NCT #: NCT05868382

ModernaTX, Inc.

Protocol mRNA-CRID-004

A Phase 2, randomized, active controlled, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccine candidate variations in healthy adults 18 to 49 years of age.

Statistical Analysis Plan

SAP Version 2.0
Version Date of SAP: 27 Jan 2024

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DOCUMENT HISTORY

Version	Date	Description of main modifications
1.0	26 September 2023	Original Version (Version 1.0)
2.0	23 January 2024	Amendment 1 (Version 2.0) • Section 6.1: updated the imputation rule of antibody levels/concentrations that are >ULOQ; • Section 9.2: adjusted the analysis windows for immunogenicity data. • Section 9.7: updated terms in AE of Clinical Interest by SMQ due to MedDRA up-versioning to 26.1

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AR	Adverse reaction
BMI	Body mass index
CEAC	Cardiac Event Adjudication Committee
CI	Confidence interval
CSP	Clinical study protocol
CSR	Clinical study report
eCRF	Electronic case report form
eDiary	Electronic diary
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration
GLSM	Geometric least square means
GMFR	Geometric mean fold-rise
GMR	Geometric mean ratio
GMT	Geometric mean titer
HAI	Hemagglutination inhibition
IA	Interim analysis
ICF	Informed consent form
IST	Internal safety team
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification
MMRM	Mixed model repeated measures
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred term
RTPCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
ULOQ	Upper limit of quantification

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-CRID-004, is based on the most recent approved clinical study protocol (CSP), dated 12-Apr-2023 and the electronic case report form (eCRF), dated 24-Aug-2023.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 9) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-CRID-004 is a Phase 2, randomized, active-controlled, observer-blind, dose-ranging study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccine candidate variations in healthy adults 18 to 49 years of age.

DuBu Research Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, and immunogenicity data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the first interim analysis (IA) clinical database lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

2. Study Objectives

2.1. Primary Objective

The primary objective is the following:

- To evaluate the safety and reactogenicity of mRNA 1010 vaccine candidate variations.

2.2. Secondary Objectives

The secondary objective is the following:

- To evaluate the humoral immunogenicity of mRNA 1010 vaccine candidate variations at evaluable humoral immunogenicity timepoints.

2.3. Exploratory Objectives

CCI [redacted]

- CCI [redacted]

3. Study Endpoints

3.1. Primary Endpoints

The primary objective will be evaluated by the following endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after study intervention.
- Unsolicited adverse events (AEs) through 28 days after study intervention.
- Medically attended AEs (MAAEs) from Day 1 to end of study (EoS).
- Adverse events of special interest (AESIs) from Day 1 to EoS.
- Serious adverse events (SAEs) from Day 1 to EoS.
- AEs leading to study or treatment discontinuation from Day 1 to EoS.

3.2. Secondary Endpoint

The secondary objective will be evaluated by the following endpoints:

- Geometric mean titer (GMT) at indicated timepoints as measured by hemagglutination inhibition (HAI) assay.
- Geometric mean fold rise (GMFR), comparing each timepoint with D1 (Baseline) as measured by HAI assay.
- Percentage of participants with seroresponse for mRNA1010 at indicated timepoints, as measured by HAI assay.

3.3. Exploratory Endpoints

CCI [redacted]

- CCI [redacted]

4. Study Design

4.1. Overall Study Design

This will be a randomized, observer-blind, Phase 2 study to evaluate the safety, reactogenicity and immunogenicity of mRNA-1010 vaccine candidate variations using a systems biology approach in healthy adults 18 to 49 years of age.

Three mRNA-1010 vaccine candidate versions will be evaluated:

- mRNA-1010: CCI [redacted]
- mRNA-1010.4: CCI [redacted]
- mRNA-1010.6: CCI [redacted]

This study will initially enroll approximately 270 participants 18 to 49 years of age. Participants will be randomly assigned to study arms 1, 2, 3, 4, 5, and 6 in a ratio of 2:1:2:1:1:2 to receive a single dose of 1 of the 3 mRNA-1010 vaccine candidate variations (ie, mRNA-1010, mRNA-1010.4, or mRNA-1010.6). The different arms will include different dose levels for mRNA-1010.4 and mRNA-1010.6. See Table 1 for study arms and number of participants per study arm.

Table 1: Study Arms and Dosing Regimens

Study Arm	Group Name	Antigens	Dose (Total)	N (Total)	Dose Schedule
1	mRNA-1010 (Single dose)	Influenza HA, quadrivalent for NH	CCI [redacted]	60	D1
2	mRNA-1010.4 (Single dose)			30	D1
3	mRNA-1010.4 (Single dose)			60	D1
4	mRNA-1010.6 (Single dose)			30	D1
5	mRNA-1010.6 (Single dose)			30	D1
6	mRNA-1010.6 (Single dose)			60	D1

Except for appropriately delegated unblinded pharmacists, vaccine administrators, and monitors, all personnel involved in the conduct of the study will remain blinded to individual treatment assignment until planned study unblinding.

Study visits for all participants will consist of a Screening Visit (up to 28 days before the D1 visit), a Study Intervention Visit at D1, and Clinic Visits CCI [redacted] The duration of study participation for all participants is up to 7 months from the Screening Visit.

4.2. Statistical Hypotheses

There is no hypothesis testing in this study.

4.3. Sample Size and Power

The number of proposed participants is considered sufficient to provide a descriptive summary of the safety, reactogenicity, and immunogenicity of the mRNA-1010 vaccine product variables.

With 60 participants in the CCI study arms, there is an approximately 95% probability to observe at least 1 participant with an AE if the true incidence of the AE is 5%; if the true incidence rate is 3%, then the probability to observe an AE is approximately 84%.

