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## I. BACKGROUND

This document provides a review of the safety management planning for mRNA-1273. It is prepared according to the format and expectations of the *Guidance for Industry ICH E2E Pharmacovigilance Planning FDA April 2005*. It describes a method for summarizing the important identified risks of a medicine, important potential risks, and important missing information, including the potentially at-risk populations and situations where mRNA-1273 product is likely to be used that have not been studied preapproval. It describes the risks associated with the clinical use of mRNA-1273 at the time of the data lock of the clinical studies for the Emergency Use Authorization (EUA) submission in the US. This plan will subsequently be updated to incorporate additional information received during the Emergency Use experience and from the continuation of the ongoing clinical studies.

At this time, Moderna has conducted a review of the non-clinical data and ongoing clinical safety data to characterize the safety specification that will form the basis of the RMP in the EUA. Should any important benefit or risk information emerge during the course of implementing the RMP, the safety specifications may be updated, and additional pharmacovigilance and risk minimization measures may be developed.

To date, based on the available data, the specification, pharmacovigilance plan and risk minimization measures that inform the PV Planning starting at the time of the EUA are described as follows.

## **II. SAFETY SPECIFICATION**

### **A. Elements of the Safety Specification**

#### **1. Nonclinical Specification**

To evaluate the theoretical concern of enhanced respiratory disease (ERD), non-clinical studies in several species have been performed with mRNA-1273 (e.g., disease pathology, immune profiling). These mRNA-1273 vaccine study results show immune signatures not predicted to associate with ERD and a lack of vaccine-enhanced viral replication or pulmonary pathology after challenge with SARS-CoV-2 in relevant animal species.

The non-clinical package, which consisted of both studies performed with mRNA-1273 and mRNA vaccines formulated in the same SM-102 LNP vaccine matrix, has been completed to support mRNA-1273 use in humans. A developmental and reproductive study with mRNA-1273 in female Sprague-Dawley rats was completed in December 2020 with no adverse findings. No important identified or potential risks have been identified from the non-clinical studies that support mRNA-1273 vaccine (Module 2.4 of IND#19745).

#### **2. Clinical**

##### **a. Exposure in clinical trials**

Three clinical trials investigating the efficacy, immunogenicity, and safety of mRNA-1273 are ongoing.

A dose finding Phase 1 study (DMID NCT04283461) has enrolled 120 healthy adults to receive either 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273. Participants are administered 2 doses of mRNA-1273 given 28 days apart and will be followed up until Day 394.

A Phase 2 study (mRNA 1273 P201) has enrolled 600 healthy adults 1 randomized 1:1:1 to receive either placebo or mRNA-1273 either 50 µg or 100 µg. The study is divided into 2 cohorts by age, Cohort 1 with 300 participants ( $\geq 18$  to  $< 55$  years old) and Cohort 2 with 300 participants ( $\geq 55$  years old). Participants are administered 2 doses of mRNA-1273 or placebo given 28 days apart and will be followed up until Day 394.

The phase 3 study (mRNA 1273 P301) is a large US randomized, stratified, observer-blind, placebo-controlled, study to evaluate safety, efficacy, and immunogenicity of mRNA-1273 in

adults  $\geq 18$  years of age. This study enrolled 30,418 participants with no known history of SARS-CoV-2 infection, but whose location or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infection. Participants were randomly assigned to receive injections of either 100  $\mu$ g of mRNA-1273 vaccine or a placebo control in a 1:1 ratio. Additionally, study participants at increased risk of complications from COVID-19 have been included. Participants  $\geq 65$  years of age have been enrolled, as increasing age is in itself a risk factor for severe COVID-19 disease. The trial also enrolled participants  $\geq 18$  and  $<65$  years of age with underlying medical conditions which further increases their risk of severe COVID-19 such as chronic lung disease, significant cardiac disease, severe obesity diabetes and liver disease. As of 11 Nov 2020, 15,180 (99.8%) participants in the mRNA-1273 group and 15,170 (99.7%) participants in the placebo group received the first injection, and 13,982 (91.9%) participants in the mRNA-1273 group and 13,916 (91.5%) participants in the placebo group received the second injection. The trial has enrolled a diverse population with subjects of 65 years of age and above (N= 7,533). There is about the same incidence of females and males (47.3% and 52.7%, respectively). In addition, subjects with underlying co-morbidities that make them at increased risk for severe COVID 19 disease have been represented (diabetes 35.5%, severe obesity 24.9%, significant cardiac disease 18.7%, liver disease 2.3%). In the ongoing phase 3 trial, race is represented by Caucasian with 79.2% of the subjects, 10.2% are black or African Americans, 4.6% are Asian and to a lesser extent there are representatives from multiracial origin. Among trial participants, 20.5% reported Hispanic ethnicity.

