16.1.9. DOCUMENTATION OF STATISTICAL METHODS

16.1.9.1. Documentation of Statistical Methods Statistical Analysis Plan (SAP)

- **C4781013 Substudy A Statistical Analysis Plan V2, Clean Copy 12Jun2024**
- **C4781013 Substudy B Statistical Analysis Plan, V2, Clean Copy, 12Jun2024**
- **C4781013 Substudy C Statistical Analysis Plan V2 Clean Copy, 12Jun2024**

16.1.9.2. Statistical Output (Not Applicable)

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Protocol C4781013 – Substudy A

A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MODIFIED RNA VACCINES AGAINST INFLUENZA IN HEALTHY ADULTS

Statistical Analysis Plan (SAP)

Version: 2

Date: 12 Jun 2024

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APPENDICES

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 18 Apr 2024	Original 12 Mar 2024	N/A	N/A
2 12 Jun 2024	1 26 Apr 2024	• To update the monitoring and collection period for myocarditis and pericarditis per protocol amendment 1. • To update the analysis population for CCI [redacted] for consistency with the protocol. • To make updates and clarifications on the reactogenicity events collected in the e-diary and CRF per regulatory comments. • To add a sensitivity analysis for the summary of reactogenicity events by maximum severity per regulatory comments.	• Section 3.1.3 and Section 6.3.3: Updated the monitoring and collection period for myocarditis and pericarditis from "14 days after vaccination" to "28 days after vaccination." • Section 2.2, Section 2.2.3, Section 4, Section 5.2, Section 6.4.1.1, Section 6.4.2.1, and Section 6.4.3.1: Updated the analysis population for CCI [redacted] for consistency with the protocol. • Section 2.3, Section 3.1.1, Section 3.1.2, Section 3.5.2, Section 5.3.1.1, Section 6.1.1.1, and Section 6.3.1: Clarified the reactogenicity data collected in the e-diary and CRF and the analysis of reactogenicity events. • Section 6.1.1.2: Added a sensitivity analysis for the summary of reactogenicity events by maximum severity.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4781013 – Substudy A. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

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2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
Primary safety	To define the safety and tolerability profile of tIRVs in participants 18 through 64 years of age	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs • MAEs • NDCMCs	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination
Secondary immunogenicity	To describe the immune response elicited by tIRVs in participants 18 through 64 years of age	• HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines	In participants complying with the key protocol criteria (evaluable immunogenicity population [HAI CCI [redacted]]): • HAI GMTs at baseline and 4 weeks after vaccination • HAI GMFRs from before vaccination to 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] for each strain at 4 weeks after vaccination • The proportion of participants with HAI titers ≥1:40 for each strain at baseline and 4 weeks after vaccination

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Type	Objective	Endpoint	Estimand
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Type	Objective	Endpoint	Estimand
CCI [redacted]			

a. Seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the time point of interest, or an HAI titer ≥1:10 prior to vaccination with at least a 4-fold rise at the time point of interest.

2.2.1. Primary Estimand(s)

The primary estimands for the primary objective (safety) will use the treatment policy strategy and estimate the safety event rate (reactogenicity, AEs/SAEs/MAEs/NDCMCs) regardless of whether an intercurrent event occurs.

- The reactogenicity estimands (local reactions and systemic events) have the following 5 attributes:
  - **Treatment condition:** Vaccination with 3 different formulations of tIRV (tIRV1, tIRV2, and tIRV3), QIV1 (CCI [redacted], and qIRV1 as defined in Section 2.3.
  - **Population:** Participants 18 through 64 years of age who receive the study intervention.
  - **Variables:** Local reactions and systemic events from the e-diary up to 7 days following vaccination.
  - **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, use of rescue medication, missing e-diary entries on certain days, study discontinuation), if collected, will be included.
  - **Population-level summary:** The rates of reporting each prompted reactogenicity item, and the associated 2-sided 95% CIs, by study intervention group (in the tIRV1, tIRV2, tIRV3, QIV1 and qIRV1 vaccine groups, separately).
- The AE, SAE, MAE and NDCMC estimands have the following 5 attributes:
  - **Treatment condition:** Vaccination with 3 different formulations of tIRV (tIRV1, tIRV2, and tIRV3), QIV1 (CCI [redacted], and qIRV1 as defined in Section 2.3.
  - **Population:** Participants 18 through 64 years of age who receive the study intervention.

