NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Post Authorization Safety Study (PASS) information

Title	Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity
Protocol version identifier	3.2
Date of last version of protocol	26 Aug 2021
EU PAS register number	EUPAS41392
Active substance	COVID-19 mRNA-1273 vaccine (nucleoside modified)
Medicinal product	COVID-19 mRNA-1273 vaccine
Product reference	
Procedure number	N/A
Marketing authorisation holder(s)	Moderna Inc.
Joint PASS	No
MAH contact	(b) (6) @modernatx.com
Research question and objectives	This study aims to augment ongoing active and passive safety signal detection through signal refinement and, where warranted, evaluation of potential safety signals associated with the introduction of SARS-CoV-2 mRNA-1273 vaccine. The objectives of this study are to: 1. Estimate crude and age/sex adjusted incidence rates (IR) and incidence rate ratios (IRR) at key time periods and among key populations a. Estimate background incidence rates of myocarditis and other AESIs i. in the general population and influenza-vaccinated individuals during the pre-COVID period

	ii. in the general population during the active-COVID but pre-vaccine COVID-19 EUA periods b. Estimate incidence rates for myocarditis and other AESIs among mRNA-1273-vaccinated individuals in post-EUA period. Estimate IRR by comparing post vaccine IR to background IR in two periods (pre-COVID, active- COVID) estimated in Objective 1(a) c. Estimate crude and age/sex adjusted incidence rates and incidence rate ratios for additionally-identified AESIs 2. Estimate age/sex adjusted observed to expected ratio for myocarditis and other specific AESIs meeting pre-specified evaluation threshold from Objective 1b (completed as needed) 3. Estimate relative risk for myocarditis and other specific AESIs meeting pre-specified evaluation threshold from Objective 2 via self-controlled risk interval (SCRI) analyses (completed as needed)
Country(-ies) of study	United States.
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2. List of Abbreviations

Abbreviations	Definition
ACCESS	vACcine Covid-19 monitoring readinESS
AE	Adverse Event
AEP	Aetion Evidence Platform
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical

CBER	Center for Biologics Evaluation and Research
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
CMS	Center for Medicare & Medicaid Services
CPT	Current Procedural Terminology
CSVT	Cerebral Sinus Venous Thrombosis
EMA	European Medicine Agency
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GPP	Good Pharmacoepidemiological Practice
HIPAA	Health Insurance Portability and Accountability Act
ICD	International Classification of Disease
ICMJE	International Committee of Medical Journal Editors
IR	Incidence Rate
IRR	Incidence Rate Ratio
O/E	Observed to Expected
OTC	Over-the-counter
PHI	Protected health information
PII	Personal identifying information
RR	Relative Risk
SAP	Statistical Analysis Plan
SCRI	Self-controlled risk interval
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States
VAC4EU	Vaccine monitoring Collaboration for Europe
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink

3. Responsible Parties

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4. Abstract

Title	Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity
Rationale and background	In the context of pandemic COVID-19 disease, Moderna has rapidly developed the SARS-CoV-2 mRNA-1273 vaccine. The present study aims to augment ongoing active and passive signal detection by estimating background rates of Adverse Events of Special Interest (AESIs) prior to the first emergency use authorization (EUA) for any SARS-CoV-2 vaccine (11 December 2020) and then after EUA in the US population and in specific subgroups of interest.[1] Post-authorization data have demonstrated increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is highest among younger males. This study will contextualize the risk of myocarditis and other potential safety signals and inform the need for further safety evaluation and signal refinement, notably using observed-to-expected (O/E) analyses where a safety concern has been raised from literature or medical reviews, disproportionate reporting or unexpected temporal relationship. In the event that O/E analysis results show observed values higher than expected, self-controlled risk interval (SCRI) analyses will be conducted to further evaluate the signal.
Research question and objectives	This study aims to augment ongoing active and passive safety signal detection through signal refinement and, where warranted, evaluation of potential safety signals associated with the introduction of SARS-CoV-2 mRNA-1273 vaccine. The objectives of this study are to: 1. Estimate crude and age/sex adjusted incidence rates (IR) and incidence rate ratios (IRR) at key time periods

	and among key populations a. Estimate background incidence rates of myocarditis and other AESIs i. in the general population and influenza-vaccinated individuals during the pre-COVID period ii. in the general population during the active-COVID but pre-vaccine COVID-19 EUA period b. Estimate incidence rates for myocarditis and other AESIs among mRNA-1273-vaccinated individuals in post-EUA period. Estimate IRR by comparing post vaccine IR to background IR in two periods (pre-COVID, active- COVID) estimated in Objective 1a c. Estimate crude and age/sex adjusted incidence rates and incidence rate ratios for additionally-identified AESIs 2. Estimate age/sex adjusted observed to expected ratio for myocarditis and other specific AESIs meeting pre-specified evaluation threshold from Objective 1b (completed as needed) 3. Estimate relative risk for myocarditis and other specific AESIs meeting pre-specified evaluation threshold from Objective 2 via self-controlled risk interval (SCRI) analyses (completed as needed)
Study design	Retrospective observational cohort study with active vaccine surveillance using a self-controlled risk interval design.
Population	To support the study objectives, three primary cohorts of interest will be formed: **Cohort 1a:** Entire (adult/pediatric) cohort meeting eligibility in Pre-COVID period (**Time Period 1)** from 1 Dec 2018 to 30 Nov 2019 Cohort 1b: Entire (adult/pediatric) cohort with evidence of an influenza vaccination and meeting eligibility in Time Period 1 **Cohort 2:** Entire (adult/pediatric) cohort meeting eligibility in Active-COVID, Pre-EUA period (**Time Period 2)** from 1 Dec 2019 to 10 Dec 2020 (one day prior to first US SARS-CoV-2 vaccine EUA) **Cohort 3:** Entire (adult/pediatric) cohort meeting eligibility in Post-EUA period (**Time Period 3)** from date of first US

	SARS-CoV-2 vaccine EUA to 31 Dec 2022 comprised of mRNA-1273 vaccinated patients.
Variables	**Exposures**: at least one dose of mRNA-1273 **Outcomes**: myocarditis and other predefined AESIs and additional events to be identified by the Sponsor based on active or passive surveillance signal detection **Key Covariates**: age group, sex
Data sources	This retrospective observational cohort study will use secondary, de-identified individual-level medical and pharmacy claims data provided by HealthVerity. This data source includes more than 140 million patients insured under commercial, Medicare or Medicaid plans, and/or served by providers participating in several large US medical and pharmacy insurance claims submission systems. The data will be refreshed biweekly throughout the study period.
Study size	The analysis population for background rates will include a sample of patients from the HealthVerity database (See Section 9.2). The population for vaccinated individuals will be formed from the entirety of available HealthVerity data.
Data analysis	The following analyses will per performed overall and stratified by age, sex, and dose of vaccine (1st, 2nd, and any additional doses) 1. Crude and age/sex adjusted incidence rate ratios using background (referent) IR and post-vaccine (exposed) IR for predefined AESIs. 2. Observed / expected ratios comparing observed event counts to expected event counts for myocarditis and other AESIs as needed. 3. Self-controlled risk interval analysis for myocarditis and other AESIs as needed.
Milestones	Final Protocol: 26 August 2021 Interim results: every 3 months until Dec 2022 Final report: end of June 2023

5. Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
V2.0	25-03-2021	6: Milestones	Update to the final protocol actual date	Revisions were required based on regulatory feedback.

V2.0	25-03-2021	7: Rationale and Background	Additional details were provided on current approval status, identified important risks, and key elements of missing information	Revisions were required based on regulatory feedback.
V2.0	25-03-2021	8: Research Question and Objective	Text of the study objectives has been clarified to more explicitly reflect the planned analyses	Revisions were required based on regulatory feedback.
V2.0	25-03-2021	9.1: Study Design 9.7: Data Analysis Plan	Reference to assessment of incidence rates in presumed unvaccinated individuals in Time Period 3 has been removed.	Per regulatory feedback, misclassification of exposure status limits the interpretability of rates in the presumed unvaccinated.
V2.0	25-03-2021	9.1: Study Design	Clarification and citations were added explaining planned thresholds that will trigger execution of additional analyses for a given outcome. Analyses will only be conducted for outcomes where the total exposed event count is >5.	Clarifications were required based on regulatory feedback. Inclusion of a minimum event count will limit execution of analyses that are based on data too sparse to support interpretation.
V2.0	25-03-2021	9.1: Study Design	Text throughout the section was revised for clarity and consistency with the amended protocol objective section.	Revisions were required based on regulatory feedback.
V2.0	25-03-2021	9.2: Setting	Clarifying text has been added to distinguish the underlying database from the subset of patients that are included in planned analyses.	Clarifications were required for transparency in the proposed study design.
V2.0	25-03-2021	9.2: Setting, 9.2.2: Study Population	In order to ensure that follow-up care for existing outcomes is not identified as a new event, study entry criteria were modified to require 365 days of continuous health plan enrollment. This facilitates use of clean periods when defining incident AESI.	Change required to align the outcomes included in this assessment with the ACCESS protocols per regulatory feedback.
V2.0	25-03-2021	9.3.2: Outcomes	Additional predefined AESIs have been added for consistency with the ACCESS project.	Revisions were required based on regulatory feedback.
V2.0	25-03-2021	9.3.4: Data Sources	Clarification has been received by the MAH that death data are not presently available within the study population. As such, reference has been removed.	Revisions were required based on new information concerning the data source.
V2.0	25-03-2021	Annex 1	The Annex describing AESI was amended to include additional outcomes and their codes. A proposed clean period was also specified for each AESI.	Revisions were required based on regulatory feedback.
V2.0	25-03-2021	Annex 2	A new Annex provides examples of planned risk windows and time varying covariates for consideration in SCRI analyses. Appendices with full details of planned SCRI analyses will be shared	Revisions were required based on regulatory feedback.

			with regulatory agencies should their execution be required.	
V2.0	25-03-2021	All	Text throughout the document was revised for clarity and consistency with the amended protocol objectives and changes identified above.	Revisions were required based on regulatory feedback.
v3.0	26-08-2021	4	Abstract update for changes in Protocol v3.0	Alignment of the protocol to Version 3.0 changes
v3.0	26-08-2021	7	Update in current vaccine authorization status	Updated information available at time of protocol amendment.
v3.0	26-08-2021	8 & 9	The age range was expanded to capture individuals of all ages with subgroups for children, adolescents and adults.	Use of Spikevax has been observed in younger individuals, and indicated ages may change over the course of the study.
v3.0	26-08-2021	8 & 9	- Expanding beyond adult population - Adding a T1 flu vaccinated comparator group - Minor edits to analytic dataset	- In anticipation of potential future use in younger age groups - per FDA CBER comment - More information on dataset available
v3.0	26-08-2021	8 & 9	- Expanding beyond adult population - Adding a T1 flu vaccinated comparator group - Minor edits to analytic dataset	- In anticipation of potential future use in younger age groups - per FDA CBER comment - More information on dataset available
v3.0	26-08-2021	Annex 1	Update in references	Revisions were required based on regulatory feedback.
v3.0	26-08-2021	Annex 2	Addition of risk and control periods were specified and clarification of time varying covariates implemented	Revisions were required based on regulatory feedback.
v3.1	26-08-2021	9.5	Revised sample size estimates were included	Revisions were required based on regulatory feedback.
v3.1	26-08-2021	9.7	Additional sensitivity analyses were described	For potential considerations around healthcare utilization, heterologous vaccine schedule, and stratification by dose and/or immunocompromised status
V3.2	27-10-2021	Throughout	Myocarditis has been specified as primary outcomes, additional supporting background context has been included, and dose stratified analyses have been designated as mandatory regardless of sample size.	Revisions were required based on regulatory feedback.
V3.2	27-10-2021	9.5, 9.7	Revised sample size estimates were included based on the need to include myocarditis and reduce the proposed duration	Revisions were required based on regulatory feedback.

			proposed control windows for SCRI analyses.	
V3.2	27-10-2021	9.7	Additional analyses were described, including stratification by dose and inclusion of mild to moderate health states in analyses designed to characterize the potential impact of changes in healthcare utilization on study results.	Revisions were required based on regulatory feedback.