With 30 participants in the CCI [redacted] study arms, there is an approximately 95% probability to observe at least 1 participant with an AE if the true incidence of the AE is 9.5%; if the true incidence rate is 7.5%, then the probability to observe an AE is approximately 90%.

4.4. Randomization

All participants will be centrally assigned to randomized study intervention using an interactive voice response system (IVRS) / interactive web response system (IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

This study will initially enroll approximately 270 participants 18 to 49 years of age. Participants will be randomly assigned to study arms 1, 2, 3, 4, 5, and 6 in a ratio of 2:1:2:1:1:2 to receive a single dose of 1 of the 3 mRNA-1010 vaccine candidate variations (ie, mRNA-1010, mRNA-1010.4, or mRNA-1010.6). The different arms will include different dose levels for mRNA-1010.4 and mRNA-1010.6.

4.5. Blinding and Unblinding

This is an observer-blind study. The details of blinding and unblinding are presented in Section 6.4 and 9.1 in Protocol.

5. Analysis Populations

The following analysis sets are defined: Randomization Set, Solicited Safety Set, Safety Set, Full Analysis Set (FAS), Per-Protocol Set (PPS).

5.1. Randomization Set

The Randomization Set consists of all participants who are randomized in the study, regardless of the participant's treatment status in the study. Participants will be included in the treatment group to which they are randomized.

5.2. Safety Set

The Safety Set consists of all participants who receive one dose of study intervention. The Safety Set will be used for all analyses of safety except for the solicited ARs. Participants will be included in the study arm corresponding to the study intervention that they actually received.

5.3. Solicited Safety Set

The Solicited Safety Set consists of all participants in the Safety Set who contribute any solicited AR data (ie, have at least one post-baseline solicited safety [eDiary] assessment). The Solicited Safety Set will be used for the analyses of solicited ARs. Participants will be included in the treatment group corresponding to the study intervention that they actually received.

5.4. Full Analysis Set

The FAS consists of all randomized participants who receive the study intervention. Participants will be included in the study arm to which the participant is randomized.

5.5. Per-Protocol Set

The Per-Protocol Set consists of all participants in the FAS who comply with the injection schedule, comply with the timing of immunogenicity blood sampling to have a Baseline (D1), have at least 1 post-injection assessment, have a CCI assessment that is within CCI after injection (-7 or +14 days of CCI), have no important protocol deviations which impact the immune response, and do not use prohibited medication or non-study vaccines against influenza (Please see the details in Section 6.4.3 Table 3). Important protocol deviations that cause a subject to be removed from the PPS will be determined prior to database lock with the exception of deviations that can only be identified after unblinding such as dosing errors. Receiving a vaccine product different from randomized (e.g. randomized to mRNA-1010 but received mRNA-1010.4) will warrant a participant's exclusion from the PP set. Receiving ≤ 75% or > 150% of the randomized vaccine product dose level will exclude a participant from the PP set based on the following rule ('Y' indicates exclusion):

Table 2: PP Set Exclusion Criteria for Dosing Errors

mRNA-1010

Actual Dose Received	Actual Dose Assigned	Randomized Dose
CCI		CCI
		Y
		Y

mRNA-1010.4

Actual Dose Received	Actual Dose Assigned	Randomized Dose	
CCI		CCI	
		Y	Y
			Y
		Y	
		Y	Y

mRNA-1010.6

Actual Dose Received	Actual Dose Assigned	Randomized Dose		
CCI		CCI		
		Y	Y	Y
			Y	Y
		Y		Y
		Y	Y	
		Y	Y	Y

The PPS will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they were randomized.

6. Statistical Analysis

6.1. General Considerations

The schedule of events is provided in Appendix E.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before study vaccination.

For immunogenicity tests, the baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the date of first dose of IP.

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in that treatment group within the analysis set of interest, unless otherwise specified.

Study day relative to injection will be calculated as below:

a) study day prior to injection will be calculated as: date of assessment/event – date of injection;

b) study day on or after the date of injection will be calculated as: date of assessment/event – date of injection + 1.

For calculation regarding antibody levels/concentrations, antibody values reported as below lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. For values that are greater than the upper limit of quantification (ULOQ), if actual values are reported from the testing lab, the actual values will be used in analysis (not the assigned ULOQ value); if actual values are not reported by the testing lab and results are reported as '>ULOQ', the assigned value of ULOQ will be used in analysis. Missing results will not be imputed.

The following **analysis periods for safety analyses** will be used in this study:

- Up to 7 days after vaccination injection: this period starts at the day of injection and continues through 6 subsequent days. This analysis period will be used for analyses of solicited ARs.

- Up to 28 days after vaccination injection: this period starts at the day of injection and continues through 27 subsequent days. This analysis period will be used as the primary analysis period for analyses of unsolicited AEs, unless specified otherwise.

