

RESPONSE TO FDA COMMENTS ON SAFETY RECEIVED ON JULY 14, 2021

The Sponsor acknowledges FDA comments on SAFETY topics (in **BOLD**)

We have completed the review of Post-Authorization Safety Protocol mRNA 1273-P903 submitted in amendment 129 to EUA 27073, and have the following comments:

ITEM 1:

Page 11, Section 9.1. “In Objective 1.b, vaccine exposed IRs for predefined AESIs will be estimated in Time Period 3 among mRNA-1273-vaccinated individuals. Further, crude and age/sex adjusted IRRs will be estimated to compare IRs for mRNA-1273- vaccinated (exposed) individuals in Time Period 3 to the background (referent) IRs estimated in Time Periods 1 and 2 as part of Objective 1a above..”

FDA Comment # 1:

The referent background IRs will be estimated using individuals in Time Periods 1 and 2, and vaccine exposed IRs will be estimated using SARS-CoV-2 mRNA- 1273 vaccinated individuals in Time Period 3.

Individuals included in Time Periods 1 and 2 may not be comparable with the exposed individuals in Time Period 3. For Time Periods 1 and 2, no COVID-19 vaccines were available, however, other types of vaccines such as influenza vaccines were available. Vaccinated and unvaccinated individuals could have different health seeking behaviors or medical conditions. Please clarify how to mitigate against biases due to the differences between Cohorts 1&2 and Cohort 3.

Time varying confounders could potentially bias the results. For example, the COVID-19 pandemic could have long-term and short-term impact on people’s health seeking behavior. Please clarify how to mitigate against biases due to time varying confounders such as change of health seeking behavior.

Sponsor Response:

The Sponsor agrees that there is potential for bias when comparing vaccinated patients in the post-EUA time period to non-vaccinated patients in the pre-COVID and peri-COVID time periods. Therefore, in addition to estimating background AESI rates in T1 (pre-COVID), T2 (peri-COVID), and T3 (Moderna vaccinated), the study will additionally estimate background rates in T1 among patients who have received an influenza vaccine. This rate will be compared to T3 (Moderna vaccinated) and may trigger O/E in those populations, which may then trigger SCRI analysis of the specific AESI. Details of this additional analysis and triggering criteria have been added to Protocol v3.1. Additionally, descriptive analyses to understand differences that may exist between patients who receive the mRNA-1273 vaccination and those who received the influenza vaccine during a pre-COVID era will be implemented.

To understand the potential for bias from time-varying confounders such as healthcare utilization over the study periods, the rates of medical conditions and procedures expected to be consistent over time (e.g. brain surgery, heart attack, revascularization procedure) will be examined over each of the three study time periods. This will provide context on the potential quantity of bias that may be introduced by changes in healthcare resource utilization over time.

Furthermore, if an SCRI analysis is triggered for a specific AESI, control for potential time-varying confounding will be considered and documented in the Protocol Annex 2.

ITEM 2:

Page 13, Section 9.1. “In the SCRI design, the length of the risk and control periods are fixed but may be unequal. Each AESI will be assigned specific risk and control periods based on biologically plausible mechanisms.”

FDA Comment # 2:

Please specify the risk and control periods for each AESI. Annex 2 on Page 32 and 33 only provided the risk window for some of the AESIs.

Sponsor Response:

Protocol v3.1 Annex 2 has been updated to specify the risk window for each AESI. These risk windows are aligned with the FDA and/or CDC COVID-19 vaccine safety surveillance protocols and will be utilized in the case an O/E analysis is triggered. As noted in the updated Protocol v3.1, these are suggested starting points, and upon an AESI-specific trigger for a SCRI analysis, the length of the risk period will be re-evaluated considering current literature, publicly available protocols, and biologic feasibility, and potentially updated in a corresponding Protocol Annex 2.

For the control period, a 183-day window will be applied consistently across all AESIs. This is aligned with the FDA’s COVID-19 vaccine safety surveillance protocol and is documented in Annex 2 of Protocol v3.1. Upon an AESI-specific trigger for a SCRI analysis, the length of the control period will be re-evaluated and potentially updated. Further, an optional washout period (if applicable) will be defined. These will be documented in Annex 2 of the protocol and submitted to the Agency prior to conducting the SCRI analysis.