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- **Variables:**
  - AEs reported through 4 weeks after vaccination.
  - SAEs reported through 6 months after vaccination.
  - MAEs reported through 6 months after vaccination.
  - NDCMCs reported through 6 months after vaccination.
- **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, use of rescue medication, study discontinuation), if collected, will be included.
- **Population-level summary:** The rates of AEs, SAEs, MAEs and NDCMCs, and the associated 2-sided 95% CIs, by study intervention group (in the tIRV1, tIRV2, tIRV3, QIV1 and qIRV1 vaccine groups, separately).

2.2.2. Secondary Estimand(s)

The secondary estimands for the secondary objective (immunogenicity) will use the hypothetical strategy and estimate the vaccine immune response when an intercurrent event does not occur. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed.
It includes the following 5 attributes:

- **Treatment condition:** Vaccination with 3 different formulations of tIRV (tIRV1, tIRV2, and tIRV3), QIV1 (CCI [redacted]), and qIRV1 as defined in Section 2.3.
- **Population:** Participants 18 through 64 years of age, as defined by the inclusion and exclusion criteria.
- **Variables:**

  HAI CCI [redacted].

  - HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines:
    - HAI titers at baseline and 4 weeks after vaccination.
    - HAI titer fold rise from before vaccination to 4 weeks after vaccination.
    - Presence of HAI seroconversion for each strain at 4 weeks after vaccination.
    - Presence of HAI titers ≥1:40 for each strain at baseline and 4 weeks after vaccination.

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- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:
  - Not meeting the study inclusion criteria or meeting the exclusion criteria.
  - Not receiving the study intervention as randomized.
  - Blood for assay testing is taken outside of the defined window (<26 days or >35 days after vaccination).
  - Having major protocol deviations (received prohibited vaccine or treatment that may alter the immune response and subsequently impact the vaccine protection).

  All data after the above intercurrent events, if collected, will be excluded from analysis.

- **Population-level summary:** HAI GMTs, and the associated 2-sided 95% CIs, at baseline and 4 weeks after vaccination; HAI GMFRs, and the associated 2-sided 95% CIs, from before vaccination to 4 weeks after vaccination; the proportion of participants achieving HAI seroconversion at 4 weeks after vaccination, and the associated 2-sided 95% CIs; and the proportion of participants with HAI titers ≥1:40 for each strain at baseline and 4 weeks after vaccination, and the associated 2-sided 95% CIs, will be summarized by study intervention.