- Throughout the study: this period starts at injection on Day 1 and continues through the earliest date of (study completion, discontinuation from the study, or death). This analysis period will be used for analyses of unsolicited AEs including any SAEs, MAAEs, AEs leading to discontinuation of study vaccine and/or study participation, and AESIs.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline.
- In the derivation of maximum/minimum values and maximum/minimum change from baseline values for safety analyses.
- In individual participant data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data:

- Imputation rules for missing dates of prior/concomitant medications and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- Imputation rules for solicited adverse reactions (SAR) are provided in Appendix I.
- For safety hematology/chemistry laboratory results containing '<' or '>' sign,

  '<x' case: for each lab test, set to x/2

  '>x' case: for each lab test, set to x + 1/10^y, where y is the decimal place number of x. For example, >4.01, display as 4.02 (i.e. 4.01+0.01).
- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups:

The following treatment groups will be used for summary purposes:

- mRNA-1010 vaccine: CCI

- mRNA-1010.4 vaccine: CCI
- mRNA-1010.4 vaccine: CCI
- mRNA-1010.6 vaccine: CCI
- mRNA-1010.6 vaccine: CCI
- mRNA-1010.6 vaccine: CCI

6.2. Background Characteristics

6.2.1. Participant Disposition

The number and percentage of participants in the following categories will be summarized by treatment group as defined in Section 6.1 based on Randomization Set:

- Randomization Set
- Solicited Safety Set
- Safety Set
- Full Analysis Set
- Per-Protocol Set

The percentage will be based on participants in the Randomization Set.

The number of participants in the following categories will be summarized:

- Participants screened
- Screen failure participants
- Individual reasons for screen failure

The percentage of participants who screen failed will be based on the number of participants screened. The percentage of participants reporting each reason for screen failure will be based on the number of participants who screen failed.

The number and percentage of participants in each of the following disposition categories will be summarized overall and by treatment group based on the Randomization Set:

- Received study vaccine
- Completed study

- Prematurely discontinued the study and the reason for discontinuation

The number and percentage of participants will be summarized by site based on Randomization Set.

A participant disposition listing will be provided, including informed consent, participants who received study vaccine, participants who completed study, participants who discontinued from participation in the study, with reasons for discontinuation. A separate listing will be provided for screen failure participants with reasons for screen failure.

In addition, randomized participants with any inclusion and exclusion criteria violation will also be provided in a listing.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Number and percentage of participants will be provided for categorical variables such as gender, race, ethnicity, and age. The summaries will be presented by overall and treatment group based on the Safety Set, FAS, and PPS.

For screened failure participants, age (years), as well as gender, race, ethnicity will be presented in a listing.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order (Appendix F). PT will be displayed in descending order of frequency of the overall group and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of concomitant medications will be based on the Safety Set.

Imputation rules for missing/partial dates of medications are detailed in Appendix C. Categorization of prior and concomitant medications are defined below:

- A medication taken before the study vaccine injection date is considered a "prior" medication, regardless of when the medication ended;
- A medication continued or newly received at or after injection of study vaccine injection through the last study visit is considered a "concomitant" medication.

An overall summary of concomitant medications including the number and percentage of participants who take the following will be presented by treatment group:

- Any concomitant medications or non-study vaccination within 28 days post injection
- Any non-study vaccination within 28 days post injection
- Any non-study seasonal influenza vaccinations with 28 days post injection
- Any non-study investigational or nonregistered product
- Systemic steroids (>=10 mg/day prednisone or equivalent), immunosuppressants, immunoglobulins, dupixent, and/or blood products administered at any time within 28 days post injection

A summary table of concomitant medications that continued or newly received within 28 days post-injection will be provided by ATC levels 1 and 2 in descending frequency in the overall group.

Medications taken to prevent pain or fever will be collected on eDiary and summaries will be provided based on the Solicited Safety Set by treatment group including within 7 days after injection.

Prior and concomitant medications will be presented in a listing.

Concomitant Procedures will be presented in a listing.

6.2.5. Study Exposure

Study investigational product administration data will be presented in a listing. Dosing error data will also be presented in a listing.

6.2.6. Important Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Important protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the participants with each important protocol deviation type will be provided by treatment group and overall based on the Randomization Set.

Important protocol deviations may impact immune response corresponding to the immunogenicity objective, and participants with such deviations will be excluded from the Per-Protocol Set for immunogenicity analyses; these important protocol deviations will be determined and documented by Sponsor prior to DBL and unblinding. Reasons of exclusion from Per-Protocol Set will be summarized and listed.

Important protocol deviations will be presented in a listing.

6.3. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESIs, AEs leading to withdrawal from study participation, clinical laboratory test results, vital signs, and physical examination findings. The total number and percentage of participants that died based on AE data and other data source (e.g. End of Study Form) will be summarized. Descriptive statistics of time of death from injection will be calculated. The number and percentage of participants for each category of time of death from injection will also be summarized. A listing of death will be provided.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by the treatment group unless otherwise specified.

For Solicited Safety Set and Safety Set, participants receiving a treatment different than planned will be summarized under the actual treatment received. If non-protocol dosage

was administered in error, a mid-point rule will be used to determine a participant's actual treatment:

- mRNA-1010 CCI If the received dose of mRNA-1010 is > CCI
- mRNA-1010.4 CCI : If the received dose of mRNA-1010.4 is > CCI and ≤ CCI
- mRNA-1010.4 CCI If the received dose of mRNA-1010.4 is > CCI
- mRNA-1010.6 CCI : If the received dose of mRNA-1010.6 is > CC and ≤ CCI
- mRNA-1010.6 CCI : If the received dose of mRNA-1010.6 is > CCI and ≤ CCI
- mRNA-1010.6 CCI : If the received dose of mRNA-1010.6 is > CCI

6.3.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans whether it is considered drug related or not. Summaries and analyses of AE newly occurred after study vaccination or any AE already present that worsens after exposure to study vaccination will be provided. Adverse events will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

Unsolicited AEs will be collected for up to 28 days after injection; SAEs, MAAEs, AESIs, and AEs leading to discontinuation of study participation will be collected throughout the study.

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by treatment group. Separate summaries will be provided for unsolicited AEs up to 28 days after injection and similarly for those throughout the study, unless otherwise specified.