6. Milestones

Milestone	Planned date	Actual date	Comments
Protocol v2.0	31 January 2021	25 March 2021	Protocol revisions were required based on regulatory feedback following submission of Protocol version 1.0
Protocol v3.0	Not applicable	26 Aug 2021	Protocol revisions were made based on regulatory feedback following submission of Protocol version 2.0 as well as continued refinement of study methodology
Protocol v3.2	Not applicable	27 October 2021	Protocol revisions were made based on regulatory feedback following submission of Protocol version 3.0 as well as continued refinement of study methodology
Interim results	Every 3 months through the end of the study period (31 December 2022)		
Final report	30 June 2023		

7. Rationale and Background

In the context of pandemic COVID-19 disease, Moderna has rapidly developed the SARS-CoV-2 mRNA-1273 vaccine. Phase 1 (NCT04283461) efficacy results were positive, notably in the elderly population (65 years old and above).[2,3] A dose-confirmation phase 2a trial (NCT04405076) was then conducted followed by a phase 3 trial (NCT04470427) which has shown a vaccine efficacy rate of 94.1% in adults.[4]

As of 31 July 2021, mRNA-1273 vaccine has not been licenced in any country/region. Emergency use authorisation was obtained in the US on 18 December 2020 and has since been granted in countries including Canada, Israel, the United Kingdom, Switzerland, Singapore, Japan, India, Qatar, Paraguay, Brunei, Botswana, Taiwan, Philippines, Thailand, South Korea, Jordan, Bhutan, United Arab Emirates, Colombia, Saudi Arabia, Vietnam, Sri Lanka, Haiti, Indonesia, Ukraine, Tunisia, and Algeria as well as by the World Health Organization and the European Union for active immunization to prevent COVID-19 in individuals 18 years of age and older. While the current EUA in the United States is for the adult population, Moderna is currently studying the safety and effectiveness of the mRNA-1273 vaccine in younger age groups, and has received authorization in adolescents in the European Union and Japan. In anticipation of potential future post-market safety needs, the study is expanded to include all ages, and <18 age groups will be included as subgroups if/when the vaccine is authorized for such use in the US.

Myocarditis refers to inflammation of the myocardium and may be due to any one of numerous etiologies (e.g., infectious pathogens, toxins, drugs, and autoimmune disorders) that may resolve spontaneously, cause sudden cardiac death, or evolve into dilated cardiomyopathy. The most common etiology of myocarditis, especially among younger people, is viral infection (with numerous viruses, including SARS-CoV-2, implicated). The actual prevalence of the disease remains uncertain because of the difficulty of reaching a confirmatory diagnosis in many cases. For reasons that are unclear, myocarditis tends to occur disproportionately among younger males (approximately 20-40 years of age). Reliable and accessible diagnostic tools for the early diagnosis of acute myocarditis are an unmet clinical need at this time (Blanco-Dominguez 2021). Rare cases of myocarditis and pericarditis have been observed following vaccination with mRNA vaccines targeting SARS-CoV-2, including SPIKEVAX. Most of these cases have occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men.

Anaphylaxis is also recognized as an important identified risk, and provider instructions include warnings that appropriate medical treatment to manage immediate allergic reactions must be available in the event of an acute anaphylactic reaction following administration of the Moderna COVID-19 Vaccine. Other potential risks include vaccine-associated enhanced disease. Areas not assessed in the phase 3 trial included risks related to use in pregnant or lactating women, long-term safety, use in immunocompromised or frail subjects, use in populations with unstable health conditions and comorbidities, interaction with other vaccines, and long-term safety.

The Risk Management Plan (RMP) also prespecifies that adverse events of special interest (AESI) identified by regulatory agencies and vaccine expert groups will be monitored via routine and enhanced pharmacovigilance activities. The vaccine exposed population of the Phase 3 P301 study allowed the detection of rare events with a frequency of 1/10,000 persons or 0.01%. However, most rare adverse events of special interest (AESIs) for post-marketing safety surveillance have incidence rates lower than 2/10,000 persons or 0.02%. As such, additional

safety surveillance and evaluation is needed in the post-marketing setting. This is especially critical as safety concerns have been raised in the past following mass vaccination campaigns either with existing or new vaccines.

The present study aims to augment ongoing active and passive signal detection by estimating background rates of Adverse Events of Special Interest (AESIs) prior to the first emergency use authorization (EUA) for any SARS-CoV-2 vaccine (11 December 2020) and then after EUA in an overall US population and in specific subgroups of interest.[1] This will contextualize potential safety signals and inform the need for further safety evaluation and signal refinement, notably using observed-to-expected (O/E) analyses where a safety concern has been raised from literature or medical reviews, disproportionate reporting, or unexpected temporal relationships. In the event that O/E analysis results indicate observed values higher than expected, self-controlled risk interval (SCRI) analyses will be conducted to further evaluate the signal.

8. Research Question and Objectives

This study aims to augment ongoing active and passive safety signal detection through signal refinement and, where warranted, evaluation of potential safety signals associated with exposure to the SARS-CoV-2 mRNA-1273 vaccine.

The objectives of this study are to:

1. Estimate crude and age/sex adjusted incidence rates and incidence rate ratios
    a. Estimate crude and age/sex adjusted incidence rates (IR) and incidence rate ratios (IRR)
        i. Estimate background incidence rates of myocarditis and other AESIs during the pre-COVID period (“Time Period 1”) overall and for individuals who received an influenza vaccination during Time Period 1
        ii. Estimate background incidence rates of myocarditis and other AESIs during the active-COVID but pre-vaccine COVID-19 EUA periods (“Time Period 2”)
    b. Estimate incidence rates for myocarditis and other AESIs among mRNA-1273-vaccinated individuals:
        i. Estimate post vaccine (exposed) incidence rates in the era following the first COVID-19 vaccine EUA (“Time Period 3”)
        ii. Compare post vaccine (exposed) incidence rates to background (referent) incidence rates in two periods (Time Periods 1 and 2) estimated in Objective 1a(i-ii)
    c. Estimate crude and age/sex adjusted incidence rates and incidence rate ratios for additionally-identified AESIs:
        i. Complete Objective 1a analyses for additionally-identified AESIs
        ii. Complete Objective 1b analyses for additionally-identified AESIs
2. Estimate age/sex adjusted observed to expected ratios for myocarditis and other specific AESIs meeting pre-specified evaluation threshold from Objective 1b (completed as needed)
3. Estimate relative risk for myocarditis and other specific AESIs meeting pre-specified evaluation threshold from Objective 2 via self-controlled risk interval (SCRI) analyses (completed as needed)

9. Research Methods

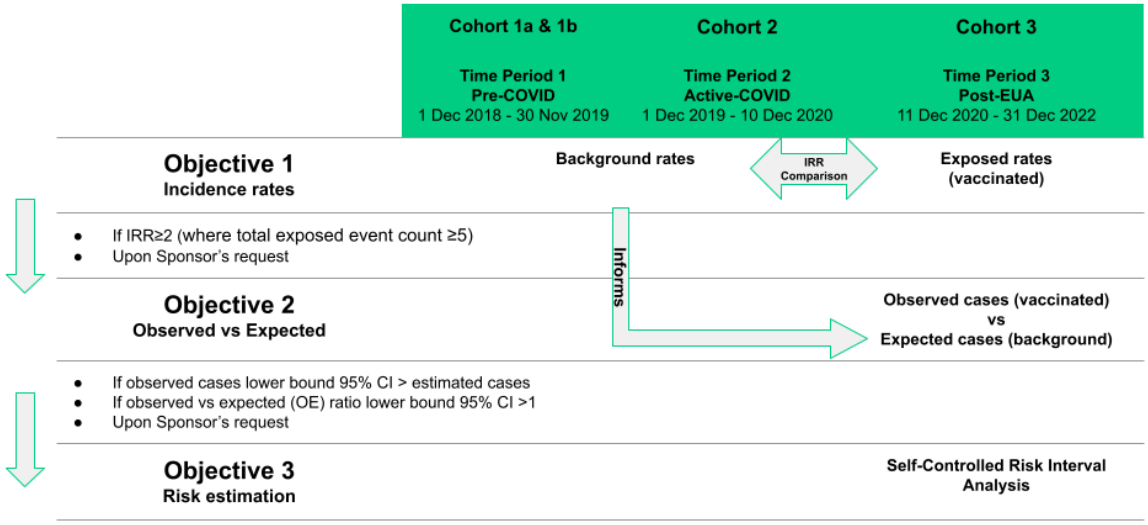
9.1. Study Design

The description of research methods below will reference several concepts:

- **Pre-defined AESIs**: a list of predefined AESIs is proposed in this protocol in Section 9.3.2. These AESI include myocarditis, which is a primary outcome for this study.
- **Additionally-Identified AESIs:** AESIs which may be identified by regulatory agencies or the sponsor after this protocol has been implemented. Additionally-Identified AESIs will be identified in protocol revisions.
- **Time Periods**: For consistency, we reference three time periods of interest. The specific dates of each time period are noted in Section 9.2.
    - **Time Period 1 (Cohort 1a and 1b** assessment**)** is defined as the era that is immediately preceding the emergence of COVID-19.
        - Cohort 1a assessment will be for the general population
        - Cohort 1b assessment will be for the population with evidence of receiving an influenza vaccination during Time Period 1
    - **Time Period 2 (Cohort 2** assessment**)** is defined as the era following the emergence of COVID-19 but before the first COVID-19 vaccine EUA.
    - **Time Period 3 (Cohort 3** assessment**)** is defined as the era following the first COVID-19 vaccine EUA.

The three Objectives outlined in this protocol correspond to a stepwise approach summarized in Figure 1. All Objectives will be completed as soon as they are feasible, based on data availability.

Figure 1. Study Design



*Cohort 1a consists of all eligible individuals in Time Period 1, Cohort 1b consists of all eligible influenza vaccine recipients during Time Period 1.

In **Objective 1** crude and age/sex adjusted IRs and IRRs will be estimated. All rates and ratios will be estimated in the overall population, and in subgroups defined by age group and sex. Additional subgroups may be considered. All analyses are defined in full in the statistical analysis plan (SAP).