b. Populations not studied in the preapproval phase

Due to exclusion criteria in the trials, special populations not studied included the pediatric age group ( $<18$ -year-old) as well as pregnant and breastfeeding women. A pediatric study plan has been agreed upon by CBER with the clinical development plan for the evaluation of safety and effectiveness in the pediatric population. The Phase 3 P301 study included participants with age  $> 65$ , comorbidities, diversity with respect to race and ethnicity. (see section a. Exposure in clinical trials).

c. Limitations of the human safety database

In both the mRNA-1273 group and the placebo group, the median follow-up time after the first injection was 78.0 days (11 weeks) and the median follow-up time after the second injection was 49.0 days (7 weeks). Relevant exclusion criteria in the phase 3 P301 study are included in [Table 1](#). The implication of these exclusions criteria is described in section c. Adverse events/adverse drug reactions.

**Table 1: Important Exclusion Criteria in Phase 3 P301**

Pediatric subjects.
Pregnant/Lactating women.
Acutely ill/febrile (temperature >38 C/100.4F) prior to screening visit.
Known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients.
Bleeding disorder considered a contraindication to intramuscular injection or phlebotomy.
Known history of SARS-CoV-2 infection  Of note, in Phase 3 seropositive subjects are not excluded from enrolment, although they are excluded from the Per Protocol cohort.
Has received or plans to receive a non-study vaccine within 28 days prior to or after any dose of IP (except for seasonal influenza vaccine which is not permitted within 14 days before or after any dose of vaccine.
Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (HIV positive participants with CD4 count $\geq 350$ cells/mm <sup>3</sup> and an undetectable HIV viral load within the past year [low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy [ART] are permitted]).
Has received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to Screening (for corticosteroids $\geq 20$ mg/day of prednisone equivalent).
Has received systemic immunoglobulins or blood products within 3 months prior to the day of screening.
Has donated $\geq 450$ mL of blood products within 28 days prior to Screening.

d. Adverse events (AEs)/adverse drug reactions (ADRs)

Solicited local ARs were reported by a majority of participants in the mRNA-1273 group and were reported at a higher incidence in the mRNA-1273 group than in the placebo group after each injection (Table 15 and mRNA-1273-P301 Table 14.3.1.1.3). In the mRNA-1273 group, the most common solicited local AR was pain, and the incidence was similar after the first and second injection (83.7% versus 88.4%, respectively). The majority of solicited local ARs were grade 1 to grade 2 in severity. In the mRNA-1273 group, grade 3 solicited local ARs were more common after the second injection than after the first injection (7.0% versus 3.5%); the most

common grade 3 solicited local AR after the second injection was pain (575 [4.1%] participants). No grade 4 solicited local ARs were reported, and only grade 3 pain was reported at a frequency > 2% after either injection.

Solicited systemic ARs were reported by the majority of participants in the mRNA-1273 group and were more prevalent in the mRNA-1273 group than in the placebo group after each IP injection (Table 16 and mRNA-1273-P301 Table 14.3.1.1.3). In the mRNA-1273 group, the incidence and severity of solicited systemic ARs appeared to increase after the second injection. In the mRNA-1273 group, the most common solicited systemic ARs after the first injection were fatigue and headache, and the frequency of reported events increased after the second injection. Frequently reported events after the second injection also included myalgia, arthralgia, and chills. The majority of solicited systemic ARs were grade 1 to grade 2 in severity. In the mRNA-1273 group, the most common grade 3 solicited systemic ARs after the second injection included fatigue, myalgia, headache, and arthralgia.

Local ARs were more commonly reported by younger adults ( $\geq 18$  to  $< 65$  years; 87.4% and 90.5% after the first and second injection of mRNA-1273, respectively) than older adults ( $\geq 65$  years; 74.6% and 83.9% after the first and second injection of mRNA-1273, respectively) (mRNA-1273-P301 Table 14.3.1.1.4, Table 14.3.1.1.5, and Table 14.3.1.1.6). Systemic ARs were also more commonly reported by younger adults ( $\geq 18$  to  $< 65$  years; 57.0% and 81.9% after the first and second injection of mRNA-1273, respectively) than older adults ( $\geq 65$  years; 48.3% and 71.9% after first and second injection of mRNA-1273, respectively) (mRNA-1273-P301 Table 14.3.1.1.4 and Table 14.3.1.1.5).