SCRI risk window for each AESI

Note: Day 0 = the day of the vaccine dose; Day 1 = the day after the vaccine dose

AESI	Risk window (days)
Acute aseptic arthritis	1-28
Acute disseminated encephalomyelitis (ADEM)	1-21
Acute kidney injury	1-28
Acute liver injury	1-28
Acute myocardial infarction (AMI)	1-28
Acute respiratory distress syndrome (ARDS)	1-21
Anaphylaxis	0-11
Anosmia, ageusia	1-28
Arrhythmia	1-28
Aseptic meningitis ²²	8-35
Bell’s palsy ^{24,25}	1-60
Cerebral sinus venous thrombosis	1-28
Chilblain-like lesions	1-28
Coagulation disorders	1-28
Deep vein thrombosis (DVT)	1-28
Disseminated intravascular coagulation (DIC)	1-28
Encephalitis / Encephalomyelitis ²⁵	1-42

Erythema multiforme	1-28
Gestational diabetes	1-28
Guillain-Barré Syndrome (GBS) ^{13,25,26}	1-42
Heart failure	1-28
Immune thrombocytopenia ²⁷	1-42
Ischemic heart disease	1-28
Kawasaki disease	1-21
Meningoencephalitis	1-21
Microangiopathy	1-28
Multisystem Inflammatory Syndrome	1-42
Myocarditis	1-42
Narcolepsy / Cataplexy	1-42
Pericarditis	1-42
Preeclampsia	1-28
Preterm labor	1-28
Pulmonary embolism (PE)	1-28
Seizures/convulsions	0-1
Single organ cutaneous vasculitis	1-28
Spontaneous abortion	1-28
Stillbirth	1-28
Stroke, hemorrhagic	1-28
Stroke, non-hemorrhagic	1-28
Thrombosis with thrombocytopenia	1-42
Transverse myelitis	1-42

ITEM 3:

Page 14, Section 9.2., Figure 3. “Patients with at least 28 days continuous enrollment after 2019-01-01”.

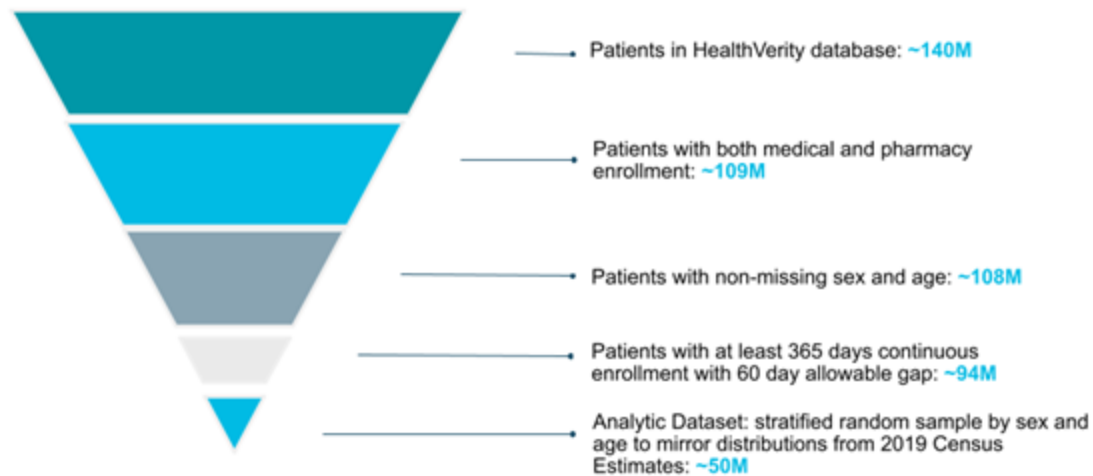
FDA Comment # 3:

Time Period 1 starts on 2018-12-01, and Figure 1 mentioned “EXCLUDE: No continuous enrollment during AESI clean period” “*At earliest starts 2017-12-01”. Please clarify why the date 2019-01-01 was chosen for analytic dataset for background rates in Figure 3.