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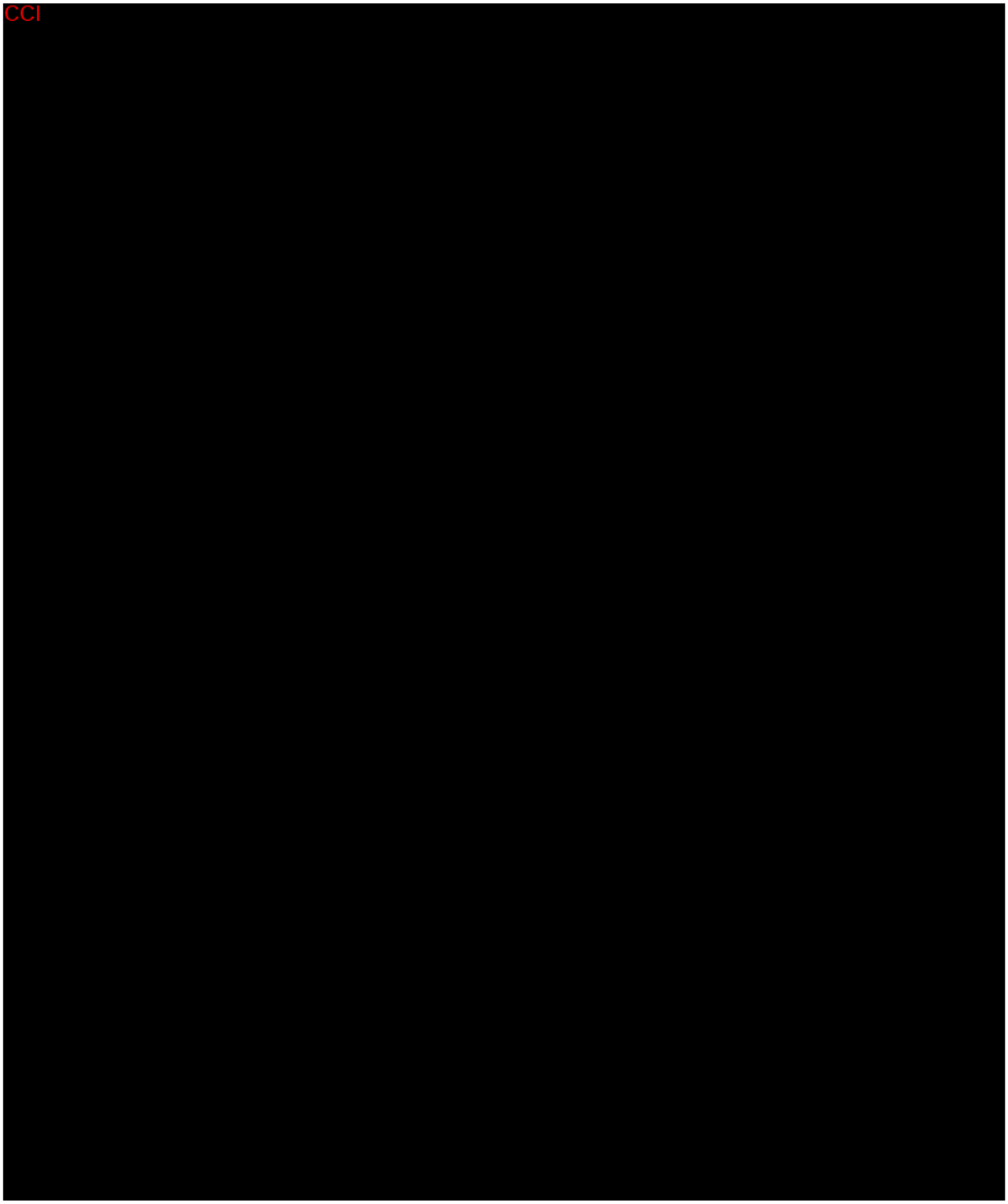
CCI



