COV2.S boosters will be excluded when the administration code indicates a booster dose while the chronology indicates a first dose.

4.7 Incident Rate Ratio Analysis

For the incident rate ratio (IRR) analysis, the risk of the AESI following a third or booster dose will be evaluated for the two mRNA vaccines. The analysis will compare the AESI rates in a database-specific historical control population to the risk of the AESI in the risk window after the vaccination. For the Medicare (65+ years old) population, one sided tests will be conducted where the null hypothesis (H0) is

IRR=1, the alternative hypothesis (Ha) is IRR>1, and the alpha is 2.5%. For the commercial claims population (18-64), one-sided tests will be conducted where the alpha is 2.5% and the null and alternative hypotheses are listed below to align with the selection of test margins outlined in the Active Monitoring Master Protocol (section 4.6.7).

- H0: IRR = 1.25; Ha: IRR > 1.25 – all AESIs except for the AESIs listed in other categories below
- H0: IRR = 1.5; Ha: IRR > 1.5 – anaphylaxis, transverse myelitis, myocarditis/pericarditis
- H0: IRR = 2.5; Ha: IRR > 2.5 – encephalomyelitis, narcolepsy, Guillain-Barré syndrome (GBS)

4.7.1 Primary Analysis

For each outcome, the following statistics will be calculated:

- Observed cases
- Expected cases (based on historical background rates)
- Observed person-time in years (adjusted for claims processing delay)
- Observed incidence rate (IR) per 100,000 person-years, 95% CI
- Expected IR per 100,000 person-years
- IRR of observed IR vs. expected IR, 95% CI
- Risk difference, 95% CI

4.7.1.1 Adjustment

The expected rates will be adjusted by the following subgroups among the observed doses (if sufficient counts are observed in the background rates): age and sex (all data sources), nursing home residency and race/ethnicity (CMS only; race/ethnicity and nursing home residency status data elements are missing at a high proportion in the commercial claims databases). The analysis will additionally be adjusted for claims-delay based on estimates of observation delay from historical data. Please reference the Active Monitoring Master Protocol (section 4.6.5) for more details.

4.7.1.2 Rate Calculation

The expected IRs are calculated as the average of the expected IRs among each of the aforementioned subgroups weighted by the proportion of that subgroup in the vaccinated population as described in the Active Monitoring Master Protocol. Observed IRs are calculated by dividing observed IRs by expected IRs.

Analyses for myocarditis/pericarditis will be stratified by age 18-45 and 46-64 years in the commercial claims population to more granularly assess risk by age as other analyses have indicated an increased risk of myocarditis/pericarditis following COVID-19 vaccination particularly amongst younger males.[32-45]

A follow up analysis will be conducted to stratify this outcome by ages 18-49 and 50-64 to more closely align with FDA authorizations of additional booster doses.

4.7.1.3 Confidence Interval Calculation

95% CIs for IRRs are calculated using a Poisson distribution.[46]

$$CI_{low} = \frac{\frac{1}{2}\, ChiInv\left(\frac{\alpha}{2}, 2 * observed\ events\right)}{expected\ events}$$

$$CI_{high} = \frac{\frac{1}{2}\, ChiInv\left(1 - \frac{\alpha}{2}, 2 * (observed\ events + 1)\right)}{expected\ events}$$

Where α = 0.05 and Chi Inv(p,n) is the inverse of the chi-squared distribution function evaluated at p with n degrees of freedom.

4.7.1.3 Risk Difference Calculation

Risk difference is calculated by subtracting the expected number of cases from the observed number of cases per million doses. The number of cases per million doses is obtained by multiplying the observed and expected IRs per day by the length of risk window and by 1 million such that the units are cases per million doses. The lower/upper bound of the 95% CI for the risk difference is obtained by subtracting the expected IR per day from the lower/upper bound of the 95% CI for the observed IR per day and multiplying by the length of the risk window and by 1 million such that the units are cases per million doses.

4.7.1.4 Output Statistics

Example statistics produced by the analysis are presented in Table 5. A statistical signal will be observed when the estimated IRR exceeds H0 and when H0 is not within the IRR 95% CI.