In **Objective 1a**, background IRs for predefined AESIs will be estimated in (i) Time Period 1 for Cohorts 1a (general population) and 1b (those receiving an influenza vaccine) and (ii) Time Period 2 for Cohort 2. IRs for a particular AESI will be estimated by dividing the number of observed cases (unique per patient) by the cumulative person-time.

In **Objective 1b**, 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 (Cohorts 1a and 1b) and 2 (Cohort 2) as part of Objective 1a above.

Estimation of background incidence rates will occur as soon as possible after the mRNA-1273 EUA, and exposed incidence rates estimation will occur as soon as a sufficient number of individuals have been vaccinated with mRNA-1273 vaccine. Vaccine uptake will be monitored on a biweekly basis. The vaccine exposed incidence rates will be estimated periodically as data become available during Time Period 3.

Given the importance of collecting information from vaccinated individuals in an expedited manner, both closed and open insurance claims data will be leveraged during Time Period 3 to estimate the vaccine exposed AESI rates among mRNA-1273 vaccinated individuals. Subsequent descriptive and comparative analyses will only use closed claims (see Sections 9.4 and 9.9 for further details).

As incidence rate ratios are estimated in Objectives 1b and 1c, they will be evaluated to determine whether further study is warranted. Objective 2 will be triggered for a given AESI if any of the following criteria are met:

- The overall IRR reaches a threshold of ≥2 and the total exposed event count is ≥5
- The IRR in any subgroup a threshold of ≥2 and the total exposed event count is ≥5
- The sponsor determines that this analysis will assist with safety signal validation and/or assessment

The above-mentioned threshold of ≥2 was determined a priori based on a conservative definition of a weak signal threshold (RR=2) from published safety surveillance research.[5,6]

In **Objective 2**, an observed versus expected ratio will be estimated for those specific AESIs identified by the criteria in Objective 1. The number of observed cases of specific AESIs will be counted among the mRNA-1273 vaccinated population in Time Period 3. Estimates of the expected number of cases among vaccinated individuals will be computed using the

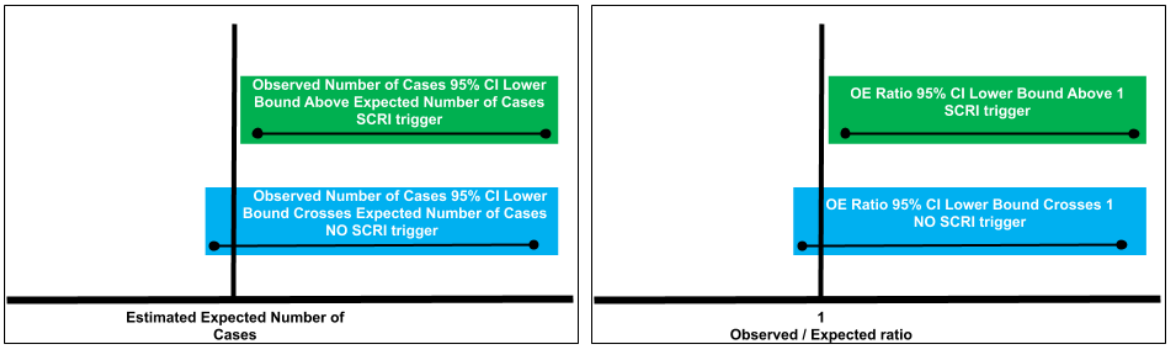
background rates for Time Periods 1 and 2, as assessed for Objective 1a, and the total person-time at risk during the risk period determined for each specific AESI.

The observed and estimated expected numbers of AESI events among mRNA-1273 vaccinated individuals in Time Period 3 will be compared, then the O/E (observed to expected) ratio measure will be calculated, and a confidence interval (CI) estimated. CIs will also be estimated around the number of events observed in the risk period. The O/E ratio will be stratified by age group and sex as observed in the vaccinated population (see Section 9.7 for further details).

Objective 3 self-controlled risk interval (SCRI) analyses will be triggered if any of the following criteria are met (Figure 2):

- The lower bound of the 95% CI of the observed number of cases is higher than the estimated number of expected cases as measured for Objective 2 (Time Period 3)
- The lower bound of the 95% CI of the O/E ratio is greater than 1
- The sponsor determines that this analysis will assist with safety signal validation and/or assessment

Figure 2. Observed / Expected Triggers for Self-Controlled Risk Interval Analysis



In **Objective 3**, the relative risk will be estimated for AESIs identified for further study. The potential risk associated with mRNA-1273 vaccine and specific AESIs will be estimated using a SCRI analysis of mRNA-1273 exposed cases identified in Time Period 3. This analysis will be run when a sufficient number of cases have been reached based on sample size estimates for each specific AESI (see Section 9.5 for further details). The SCRI design has been widely used for post-licensure vaccine safety monitoring to detect potential elevated risks of adverse events following vaccination.[7,8] The main advantage of this design is that it adjusts implicitly for fixed non-time-varying covariates as only exposed cases are being used. However, adjustment may be needed for time-varying covariates. Compared to cohort designs that use large amounts of historical or concurrent data on unexposed individuals or self-control case series methods, the SCRI design has less statistical power.[9,10] 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.

9.2. Setting

The study population will be selected from HealthVerity's aggregated medical and pharmacy claims database that represents healthcare utilization for over 140 million patients between 1 Dec 2017 and the end of the study period (see Section 9.2.1). Objectives 1 and 2 will utilize historical medical and pharmacy claims data to support estimation of background rates. Upon vaccine launch and administration, a biweekly refresh of medical and pharmacy claims for specific patient cohorts will accumulate throughout the study period to support Objectives 1, 2, and 3.

Analytic Dataset

For time periods 1 and 2, a subset of the historical medical and pharmacy claims data will make up the analytic dataset for estimating the background incidence rates. Patient data will be included into this analytic dataset from the larger HealthVerity database if the following inclusion criteria are met: patients have both medical and pharmacy benefit coverage, have at least 365 days of continuous enrollment (60-day allowable gap) during the period 1 Dec 2017 through 10 Dec 2020, and have non-missing values for both sex and age. From the patients meeting inclusion criteria, a stratified random sample will be generated based on sex and age to mirror distributions from 2019 Census Estimates (see Figure 3). Data use and licensing for the HealthVerity database allow for use of up to 40% of the total patient population for the background rate analytic dataset, which will result in approximately 50 million patients for the background rate time periods. For Time Period 3, there will be no sampling of patients; all vaccinated individuals present in the HealthVerity database meeting study entry criteria will be included (see Figure 4).

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

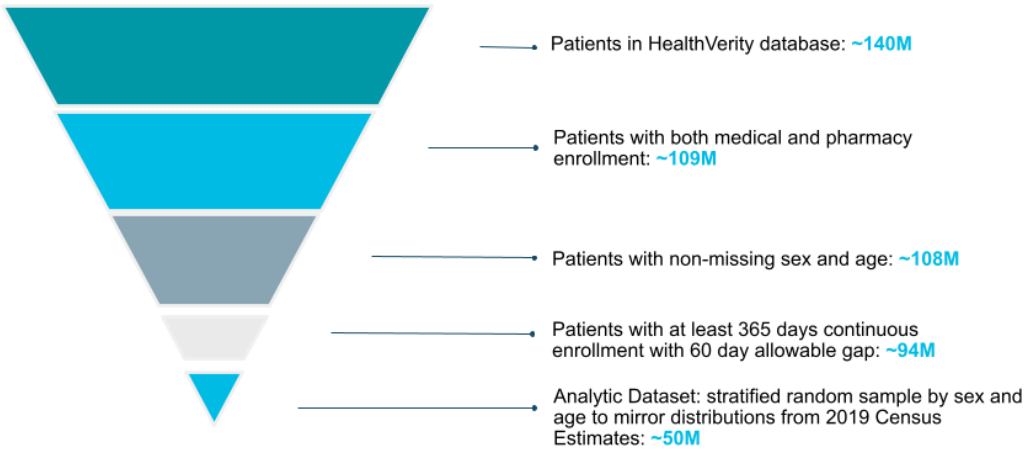
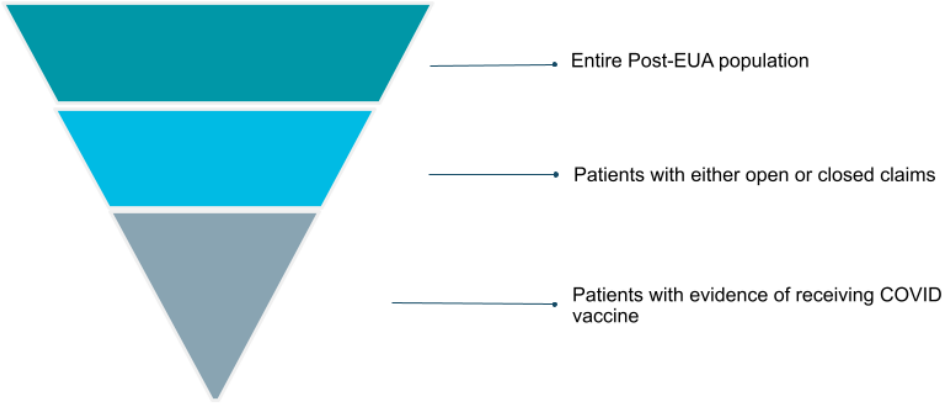


Figure 4. Analytic Dataset for Vaccine Exposed Rates (Time Period 3)



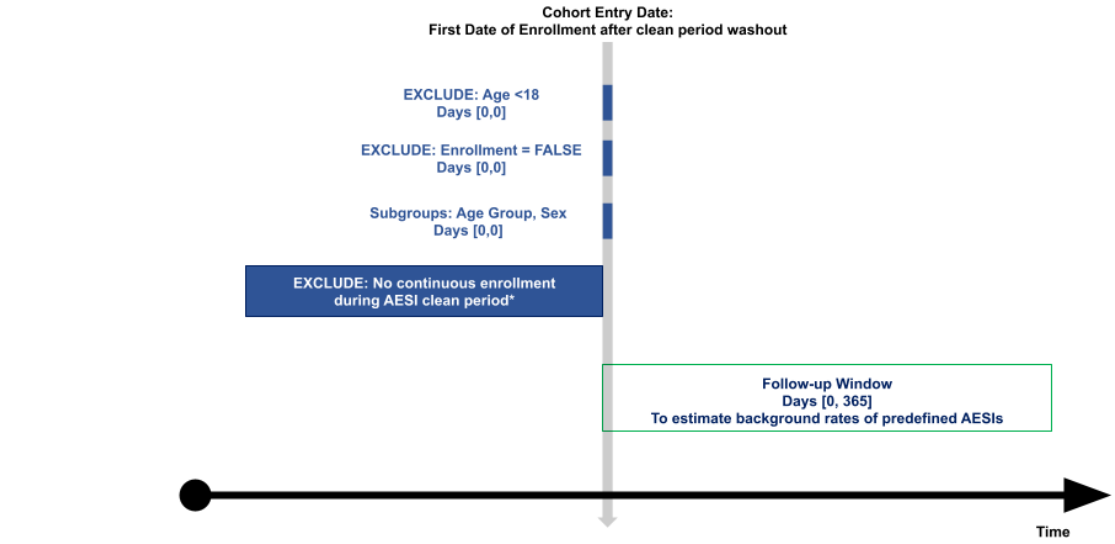
Study cohorts

To support the study Objectives, four primary cohorts of interest will be formed from the analytic datasets described above. Cohort 1a, 1b, and 2 will be drawn from the analytic dataset for Time Period 1 & Time Period 2 baseline rates described in Figure 3. Cohort 3 will be drawn from the analytic dataset for vaccine exposed rates during Time Period 3 described in Figure 4. Each of

the four cohorts will be built separately among an adult population and among a pediatric population (6 months -17 years).