All summary tables (except for the overall summary of AEs) for unsolicited AEs newly occurred after study vaccination or already present that worsens after exposure to study vaccination will be presented by SOC and PT with counts of participants included. SOC will be displayed in internationally agreed order (Appendix F). PT will be displayed in descending frequency in the overall group and then alphabetically within SOC. When summarizing the number and percentage of participants with an event, participants with

multiple occurrences of the same AE or a continuing AE will be counted once. Participants will be presented according to the highest severity (the strongest relationship) in the summaries by severity (of related AEs), if participants reported multiple events under the same SOC and/or PT.

Percentages will be based upon the number of participants in the Safety Set within each treatment group.

6.3.1.1. Incidence of Adverse Events

An overall summary of unsolicited AEs newly occurred after study vaccination or already present that worsens after exposure to study vaccination, including the number and percentage of participants who experience the following will be presented by vaccination group:

- Any unsolicited AEs
- Any serious AEs
- Any fatal AEs
- Any unsolicited medically attended AEs
- Any unsolicited AEs leading to discontinuation from participation in the study
- Any unsolicited severe AEs
- Any AESI

The table will also include the number and percentage of participants with unsolicited AEs that are treatment-related in each of the above categories.

The overall summary will be provided for unsolicited AEs up to 28 days after injection and those up to EoS throughout the study, respectively.

In addition, separate listings containing individual participant AE data for unsolicited AEs, unsolicited treatment-related AEs, unsolicited severe AEs, unsolicited treatment-related severe AEs, serious AEs, treatment-related serious AEs, unsolicited AEs leading to discontinuation from participation in the study, unsolicited medically-attended AEs and AESIs will be provided separately.

6.3.1.2. AEs by System Organ Class and Preferred Term

The following summary tables of AE newly occurred after study vaccination or any AE already present that worsens after exposure to study vaccination will be provided by MedDRA SOC and PT using frequency, counts, and percentages (i.e., number and percentage of participants with an event):

- All unsolicited AEs up to 28 days after injection
- All unsolicited treatment-related AEs up to 28 days after injection and up to EoS throughout the study
- All unsolicited AE up to 28 Days After Injection with Occurrence in >=1% of Participants in Any Vaccination Group
- All serious AEs up to 28 days after injection and up to EoS throughout the study
- All serious AEs that are treatment-related up to 28 days after injection and up to EoS throughout the study
- All unsolicited AEs leading to discontinuation from participation in the study up to 28 days after injection and up to EoS throughout the study
- All unsolicited severe AEs up to 28 days after injection
- All unsolicited severe AEs that are treatment-related up to 28 days after injection
- All unsolicited medically attended AEs up to 28 days after injection and up to EoS throughout the study
- All unsolicited medically attended AEs that are treatment-related up to 28 days after injection and up to EoS throughout the study
- All AESIs up to 28 days after injection and up to EoS throughout the study
- All non-serious AEs up to 28 days after injection
- All non-serious severe AEs up to 28 days after injection

6.3.1.3. AEs by Preferred Term

A summary table by PT will be provided for all unsolicited AEs newly occurred after study vaccination or any AE already present that worsens after exposure to study vaccination up to 28 days after injection. AEs with fatal outcome up to 28 days after injection and up to EoS throughout the study will also be summarized by PT.

PTs will be sorted in a descending order according to the frequency in the overall group.

6.3.1.4.AEs by System Organ Class, Preferred Term and Severity

The following summary tables will be provided for all unsolicited AEs newly occurred after study vaccination or any AE already present that worsens after exposure to study vaccination up to 28 days after injection by SOC, PT, and maximum severity using frequency counts and percentages:

- All unsolicited AEs
- All unsolicited AEs that are treatment-related

6.3.1.5. Selected AEs of Clinical Interests by SMQ and Preferred Term

The number of participants with occurrences of selected AEs of clinical interests identified by SMQ up to 28 days and up to EoS throughout the study will be summarized, respectively. Only AEs newly occurred after study vaccination or any AE already present that worsens after exposure to study vaccination will be summarized. SMQ will be summarized by PT, if applicable. Detailed description of SMQ is presented in Appendix G Table 5 and Table 6. Additional SMQs may be summarized, as necessary.

In addition, the number of participants with anaphylactic reaction up to 28 days and up to EoS throughout the study is summarized by vaccination groups, respectively.

6.3.1.6. Independent Cardiac Event Adjudication Committee

An independent CEAC of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis and pericarditis to determine if they meet CDC criteria of "probable" or "confirmed" events, and to assess severity (see more details in the protocol Section 10.1.6.2) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review can be found in the CEAC charter.

CEAC will be presented in a listing.

6.3.2. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term "Solicited Adverse Reactions" refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period

(day of injection and 6 subsequent days). The solicited ARs are recorded by the participant in eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist in the eDiary (i.e., solicited ARs). Any solicited ARs occurring within 7 days after injection, if not entered in the eDiary in the required input time window, should be reported in the Reactogenicity eCRF. Solicited ARs reported in both the eCRF and eDiary will be included in the evaluation of solicited ARs.

The following local ARs will be solicited: pain at injection site, erythema (redness) at injection site, swelling/induration (hardness) at injection site, and axillary (underarm) swelling or tenderness ipsilateral to the side of injection.

The following systemic ARs will be solicited: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (joint aches in several joints), nausea/vomiting, chills, and fever.

The solicited ARs will be graded based on the grading scales presented in Table 7 in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). Investigator will assess Grade 4 events (with exception of fever).

If a participant reports a solicited AR with onset during the solicited period, but they did not record the event in the eDiary, then the event should be recorded by study staff in the EDC where reactogenicity is collected.