The incidence of solicited local ARs after the first injection in participants baseline negative for SARS-CoV-2 at baseline was 84.5% in the mRNA-1273 group and 19.7% in the placebo group. In baseline positive participants, the incidence was 71.8% and 17.4%, respectively (mRNA-1273-P301 Table 14.3.1.1.7). After the second injection, in baseline negative participants, the incidence of solicited local ARs was 89.0% in the mRNA-1273 group and 18.7% in the placebo group. In baseline positive participants at baseline, the incidence was 74.4% and 17.5%, respectively (mRNA=1273-P301 Table 14.3.1.1.8). The incidence of solicited systemic ARs after the first injection in participants baseline negative for SARS-CoV-2 at baseline was 54.6% in the mRNA-1273 group and 42.2% in the placebo group. In baseline positive participants, the incidence was 61.2% and 35.3%, respectively (mRNA-1273-P301 Table 14.3.1.1.7). After the second injection, the incidence of solicited systemic ARs in baseline negative participants was 79.5% in mRNA-1273 group and 36.5% in the placebo group, and in baseline positive participants, the incidence was 66.5% and 31.0%, respectively (mRNA=1273-P301 Table 14.3.1.1.8).

Overall, the frequency or severity of solicited local and systemic ARs was not higher in baseline positive participants than in baseline negative participants.

During the study, several participants reported injection site reactions after Day 7 that were characterized by erythema, induration, and often pruritis. A review of these events showed that the vast majority of the unsolicited TEAEs categorized as local injection or vaccination site reactions in the second week after immunization were a subset of the solicited local AR with a duration beyond Day 7 (mRNA-1273-P301 Table 14.3.1.6.1 and Table 14.3.1.6.2).

To date, no Important Identified risk has been identified.

### **Important Potential risks:**

Vaccine-enhance respiratory disease (VAERD):

There is a theoretical concern over the potential for vaccine-associated disease enhancement associated with vaccines against SARS-CoV-2. The concern is that a SARS-CoV-2 vaccine could theoretically cause enhanced disease and specifically ERD in vaccinees that are subsequently exposed to wild-type SARS-CoV-2. The potential for vaccination against SARS-CoV-2 to be associated with disease enhancement is a theoretical concern, given similar observations with other respiratory viruses in general, and in animal models of some highly pathogenic coronaviruses. This concern has been triggered by preclinical work on SARS-CoV and MERS-CoV vaccines, the experience with feline infectious peritonitis virus and vaccines in cats, and enhanced disease seen with RSV, measles, and dengue vaccines in humans.

Importantly, VAED has not been seen following SARS or MERS vaccines given to humans, albeit the number of people who received these experimental vaccines remains very small.

To evaluate the theoretical concern of enhanced respiratory disease (ERD) with mRNA-1273, non-clinical studies in several species have been performed (e.g., disease pathology, immune profiling). These mRNA-1273 vaccine study results show immune signatures not predicted to associate with ERD and a lack of vaccine-enhanced viral replication or pulmonary pathology after challenge with SARS-CoV-2 in relevant animal species. The phase 3 P301 study was designed to assess the risk of enhanced disease with prespecified rules for harm as defined in the analysis plan and evaluated through by the DSMB. No such safety concerns have been identified, and all cases of severe COVID-19 disease included in the first interim analysis (IA) of efficacy occurred in the placebo group.

Anaphylactic reactions (including anaphylaxis):

As with all injectable vaccines, immediate systemic and severe allergic reactions to vaccination can occur. These events can occur after any vaccination. Most persons recover fully with treatment, but serious complications can occur. Reporting from selected health care

organizations in the United States found an overall rate of anaphylaxis after vaccination of 1.3 cases per million doses administered to both children and adults. Available data seem to suggest a particular patient profile for persons who experience anaphylaxis after vaccination: the vast majority have a history of atopy, but they can occur among persons with no known history of hypersensitivity.

In the ongoing clinical development program, no case of anaphylaxis has been observed to date.

The mRNA-1273 formulation does not contain gelatin, egg protein known to increase the risk of allergy. Within the context of a mass vaccination the risk of anaphylactic reaction including anaphylaxis remains to be monitored and characterized.