Sponsor Response:

Figure 3 has been updated in Protocol v3.1, Section 9.2 (and copied below) to reflect changes to the continuous enrollment requirement. Previously, patients were required to have at least 28 days of continuous enrollment after January 1, 2019 to be included in the Time Period 1 & 2 Analytic Dataset. Following exploration of an updated cut of the Healthverity database, the Analytic Dataset criteria has been updated so that patients are required to have continuous enrollment (allowing for a maximum 60-day gap) for at least 365 days any point during Time Period 1 and Time Period 2. This update maintains the initial dataset size for Time Period 1 & Time Period 2 of approximately 50M patients, consisting of ~39M adults and ~11M pediatric patients (to support the expanded patient population as documented in Protocol v3.1).

Figure 3. Analytic Dataset for Background Rates (Time Period 1 & Time Period 2)



ITEM 4:

Page 15, Section 9.2. “Cohort 1: Entire cohort meeting eligibility per Figure 5 in Time Period 1: Pre-COVID period from 1 Dec 2018 to 30 Nov 2019”. Page 16, Figure 5, “Allowable cohort entry date range: 2018-12-01 through 2012-02-29”.

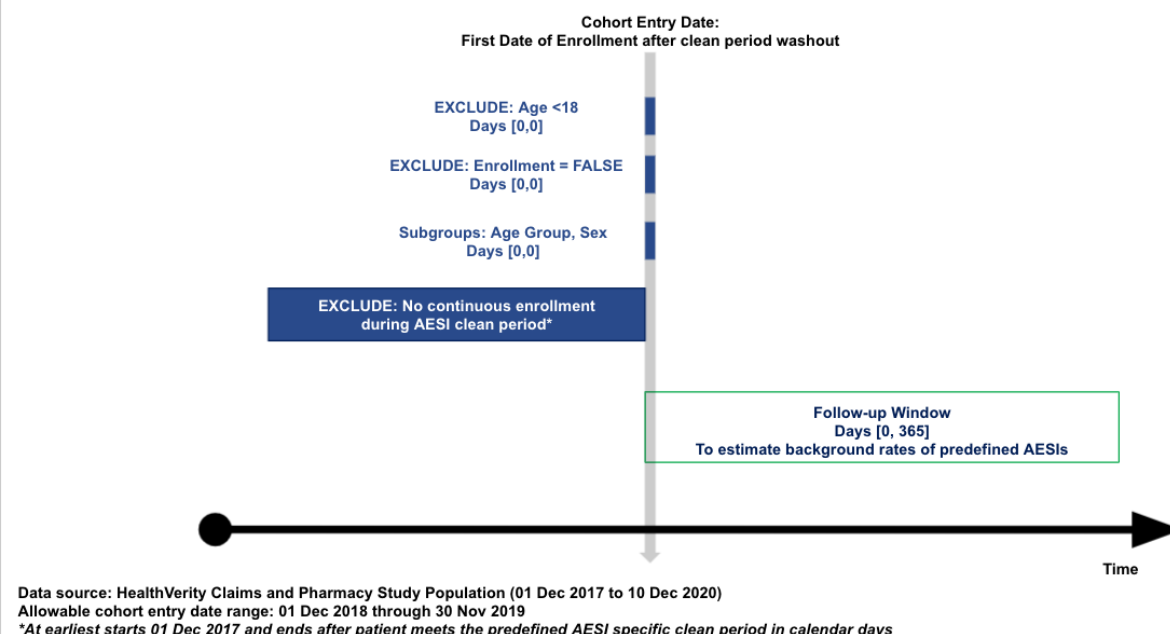
FDA Comment # 4:

Please clarify the discrepancy between these two cohort entry date ranges. In Figure 5, the allowable cohort entry end date for Cohort 1 is 2012-02-29. If this is incorrect, please provide a correct date

Sponsor Response:

The date in the Figure 5 footnote contained a typographical error. It has been updated in Figure 5 in Protocol v3.1 (and copied below) with allowable cohort entry dates between 01 Dec 2018 and 30 Nov 2019.