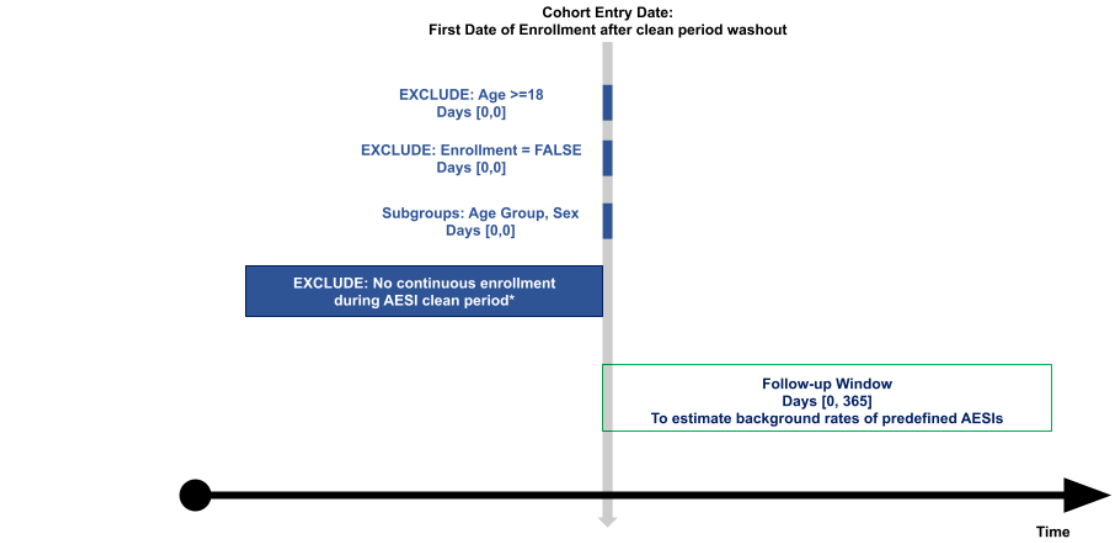
<u>Cohort 1a:</u> Static (adult/pediatric) cohort meeting eligibility per Figure 5-6 in Time Period 1**:** Pre-COVID period from 1 Dec 2018 to 30 Nov 2019

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



Data source: HealthVerity Claims and Pharmacy Study Population (01 Dec 2017 to 10 Dec 2020)
Allowable cohort entry date range: 01 Dec 2018 through 30 Nov 2019
**At earliest starts 01 Dec 2017 and ends after patient meets the predefined AESI specific clean period in calendar days*

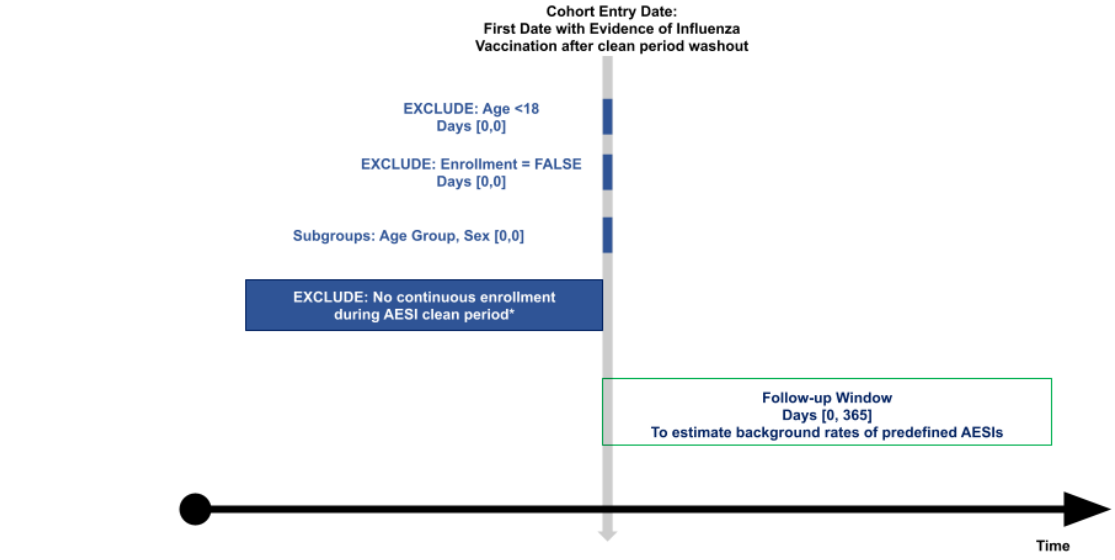
Figure 6. Cohort 1a: Static Pediatric Cohort (Time Period 1)



Data source: HealthVerity Claims and Pharmacy Study Population (01 Dec 2017 to 10 Dec 2020)
Allowable cohort entry date range: 01 Dec 2018 through 30 Nov 2019
**At earliest starts 01 Dec 2017 and ends after patient meets the predefined AESI specific clean period in calendar days*

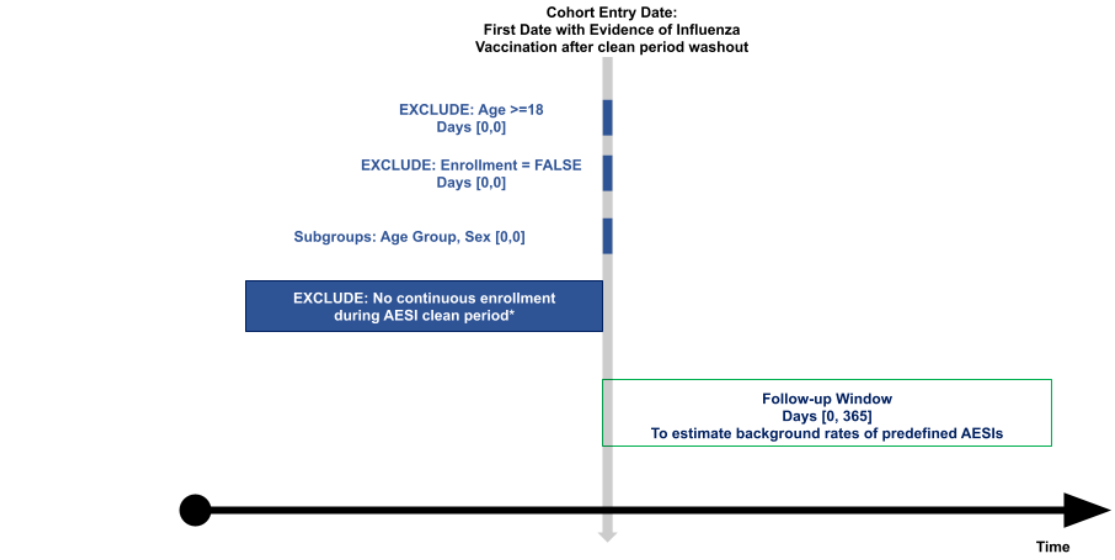
Cohort 1b: Static (adult/pediatric) cohort with evidence of an influenza vaccination and meeting eligibility per Figure 7-8 in Time Period 1: Pre-COVID period from 1 Dec 2018 to 30 Nov 2019

Figure 7. Cohort 1b: Static Influenza Vaccinated Adult Cohort (Time Period 1)



Data source: HealthVerity Claims and Pharmacy Study Population (01 Dec 2017 to 10 Dec 2020)
Allowable cohort entry date range: 01 Dec 2018 through 30 Nov 2019
**At earliest starts 01 Dec 2017 and ends after patient meets the predefined AESI specific clean period in calendar days*

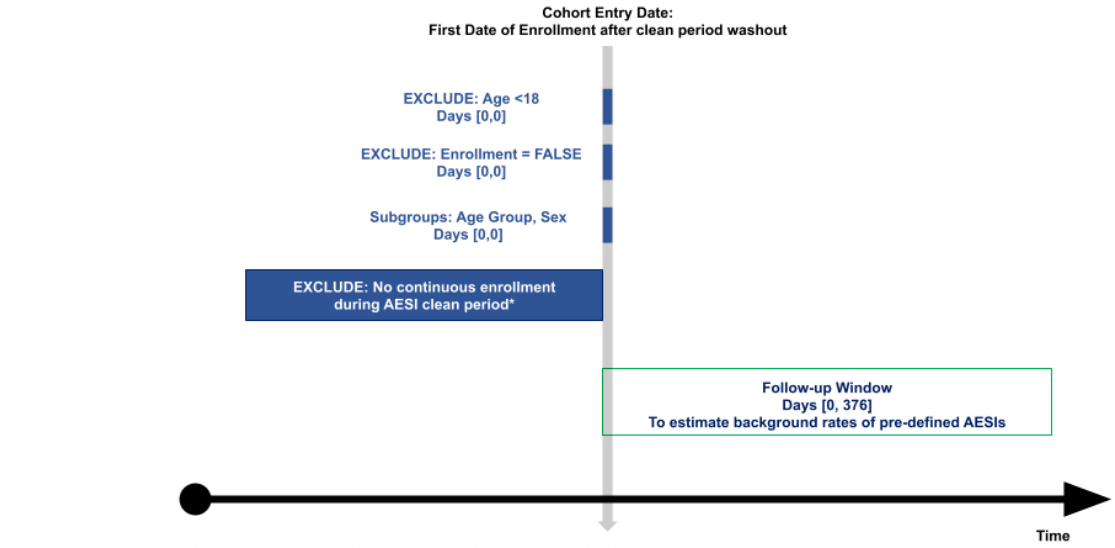
Figure 8. Cohort 1b: Static Influenza Vaccinated Pediatric Cohort (Time Period 1)



Data source: HealthVerity Claims and Pharmacy Study Population (01 Dec 2017 to 10 Dec 2020)
Allowable cohort entry date range: 01 Dec 2018 through 30 Nov 2019
**At earliest starts 01 Dec 2017 and ends after patient meets the predefined AESI specific clean period in calendar days*