### **Important Missing Information:**

Use in Pregnant and breast-feeding women:

The target indication for mRNA-1273 is adults  $\geq 18$  year of age thus will include women of childbearing potential, although the fact sheet will note that administration in pregnant women has not been studied. Pregnant women were excluded from the clinical trials, through a small number of pregnancies has been reported in the mRNA-1273 clinical program.

Use in the pediatric population:

The safety of the vaccine has not yet been established in pediatric subjects  $<18$  year of age. The mRNA-1273 vaccine will be evaluated in pediatric subjects in a separate clinical plan.

Long term safety

The long-term safety profile is to be characterized through continued trial follow up, active surveillance for safety, and routine pharmacovigilance.

Long-term efficacy:

Vaccine efficacy has been demonstrated at the first IA with overwhelming results in the phase 3 P301. However, the duration of immunity which continues to provide protection against the COVID-19 disease remains to be evaluated. It is known that antibody levels to other coronaviruses wane over time and reinfections have been documented. Thus, the long-term efficacy and safety profile is to be characterized through continued trial follow up, as well as a noninterventional study to inform on long-term effectiveness and co-administration with influenza vaccine.

Immunogenicity in subjects with immunosuppression:

In the clinical development program, no subjects with immunosuppression have been enrolled. In study P301 subjects with HIV who did not meet the exclusion criteria have been enrolled. In general, it is expected that subjects with immunocompromised status may not reach the

protective antibody level achieved in healthy individuals with vaccines. However, in the phase 3 study P301, the IA shows an overwhelming vaccine efficacy in the overall population of the trial. mRNA-1273 vaccine is not a live attenuated vaccine nor does it contain a viral vector. Therefore, no risk of transmission of an infection due to the vaccine construct is expected in this population. This population will be monitored via routine pharmacovigilance.

Concomitant administration with non-COVID vaccines (e.g., seasonal flu vaccine):

Due to the exclusion criteria in the mRNA-1273 clinical program no experience exists with vaccines within 28 days prior to the first dose or any dose of mRNA-1273 except for seasonal influenza vaccine <14 days. It is common medical practice to administer vaccines concurrently. There is the theoretical question as whether a vaccine can create interference in the immune response to either vaccines or induce safety concerns. Patients receiving mRNA-1273 may be administered seasonal flu vaccines during the vaccination period of the pandemic. A noninterventional study will inform on long-term effectiveness and co-administration with influenza vaccine.

A summary of these safety concerns is included in [Table 2](#).

#### A. Summary of Safety Concerns

**Table 2: mRNA-1273 Summary of Safety Concerns**

Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	Vaccine associated enhanced respiratory disease Anaphylactic reactions (including anaphylaxis)
Missing Information	Pregnant and breast-feeding women Use in the pediatric population Long-term safety Long-term effectiveness Immunogenicity in subjects with immunosuppression Concomitant administration with non-COVID vaccines (e.g. seasonal flu vaccine)



### III. PHARMACOVIGILANCE PLAN

#### A. Structure of the Pharmacovigilance Plan

##### 1. Summary of ongoing issues

The pharmacovigilance plan addresses the important safety concerns and missing information in [Table 2](#).

##### 2. Routine pharmacovigilance activities

Routine pharmacovigilance will be conducted for mRNA-1273, and due to the special circumstances of the pandemic, enhancement of routine activities will be undertaken. Moderna has a safety surveillance and reporting system in place to organize the collection, data entry in the company global safety database and evaluation of any adverse events reported to Moderna. Cases will be entered into the global safety database. Duplicate detection as well as queries to reporters will follow. Inadvertent exposure to the vaccine during pregnancy will include follow up queries. Moderna will engage in continuous monitoring of the safety profile of mRNA-1273 including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities.

Post-authorization reporting to VAERS of all serious adverse events, COVID disease requiring hospitalization, vaccination administration errors, and Multisystem Inflammatory Syndrome (MIS) will occur through 15 day alert reports to FDA. Periodic reporting to FDA will occur quarterly or at another interval specified by the agency. In addition, all Suspected Unexpected Serious Adverse Reactions (SUSAR) from the ongoing clinical trials will be continue to be expedited to the Agency.

An overview of Moderna's signal detection strategy for the mRNA-1273 vaccine is described in [Table 3](#).

**Table 3: mRNA-1273 Signal Data Sources and Periodicity of Assessment**

Data source	Periodicity
Company global safety database	Ongoing monitoring of individual cases including potential SUSARs and AESI. Weekly aggregated review of AE cases for trend analyses  Review of disproportionate reporting of Preferred Terms (PT) during RP as compared to data prior to the RP.