Figure 5. Cohort 1a: Static Adult Cohort (Time Period 1)



ITEM 5:

Page 18, Section 9.3.2. “AESIs will be identified in claims data and defined using ICD-10 and ATC codes. To the extent possible, existing validated algorithms have been or will be used to define those outcomes (e.g., protocols from FDA CBER, VAC4EU11, FDA Sentinel). Algorithms may be adapted from other sources or created for this study based on literature review.”

FDA Comment # 5:

Please specify how to validate outcomes. Please provide information including a list of AESIs with existing validated algorithms and details of the validation algorithms. Please specify how to handle AESIs without existing validated algorithms.

Sponsor Response:

The sponsor appreciates the importance of utilizing validated measures when possible. Annex 1 in Protocol v3.1 (and copied below) has been updated with the reference for each AESI algorithm. The study will utilize algorithms aligned with those listed in the FDA and/or ACCESS protocols. If not available in those sources, algorithms from literature are used.

The AESIs of interest are defined using ICD-10 diagnosis codes, and several existing validated AESI algorithms are based on ICD-9 diagnosis codes alone. Conducting specific validation exercises across all of the AESI would delay the potential detection of safety issues through active surveillance activities in Objectives 1 & 2 (comparison of incidence rates & O/E analyses).

If/when Objective 3 (SCRI) is triggered for signal refinement, the literature and public protocols available at the time will be reviewed again for validated algorithms, and the algorithm for the triggered AESI will be aligned with Agency via Annex 2 before conducting the analyses.

Annex 1. List of Clean Period and ICD-10/ATC codes to identify predefined AESIs

Preliminary - may be updated in future protocols based on latest literature and publicly available protocols

Predefined AESI	Clean Period	Codes	Source
Acute aseptic arthritis	365 days	ICD-10: M10, M10.0, M10.00, M10.9, M11.9, M13.9, M19.90	ACCESS
Acute disseminated encephalomyelitis (ADEM)	365 days	ICD-10: G04.00, G04.01, G04.02	ACCESS
Acute kidney injury	365 days	ICD-10: D59.3, K76.7, N00.x, N10.x, N11.x, N12.x, N13.x, N14.x, N15.x, N16.x, N17, N17.0, N17.2, N17.9, N19, N28.9, O08.4, O90.4, R39.2, S37.0, S37.00, T79.5	ACCESS
Acute liver injury	365 days	ICD-10: K71, K71.0, K71.1, K71.2, K71.6, K71.7, K71.8, K71.9, K72, K72.0, K72.01, K72.9, K72.91, K75.9, B17.9	ACCESS
Acute myocardial infarction (AMI)	365 days	ICD-10: I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9	FDA
Acute respiratory distress syndrome (ARDS)	365 days	ICD-10: J80, J96.9, R06.03	ACCESS
Anaphylaxis ²¹	30 days	Criterion A: inpatient or emergency department encounter with any of the following ICD-10 codes: T78.2, T78.2XXA, T78.2XXD, T78.2XXS, T88.6, T88.6XXA, T88.6XXD, T88.6XXS, T80.5, T80.51, T80.51XA, T80.51XD, T80.51XS, T80.52, T80.52XA, T80.52XD, T80.52XS, T80.59, T80.59XA, T80.59XD, T80.59XS OR Criterion B: outpatient encounter with any of the following ICD-10 codes: T78.2, T78.2XXA, T78.2XXD, T78.2XXS, T88.6,	Beachler DC, Taylor DH, Anthony MS, et al. Development and validation of a predictive model algorithm to identify anaphylaxis in adults with type 2 diabetes in U.S. administrative claims data. Pharmacoepidemiol Drug Saf. 2021;30:918–926. https://doi.org/10.1002/pds.5257