If a solicited local or systemic AR continues beyond 7 days post injection, the participant should notify the site to provide an end date and close out the event in the EDC where reactogenicity is collected.

All solicited ARs (local and systemic) will be considered causally related to injection.

All solicited ARs analyses will be based on Solicited Safety Set and will be provided by treatment group, unless otherwise specified.

An overall summary of solicited ARs including the number and percentage of participants who reported any solicited AR, any solicited local AR, and any solicited systemic AR within 30 minutes and 7 days after injection, grade 3 or grade 4 Solicited AR will be summarized.

The number and percentage of participants who reported any solicited AR, any solicited local AR, and any systemic solicited AR within 7 days after injection will be tabulated with a two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method.

The number and percentage of participants who reported any solicited AR, any solicited local AR, any systemic solicited AR and individual solicited ARs (has a severity grade of Grade 1 or greater) within 7 days after injection will be tabulated and plotted by severity grade. Participants are counted under the maximum severity grade within each event.

The number and percentage of participants experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral, axillary, or tympanic route) by severity grade will be provided. Participants are counted under the maximum severity grade within each event.

The onset day of an individual solicited AR is defined as the time point at which the solicited AR first occurred. The number and percentage of participants who reported any solicited AR, any solicited local AR, systemic solicited AR and individual solicited ARs (has a severity grade of Grade 1 or greater) within 7 days after injection will be summarized by onset day.

The duration (days) of each solicited AR will be summarized. Duration will be calculated as end date of solicited AR – onset date of solicited AR + 1, no matter if it is intermittent or continued or if the solicited AR continues beyond 7 days.

All solicited ARs that continue beyond 7 days after injection will be summarized and presented in separate data listings.

6.3.3. Clinical Laboratory Evaluations

The pregnancy testing results using highly sensitive serum or urine hCG will be performed as needed for person of childbearing potential, and follicle stimulating hormone and estradiol tests will be performed as needed for person of nonchildbearing potential. These results will be listed.

6.3.4. Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures, pulse, respiratory rate, and temperature, will be presented in a data listing.

Observed values and changes from baseline for all vital sign measurements will be summarized at each scheduled visit by the treatment groups. Vital sign measurements will

also be summarized using a shift grading table from pre-dose to post-dose by vaccination group according to the toxicity grading criteria in Appendix H.

6.4. Immunogenicity Analysis

The analysis of immunogenicity will be analyzed by vaccination group based on the PPS. If the number of participants in the FAS and PPS differ (defined as the difference divided by the total number of participants in the PPS by more than 10%), supportive analyses of immunogenicity may be conducted using the FAS. Supportive analysis is required if the condition is met at end of study; it is optional for the IA.

6.4.1. Immunogenicity Assessments

There will be two types of immunogenicity assessments:

- Vaccine-specific humoral immune responses, including serum antibody levels as measured by the HAI assay. Additional vaccine-specific humoral immune response assessments may include analysis of neutralizing antibody titers, antibody functionality, epitope specificity, and affinity.
- CCI [redacted]

6.4.2. Analysis of Humoral Immunogenicity Endpoints

Immunogenicity assessments of serum antibody levels as measured by HAI assay at CCI [redacted] will be included in the analyses below.

Data collected following intercurrent events (Section 6.4.3) will not be included in data summaries or inferential analyses described in this section.

6.4.2.1 Geometric Mean Titer and Geometric Mean Fold Rise

- The following immunogenicity endpoints will be evaluated: Geometric mean titer (GMT) at indicated timepoints as measured by HAI assay.
- Geometric mean fold rise (GMFR), comparing each timepoint with D1 (Baseline) as measured by HAI assay.

The GMT will be calculated using the following formula:

$$2^{\left\{\frac{\sum_{i=1}^{n} log_2(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers.

The GMFR measures the changes in immunogenicity titers within participants. The GMFR will be calculated using the following formula:

$$2^{\left\{\frac{\sum_{i=1}^{n} log_2\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 2^{\left\{\frac{\sum_{i=1}^{n} log_2(v_{ij}) - log_2(v_{ik})}{n}\right\}}$$

where, for n participants, v_{ij} and v_{ik} are observed immunogenicity titers for participant i at time points j and k, $j \neq k$ and k is baseline. The 95% CIs for GMT and GMFR will be calculated based on the t distribution of the log-transformed values and then back transformed to the original scale for presentation.

- The following evaluations will be performed at baseline (Day 1) and each post-baseline time point: GMT of antibody levels with corresponding 95% CI will be provided at CCI [redacted]. GMTs with 95% CI will be plotted at each time point. The following descriptive statistics will also be provided at CCI [redacted] the number of participants (n), median, minimum, and maximum.
- GMFR of antibody levels with corresponding 95% CI will be provided at CCI [redacted] over pre-injection at (Day 1 [baseline]). GMFRs and corresponding 95% CI will be plotted at each post-baseline time point.

6.4.2.2 Comparisons between mRNA-1010 and Comparator Groups

CCI [redacted]

CCI [redacted]

6.4.2.3 Seroresponse

The immunogenicity endpoint of seroresponse is defined as the proportion of participants with an increase of antibody titers and concentrations from baseline below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise from baseline if baseline is ≥LLOQ.

- The number and percentage of participants with seroresponse from Day 1 (baseline) to CCI [redacted] will be provided with 2-sided 95% CI using the Clopper-

Pearson method. Seroresonse rate and corresponding 95% CI will be plotted at each post-baseline time point.

- CCI [redacted]

6.4.2.4 Proportion of participants with HAI titer ≥ 1:40

The number and percentage of participants with a HAI titer ≥ 1:40 at CCI [redacted] will be provided with 2-sided 95% CI using the Clopper-Pearson method.