	Aggregate review of endpoints of interest
Literature	Weekly global literature review
Eudravigilance and other international passive surveillance data	Continuous monitoring when applicable subject to sponsor access to data
VAERS	Frequency of review (bi-weekly or monthly) will depend on public availability of VAERS extract and manual effort necessary to upload in Empirica Signal.  Generation of disproportionality scores using Empirical Bayesian Geometrical Mean (EBGM) and its 90% credibility intervals
Health Authority websites	Ongoing review of data published on the Safety Web Portals of selected major regulatory agencies to identify required actions regarding the product, products in same class.

# 1. Action plan for safety issues

## Vaccine associated enhanced respiratory disease

- Objective: Assess evidence that might suggest Vaccine Enhanced Disease is a clinical entity rather than a theoretical potential risk
- Actions: Continued clinical trial follow-up; expedited reporting for cases of COVID disease requiring hospitalization to VAERS
- Rationale: Vaccine enhanced respiratory disease is an important potential risk in the Plan. However, when considering an individual COVID-19 case, the broad spectrum of the COVID-19 disease manifestations in different populations and age groups makes it impossible to determine how severe COVID-19 infection would have been in the absence of vaccination. As a result, there is no uniformly accepted definition of VAED or VAERD based solely on individual clinical characteristics, and no single or combination of specific confirmatory tests to diagnose VAED. This creates substantial measurement error for any potential observational epidemiology activity. To date the clinical trial program suggests quite the opposite, there is a clear imbalance of severe COVID cases in the placebo group.
- Milestones for evaluation and reporting: ongoing harm monitoring in the Phase 3 trial with respect to severe COVID case counts, ongoing evaluation of VAERS and other

passive surveillance systems as applicable for clinical descriptions from reporters combined with evaluation of disproportional clusters if applicable.

#### Anaphylactic reactions (including anaphylaxis)

- Objective: Identify cases of anaphylaxis
- Actions: Continued clinical trial follow-up; expedited reporting for cases of COVID disease requiring hospitalization to VAERS
- Rationale: Reporting from selected health care organizations in the United States found an overall rate of anaphylaxis after vaccination of 1.3 cases per million doses administered to both children and adults.
- Milestones for evaluation and reporting: continuous monitoring in the clinical development program and ongoing evaluation of VAERS and other passive surveillance systems as applicable

## 2. Summary of Actions to be completed, Including Milestones

In addition to actions targeted at potential risks listed in the safety specification, the sponsor intends to address safety through the continued clinical development program and a plan for active surveillance of safety for individuals who receive the Moderna mRNA-1273 SARS-CoV-2 Vaccine under an EUA as the “active follow-up for safety” referenced in the Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020). The sponsor is also proposing to establish a pregnancy cohort and conduct a long-term effectiveness and co-administration study.

### **Continued Clinical Trials Follow-up**

The Phase 1 study DMID 20-0003 and P201 are ongoing and unblinded and continue with a planned safety follow up period of 13 months. The Phase 3 P301 trial is ongoing, and Moderna expects that participants, including approximately 25% who are healthcare workers, may request unblinding to receive mRNA-1273 or another vaccine potentially available under EUA external to the trial. More extensive participant-driven crossover would be expected to alter the composition of the trial population, with greatly increased subject drop-out due to a large proportion of participants belonging to priority vaccination groups desiring or being mandated to be vaccinated with active vaccine.

Alternatively, the sponsor is evaluating the opportunity to amend the protocol and proactively reconsent participants. Should mRNA-1273 be authorized in the US for EUA, participants who received placebo would be offered mRNA-1273 vaccination and remain in the trial, enabling Moderna to continue to collect the relevant safety and effectiveness data over the

entire two years of follow-up while increasing the likelihood of retaining participants on trial. Adverse events among those vaccinated within the trial will be captured, regardless of the treatment group to which the subjects were originally allocated, over the entire clinical trial follow-up period of 24 months.