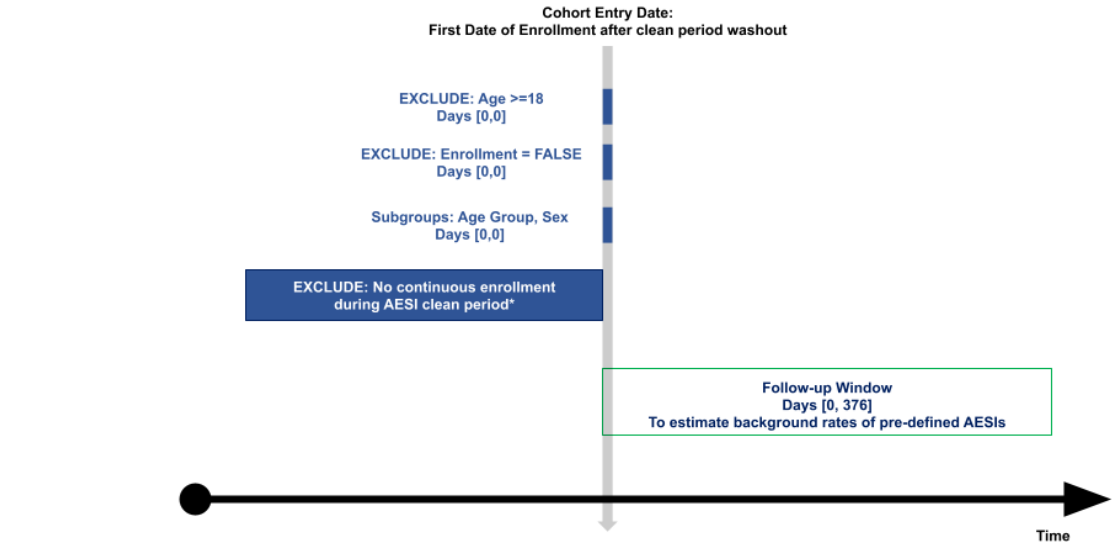
Cohort 2: Static (adult/pediatric) cohort meeting eligibility per Figure 9-10 in Time Period 2: Active-COVID, Pre-EUA period from 1 Dec 2019 to 10 Dec 2020 (one day prior to first US SARS-CoV-2 vaccine EUA)

Figure 9. Cohort 2: Static Adult Cohort (Time Period 2)



Data source: HealthVerity Claims and Pharmacy Study Population (01 Dec 2017 to 10 Dec 2020)
Allowable cohort entry date range: 01 Dec 2019 through 10 Dec 2020 (1 day before First US EUA Date [11 Dec 2020])
**At earliest starts 01 Dec 2018 and ends after patient meets the predefined AESI specific clean period in calendar days*

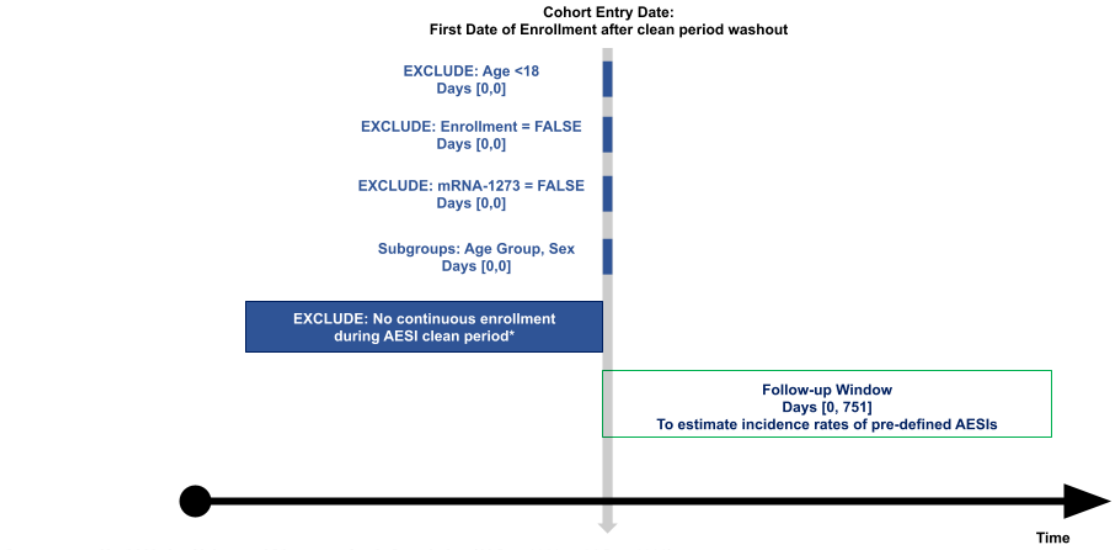
Figure 10. Cohort 2: Static Pediatric Cohort (Time Period 2)



Data source: HealthVerity Claims and Pharmacy Study Population (01 Dec 2017 to 10 Dec 2020)
Allowable cohort entry date range: 01 Dec 2019 through 10 Dec 2020 (1 day before First US EUA Date [11 Dec 2020])
**At earliest starts 01 Dec 2018 and ends after patient meets the predefined AESI specific clean period in calendar days*

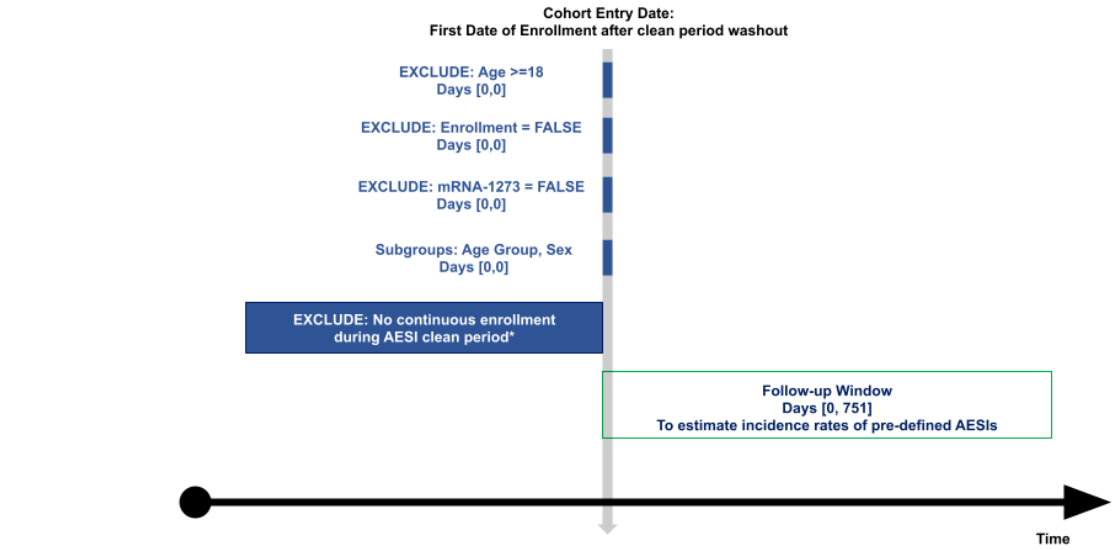
Cohort 3: Entire (adult/pediatric) cohort meeting eligibility per Figure 11-12 in Time Period 3: Post-EUA period from date of first US SARS-CoV-2 vaccine EUA to 31 Dec 2022 comprised of mRNA-1273 vaccinated patients.

Figure 11. Cohort 3: Adult Cohort (Time Period 3)



Data source: HealthVerity Claims and Pharmacy Study Population (11 Dec 2020 to 31 Dec 2022)
Allowable cohort entry date range: First US EUA Date [11 Dec 2020] through 31 Dec 2022
**At earliest starts 01 Dec 2019 and ends after patient meets the predefined AESI specific clean period in calendar days*

Figure 12. Cohort 3: Pediatric Cohort (Time Period 3)



Data source: HealthVerity Claims and Pharmacy Study Population (11 Dec 2020 to 31 Dec 2022)
Allowable cohort entry date range: First US EUA Date [11 Dec 2020] through 31 Dec 2022
**At earliest starts 01 Dec 2019 and ends after patient meets the predefined AESI specific clean period in calendar days*

The cohort entry date will be defined as the first date during the cohort time period that the patient has evidence of enrollment (all cohorts) or claims activity (cohort 3) in the data and meets the AESI specific continuous enrollment (60-day gap allowed) clean period (see Annex 1) without evidence of the AESI. For Cohort 1b, the cohort entry date will be the first

date during the cohort time period that the patient has evidence of influenza vaccination and meets the AESI specific continuous enrollment clean period.

9.2.1. Study Period

The study will include data drawn from 1 Dec 2017 until 31 Dec 2022.

9.2.2. Study Population

Cohorts 1a, 1b, and 2 will be created for each AESI representing time prior to mRNA-1273 vaccine EUA. They will serve to estimate background incidence rates across Time Period 1 and Time Period 2 for Objective 1a(i-ii) and will be leveraged for Objective 2 (where warranted).

Cohort 3 will be a cohort with vaccinated individuals from the time after mRNA-1273 vaccine EUA up to 31 Dec 2022. Cohort 3 data will be updated biweekly; updates will both extend follow-up time for existing patients and may include new patients. Cohort 3 will serve to estimate IRs after mRNA-1273 vaccine EUA (for Objectives 1a and 1b) and will be leveraged for Objectives 2 and 3 where warranted.

Subgroups will be defined based on age group and sex. Other clinical and non-clinical factors may be added as needed.

9.2.3. Inclusion Criteria

To be included in this study, participants must meet the following criteria:

- Included in a health plan covered by HealthVerity database (see Section 9.4)
- Covered by a health plan during at least one period of interest (pre-COVID-19, active COVID-19 and post-EUA periods), but not necessarily the full period
  - Individuals will contribute follow-up time to each time period for which they are eligible
- Demonstrate an AESI specified clean period of continuous baseline enrollment or claims activity before the period of interest (pre-COVID-19, active COVID-19 and post-EUA periods) during which the patient is covered.

On cohort entry date, patients will have evidence of enrollment or claims activity in a health plan. Their age group and sex will be assigned for the remainder of the follow-up. Patients will also, for each AESI, meet a required continuous enrollment clean period described in Annex 1.

9.2.4. Exclusion Criteria

None.

9.3. Variables

9.3.1. Exposures

The mRNA-1273 vaccination schedule consists of two 100 µg doses within a one month period, with the second dose likely between 28 and 31 days of the first. Exposure to mRNA-

1273 vaccine will be identified through specific CPT code 91301 and modifiers 0011A (1st dose) and 0012A (2nd dose) and 0013A (3rd dose) or NDC 10/11 code (80777-273-10, 80777-0273-10, 80777-273-15, 80777-273-99), noting that codes will be reviewed prior to execution of each interim analysis and updated to include newly identified entries. CPT codes and modifiers are expected to be fully reported as a result of insurance reimbursement requirements set by CMS and others. However, exposure status may be missed when vaccinations occur outside of conventional healthcare settings. This study will consider a patient with evidence of at least one dose of mRNA-1273 as exposed (i.e., vaccinated), with exposure date determined as the first date of vaccination claim's date of service.

In Time Period 3, all individuals receiving mRNA-1273 will be identified. However, subgroups may be based on (1) dose observed (e.g., first, second, third, etc recognizing that real-world utilization may vary from the schedule authorized at the time of protocol development), and (2) receipt of a heterologous vaccine schedule in which multiple COVID-19 vaccine brands are used. While the primary analysis will consider AESI rates following receipt of mRNA-1273 restricted to individuals that did not receive other COVID-19 vaccines, analyses of other populations may be conducted where sample size is sufficient to obtain meaningfully precise estimates.

9.3.2. Outcomes

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, VAC4EU[11], FDA Sentinel). Algorithms may be adapted from other sources or created for this study based on literature review.