CCI [redacted]

6.4.3. Handling of Intercurrent Events

Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

The potential intercurrent events for this study are listed in Table 3.

Table 3: Intercurrent Events

Intercurrent Event	Identification Method
Intercurrent infections	Captured from RTPCR, and from the adverse events (AE) page through a manual review based on dictionary-derived terms (preferred terms). Immunogenicity data collected after the first occurrence of intercurrent infections will be excluded (censored) from analysis.
Use of prohibited medication or non-study vaccines	Collected on the concomitant therapies case report form or protocol deviation form. Non-study vaccines only include vaccines against influenza. Subject will be excluded from PPS.
Visit window important deviations	Collected from protocol deviation form Subject will be excluded from PPS.

6.4.4. Subgroup Analyses

No subgroup analyses are planned for the study.

6.4.5. Nasopharyngeal Swab for Virus Detection

Nasopharyngeal swab for virus detection and available results will be listed.

6.5. Planned Analyses

CCI [redacted]

CCI [redacted]

The final CSR will include full unblinded analyses of all safety and immunogenicity with individual unblinded listings through EoS.

7. Changes from Planned Study Design and Analyses in Protocol

Randomization will not be stratified by Receipt of a 2022-2023 NH influenza vaccine (Yes/No). No stratification factor will be used in this study.

For immunogenicity analysis, the number and percentage of participants with >2-, 3-fold increases from Baseline (if ⩾LLOQ) or with >2-, 3-fold increases from LLOQ (if <LLOQ) will not be analyzed with 2-sided 95% CI per Protocol.

8. References

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. September 2007 [cited 2020 Oct 28] [10 screens]. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf

9. List of Appendices

9.1. Appendix A Standards for Safety and Immunogenicity Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean, median, Q1 and Q3 will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to 1 decimal place.

9.2. Appendix B Analysis Visit Windows for Safety and Immunogenicity Analysis

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window for post injection assessments:

Step 1: If the assessments are collected at a scheduled visit, the collected data will be mapped to the nominal scheduled visit.

Step 2: If the assessments are collected at an unscheduled visit, the collected data will be mapped using the analysis visit windows described in Table 4 below.

If a participant has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within both scheduled visit and unscheduled visit, the assessment collected at scheduled visit will be used.
- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments with equal distance to the target study day, the last assessment will be used.

CCI

Visit	Target Study Day	Visit Window in Study Day
CCI		

9.3. Appendix C Imputation Rules for Missing Dates of Prior/Concomitant Medications

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
   - If only Day is missing, use the first day of the month, unless:
     - The medication end date is after the date of injection or is missing AND the start month and year of the medication coincide with the start month and year of injection AND the medication is not known to be taken prior to study administration (e.g. answer to the question of "Was the medication taken prior to study administration?" in CRF is not Yes). In this case, use the date of injection.
   - If Day and Month are both missing, use the first day of the year, unless:
     - The medication end date is after the date of injection or is missing AND the start year of the medication coincides with the start year of injection AND the medication is not known to be taken prior to study administration (e.g. answer to the question of "Was the medication taken prior to study administration?" in CRF is not Yes). In this case, use the date of injection.
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the injection for purposes of determining status as prior or concomitant. If the medication is known to be not taken prior to study administration (e.g. answer to the question of "Was the medication taken prior to study administration?" in CRF is No), the medication will be treated as though it began after the injection for purposes of determining status as prior or concomitant.
2. Missing or partial medication stop date:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

9.4. Appendix D Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

1. Missing or partial AE start date:
    - If only Day is missing, use the first day of the month, unless:
        - The AE end date is after the date of injection or is missing AND the start month and year of the AE coincide with the start month and year of injection. In this case, use the date and time of injection, even if AE start time is collected.
    - If Day and Month are both missing, use the first day of the year, unless:
        - The AE end date is after the date of injection or is missing AND the start year of the AE coincides with the start year of injection. In this case, use the date and time of injection, when time is available.
    - If Day, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered to occur after exposure to study vaccination.
2. Missing or partial AE end dates will not be imputed.

9.5. Appendix E Schedule of Events

Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**USV[a]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**SC**	**C**	**C**
Month Timepoint		CCI											
Study Visit Day	**Screening[b]**												
Window Allowance (Days)	**-28**	**NA**	**NA**	**0**	**±1**	**-1 to +3**	**-7 to +3**	**±5**	**±5**	**±5**	**±5**	**±14**	**NA**
Days from Last Study Intervention		CCI											
ICF, demographics, concomitant medications, medical history	X	X											
Inclusion/exclusion criteria	X	X											
Physical examination[d]	X	X											
Vital signs[e]	X	X											
Pregnancy testing[f]	X	X											

Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**USV[a]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**SC**	**C**	**C**
Month Timepoint		CCI											
Study Visit Day	**Screening[b]**												
Window Allowance (Days)	**-28**	**NA**	**NA**	**0**	**±1**	**-1 to +3**	**-7 to +3**	**±5**	**±5**	**±5**	**±5**	**±14**	**NA**
Days from Last Study Intervention		CCI											
Blood for humoral immunogenicity[g]		X				X	X		X			X	
CCI													
NP swab for virus detection[h]		X											X
Randomization		X											

Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**USV[a]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**SC**	**C**	**C**
Month Timepoint		CCI											
Study Visit Day	**Screening[b]**												
Window Allowance (Days)	**-28**	**NA**	**NA**	**0**	**±1**	**-1 to +3**	**-7 to +3**	**±5**	**±5**	**±5**	**±5**	**±14**	**NA**
Days from Last Study Intervention		CCI											
Study intervention (including 30-minute postdosing observation period)		X											
eDiary activation for recording solicited ARs (7 days)[i]		X											
Review of eDiary ARs[j]						X							
Follow-up safety calls[k]								X		X	X		