### **Active follow-up for safety**

The Active Follow-up for Safety activity will use secondary, de-identified individual-level medical and pharmacy claims data that represent more than 100 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. These data sources include Veradigm data and other HealthVerity data partners, including provider-submitted claims, adjudicated insurance claims, and pharmacy billing managers. The data are tokenized which allows linkage and de-duplication at the patient level across data sources. Of note, this population complements but does not duplicate the populations under observation in the CDC's Vaccine Safety DataLink and the FDA's CMS programs. The data will be refreshed every two weeks in a prospective fashion throughout the two-year study period. Retrospective analyses will address three core objectives: estimation of background rates, assessment of observed versus expected rates, and self-controlled risk interval analyses for prespecified adverse events that meet criteria described below. In addition, the flexibility of the Aetion evidence platform will enable the sponsor to address emerging EUA and postmarketing safety issues as they arise through additional analyses even if they were not on the original AESI list. After protocol approval by FDA, AESIs will be observed from the first mRNA-1273 vaccine dose administered among US adults through 31 December 2022. This activity was designed in response to FDA's description of the need for "active follow-up for safety" referenced in the Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020).

***First-stage descriptive analysis (Objective 1).*** A list of predefined AESIs is proposed in [Table 4](#). The incidence rate (IR) of AESIs will be assessed prior to mRNA-1273 vaccine EUA over two time periods. Time Period 1 is defined as the era that is immediately pre-COVID-19 (1 Jan 2019 to 31 Dec 2019). Time Period 2 is defined as the era following the emergency of COVID-19 but before widespread availability of vaccines (1 Jan 2020 to 10 Dec 2020). Background rates will be stratified by sex, age group, payer type, calendar month, and will be described by predefined subgroups of interest.

Observed IRs will be measured in Time Period 3, defined as the era following the emergence of SARS-CoV-2 vaccines as sufficient numbers of vaccinated individuals have been reached.

Crude, unstratified observed versus background incidence rate ratios (IRRs) will be computed in the overall adult population as follows:

- Observed IR (Time Period 3) versus background IR in the pre-COVID-19 era (Time Period 1)
- Observed IR (Time Period 3) versus background IR in the COVID-19 era (Time Period 2)

***Second-stage descriptive analysis (Objective 2).*** The second-stage analysis will be triggered if one of the following criteria is met, including but not limited to:

- Any estimated IRR from the first stage analysis reaches a threshold of  $\geq 2$
- The sponsor determines that this analysis will assist with safety signal validation and/or assessment

The number of observed and expected cases of specific AESIs will be estimated among the mRNA-1273 vaccinated population in Time Period 3. Estimates of the expected number of cases will be computed using the background rates assessed over Time Periods 1 and 2, and the total person-time at risk during the risk period. Estimates will be stratified by age and sex and frailty classification, geographic region and calendar time as observed in the vaccinated population.

The observed and estimated expected numbers of AESI events among mRNA-1273 vaccinated adults in Time Period 3 will be compared and the O/E ratio measure will be calculated.

Confidence intervals (CI) will be calculated around the number of events observed in the risk period.

***Third-stage comparative analysis (Objective 3).*** The third-stage analysis will be triggered if one of the following criteria is met:

A third-stage analysis will be triggered if either of the following criteria are met:

- The lower bound of the 95% CI of the observed number of cases is higher than the estimated number of cases in 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 assessment

The potential association between mRNA-1273 vaccine and specific AESIs will be estimated using a self-controlled risk interval (SCRI) analysis of mRNA-1273 exposed cases identified after EUA. The SCRI design has been widely used for post-licensure vaccine safety monitoring to detect potential elevated risks of adverse events following vaccination. 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 needs to be made for time-varying covariates. 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.

## Exposures

The mRNA-1273 vaccination schedule consists of two 100 µg doses expected to be administered approximately one month apart. Exposure to mRNA-1273 vaccine will be identified through specific CPT code 91301 and modifiers 011A (1st dose) and 012A (2nd dose). CPT codes and modifiers are expected to be fully reported as a result of insurance reimbursement requirements set by CMS and others.

## Outcomes

AESIs will be identified in claims data and defined using ICD-10 codes. To the extent possible, existing validated algorithms will be used to define those outcomes. Algorithms may be adapted from other sources such as the VAC4EU initiative (<https://vac4eu.org/covid-19-vaccine-monitoring/>) or created for this study. The operational definition for each outcome will be presented as an annex of the full study protocol.

The below table provides the list of predefined AESIs for which Objective 1 IRs will be calculated. Several sources have been considered to define this list: CDC/FDA's VAERS and VSD, and the ACCESS project endorsed by EMA.