Table 1 below provides the list of predefined AESIs for which Objective 1 IRs will be estimated (see Annex 1 for corresponding code list). Several sources have been considered to define this list: CDC/FDA's VAERS and VSD, and the ACCESS project endorsed by EMA. Additional AESIs may be added as described in Section 9.1.

Table 1. Predefined AESIs

Predefined AESIs
Acute aseptic arthritis
Acute disseminated encephalomyelitis (ADEM)
Acute kidney injury
Acute liver injury
Acute myocardial infarction (AMI)
Acute respiratory distress syndrome (ARDS)
Anaphylaxis
Anosmia, ageusia

Arrhythmia
Aseptic meningitis
Bell’s palsy
Chilblain-like lesions
Coagulation disorders
Cerebral sinus venous thrombosis
Deep vein thrombosis (DVT)
Disseminated intravascular coagulation (DIC)
Encephalitis / Encephalomyelitis
Erythema multiforme
Gestational diabetes (among pregnant women)
Guillain-Barré Syndrome (GBS)
Heart failure
Immune thrombocytopenia
Ischemic heart disease
Kawasaki disease
Meningoencephalitis
Microangiopathy
Multisystem Inflammatory Syndrome
Myocarditis
Narcolepsy / cataplexy
Pericarditis
Preeclampsia (among pregnant women)
Preterm labor (among pregnant women)
Pulmonary embolism (PE)
Seizures/convulsions
Single organ cutaneous vasculitis
Spontaneous abortion (among pregnant women)
Stillbirth (among pregnant women)
Stroke, hemorrhagic
Stroke, non-hemorrhagic
Thrombosis with thrombocytopenia
Transverse myelitis
Type 1 Diabetes

9.3.3. Key Covariates

The following covariates will be considered for subgrouping or adjustment in this study:

- Age group: <12, 12-16 , 17, 18-24, 25-39, 40-49, 50-64, 65-74, 75+
  - Note: 17-year old patients will be considered separately given that age availability in whole years limits ability to classify these individuals as adolescent or adult.
- Sex
- Dose (dose 1, dose 2, and any booster or additional doses observed)

Identifying Pregnancy Episodes
To determine time at risk for a pregnancy-related AESI, pregnancy endpoints (live birth, still birth, delivery of unknown outcome, trophoblastic and other abnormal products of conception, ectopic pregnancy, elective abortion, and spontaneous abortion) among females of childbearing age (12-55 years) will be identified. The pregnancy outcomes will be identified in hierarchical order to identify individual pregnancy episodes. The length of the pregnancy episode will be defined as the maximum pregnancy term[12], with day 1 identified as the pregnancy start date. The corresponding code lists and maximum pregnancy term will be detailed in the SAP.

9.3.4. Other Covariates

For AESIs which trigger an SCRI analysis, additional adjustment for the below covariates such as seasonality and health-care resource utilization, and potential time-varying confounders will be considered and will be detailed in Protocol Annex 2.

The operational definition for each covariate will be presented in the SAP.

9.4. Data Sources

This retrospective observational cohort study will use secondary, de-identified individual level medical and pharmacy claims data provided by HealthVerity. The data represent more than 140 million patients insured under commercial, Medicare or Medicaid plans, and/or served by providers participating in several large US medical and pharmacy insurance claims submission systems.

HealthVerity data contains near real-time medical claims and outpatient pharmacy transactions, including drugs, diagnoses, and procedures. This data is drawn from a variety of US sources which include Veradigm and over 70 other data partners. Data elements include provider-submitted claims, adjudicated insurance claims, and pharmacy billing manager claims submissions. They update in near real-time, with minimal lag between time of claim submission and time of inclusion in the database. Over 12 months of historical data is available for many patients. Hospitalizations are included in the data at a summary level. Vaccinations will be captured via manufacturer-specific CPT codes. Drugs dispensed by a pharmacy are generally well captured, while OTC medications are not.

The medical claims used for this study will include open and closed medical claims.

Open claims are adjudicated or unadjudicated claims submitted by providers or facilities for consideration for payment by payers. The claims are captured in clearing houses or practice management or revenue cycle management systems. Because they often are not yet associated with a particular insurer, there is no associated enrollment/eligibility file, the registry of who is and who is not covered under a plan. As such, with open claims, the total number of patients available for analysis (i.e., denominator) must be estimated. This is typically done by assuming coverage based on a patient's claims activity; however, as there is not an associated enrollment file, a complete record of a patient's activity with the healthcare system (observability) is not possible and there is the potential for missing information (diagnoses, procedures, or prescription fills). Open claims are processed and available in near real time.

Closed claims data, sometimes referred to as payer data, represent claims accepted by and paid by health insurance companies. Because insurers generally pay for all of a patient's care, or at least record all care for payment decisions on future claims, closed claims present a fully complete view of services. The total number of patients available for analysis (i.e. denominator) is available from the enrollment file. Closed claims generally lag by 3-6 months.

To create linkages across databases to ensure de-identified, longitudinal, de-duplicated patient data, all data partners use the HealthVerity technology within their system to create a unique, secure, encrypted, and non-identifiable patient token. This token is then employed as a consistent linkage key across datasets. The linkage of patients has high accuracy: 99.7% of linkages made are made correctly (0.3% false positives), and 96% of possible linkages are made (4% false negative) according to HIPAA regulations. With real-time assembly of data requiring the use of multiple sources, this approach appropriately balances timeliness with fidelity of linkage.

All data include key factors such as patient age, sex, and 3-digit zip level. Race and ethnicity information is not available. Use of data and the precise granularity available is controlled by HIPAA requirements or application of public health exemption. No PHI (protected health information) or PII (personal identifying information) leaves the data owner's possession, and all research data were certified HIPAA compliant by expert determination.

9.5. Study Size

The analysis cohorts for background incidence rates will be drawn from approximately 50 million patients from the HealthVerity database (See Section 9.2, Figure 3). The cohort for vaccinated individuals will be formed from the entirety of available HealthVerity data from over 140 million patients.

AESI-specific sample size calculations will be performed when a particular AESI enters the Objective 3 analysis. For illustration, Table 2 below provides example sample size estimates for 4 AESIs (Myocarditis, Guillain-Barré syndrome [GBS], acute myocardial infarction, and anaphylaxis), and is based on the following simplifying assumptions and parameters:

- Administration of 1 dose of vaccine AESI-specific risk period

    - Myocarditis: 1-7 days
    - GBS: 1–42 days
    - Acute myocardial infarction (MI): 1–28 days
    - Anaphylaxis: 1 day
- 42 -day control period
- 0.80 power
- α=5%
- Total observation period = AESI-specific risk period + 42 -day control period
    - Minimal detectable risk ratio (RR) = 1.5, 2 or 3
- 15.1 million individuals with at least one mRNA-1273 dose in the HealthVerity database (as of August 26, 2021)

Table 2. Example sample size estimates

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
Myocarditis	2.2 cases per 100,000 vaccine recipients	332	7	49	333	103	36
GBS	1.2 - 3.0 cases per 100,000 inhabitants annually[13]	181-453	42	84	194	69	29
Acute myocardial infarction (MI)	805,000 MI's in the US per year (242.9 events per 100,000 persons per year)[14]	36.678	28	70	193	66	27
Anaphylaxis	42 cases per 100,000 person-years over 10 years[15]	6,342	1	43	1,684	491	156

[a] Estimated US incidence x approximately 15.1 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 + 42 days 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.[16,17]

The simplifying assumptions and parameters above may be varied in the actual sample size calculations for a particular AESI entering Objective 3 analysis.

9.6. Data Management

All data management will be conducted using the Aetion Evidence Platform® (AEP) which is a software system developed by Aetion, Inc. (http://www.aetion.com) for real-world data analysis. The AEP is an analytic platform on which data can be used to generate evidence by executing analyses in a transparent and reproducible manner that has been validated for a range of studies. The AEP has been accepted for use in FDA context previously, i.e., for the RCT DUPLICATE project and in an COVID-19 Research Collaborative Agreement and the COVID-19 Evidence Accelerator.[18,19]

FDA reviewers can be provided access to AEP to review the results and access the underlying data, upon submission of the interim and final study reports. All components of the study (e.g., cohorts, defined outcomes/covariates, results) will be available for review through the AEP.

9.7. Data Analysis Plan

A separate SAP will include additional details pertaining to operational execution of the planned analyses. For all analyses, adult and pediatric patients will be analysed separately. Formation of each cohort will be described showing attrition based on each study entry criterion, and descriptive analyses will be presented characterising the cohort based on demographic characteristics and baseline medical history.

An additional descriptive table will be presented describing individuals with events of myocarditis observed following receipt of mRNA-1273 . This subpopulation will further be described in terms of baseline characteristics, healthcare utilization and subsequent cardiac hospitalizations or new diagnoses. Descriptive analyses will include stratification by age, sex, dose, and time since most recent vaccination (1-7 days vs. >7 days).

For **Objective 1**, AESI IRs will be descriptively reported. Background IRs per 100,000 person-years will be estimated with 95% CI for Time Period 1 and Time Period 2 and, among the vaccine-exposed, estimated for Time Period 3. Background and vaccine-exposed IRs in the US population will be stratified by age group and sex.

Both background and vaccine-exposed IRs will be estimated from detection of new onset or first diagnosis of the AESI, as the count of exposed individuals allows. Sensitivity analyses will be considered, such as requiring that an AESI be observed at least twice in 30 days.

The incidence rate ratio (IRR) with 95% CI will be calculated to estimate the relative change in IRs pre/post mRNA-1273 vaccine EUA. This will be performed separately for Time Period 1 and Time Period 2. IRRs will be calculated overall and may be stratified as above.

The clean periods for pregnancy-related AESI's will be applied on the day prior to the pregnancy start date. Among the sub-cohort of pregnant patients, the risk period for the pregnancy-related AESI's will begin on the estimated pregnancy start date. If a patient's pregnancy window crosses multiple timepoints, only the days of the pregnancy episode which are included in the specific time period of interest will be considered at risk.

For **Objective 2**, when the pre-specified criteria are met for a particular AESI, the observed vs expected event ratios (O/Es) and corresponding 95% CI will be calculated, as the ratio of the number of events among those vaccinated with mRNA-1273 to the number of events expected in this population from background rates.

The number of events among those vaccinated will be enumerated as the observed value. The expected value will be calculated as follows:

$$\text{Number Expected (NE)} = \sum_s [\text{Background IR}^a]_s \times [\text{Exposed persons}]_s \times \text{time at risk}$$

- where a is the IR calculated in Time Period 1 and Time Period 2 separately
- where s is the age group, sex, and calendar period stratum
- The time at risk is the cumulative sum of days for all persons exposed to the vaccine during which there is medical plausibility that there is a vaccine-associated increased risk of experiencing an event. The time at risk will be calculated by summing the days after a dose is administered (risk interval). This considers the real-world implication that persons are not fully adherent and do not receive both doses of vaccine.