		<p>T88.6XXA, T88.6XXD, T88.6XXS, T80.5, T80.51, T80.51XA, T80.51XD, T80.51XS, T80.52, T80.52XA, T80.52XD, T80.52XS, T80.59, T80.59XA, T80.59XD, T80.59XS PLUS a code for one of the following symptoms/procedures/treatments within 2 days:</p> <p>i. Screening B Treatment (ICD-10: J98.01, R06.1, I95.9; HCPCS: J01.70, J01.71, J12.00; ICD-10 PCS: 5A1.2012; CPT: 929.50, J10.20, J10.30, J10.40, J29.20, J29.30, J17.00, J17.10, J17.20) or</p> <p>ii. Treatment C Treatment (HCPCS: J01.70, J01.71; CPT: J12.00, J10.20, J10.30, J10.40, J29.20, J29.30, J17.00, J17.10, J17.20) or</p> <p>iii. Skin-mucosal tissue involvement (ICD-10: H11.421, H11.422, H11.423, H11.429, H02.841, H02.842, H02.843, H02.844, H02.845, H02.846, H02.849, J39.2, J38.4, R23.2, L50.0, L50.1, L50.2, L50.3, L50.4, L50.5, L50.6, L50.8, L50.9, L29.1, L29.2, L29.3, L29.8, L29.9) or</p> <p>iv. Respiratory compromise (ICD-10: J96.00, J96.01, J96.02, J96.90, J96.91, J96.92, J80, R06.03, R06.9, R06.4, R06.01, R06.81, R06.3, R06.02, R06.82, R06.2, R06.00, R06.09, R06.3, R06.83, R06.89, R06.1, J45.20, J45.30, J45.40, J45.50, J45.22, J45.32, J45.42, J45.52, J45.21, J45.31, J45.41, J45.51, J45.909, J45.998, J45.902, J45.901) (OR</p> <p>v. Reduced blood pressure (ICD-10: I95.1, I95.0, I95.89, I95.3, I95.2, I95.81, I95.89, I95.9, R55) or</p> <p>vi. Gastrointestinal symptoms (ICD-10: K52.21, K52.22, K52.29, R11.2, R11.10, R11.11, R11.12,</p>	
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		<p> T44.5X5A, T44.6X5A, T44.7X5A, T44.8X5A, T44.905A, T44.995A, T45.0X5A, T45.1X5A, T45.2X5A, T45.3X5A, T45.4X5A, T45.515A, T45.525A, T45.605A, T45.615A, T45.625A, T45.695A, T45.7X5A, T45.8X5A, T45.8X5A, T45.95XA, T45.95XA, T46.0X5A, T46.1X5A, T46.2X5A, T46.3X5A, T46.4X5A, T46.5X5A, T46.6X5A, T46.7X5A, T46.8X5A, T46.905A, T46.995A, T47.0X5A, T47.1X5A, T47.2X5A, T47.3X5A, T47.4X5A, T47.5X5A, T47.6X5A, T47.7X5A, T47.8X5A, T47.95XA, T48.0X5A, T48.1X5A, T48.205A, T48.295A, T48.3X5A, T48.4X5A, T48.5X5A, T48.6X5A, T48.905A, T48.995A, T49.0X5A, T49.1X5A, T49.2X5A, T49.3X5A, T49.4X5A, T49.5X5A, T49.6X5A, T49.7X5A, T49.8X5A, T49.95XA, T50.0X5A, T50.1X5A, T50.2X5A, T50.3X5A, T50.4X5A, T50.5X5A, T50.6X5A, T50.7X5A, T50.7X5A, T50.8X5A, T50.995A, T50.A15A, T50.A25A, T50.A95A, T50.B15A, T50.B95A, T50.Z15A, T50.Z95A) or viii. Shock caused by anesthesia (ICD-10: T88.2XXA) or ix. Angioneurotic edema (ICD- 10: T78.3XXA) or x. Acute bronchospasm (ICD-10: J98.01) or xi. Stridor (ICD-10: R06.1) or xii. Allergy unspecified, initial encounter (ICD-10: T78.40XA) OR </p>	
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		<p>Criterion C: At least one of the following combinations</p> <p>i. (skin-mucosal tissue involvement) & (shock caused by anesthesia) or</p> <p>ii. (respiratory compromise) & (shock caused by anesthesia or angioneurotic edema) or</p> <p>iii. (acute bronchospasm or stridor) & (allergy unspecified, initial encounter) or</p> <p>iv. (reduced blood pressure) & (gastrointestinal symptoms) & (an unspecified adverse effect or allergy unspecified, initial encounter) or</p> <p>v. (reduced blood pressure) & (skin-mucosal tissue involvement) & (unspecified adverse effect or an allergy unspecified, initial encounter) or</p> <p>vi. (respiratory compromise) & (reduced blood pressure) & (an unspecified adverse effect or an allergy unspecified, initial encounter) or</p> <p>vii. (respiratory compromise) & (gastrointestinal symptoms) & (an unspecified adverse effect or an allergy unspecified, initial encounter or skin-mucosal involvement) or</p> <p>viii. (respiratory compromise) & (skin-mucosal tissue involvement) & (an unspecified adverse effect or an allergy unspecified, initial encounter)</p> <p>PLUS</p> <p>Possible anaphylaxis treatment within 2 days (ICD-10: T78.2, T78.2XXA, T78.2XXD, T78.2XXS, T88.6, T88.6XXA, T88.6XXD, T88.6XXS, T80.5, T80.51, T80.51XA, T80.51XD, T80.51XS, T80.52, T80.52XA, T80.52XD, T80.52XS, T80.59, T80.59XA, T80.59XD, T80.59XS)</p>	
Anosmia, ageusia	365 days	ICD-10: R43.0, R43.2	ACCESS
Arrhythmia	365 days	ICD-10: I45.4, I45.6, I45.9, I47.x, I48, I48.0, I48.1, I48.2, I48.3, I48.4, I48.9, I48.91,	ACCESS