**Table 4: List of Predefined AESIs**

Pregnancy and fetal adverse outcomes
Acute disseminated encephalomyelitis (ADEM)
Acute myocardial infarction (AMI)
Acute respiratory distress syndrome (ARDS)
Anaphylaxis
Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)
Diabetes type 1
Disseminated intravascular coagulation (DIC)
Encephalitis / Encephalomyelitis
Encephalopathy
Guillain-Barré Syndrome (GBS)

Kawasaki disease
Meningitis
Meningoencephalitis
Multisystem Inflammatory Syndrome in Children (MIS-C)
Myelitis
Myocarditis, pericarditis
Narcolepsy / cataplexy
Seizures/convulsions
Stroke
Thrombocytopenia
Transverse myelitis
Venous thromboembolism (VTE)

### Data considerations

Data sources include Veradigm data and other HealthVerity data partners, including provider-submitted claims, adjudicated insurance claims, and pharmacy billing managers. The data will be refreshed every two weeks.

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. 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.

Most study participants will have 12 or more months of historical information. Hospitalization claims are included bundled per patient stay. Vaccinations will be captured via manufacturer-specific CPT codes. Drugs dispensed by a pharmacy are generally very well captured, while OTC medications are not. All data include key factors such as patient age, gender, and 3-digit zip level.

## Study size

The analysis population for background and post-vaccine rates will be formed by up to 40% of the HealthVerity database. From initial feasibility estimates considering vaccine uptake, this is around 28 million adult patients of the total 70 million adults with full medical and pharmacy coverage over 2019 and 2020. The population for vaccinated individuals will be formed from the entirety of available HealthVerity data.

AESI-specific sample size calculations will be performed when a particular AESI enters the third stage analysis. For illustration, the table below provides example sample size estimates for 3 AESIs (Guillain-Barré syndrome [GBS], anaphylaxis and encephalitis), and is based on the following simplifying assumptions and parameters:

- Administration of 2 doses of vaccine within a 31-day interval
- 1-year observation period
- No effect of age on risk of the AESI
- 0.80 power
  
- $\alpha=5\%$
- Total risk period = 2 x upper bound of the post-vaccination risk periods as follows <sup>4-7</sup>:
  - 1–42 days for GBS (the risk period of the first dose ends when the second dose is administered)
  - 1–21 days for encephalitis
  - 0–2 days for anaphylaxis
- Minimal detectable risk ratio (RR) = 1.5, 2 or 3

**Table 5: Sample Size**

Outcome	Estimated US incidence	Expected events in HealthVerity <sup>a</sup>	Total risk period (days) <sup>b</sup>	Cases required by minimal detectable RR		
				RR=1.5	RR=2	RR=3
GBS	1.2 - 3.0 cases per 100,000 inhabitants <sup>6</sup>	336 - 840	73	263	83	31
Encephalitis	7.3 hospitalized	2,044	42	396	121	42



	cases per 100,000 inhabitants <sup>7</sup>					
Anaphylaxis	42 cases per 100,000 person-years <sup>8</sup>	11,760	4	3,514	1,018	319

<sup>a</sup> Estimated US incidence x 28 million adult patients (40% sample of 70 million adult patients with medical and pharmacy claims in HealthVerity)

<sup>b</sup> assuming administration of 2 doses within a 31-day interval and a one-year observation period

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

#### Anticipated timelines and milestones

We propose to provide interim study reports from the Active Follow-up for Safety activity every 3 months through the end of the study period (31 December 2022). A final report will be submitted by the end of June 2023.

#### Pregnancy Cohort

The sponsor will establish a passive pregnancy registry system upon EUA. After protocol approval by FDA, a prospective observational study to be conducted in the US could be initiated. The registry would enroll pregnant women and will follow them from enrollment until the end of pregnancy (live birth, stillbirth, termination of pregnancy, or spontaneous abortion); live-born infants will be followed from birth until 1 year of age. The study period will be three years from the start of the EUA.

Recruitment will target 1200 patients, 600 per exposure group. This sample size will provide approximately 80% power to detect a minimum risk ratio of 2.5 assuming a live birth rate of 85% and 15% loss to follow-up. This sample size will also offer >80% power to detect risk ratios of as low as 2.0 assuming a live birth rate of 75% and 15% loss to follow-up using an external comparator. The contextualization with an external comparator (e.g., Metropolitan Atlanta Congenital Defects Program) will provide supportive evidence using stable rates of adverse outcomes based on large populations. Additionally, it will mitigate potential biases that may be present with the internal comparator including potential systematic differences between women who choose to be vaccinated during pregnancy and those who choose not to be vaccinated and the operational challenge that it may become more difficult to enroll unexposed patients as uptake of COVID-19 vaccines increase.