Subsequent analysis of the potential risk associated with mRNA-1273 vaccine will be triggered by the confidence interval of the observed AESI event crossing the threshold of the estimated expected events. Confidence intervals (CI) will be calculated around the number of events observed in the risk period.[20] If the lower bound of the 95% CI of the observed number of cases is higher than the estimated expected number of cases, the observed number is deemed significantly higher than the expected and will trigger the SCRI analysis. Likewise, when the lower bound of the 95% CI of the O/E ratio is greater than 1, the observed number is deemed significantly higher than the expected and will trigger the SCRI analysis.

Therefore, if the lower bound of the observed number of cases is greater than the estimated expected number of cases, the observed is deemed higher than the expected.

For **Objective 3**, when the pre-specified criteria are met for a particular AESI or a request is made by the sponsor or regulatory authorities, the risk ratio (RR) of each AESI triggered in Objective 2 will be estimated using a self-controlled risk interval (SCRI) design and fitting a conditional Poisson regression model. For each AESI, a risk period, clean period (optional), and control period will be defined. Table 3 displays the duration of the risk windows as aligned with the FDA and CDC COVID-19 vaccine safety surveillance protocols, which will also be used for the calculation of the O/E ratio in Objective 2. For control periods, a 42-day window will be applied consistently across all AESIs. Upon an AESI-specific trigger for a SCRI analysis, the length of the risk period will be re-evaluated and potentially updated, and the length of the control period and an optional clean period (if applicable) will be re-evaluated. These will be documented in Protocol Annex 2 which will be submitted to regulatory agencies for approval prior to conducting the SCRI analysis.

The SCRI will calculate an IRR following any vaccine dose without distinguishing between doses, thus it will include both patients with only 1 dose and those with 2 doses of the mRNA-

1273 vaccine. The risk windows and control windows will be implemented as follows:

- The risk window will run until the end of its pre-specified duration or until a patient receives a second vaccine dose.
- The control period will start on the day following the end of the AESI-specific risk window.
- If a second vaccine dose is observed, an additional risk window will be included in the analysis. The following adjustments will be made for AESI risk windows with a duration less than and greater than the 28-day dosing schedule:
    - For AESIs with a risk window less than 28 days, the period between the end of the first dose risk window and start of the second dose risk window will contribute to the control period.
    - For risk windows longer than the 28-day dosing schedule, the first dose risk window will be truncated at the time of the second vaccine dose.

D ose-specific effects will be evaluated for myocarditis and for outcomes with sufficient sample size.

When criteria for a SCRI analysis are met for a particular AESI, the need to control for time-varying confounding will be determined and included in an updated Protocol Annex 2.

Sensitivity Analyses:

While duration of the risk windows are aligned with the FDA and CDC COVID-19 vaccine safety surveillance protocols, the distribution of AESIs after vaccination will be explored (e.g., median/mean number of days between vaccine dose and AESI, identifying clusters of AESIs post-vaccination) and sensitivity analyses may be performed with alternative risk windows (e.g., 30-60 days).

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 described over each of the three study time periods. While the severe outcomes are expected to be more similar to the study outcomes, they are less susceptible to changes in health seeking behaviour. As such, rates of mild and moderate conditions and procedures (e.g., colonic diverticulitis, hypertension, colonoscopies, mammograms, and cervical cancer screenings) will also be characterized.

Main analyses will be restricted to individuals that receive only the mRNA-1273 vaccine in Time Period 3. Sensitivity analyses that may be performed pending availability of a sufficient sample size include consideration of individuals with a heterologous vaccine schedule, stratification by dose, and stratification by immunocompromised status. Given that a third dose of vaccine is recommended for severely immunocompromised individuals, dose-stratified analyses will be reviewed to assess whether there is evidence of effect measure modification (which would require further stratification) or confounding (which would require adjustment) by this factor.

9.8. Quality Control

9.8.1. Data Quality Control

Data provided by HealthVerity will be examined for completeness and consistency, including identifying any issues with missing files or variations in data structure. Standard data quality checks include:

- Generating statistics for each variable including the number of records observed, the number of unique values observed, the number of null values observed and percent fill, and the most frequently occurring values
- Comparing the schema of data received with the expected schema per vendor documentation
- Creating event density distributions for new datasets and data updates in order to explore event data over time and identify possible gaps or missing files
- Checking for variables with high proportions of missing data
- Cross-checking imported record counts against original data counts
- Cross-checking patient event dates against enrollment files (where available)
- Parallel coding for final validation of data transformation before platform deployment

If any quality issues are identified, the data provider will replace any necessary files or data items, and the verification process will be repeated.

9.8.2. Analysis Results Quality Control

All results will be reviewed by the principal investigators to evaluate internal consistency of counts and totals. All calculated variables will be checked against the component variables (crosstabs) to ensure accuracy. For example, categorical age would be compared with continuous age to confirm that each category of age contained only persons of the expected age ranges within that category.

9.9. Limitations of the Research Methods

There are four general limitations associated with this analysis.

First, this study will use medical and prescription claims, which are valuable for the efficient and effective examination of healthcare outcomes but have inherent limitations. There may be some misclassification bias as a diagnosis code on a medical claim does not always constitute presence of disease. The diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease.

Second, whereas the data available for Time Period 1 and Time Period 2 are closed, adjudicated claims, Time Period 3 will be a mixture of closed and open claims for interim analyses. Closed claims capture almost every event occurring and not occurring during a patient's insurance enrollment period but are subject to a lag due to the need for data adjudication. Open claims come from a variety of data sources and do not rely on a patient maintaining the same insurance plan. However, open claims only capture patient activity in specific healthcare settings and therefore some patient activity may be missed. Open claims are near real-time and do not have substantial lag, enabling near real-time safety signal evaluation and refinement activities. There may be some misclassification bias as a result of missing patient activity in the open claims and there is a substantial delay in detecting patient

activity in the closed claims. Incidence rate estimation will be repeated periodically to help mitigate these biases as data is updated and becomes available. The final analyses and study report will be based on closed claims only.

Third, it is not possible with open claims to assess patient observability based on insurance plan membership enrollment files, as is done with closed medical and pharmacy claims. Thus, the concept of enrollment for open claims will be proxied based on the first and last date of data observable (activity) for each patient. This could bias estimation of person-time.

Fourth, in the HealthVerity data which encompasses Time Period 1 and Time Period 2, a stratified random sample will be generated based on sex and age distributions from 2019 US Census. However, the prospective data in Time Period 3 includes any patient who receives the SARS-CoV-2 vaccine and will not be weighted to be nationally representative. To mitigate this, incidence rates calculated from these data will be standardized to US Census or stratified by age group, sex, and calendar period.

Fifth, individuals in Time Period 3 will be vaccinated, while those in the Time Period 1 comparison cohort are expected to be a mixture of vaccinated and non-vaccinated patients. Any attempt to compare these two groups without sufficiently adjusting for confounding factors may lead to channeling bias, as vaccinees may have fewer comorbidities and more frequent health seeking behavior compared to non-vaccinated individuals. Additionally, these factors may change over time, both in the short and long terms, throughout the COVID-19 pandemic. In order to account for baseline differences between cohorts, descriptive analyses will be conducted and *a priori* assumptions will be made about which potential confounders to adjust for, including proxies of health seeking behavior and comorbidities. To evaluate the impact of this potential bias, incidence rates of AESI's among vaccinated patients in time period 3 will be compared to individuals with evidence of an influenza vaccine in Time Period 1. Negative controls (e.g., brain surgery, heart attack, revascularization procedure) may also be descriptively assessed as indicators of unmeasured confounding when comparing background rates in Time Period 1 with incidence among vaccinated patients in Time Period 3.

Sixth, there is the potential for misclassification bias when identifying diseases based on medical claims. To minimize bias, validated algorithms will be used whenever possible and algorithms will be drawn from public, credible sources such as the CBER protocol, FDA Sentinel, or EMA ACCESS. For those diseases not found in any of these sources, peer-reviewed literature will be used. Clinician review and resulting adjustments to the algorithms may be required for further refinement.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

This study was designed and shall be implemented and reported in accordance with Good Pharmacoepidemiology Practice (GPP), with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. Given this is a retrospective database study using de-identified data, informed consent is not required.

11. Management and Reporting of Adverse Events / Adverse Reactions

Individual cases of above specified safety outcomes possibly associated with mRNA-1273 vaccination during this study will not be reported as it is a retrospective database study. Data will be reported as per study design and milestones.

12. Plans for Disseminating and Communicating Study Results

The results of this study will be submitted for publication as scientific papers in peer-reviewed journals. The manuscripts will be prepared in accordance with the current guidelines including Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and ICMJE authorship guidelines.

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Annex 1. 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

The table below summarizes ICD-10 codes and ATC codes (only where indicated) considered for predefined AESIs definition.

AESI	Clean Period	Code list	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, 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: 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 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 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,	See reference

		L50.4, L50.5, L50.6, L50.8, L50.9, L29.1, L29.2, L29.3, L29.8, L29.9) or 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) v. Reduced blood pressure (ICD-10: I95.1, I95.0, I95.89, I95.3, I95.2, I95.81, I95.89, I95.9, R55) or vi. Gastrointestinal symptoms (ICD-10: K52.21, K52.22, K52.29, R11.2, R11.10, R11.11, R11.12, R10.0, R10.9, R10.11, R10.12, R10.31, R10.32, R10.33, R10.13, R10.84, R10.10, R10.2, R10.30) or vii. Unspecified adverse effect (ICD-10: T50.905A, T78.41XA, T41.0X5A, T41.1X5A, T41.205A, T41.295A, T41.3X5A, T41.45XA, T88.53XA, T88.59XA, T38.3X5A, T88.52XA, T50.995A, T36.0X5A, T36.1X5A, T36.2X5A, T36.3X5A, T36.4X5A,T36.5X5A, T36.6X5A, T36.7X5A, T36.8X5A, T36.95XA, T37.0X5A, T37.1X5A, T37.2X5A, T37.3X5A, T37.4X5A, T37.5X5A, T37.8X5A, T37.95XA, T38.0X5A, T38.1X5A, T38.2X5A, T38.4X5A, T38.5X5A, T38.6X5A, T38.7X5A, T38.805A, T38.815A, T38.895A, T38.905A, T38.995A, T39.015A, T39.095A, T39.1X5A, T39.2X5A, T39.315A, T39.395A, T39.4X5A, T39.8X5A, T39.95XA, T40.0X5A, T40.2X5A, T40.3X5A, T40.4X5A, T40.5X5A, T40.605A, T40.695A, T40.7X5A, T40.905A, T40.995A, T41.5X5A, T42.0X5A, T42.1X5A, T42.2X5A, T42.2X5A, T42.3X5A, T42.4X5A, T42.5X5A, T42.6X5A, T42.6X5A, T42.75XA, T42.75XA, T42.8X5A, T43.015A, T43.025A, T43.1X5A, T43.205A, T43.215A, T43.225A, T43.295A, T43.3X5A, T43.4X5A, T43.505A, T43.595A, T43.605A, T43.615A, T43.625A, T43.635A, T43.695A, T43.8X5A, T43.95XA, T44.0X5A, T44.1X5A, T44.2X5A, T44.3X5A, T44.4X5A, 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 Criterion C: At least one of the following combinations i. (skin-mucosal tissue involvement) & (shock caused by anesthesia) or ii. (respiratory compromise) & (shock caused by anesthesia or angioneurotic edema) or iii. (acute bronchospasm or stridor) & (allergy unspecified, initial encounter) or iv. (reduced blood pressure) & (gastrointestinal symptoms) & (an unspecified adverse effect or allergy unspecified, initial encounter) or v. (reduced blood pressure) & (skin-mucosal tissue involvement) & (unspecified adverse effect or an allergy unspecified, initial encounter) or vi. (respiratory compromise) & (reduced blood pressure) & (an unspecified adverse effect or an allergy unspecified, initial encounter) or vii. (respiratory compromise) & (gastrointestinal symptoms) & (an unspecified adverse effect or an allergy unspecified, initial encounter or skin-mucosal involvement) or viii. (respiratory compromise) & (skin-mucosal tissue involvement) & (an unspecified adverse effect or an allergy unspecified, initial encounter) PLUS 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)	
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, I48.92, I49.0, I49.01, I49.02, I49.1, I49.3, I49.5, I49.8, I49.9	ACCESS