		I48.92, I49.0, I49.01, I49.02, I49.1, I49.3, I49.5, I49.8, I49.9	
Aseptic meningitis ²²	365 days	ICD-10: A87.0, A87.1, A87.2, A87.8, A87.9, B26.1, G02.0, G03.0, G03.8, G03.9	See reference
Bell's palsy	183 days	ICD-10: G51.0	FDA
Cerebral Sinus Venous Thrombosis (CSVT) ²³		ICD-10: G08.X, O22.5, I67.6, I63.6, O87.3	See reference
Chilblain-like lesions	365 days	ICD-10: T69.1, T69.1XXA, T69.1XXD	ACCESS
Coagulation disorders	365 days	ICD-10: D65.x, D66.x, D67.x, D68.x, D69.x	ACCESS
Deep vein thrombosis (DVT)	365 days	ICD-10: I82.220, I82.3, I82.401, I82.402, I82.403, I82.409, I82.411, I82.412, I82.413, I82.419, I82.421, I82.422, I82.423, I82.429, I82.431, I82.432, I82.433, I82.439, I82.441, I82.442, I82.443, I82.449, I82.451, I82.452, I82.453, I82.459, I82.461, I82.462, I82.463, I82.469, I82.491, I82.492, I82.493, I82.499, I82.4Y1, I82.4Y2, I82.4Y3, I82.4Y9, I82.4Z1, I82.4Z2, I82.4Z3, I82.4Z9, I82.621, I82.622, I82.623, I82.629	FDA
Disseminated intravascular coagulation (DIC)	365 days	ICD-10: D65	FDA
Encephalitis / Encephalomyelitis	183 days	ICD-10: G04.00, G04.02, G04.81, G04.90, G05.3	FDA
Erythema multiforme	365 days	ICD-10: L51.x	ACCESS
Gestational diabetes (among pregnant women)	365 days	ICD-10: O24.4x	ACCESS
Guillain-Barré Syndrome (GBS)	365 days	ICD-10: G61.0	FDA
Heart failure	365 days	ICD-10: I50.x, I09.81, I11.0, I13.0	ACCESS
Immune thrombocytopenia	365 days	ICD-10: D69.3	FDA
Ischemic heart disease	365 days	ICD-10: I20.x, I21.x, I22.x, I23.x, I24.x, I25.x	ACCESS
Kawasaki disease	365 days	ICD-10: M30.3	FDA
Meningo-encephalitis	365 days	ICD-10: A69.22, G04, G04.9, G36, G93.4, G93.40	ACCESS
Microangiopathy	365 days	ICD-10: M31.1	ACCESS