The sponsor proposes to provide interim study reports every three months from the initiation of recruitment after FDA approval of the protocol through the end of the study period (December 2023). A final report will be submitted by the end of June 2024.

### **Real World Effectiveness Study**

Moderna proposes to conduct the study at Kaiser Permanente Southern California (KPSC). The health plan's population includes more than 4.5 million Southern California residents who represent 260 different ethnicities and speak about 118 different languages. This study will be a prospective cohort study to evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing the following outcomes of interest, including laboratory confirmed and clinically diagnosed COVID-19 infection, hospitalization for COVID-19 infection, and mortality (in hospital or within 30 days after discharge). Comparison groups may include KPSC members of the same age who are not vaccinated with Moderna COVID-19 vaccine. The vaccinated subjects included in the study will be those receiving Moderna COVID-19 vaccine between January 1, 2021 (or possibly as early as December 2020) and December 31, 2021. The Phase 1 populations proposed by the ACIP COVID-19 Vaccines Work Group to receive COVID-19 vaccine first include health care personnel, long-term care facility residents, essential workers, adults with high-risk medical conditions, and adults 65 years and older. Considering the feasibility of identifying appropriate subjects for the study during Phase 1, we will include KPSC health care workers and adults 65 years and older. Vaccination can be expanded to other populations when further ACIP recommendations are issued and supply becomes adequate, which is expected to occur by the second half of 2021.

The first vaccinated subject included in the study is expected to receive the first dose of Moderna COVID-19 vaccine in January 2021 (or possibly as early as December 2020) and the last subject will receive his/her 2nd dose of Moderna COVID-19 vaccine no later than December 31, 2021. The entire follow-up period will end on December 31, 2023. This would allow a maximum follow-up time of approximately almost 3 years.

### **Objectives**

#### **Primary objectives:**

- To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19
- To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease

#### **Secondary objectives:**

- To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 by age and by sex
- To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 by race/ethnicity groups
- To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 in patients with chronic diseases, (e.g. chronic kidney disease, chronic obstruction pulmonary disease (COPD), diabetes)
- To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19
- To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease
- To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing COVID-19
- To evaluate the durability of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease
- To estimate the VE of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19, by presence of concomitant vaccination in adults (e.g., receipt of influenza vaccine, pneumococcal vaccine, or tetanus, diphtheria and pertussis vaccine [Tdap]) at the time of receiving either the first or second dose of Moderna COVID-19 vaccine).

#### Anticipated sample size

We expect health care workers (HCWs) and adults ages  $\geq 65$  years to be included among the initial populations recommended by ACIP for COVID-19 vaccination during Phase 1, when COVID-19 vaccine supply may be limited. Therefore, we anticipate studying these two populations during Phase 1 of the proposed study. Moderna will provide KPSC with 750,000 doses of Moderna COVID-19 vaccine over the first 6 months after an EUA is granted, based on calculations below. Depending on supply and uptake, additional doses may be supplied by Moderna to facilitate implementation of the study.

- Approximately 730,000 members (50K HCWs and 680K adults ages  $\geq 65$  years)
- Reaching 35% coverage within 6 months ( $730,000 \times 35\% = 255,500$ )
- Times 2 doses (approximately 511,000 doses; this is over-estimating the 2-dose completion rate)
- Plus 20% buffer =  $511,000 + 102,200 = 613,200$
- An additional 136,800 doses in case of increasing demand
- $613,200 + 136,800 = 750,000$

KPSC will not commit to a certain sample size, as uptake will be driven by a number of factors including availability of COVID-19 vaccine, other COVID-19 vaccine products, ACIP prioritization, vaccine hesitancy, etc.

#### Anticipated timelines and milestones

In order to provide timely VE results during the accrual and follow-up period, we propose to perform interim analyses every 3 months in the first year starting from the 7th month of accrual (7/1/2021). In the first interim analysis, we will include vaccinated subjects that are accrued in the first ~3 months of the study (1/1/2021-3/31/2021) and followed for at least 3 months after completion of the 2nd dose. The second and third interim analyses will be performed in the 10th and 13th months with cumulative accrual from 1/1/2021-6/30/2021 and 1/1/2021-9/30/2021, respectively. Accrual will be finalized on December 31, 2021. The sequential interim analysis will be performed every 6 months in the second and the third year. The end-of-study analysis will be performed between April 1, 2024 and September 30, 2024. The final report will be submitted by the end of March 2025.