Visit Number		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**USV[a]**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**SC**	**SC**	**C**	**C**
Month Timepoint		CCI											
Study Visit Day	**Screening[b]**												
Window Allowance (Days)	**-28**	**NA**	**NA**	**0**	**±1**	**-1 to +3**	**-7 to +3**	**±5**	**±5**	**±5**	**±5**	**±14**	**NA**
Days from Last Study Intervention		CCI											
Unsolicited AEs[l]		X	X	X	X	X	X						
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
AESIs, MAAEs, and AEs leading to withdrawal from the study[m]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and nonstudy vaccinations[m]		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; AESI=adverse event of special interest; AR=adverse reaction; BMI=body mass index; C=clinic; COVID-19=coronavirus disease 2019; D=Day; EoS=end-of-study; eDiary=electronic diary; FDA=Food and Drug Administration; FSH=follicle-stimulating hormone; ICF=informed consent form; M=month; MAAE=medically attended AE; NA=not applicable; NP=nasopharyngeal; SAE=serious adverse event; SC=safety call; USV=unscheduled visit.

Note: In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency"(DHHS 2020), Investigators may convert study site visits to telemedicine visits with the approval of the Sponsor.

a. Participants may experience AEs that necessitate a USV. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study.
b. The Screening Visit and Day 1 may be performed on the same day or a different day. Additionally, the Screening Visit may be performed over multiple visits if within the 28-day screening window. If a participant returns for the D1 visit more than 28 days after their Screening Visit for any reason and continues to provide consent to participate in the study, the participant may be rescreened, for study eligibility. All assessments for eligibility must be repeated.
c. A blood draw will be collected at 6 hours post vaccine injection on D1.
d. A full physical examination, including height, weight, and BMI will be performed at Screening. Symptom-directed physical examinations may be performed at other timepoints at discretion of the Investigator. On each dosing day before injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified by a healthcare professional during study visits should be reported as an MAAE.
e. Vital signs measurements: Systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The preferred route of temperature assessment is oral. On the day of vaccination, vital signs will be collected once before vaccination and once at least 30 minutes after vaccination. Vital signs may be collected at other clinic visits in conjunction with a symptom-directed physical examination.
f. A pregnancy test either via blood or point-of-care urine test will be performed at the Screening Visit and before the vaccine dose on Day 1, if Day 1 is not on the same day as the Screening Visit. At the discretion of the Investigator, a pregnancy test either via blood or point-of-care urine can be performed at any time. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. The participant's FSH level may be measured at the Screening Visit, as necessary, and at the discretion of the Investigator, to confirm postmenopausal status.
g. D1 (Baseline) blood samples for CCI [redacted]
h. An NP swab specimen for viral respiratory pathogens will be collected prior to the study intervention administration on Day 1. At USVs participants with symptoms of respiratory tract infection may be tested by NP swab for respiratory viruses at the Investigator's discretion to include influenza, RSV and SARS-CoV-2, which may impact analyses of reactogenicity and immunogenicity.
i. eDiary entries will be recorded by the participant at approximately 30 minutes after vaccination while at the clinic with instruction provided by study staff. Study participants will continue to record in the eDiary each day, preferably in the evening and at the same time each day, on the day of vaccination and for 6 days following vaccination. Any solicited AR that is ongoing beyond Day 7 will be reported until resolution.
j. Solicited ARs recorded in the eDiaries that is ongoing beyond 7 days after injection will be followed up by the study site staff at the next scheduled telephone call or at the next study site visit. Any medication recorded in eDiaries that is taken to prevent or treat pain or fever will also be reviewed at this time.
k. Trained study personnel will call all participants to collect information relating to any MAAEs, AESIs, AEs leading to withdrawal from the study, SAEs, information on concomitant medications associated with those events; receipt of any nonstudy vaccinations; and receipt of any systemic steroids, immunosuppressive therapies (drugs or biologics), immunoglobulins, and/or blood products.
l. All unsolicited AEs will be recorded starting the day of each study intervention, and through 28 days following each study intervention.
m. All concomitant medications will be recorded through 28 days after vaccination. All concomitant medications relevant to or for the treatment of the SAE, AESI, MAAE, or AE leading to study withdrawal will be recorded from D1 through EoS. Any nonstudy vaccinations will be recorded from D1 through EoS.

9.6. Appendix F Internationally Agreed Order for Display of System Organ Class

1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues

9.7. Appendix G Definition of AE of Clinical Interest by SMQ

Table 5 List of AE of Clinical Interest by SMQ

AE of Clinical Interest*	Type of MedDRA Query	Broad or Narrow Search	SMQ Search Criteria
Anaphylactic Reaction	SMQ	Algorithm	A or (B and C) or (D and (B or C)), Specified PT and algorithm approach included in Table 6
Angioedema	SMQ	Narrow	Specified PT terms
Cardiac Arrhythmias	SMQ	Narrow	Specified PT terms
Cardiac Failure	SMQ	Narrow	Specified PT terms
Cardiomyopathy	SMQ	Narrow	Specified PT terms
Central Nervous System Vascular Disorders	SMQ	Narrow	Specified PT terms
Convulsions	SMQ	Narrow	Specified PT terms
Demyelination	SMQ	Narrow	Specified PT terms
Embolic and Thrombotic Events	SMQ	Narrow	Specified PT terms
Haematopoietic Cytopenias	SMQ	Narrow	Specified PT terms
Hypersensitivity	SMQ	Narrow	Specified PT terms
Immune-mediated/Autoimmune Disorders	SMQ	Narrow	Specified PT terms
Ischaemic Heart Disease	SMQ	Narrow	Specified PT terms
Noninfectious Myocarditis/Pericarditis	SMQ	Narrow	Specified PT terms
Peripheral Neuropathy	SMQ	Narrow	Specified PT terms
Vasculitis	SMQ	Narrow	Specified PT terms
*Based on MedDRA 26.1			