Myocarditis	365 days	ICD-10: B33.22, I41, I40.0, I40.1, I40.8, I40.9, I51.4	FDA
Narcolepsy / cataplexy	365 days	ICD-10: G47.4, G47.41, G47.411, G47.419, G47.421, G47.429	ACCESS
Pericarditis	365 days	ICD-10: B33.23, I30.0, I30.1, I30.8, I30.9, I32	FDA
Preeclampsia (among pregnant women)	365 days	ICD-10: O14, O14.0x, O14.1x, O14.9x	ACCESS
Preterm labor (among pregnant women)	182 days	ICD-10: O60.x, P07.0x, P07.1x, P07.2x, P07.3x	ACCESS
Pulmonary embolism (PE)	365 days	ICD-10: I26.02, I26.09, I26.92, I26.93, I26.94, I26.99	FDA
Seizures/ convulsions	365 days	ICD-10: G40.4, G40.A, G40.B, G40.89, R56, R56.9	ACCESS
Single organ cutaneous vasculitis	365 days	ICD-10: L95, L95.8, L95.9, D69.0, M31.0	ACCESS
Spontaneous abortion (among pregnant women)	42 days	ICD-10: O03.x, O02.1	ACCESS
Stillbirth (among pregnant women)	168 days	ICD-10: P95, Z37.1, Z37.3, Z37.4, Z37.7	ACCESS
Stroke, hemorrhagic	365 days	ICD-10: I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62.00, I62.01, I62.02, I62.9	FDA
Stroke, non-hemorrhagic	365 days	ICD-10: I63.00, I63.011, I63.012, I63.013, I63.019, I63.02, I63.031, I63.032, I63.033, I63.039, I63.09, I63.10, I63.111, I63.112, I63.113, I63.119, I63.12, I63.131, I63.132, I63.133, I63.139, I63.19, I63.20, I63.211, I63.212, I63.213, I63.219, I63.22, I63.231, I63.232, I63.233, I63.239, I63.29, I63.30, I63.311, I63.312, I63.313, I63.319, I63.321, I63.322, I63.323, I63.329, I63.331, I63.332, I63.333, I63.339, I63.341, I63.342, I63.343, I63.349, I63.39, I63.40, I63.411, I63.412, I63.413, I63.419, I63.421, I63.422, I63.423, I63.429, I63.431, I63.432, I63.433, I63.439, I63.441, I63.442, I63.443, I63.449, I63.49, I63.50, I63.511, I63.512, I63.513, I63.519, I63.521, I63.522, I63.523, I63.529, I63.531,	FDA

		I63.532, I63.533, I63.539, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.81, I63.89, I63.9	
Thrombosis with thrombocytopenia		Case meets both the definition of thrombosis and the definition of thrombocytopenia as specified above	
Transverse myelitis	365 days	ICD-10: G37.3	FDA
Type 1 Diabetes	365 days	ICD-10: E10.x	ACCESS

ITEM 6:

Page 20, Section 9.4. “The medical claims used for this study will include open and closed medical claims.”

FDA Comment # 6:

Since “Open claims are processed and available in near real time” and “Closed claims generally lag by 3-6 months”, please specify how to account for processing delay for the closed claims.

Sponsor Response:

The sponsor recognizes the potential impact of the processing delay of closed claims and thanks the reviewer for this comment.

Given the date range of Time Period 1, analyses within this period will utilize only closed, fully adjudicated claims and will not be impacted by processing delays. Analyses in Time Period 2 will use closed claims, and because of the lag time for full adjudication of newly adjudicated claims data, additional claims may become available throughout 2021. Thus, the background rates in Time Period 2 will be periodically re-run throughout 2021 and finalized at the end of 2021. The final rates will not be impacted by processing delays.

Given the importance of collecting information from vaccinated individuals in an expedited manner, both closed and open claims data will be leveraged during Time Period 3 to iteratively estimate the AESI rates among mRNA-1273 vaccinated individuals. At the end of Time Period 3, the final incidence rates will be calculated using closed claims only. Any triggered O/E and SCRI analyses will be conducted using only closed claims data. All final analyses and the study report will be based on closed claims only.

A summary of this information is provided in the table below.