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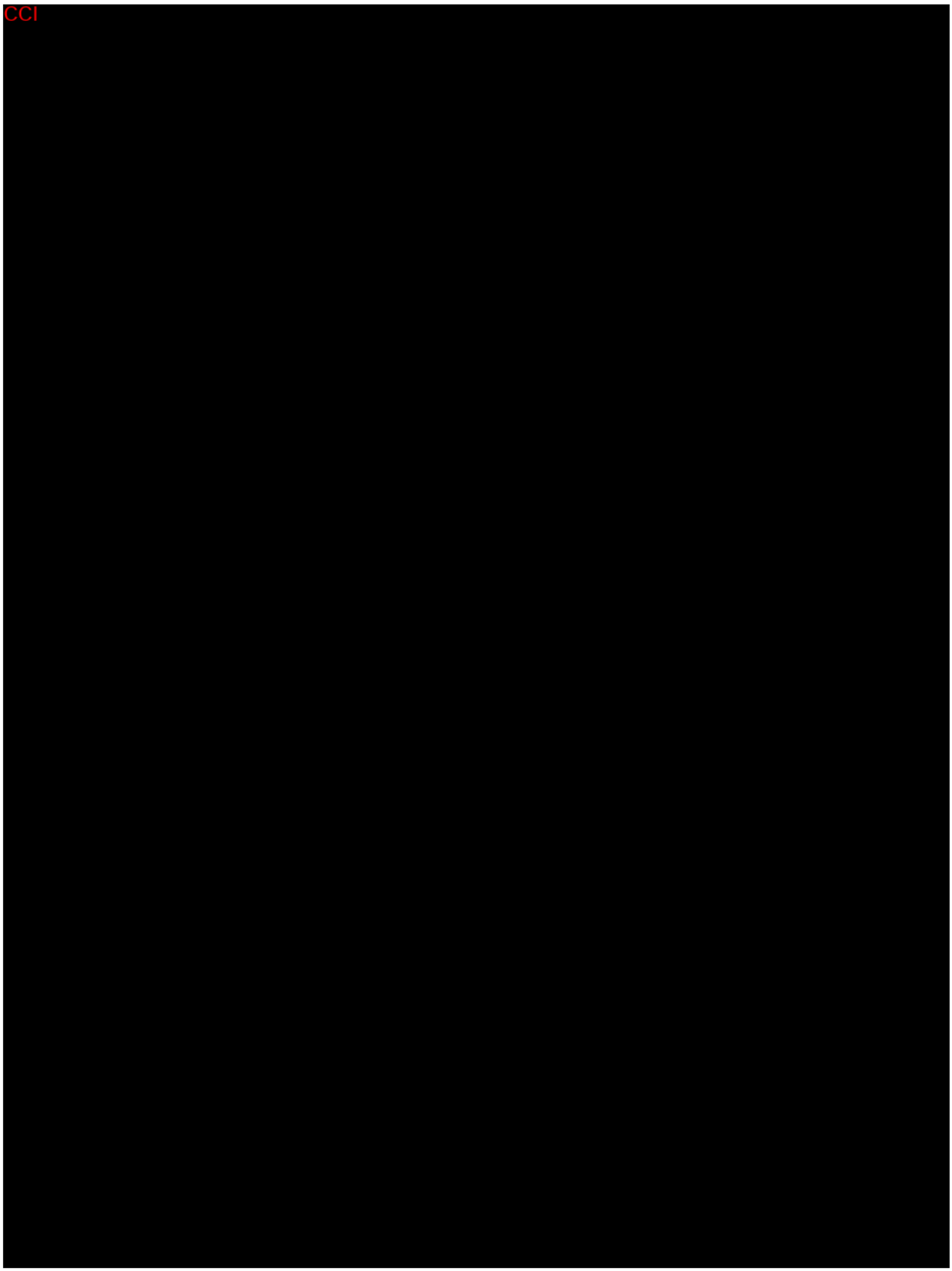
CCI



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2.3. Study Design

This is a Phase 2, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of 3 different formulations of tIRV (tIRV1 through tIRV3) encoding HA for the targeted seasonal influenza strains compared to QIV1 [redacted] and qIRV1 (encoding HA for 2 A and 2 B seasonal influenza strains) in healthy adults 18 through 64 years of age.

Up to approximately 450 participants 18 through 64 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in Table 2.

Blood samples of approximately 30 mL will be collected [redacted] prior to vaccination and at 4 weeks and 6 months after vaccination.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period after vaccination. Participants are required to complete the e-diary every evening (06:00 PM to 11:59 PM) for the 7 days following vaccination (including the day of vaccination). If participants are unable to complete the e-diary as expected on a particular day, they are allowed to retrospectively complete the missed entry within up to 3 days following the date of the missed entry (extended 72-hour e-diary reporting window).

For participants with ongoing symptoms after Day 7, subsequent e-diary entries will be followed only to monitor the duration of symptoms until resolution. The end date for the prespecified local reaction and systemic event beyond Day 7 will also be recorded on the Summary of Reactogenicity CRF page.

All AEs will be collected from informed consent signing through 4 weeks following vaccination. A subset of AEs (NDCMCs, MAEs, and SAEs) will be collected from informed consent signing through 6 months after vaccination. In addition, AEs occurring up to 48 hours after blood draws will be collected.

Table 2. Number of Participants to Be Enrolled in Substudy A – Participants 18 Through 64 Years of Age

Study Intervention	Preformulated[a]	Influenza Strains	[redacted]	Total modRNA Dose	Number of Participants
QIV1	Yes	2023-2024 northern hemisphere seasonal strains recommended by WHO for [redacted] influenza vaccines		N/A	90
tIRV1	Yes	A/H1N1		[redacted]	90
		A/H3N2			
		B/Victoria			

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Table 2. Number of Participants to Be Enrolled in Substudy A – Participants 18 Through 64 Years of Age

Study Intervention	Preformulated[a]	Influenza Strains	CCI	Total modRNA Dose	Number of Participants
tIRV2	No	A/H1N1		CCI	90
		A/H3N2			
		B/Victoria			
tIRV3	No	A/H1N1			90
		A/H3N2			
		B/Victoria			
qIRV1	Yes	A/H1N1			90
		A/H3N2			
		B/Victoria			
		B/Yamagata			

a. For tIRV2 and tIRV3 (which are not preformulated), mIRVs encoding HA for each A and B strain will be mixed at the site to generate these study interventions at the dose-level combination shown. Please see the IPM for further details.