Table 6 Algorithm Approach for Anaphylactic Reaction

The following criteria will be used to determine anaphylactic reaction:

- A term from Category A
- A term from Category B (Upper Airway/Respiratory) and a term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other.
- A term from Category D (Cardiovascular/Hypotension) and at least one of the following:

- A term from Category B (Upper Airway/Respiratory) that occurred within 24 hours of each other.
- A term from Category C (Angioedema/Urticaria/Pruritus/Flush) that occurred within 24 hours of each other.

Anaphylactic Reaction		
Category	**Scope**	**PT Search Term**
A	Narrow	Anaphylactic reaction
A	Narrow	Anaphylactic shock
A	Narrow	Anaphylactic transfusion reaction
A	Narrow	Anaphylactoid reaction
A	Narrow	Anaphylactoid shock
A	Narrow	Circulatory collapse
A	Narrow	Dialysis membrane reaction
A	Narrow	Kounis syndrome
A	Narrow	Procedural shock
A	Narrow	Shock
A	Narrow	Shock symptom
A	Narrow	Type I hypersensitivity
B	Broad	Acute respiratory failure
B	Broad	Asthma
B	Broad	Bronchial oedema
B	Broad	Bronchospasm
B	Broad	Cardio-respiratory distress
B	Broad	Chest discomfort
B	Broad	Choking
B	Broad	Choking sensation
B	Broad	Circumoral oedema
B	Broad	Cough
B	Broad	Cough variant asthma
B	Broad	Cyanosis
B	Broad	Dyspnoea
B	Broad	Enhanced respiratory disease
B	Broad	Hyperventilation
B	Broad	Irregular breathing
B	Broad	Laryngeal dyspnoea
B	Broad	Laryngeal oedema
B	Broad	Laryngospasm
B	Broad	Laryngotracheal oedema
B	Broad	Mouth swelling
B	Broad	Nasal obstruction
B	Broad	Oedema mouth
B	Broad	Oropharyngeal oedema
B	Broad	Oropharyngeal spasm
B	Broad	Oropharyngeal swelling
B	Broad	Pharyngeal oedema
B	Broad	Pharyngeal swelling

B	Broad	Respiratory arrest
B	Broad	Respiratory distress
B	Broad	Respiratory failure
B	Broad	Reversible airways obstruction
B	Broad	Sensation of foreign body
B	Broad	Sneezing
B	Broad	Stridor
B	Broad	Swollen tongue
B	Broad	Tachypnoea
B	Broad	Throat tightness
B	Broad	Tongue oedema
B	Broad	Tracheal obstruction
B	Broad	Tracheal oedema
B	Broad	Upper airway obstruction
B	Broad	Wheezing
C	Broad	Allergic oedema
C	Broad	Angioedema
C	Broad	Circumoral swelling
C	Broad	Erythema
C	Broad	Eye oedema
C	Broad	Eye pruritus
C	Broad	Eye swelling
C	Broad	Eyelid oedema
C	Broad	Face oedema
C	Broad	Flushing
C	Broad	Injection site urticaria
C	Broad	Lip oedema
C	Broad	Lip swelling
C	Broad	Nodular rash
C	Broad	Ocular hyperaemia
C	Broad	Oedema
C	Broad	Oedema blister
C	Broad	Periorbital oedema
C	Broad	Periorbital swelling
C	Broad	Pruritus
C	Broad	Pruritus allergic
C	Broad	Rash
C	Broad	Rash erythematous
C	Broad	Rash pruritic
C	Broad	Skin swelling
C	Broad	Swelling
C	Broad	Swelling face
C	Broad	Swelling of eyelid
C	Broad	Urticaria
C	Broad	Urticaria papular
D	Broad	Blood pressure decreased
D	Broad	Blood pressure diastolic decreased
D	Broad	Blood pressure systolic decreased
D	Broad	Cardiac arrest
D	Broad	Cardio-respiratory arrest

D	Broad	Cardiovascular insufficiency
D	Broad	Diastolic hypotension
D	Broad	Hypotension
D	Broad	Hypotensive crisis
D	Broad	Post procedural hypotension

9.8. Appendix H Severity Grading of Vital Sign

Vital Signs*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)** (°F)**	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 - 20	21 - 25	> 25	Intubation

Note: If the vital sign results do not meet the criteria for Grade 1-4, they will be treated as Grade 0 for the shift grading table.
* Participant should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

9.9 Appendix I Imputation Rules for Solicited Adverse Reactions (SARs)

Below are the three scenarios:

1. If the subject does not answer (missing value or shown as "NOT DONE") for any of the 7 days in eDiary period, then the subject is excluded from the Solicited Safety Set.
2. If the subject has at least one grade 1 or higher SAR for a symptom for a certain day, choose the worst response (or highest grade).
3. If the subject has some days as no symptom and some other days have missing value, set the subject as "NOT DONE", and categorize it as missing diary partially.

In terms of solicited safety set, if the subject has at least one valid eDiary or Reactogenicity form entry, then this subject will be in the solicited safety set. For scenarios 2 and 3 above, these subjects are included in the Solicited Safety Set.