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
Multisystem Inflammatory Syndrome	365 days	ICD-10: U07.1 and ICD-10: M35.8, M35.81, M35.89 up to 8 weeks after U07.1	FDA
Myocarditis	365 days	ICD-10: B33.22,I41, I40.0, I40.1, I40.8, I40.9, I51.4	FDA
Narcolepsy /	365 days	ICD-10: G47.4, G47.41, G47.411, G47.419, G47.421, G47.429	ACCESS

cataplexy			
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, I63.532, I63.533, I63.539, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.81, I63.89, I63.9	FDA
Thrombosis with thrombocytopenia		(Meets both definitions for coagulation disorders and thrombosis)	
Transverse myelitis	365 days	ICD-10: G37.3	FDA
Type 1 Diabetes	365 days	ICD-10: E10.x	ACCESS

ACCESS: http://www.encepp.eu/phact_links.shtml
FDA:https://www.bestinitiative.org/wp-content/uploads/2021/02/C-19-Vaccine-Safety-AESI-Background-Rate-Supplemental-2021.xlsx

Annex 2. SCRI analysis: example risk and control windows

The table below summarizes examples of risk windows to be considered for SCRI analysis. For control windows, 42 days will be used for all AESIs as a starting point and evaluated further.

When a particular AESI is triggered for SCRI during the course of the study, the risk and control window as well as the AESI algorithm and time-varying covariates will be reassessed and finalized. Annex 2 will be submitted to relevant regulatory agencies at that time.

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	0-1
Anosmia, ageusia	1-28
Arrhythmia	1-28
Aseptic meningitis[22]	8-35
Bell's palsy[24,25]	1-60
Cerebral Sinus Venous Thrombosis (CSVT)[23]	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- 7
Narcolepsy / Cataplexy	1-42
Pericarditis	1- 7
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- 14
Transverse myelitis	1-42
Type 1 Diabetes	1-28

*Day 0 = the day of the vaccine dose; Day 1 = the day after the vaccine dose.
*The above-mentioned risk windows are considered for the main analysis. Sensitivity analysis may be conducted on alternative risk windows considering each particular AESI.

Annex 2. SCRI analysis: Myocarditis and Pericarditis

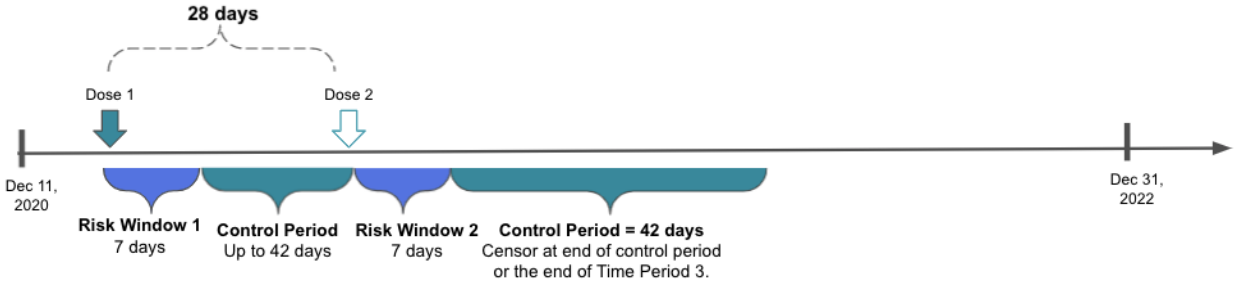
Primary SCRI Approach

The primary approach to SCRI will calculate an IRR following any vaccine dose without distinguishing between doses, thus it will include both patients with only 1 dose and those with 2 doses of the mRNA-1273 vaccine. The risk windows and control windows will be implemented as follows:

- The risk window will begin on the day following the first dose until the 7th day (day 1-7)
- The control period will be up to 42 days in length; it will start on the day following the end of the 7-day risk window (day 8) until day 50 since vaccine dose

If a second vaccine dose is observed, an additional 7-day risk window will be included in the analysis that begins on the day after the second dose. The period between the end of Risk Window 1 and the start of Risk Window 2 will contribute to the control period (Figure 1).

Figure 1. SCRI Primary Analysis, evaluate regardless of dose: Myocarditis and Pericarditis



Individuals with a heterologous vaccine dose between the first and second dose of mRNA-1273 will be censored from the SCRI analysis.

Although the current minimum required interval between the first and second dose is 7 days, we suggest expanding that to 24 days (5th percentile) and requiring a maximum time between doses of 35 days (95th percentile) given the following distributions:

Table 1a. Distribution of days between first and second dose of mRNA-1273.

Events washed out	Mean (SD)	Median (IQR)	Min	Max
Myocarditis	27.90 (6.23)	28.00 [28.00, 28.00]	1.00	170.00
Pericarditis	27.90 (6.23)	28.00 [28.00, 28.00]	1.00	170.00

Table 1b. Percentiles of days between first and second dose of mRNA-1273.

Percentile	Days to 2nd Dose
Min	1.00
5th	24.00
10th	27.00
20th	28.00
25th	28.00
30th	28.00
40th	28.00
50th	28.00
60th	28.00
70th	28.00
75th	28.00
80th	29.00
90th	31.00
95th	34.00
Max	170.00

In the SCRI analysis, the first outcome per patient will be evaluated and is assumed to be rare. The IR of myocarditis and pericarditis during the risk period will be compared with the IR during the control period; an incidence rate ratio (IRR) will be estimated using a conditional Poisson model. 95% confidence intervals from the conditional regression will be estimated using the normal approximation method based on the Wald statistic.

Dose-specific effects will also be evaluated.
For analysis of the first dose:

- The risk period will begin following the 1st dose.
- If a patient receives a 2nd dose of the vaccine, the duration of the risk window following the 2nd dose will be excluded from the analysis, and the control period will begin following the duration of the 2nd dose risk window.
- Since the risk window for myocarditis/pericarditis is <28 days (the recommended dosing window for mRNA-1273), the days between the end of the 1st dose risk window and the start of the 2nd dose risk window will be included as the control period, and the 2nd dose risk window will be excluded from the analysis.

For analysis of the second dose, the 2nd dose risk window will be included in the analysis. The control period will begin the day after the end of the 2nd dose risk window.

In the SCRI analysis, the first outcome per patient will be evaluated and is assumed to be rare. The IR of the AESI during the risk period will be compared with the IR during the control period to estimate the IRR fitting a conditional Poisson model. 95% confidence intervals from the conditional regression will be estimated using the normal approximation method based on the Wald statistic.

A sensitivity analysis will be conducted utilizing an alternative risk window of 28 days for myocarditis and pericarditis (with a 42 day control period).

Claims-Based Algorithm for Myocarditis and Pericarditis

As specified in the protocol, definitions for myocarditis and pericarditis events were identified from the FDA COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol.

AESI	Clean period	Algorithm	Diagnosis Codes
Myocarditis	365 days	At least 1 diagnosis in any setting	ICD-10: B33.22, I41, I40.0, I40.1, I40.8, I40.9, I51.4
Pericarditis	365 days	At least 1 diagnosis in any setting	ICD-10: B33.23, I30.0, I30.1, I30.8, I30.9, I32

A literature search was conducted to identify alternative claims-based algorithms for myocarditis and pericarditis, however no additional validated algorithms were identified which utilized ICD-10 diagnosis codes. We identified a systematic review of validated claims-based algorithms to identify myocarditis and pericarditis, however the algorithms identified in the review utilized ICD-9 codes [Idowua, 2013]. Comparing the full list of ICD-9 codes utilized among the algorithms identified in the systematic review (and translating those to ICD-10), all ICD-10 codes listed in the FDA algorithms for myocarditis and pericarditis are captured. Additional codes included in the algorithms captured within the systematic review are codes specific to chronic myocarditis, acute rheumatic myocarditis, and meningococcal myocarditis, conditions not relevant to vaccine-associated myocarditis.

Chart Review and Assessment of Potential Misclassification Bias

To understand the performance of the myocarditis and pericarditis algorithms within time period 3, during which the SCRI will be implemented, we will seek medical charts of individuals identified with the outcome of interest in the HealthVerity data. The results of this chart review will be submitted along with the results of updated SCRI analyses for myocarditis and pericarditis based on cases confirmed as having met the CDC case definition for myocarditis or pericarditis respectively.

Although the risk and control periods within the planned SCRI analyses for myocarditis and pericarditis are relatively short, there may be differential misclassification of an AESI in the SCRI analyses. In the case of myocarditis and pericarditis, the sensitivity of the claims-based algorithm to identify an event may be higher in the risk period, closer to receipt of a mRNA-1273 vaccine dose, than the corresponding sensitivity of the algorithm further out from receipt of a vaccine dose. This may be driven by different reporting habits relative to the recency of vaccine dose driven by public health messaging and reports regarding myocarditis/pericarditis in the media. Hypothetically, an individual experiencing symptoms of myocarditis or pericarditis may be more likely to report to a healthcare facility if he/she experiences symptoms closer to the date of vaccine dose.

To explore the impact of this differential misclassification of the claims-based algorithms to identify myocarditis and pericarditis, we will run a quantitative bias assessment across varying levels of sensitivity and specificity, assuming it is differential across groups. We will utilize the Fox & Lash quantitative bias analysis tool (https://sites.google.com/site/biasanalysis/Home?authuser=0). We propose estimating the bias adjusted measure of effect across the following range of sensitivity and specificity across the risk and control periods:

Risk Period Se	90%	90%	90%
Control Period Se	70%	80%	85%
Risk Period Sp	99%	99%	99%
Control Period Sp	99%	99%	99%

Additional Descriptive Analyses: Myocarditis and Pericarditis

Among individuals identified as having myocarditis or pericarditis events, we will describe baseline demographic and comorbid characteristics in the year prior to receipt of 1st dose. Additionally, we will describe the time from the first dose of mRNA-1273 to the myocarditis event and whether the myocarditis event required hospitalization. Details around events that required hospitalization (i.e.ICU stay, duration), as well as whether there were subsequent hospitalizations, whether those were also cardiovascular related (i.e. cardiomyopathy, heart failure, etc.), and whether there were subsequent cardiac procedures or diagnoses after hospitalization will be reported.