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- Local reactions (pain at the injection site, redness, and swelling) through 7 days following vaccination.
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) through 7 days following vaccination.
- AEs through 4 weeks after vaccination.
- SAEs through 6 months after vaccination.
- MAEs through 6 months after vaccination.
- NDCMCs through 6 months after vaccination.

3.1.1. Local Reactions

The local reactions reported in the e-diary are pain at the injection site, redness, and swelling, from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination.

If a local reaction persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and the corresponding resolution date. The investigator will enter this resolution date on the Summary of Reactogenicity CRF page.

For missing records on local reactions during the 7-day e-diary collection period, the data may be retrieved by the investigator via participant report and collected in the CRF. The local reactions collected on the Participant Reported Reactogenicity CRF page will be combined with the 7-day e-diary data and included for the below analysis (presence, maximum severity, onset day, and duration). The main reason for missing e-diary entries (missing when all reactogenicity entries are considered, including any recalled e-diary entries and data entered on the Participant Reported Reactogenicity CRF page) will be collected by the investigator on the Summary of Reactogenicity CRF page.

This section describes derivations with details for the assessment of local reactions: any presence, maximum severity, duration, and onset day of local reactions, in addition to any presence of severe local reactions.

Presence or Absence

For the data summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination, the following variables are required in order to compute the proportions:

- Presence (yes or no) of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7).
- Presence (yes or no) of each local reaction by maximum severity on any day (Day 1 through Day 7).

For each local reaction and any local reaction on any day, Table 3 and Table 4 details the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of vaccination.

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Table 3. Derived Variables for Presence of Each Local Reaction Within 7 Days After Vaccination

Variable[a]	Yes (1)	No (0)	Missing (.)[b]
Presence of each local reaction.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7)	Participant reports the reaction as "no" or "I don't recall" on all 7 days (Day 1 through Day 7) or as a combination of "no," "I don't recall," and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data on all 7 days (Day 1 through Day 7) for the reaction.

a. The variables will be derived for each of the local reactions (redness, swelling, and pain at the injection site) and for each of the severe local reactions within the interval from Day 1 through Day 7 after vaccination.
b. "Missing" means missing from both the e-diary and the Participant Reported Reactogenicity CRF page.

Table 4. Derived Variables for Presence of Any Local Reaction Within 7 Days After Vaccination

Variable[a]	Yes (1)	No (0)	Missing (.)[b]
Presence of any local reaction.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" or "I don't recall" on all 7 days (Day 1 through Day 7) or as a combination of "no," "I don't recall," and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

a. The variables will be derived for any of the local reactions (redness, swelling, and pain at the injection site) and for any of the severe local reactions within the interval from Day 1 through Day 7 after vaccination.
b. "Missing" means missing from both the e-diary and the Participant Reported Reactogenicity CRF page.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

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Table 5. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. A Grade 4 reaction that meets the definition of an SAE will be collected on the AE CRF.

For each local reaction reported, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration of Each Local Reaction (First to Last Day Reported)

For participants experiencing any local reaction (or those with a derived reaction as described in Table 3 and Table 4), the maximum duration (resolution date of reaction – start date of reaction + 1) will be derived for each study vaccination.

Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected in the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to "missing." Participants with no reported reactions have no duration.

Onset Day of Each Local Reaction

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, only the first day of reporting that specific local reaction will be counted, even if participants report a change in severity of the local reaction.

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In summary, the following variables will be derived for local reactions:

1. Presence or absence of each local reaction on each day (Day 1 through Day 7) after vaccination.

2. Presence or absence of each local reaction on any day (Day 1 through Day 7) after vaccination.

3. Presence or absence of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7) after vaccination.

4. Maximum severity of each local reaction on any day (Day 1 through Day 7) after vaccination.

5. Presence or absence of any local reaction on any day (Day 1 through Day 7) after vaccination.

6. Duration of each local reaction after vaccination.

7. Onset day of each local reaction after vaccination.

8. Onset day of any local reaction after vaccination.

3.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of vaccination.