	Date Range	Study Cohort	Initial Incidence Rates	Final Incidence Rate
Time Period 1 (Pre-COVID)	Dec 1, 2018 - Nov 30, 2019	Study Cohort 1	N/A	Date Type: Closed claims Timeline: ASAP, closed claims for TP1 will be fully adjudicated by start of study
Time Period 2 (Active-COVID)	Dec 1, 2019 - Dec 10, 2020	Study Cohort 2	Data Type: Closed claims Timeline: After June 2021	Data Type: Closed claims Timeline: After December 31, 2021*
Time Period 3 (Post-EUA)	Dec 11, 2020 - Dec 31, 2022	Study Cohort 3	Data Type: Open and closed claims Timeline: Throughout study timeline	Data Type: Closed claims Timeline: After June 2023

* While closed claims processing time is generally 3-6 months, it is possible to see claims processing delayed as long as 12 months. Given December 2021 is within the planned study timeline, a final incidence rate can be run after the 12 month period.

ITEM 7:

Page 21, Section 9.5. “AESI-specific sample size calculations will be performed when a particular AESI enters the Objective 3 analysis. For illustration, the table below provides example sample size estimates for 3 AESIs (Guillain-Barré syndrome [GBS], anaphylaxis and encephalitis)”.

FDA Comment # 7:

The sample size calculation used an R package for self-controlled case series (SCCS) studies and the observation period is 1-year. The length of the control window for the SCRI study has not been specified. Because SCCS often assigns the period other than the risk window as the control window and SCRI typically uses a fixed length control window, it is very likely that the person time was overestimated for the sample size calculation. Please specify the length of risk windows and control windows for each of the AESI.

Sponsor Response:

The Sponsor acknowledges the original sample size for the SCRI analysis was calculated leveraging a R package for the SCCS design, where a fixed control time period is not assigned. The SCRI sample size estimate has been re-calculated for 3 AESIs of interest utilizing their specific risk periods and a control period of 183 days:

- Anaphylaxis (Risk Window=0-1 days)
- Guillain-Barré Syndrome (Risk Window=1-42 days)
- Acute myocardial infarction (Risk Window=1-28 days)

Note the risk window for anaphylaxis was updated from 2-days in protocol v1.2 to 11 days in protocol v3.1. SCRI sample size was calculated for the primary analysis, following any vaccine dose. If a SCRI analysis is triggered for a specific AESI of interest, the study team will finalize the length of the risk and control periods and will provide a final sample size calculation within

the Protocol Annex 2. Annex 2 will be submitted to the Agency for review before the SCRI analysis is conducted.

Outcome	Estimated US incidence	Expected events in HealthVerity ^a	Total risk period (days)	Total observation period (days) ^b	Cases required by minimal detectable RR		
					RR=1.5	RR=2	RR=3
GBS	1.2 - 3.0 cases per 100,000 inhabitants	228-570	42	225	275	87	32
Acute myocardial infarction (MI)	805,000 MI's in the US per year (242.9 events per 100,000)	46,146	28	211	353	109	38
Anaphylaxis	42 cases per 100,000 person-years	7,980	1	194	7,007	2,024	631

^a Estimated US incidence x approximately 19 million patients with at least one mRNA-1273 vaccine dose in the HealthVerity data

^b Assuming administration of 1 vaccine dose; observation period = AESI-specific risk period + 183 day control period

Note: Sample size was calculated using the R package for self-controlled case series studies with varying observation periods per AESI. Incidence will vary by age and other patient characteristics, sample size calculations used population level rates.

ITEM 8:

Page 32 and 33, Annex 2. “Time varying covariates measured from cohort entry until end of follow-up to be considered for adjustment”. Age is listed as a time varying covariate for all the AESIs in Annex 2.

FDA Comment # 8:

For young children, age is a potential time varying confounder for self-controlled studies. Because only individuals ≥ 18 years are included in the study and most likely the age difference is small during the study period, please clarify why age is considered as a time varying covariate in Annex 2 in this study.

Sponsor Response:

The sponsor agrees that age will most likely not be a time varying confounder beyond the infant stage. Further, the sponsor recognizes the remaining list of time-varying covariates may not be applicable given the relatively short length of the risk and control periods and the frequency of data capture in a claims database. Thus, the list of potential time varying covariates has been removed from Protocol v3.1. At the time an SCRI analysis is triggered, potential time varying covariates (e.g. healthcare resource utilization, use of medications in relation to the first vaccine dose) will be considered and if relevant, specified in Protocol Annex 2. Annex 2 will be submitted to the Agency for review before the SCRI analysis is conducted.