Table 5. Example Incident Rate Ratio Statistics

Outcome	Events		Incident Rate Ratio			Signal
	Expected	Observed	H0	Estimate	95% CI	
Outcome 1	X1	Y1	1	1.20	(0.72-1.87)	No
Outcome 2	X2	Y2	1.25	1.15	(1.00-1.38)	No
Outcome 3	X3	Y3	1.5	1.6	(1.36-1.75)	No
Outcome 4	X4	Y4	2.5	2.56	(2.41-2.67)	No
Outcome 5	X5	Y5	1	1.61	(1.09-2.28)	Signal
Outcome 6	X6	Y6	1.25	1.52	(1.28-1.73)	Signal
Outcome 7	X7	Y7	1.5	1.83	(1.56-2.12)	Signal
Outcome 8	X8	Y8	2.5	2.86	(2.62-3.11)	Signal

4.7.2 Secondary Analysis

A secondary analysis stratified by history of COVID-19 diagnosis will be conducted for each AESI. Prior COVID-19 history will be identified by any diagnosis of COVID-19 in any setting (using the International Classification of Diseases, Tenth Revision, Clinical Modification: U07.1) on or following April 1, 2020. Persons are not required to be enrolled from April 1, 2020 to correspond with the COVID-19 identification period; enrollment requirements will remain consistent with the AESI clean windows. This analysis will be interpreted with the caveat that diagnosis codes may not comprehensively identify all COVID-19 infections (such as those that are not medically attended or diagnosed in settings without claims filed with the health insurance).

4.7.3 Meta-Analysis

Given a common study protocol and a standard analytical package will be used across commercial claims databases that cover populations with similar demographics, a meta-analysis will be performed to pool the commercial claims results to gain higher precision and statistical power using both random-effects and fixed-effect models.

Below, $\hat{\theta}_k$ is used to represent the estimator (log of rate ratio or log of incidence rate) estimated from each data source, where k = 1,2,3 indicates the data sources — Optum, HealthCore, CVS Health, respectively. The goal is to estimate the pooled result:

$$\hat{\theta} = \frac{\sum_{k=1}^{K} \hat{\theta}_k \omega_k}{\sum_{k=1}^{K} \omega_k}$$

where ω is a weight assigned to each estimate.

4.6.3.1 Random-Effects Meta-Analysis

We will use random-effects meta-analysis to account for the between-study heterogeneity across multiple data sources.

The random-effects model takes the form:

$$\hat{\theta}_k = \mu + \zeta_k + \epsilon_k$$

Where μ is the global true effect of interest, ζ_k is a data source specific random error term and ϵ_k is data source specific sampling error term. The pooled effect can be estimated by the inverse-variance method

$$\hat{\theta} = \frac{\sum_{k=1}^{K} \hat{\theta}_k \omega_k^*}{\sum_{k=1}^{K} \omega_k^*}$$

$$\omega_k^* = \frac{1}{s_k^2 + \tau^2}$$

where s_k^2 represents variance of $\hat{\theta}_k$ estimated for each study, and τ^2 is the variance of the distribution of true effect sizes.

The Paule-Mandel method will be used to estimate τ^2 as suggested by Veroniki (2016). [47] Bakbergenuly (2020) additionally found that the Paule-Mandel estimator is well-suited for when the number of studies is small. [48] As a sensitivity analysis, we will use the DerSimonian-Laird and restricted maximum likelihood (RMLE) estimators for τ^2 in order to assess the variation in the estimation of τ^2 due to the small number of studies.

4.6.3.2 Fixed-Effect Meta-Analysis

To address concerns that the random-effects method may not perform well when the number of studies is small, we will additionally run a fixed-effect meta-analysis. The fixed-effects model takes the form:

$$\hat{\theta}_k = \mu + \epsilon_k$$

Where μ is the global true effect of interest, and ϵ_k is data source specific sampling error term. The pooled effect can be estimated by the inverse-variance method

$$\hat{\theta} = \frac{\sum_{k=1}^{K} \hat{\theta}_k \omega_k}{\sum_{k=1}^{K} \omega_k}$$

$$\omega_k = \frac{1}{s_k^2}$$

where s_k^2 represents variance of $\hat{\theta}_k$ estimated for each study.

4.6.3.3 Evaluating Between-Study Heterogeneity

This section describes the methods we will use to evaluate between-study heterogeneity.

Forest Plots

Forest plots will be generated to visualize the variation of rate ratios and 95% CIs across data sources.

Cochran's Q

Cochran's *Q* is defined as a weighted sum of squares (WSS).

$$Q = \sum_{k=1}^{K} \omega_k \left(\hat{\theta}_k - \hat{\theta}\right)^2$$

We will use the value of *Q* to check if there is excess variation in our data. If there is no between-study heterogeneity, Q will approximately follow a chi-square distribution with K-1 degrees of freedom. As Q may be sensitive to the number of studies assessed, an additional complementary statistic will be assessed (further details below).

Higgins & Thompson's I^2 Statistic

We will also calculate Higgins & Thompson's I^2 statistic, [49] which is defined as the percentage of variability in the effect sizes that is not caused by sampling error:

$$I^2 = \frac{Q - (K-1)}{Q}$$

- I^2 = 25%: low heterogeneity
- I^2 = 50%: moderate heterogeneity
- I^2 = 75%: substantial heterogeneity

The 95% CI for I^2 will also be calculated.

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