If a systemic event persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and the corresponding resolution date. The investigator will enter this resolution date on the Summary of Reactogenicity CRF page.

The systemic events collected on the Participant Reported Reactogenicity CRF page will be combined with the 7-day e-diary data and included for the below analysis (presence, maximum severity, onset day, and duration).

The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of the event, severity level, duration, and onset day.

The variables associated with the systemic events will be computed similarly to the way local reactions are computed (see Section 3.1.1).

1. Presence (yes or no) of each systemic event on each day (Day 1 through Day 7) after vaccination.

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2. Presence (yes or no) of each systemic event on any day (Day 1 through Day 7) after vaccination.

3. Presence or absence of each severe/Grade 4 systemic event on each day and any day (Day 1 through Day 7) after vaccination.

4. Maximum severity of each systemic event on any day (Day 1 through Day 7) after vaccination.

5. Presence or absence of any systemic event on any day (Day 1 through Day 7) after vaccination.

6. Duration of each systemic event after vaccination.

7. Onset day of each systemic event after vaccination.

8. Onset day of any systemic event after vaccination.

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6.

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain

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Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

a. Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. A Grade 4 event that meets the definition of an SAE will be collected on the AE CRF.

To record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary each evening during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection period, or longer following vaccination, when fever is suspected.

Fever is defined as an oral temperature ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 7 during analysis.

Table 7. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

3.1.3. Adverse Events

The time period for actively eliciting and collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 102 in Substudy A (approximately 4 weeks after vaccination).

Additionally, MAEs, NDCMCs, and SAEs will be collected from the time the participant provides informed consent to Visit 103 in Substudy A (approximately 6 months after vaccination). In addition, AEs occurring up to 48 hours after blood draws must be recorded on the CRF.

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Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer data standard rules.

The following derivations will be included for each participant:

- Any AE reported.
- Any related AE reported.
- Any immediate AE (assess acute reactions for at least 30 minutes after study intervention administration).
- Any SAE.
- Any MAE (an MAE is defined as a nonserious AE that results in an evaluation at a medical facility).
- Any NDCMC (an NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects [eg, asthma]).
- Any severe AE.
- Any life-threatening AE.
- Any AE leading to study withdrawal.
- Any AE leading to death.
- Any AESI.
    - Confirmed diagnosis of influenza (clinical signs/symptoms and positive laboratory testing) after Day 1 through 6 months after vaccination.
    - Confirmed diagnosis of myocarditis or pericarditis occurring within 28 days after vaccination.

3.2. Secondary Endpoint(s)

- HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines at baseline and 4 weeks after vaccination.

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3.3. Other Safety Endpoint(s)

3.3.1. Physical Examinations, Vital Signs, and Medical History

A physical examination may be performed at baseline (Visit 101 in Substudy A) prior to vaccination, if clinically indicated. Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

The participant's oral temperature will be measured prior to vaccination in Substudy A. Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

Medical history will be categorized according to MedDRA.

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3.5. Baseline Variables

Measurements or samples collected prior to vaccination are considered the baseline data for the assessments. In this study, Day 1 is the baseline visit; the data from screening visit may be used as baseline only if the data on Day 1 are missing.

3.5.1. Demographics

The demographic variables are age at the first vaccination (in years), sex (male or female), race (Black/African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, not reported), and ethnicity (Hispanic/Latino/of Spanish origin, non-Hispanic/non-Latino/non-of Spanish origin, not reported), and racial designation (Japanese, other). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

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3.5.2. E-Diary Completion

An e-diary will be considered transmitted if any data for the 3 local reactions (redness, swelling, and pain at the injection site) and 8 systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain) are present on any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted.

An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

Note: Data entered as part of the 72-hour recall period will be counted for the e-diary completion/transmission.

The data from the Participant Reported Reactogenicity CRF page will not be included in the e-diary completion/transmission summary.

For transmitted e-diaries, the following variables will be defined: “Day 1,” “Day 2,” “Day 3,” “Day 4,” “Day 5,” “Day 6,” “and “Day 7.”

For completed e-diaries, the following variables will be defined: “Day 1,” “Day 2,” “Day 3,” “Day 4,” “Day 5,” “Day 6,” “Day 7,” and “Day 1-Day 7.”

“Day 1-Day 7” is the variable for participants who completed e-diaries on all 7 days.

For e-diaries that are incomplete, an indicator variable for the percentage of days without data will be derived as follows:

= 1, if data have been transmitted and are complete for 7 days (100%)

= 2, if data have been transmitted and are complete for 6 days (≥75% to <100%)

= 3, if data have been transmitted and are complete for 4 or 5 days (≥50% to <75%)

= 4, if data have been transmitted and are complete for 2 or 3 days (≥25% to <50%)

= 5, if data have been transmitted and are complete for 0 or 1 day (<25%)

3.5.3. Prior/Concomitant Vaccines and Concomitant Medications

The following concomitant medications and vaccinations will be recorded in the CRF:

- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 103).
- Last dose of licensed influenza vaccine, if received.

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- Prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine).
- Prohibited medications listed in Section 10.11.6.9.1 of the protocol, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

Nonstudy vaccines and concomitant medications will be coded using the WHODD.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per standard operating procedures.

Population	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
CCI	[redacted]
Safety	All participants who receive the study intervention.

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Important protocol deviations will be determined by clinical review. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication/treatment that might affect immune response or a medication error with a suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

The APE field will be included in the PIPD list from the CORD system and is used to help identify protocol deviations that may exclude participants from a particular population. For each reporting event, the most current endorsed version of the PIPD list must be used to generate the protocol deviation data set for analysis and reporting.

The APE flags for this study are as follows:

- YES-POP1 (participants excluded from the safety population)
- YES-POP2 (participants excluded from the evaluable immunogenicity population)
- YES-POP3 (participants identified as multiple enrollers)

Participants enrolling at multiple sites (multiple enroller): Any participant enrolling at more than 1 site in the study will be removed from the evaluable, mITT, and safety populations. These participants will be followed for safety and reported separately from the other participants.

Vaccinated but not randomized: These participants will be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received but will be excluded from the evaluable immunogenicity analyses or mITT immunogenicity analyses.

Randomized but not vaccinated: These participants will be included in the randomized population and excluded from any safety analyses and evaluable immunogenicity or mITT immunogenicity analyses.

Randomized but received incorrect vaccine: These participants will be included in the mITT populations for immunogenicity analyses if data are available and will be reported under the vaccine group based on the randomized vaccine. These participants will also be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The study is descriptive in nature, no formal statistical hypothesis testing will be performed. No decision rules will be applied.

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5.2. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Completely missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

For the immunogenicity endpoints, the main analysis will be based on the evaluable immunogenicity population. Antibody titers below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for GMT analysis. No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody titers that are below the LLOQ.

An additional analysis may be performed based on the mITT immunogenicity populations if there is a large enough difference (>10%) in sample size between the mITT immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

No formal multiplicity adjustments will be applied for the analyses in multiple endpoints or for multiple looks of the same endpoint due to the descriptive nature of this substudy.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics for binary variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson)[1] and implemented in SAS PROC FREQ.

5.2.2. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Mean Titers

The GMTs will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI based on the Student t distribution, and then exponentiating the confidence limits.

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5.2.2.2. Geometric Mean Fold Rises

GMFRs are defined as the geometric mean of the fold rise in the assay results from before to a specified time point after vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean difference. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.2.3. Geometric Mean Ratios

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using the Student t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with the line first going down and then to the right to the next assay value.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms for handling missing AE dates, AE severity, laboratory test values, and ECG values will be applied according to the Pfizer safety rules. Missing data handling rules for safety data are described in detail in the corresponding endpoint sections.

5.3.1.1. Reactogenicity Data

Completely missing reactogenicity e-diary data (no data from both the 7-day e-diary and the Participant Reported Reactogenicity CRF page) will not be imputed. For derived variables based on reactogenicity data, if any day of the 7-day e-diary data are available, the “any day (Day 1 through Day 7)” data will be considered nonmissing.

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are nonmissing.

For the “I do not recall” data in the e-diary, it will be imputed as “no” as described in Table 3 and Table 4 in Section 3.1.1. No missing reactogenicity data will be imputed other than what is described in Section 3.1.1 and Section 3.1.2.

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In summary, for any participant with all 7 days of the e-diary missing (no data from both the 7-day e-diary collection period and the Participant Reported Reactogenicity CRF page), this will not be included in the analysis (ie, assuming MCAR). If only 1 to 6 days of reactogenicity data are available, the reactogenicity data for the missing day(s) are considered as answering "no" for all reactions. This is based on the common assumption that no reports mean no events. See Table 3 and Table 4 for the derivation algorithms.

5.3.2. Immunogenicity Data

Any assay results above the LLOQ are considered accurate, and their quantitated values will be reported. Antibody titers below the LLOQ, denoted as BLQ, or below the LOD will be set to 0.5 × LLOQ for GMT analysis. No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

When calculating a fold rise, the assay results will be converted to 0.5 × LLOQ if assay results are < LLOQ, except when the prevaccination assay result is < LLOQ while the postvaccination result is ≥ LLOQ, in which case the prevaccination value will be set to LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.

If there are multiple batch assay results at baseline, the GMT will be calculated from the mean of the baseline assay results. GMFR and seroconversion will be calculated using paired baseline and postbaseline assay results from the same batch of assay data. If there is more than 1 assay value at baseline due to multiple assay result batches, the titer criterion ≥1:40 will be met if any of the assay values are ≥1:40.

Values for sera that are insufficient (QNS), IND results, or values recorded as "not done" will be set to "missing." Additionally, any time point with no blood draws will not be included in the analysis. No imputation will be done for these missing values, as MCAR is assumed for immunogenicity data.

LLOQ results for each assay used in this study will be included in the analysis specification once they are available.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Local Reactions and Systemic Events

6.1.1.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CI of the proportion of participants reporting each event, using the Clopper-Pearson method (Section 5.2.1).

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- Analysis timing: Day 1 through Day 7 after vaccination.

- Intercurrent events and missing data: All data collected after the intercurrent events will be included (Section 2.2.1). The participants without any e-diary data or reactogenicity event data on the Participant Reported Reactogenicity CRF page throughout the 7 days after vaccination will be excluded from the analysis; intermediate missing values will not be imputed. Partially missing e-diary data are imputed as "no" (Section 3.1.1, Section 3.1.2, and Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.

Reporting results:

- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for the percentage using the Clopper-Pearson method, will be presented for each study intervention group. The denominator will be the number of participants reporting at least 1 "yes" or "no" response for the local reaction after vaccination.

- Bar charts with the proportions of participants for each and any local reaction and each and any systemic event through the 7 days following vaccination will be plotted for each study intervention group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Sensitivity/Supplementary Analyses

A sensitivity analysis will be conducted for the above summary of reactogenicity events by maximum severity. A variable to indicate the time period from the planned e-diary day (11:59 PM on that calendar day) to the actual time of e-diary reporting will be derived based on FARFTDTC (reference time point, ie, the time of vaccination), FADTC (data collection time), and FATPT (time point of intended solicitation day) in the dataset. The period will be categorized in relation to the planned e-diary day, ie, within the planned day, 1 day out (1-24 hours), 2 days out (>24-48 hours), or 3 days out (>48-72 hours) from the planned e-diary day. The sensitivity analysis will exclude the participants with e-diary reports collected outside the intended solicitation (calendar) day or with data collected from the Participant Reported Reactogenicity CRF page.

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.1 and Section 3.1.2, will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction and each systemic event after vaccination.

- Onset day of each local reaction and each systemic event after vaccination.

- Presence of each and any severe local reaction and each and any severe systemic event on each of the 7 days and for "any day (Day 1 through Day 7)."

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The presentation of the results will include a basic descriptive summary without 95% CIs (Section 5.2).

These continuous endpoints will be summarized by displaying the n, mean, median, standard deviation, minimum, and maximum for each study intervention group.

In addition, the proportions of participants reporting prompted local reactions, by maximum severity level, with any e-diary errors will be included as a supplemental summary.

6.1.2. AEs, SAEs, MAEs, and NDCMCs

6.1.2.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CI of the proportion of participants reporting such events, using the Clopper-Pearson method (Section 5.2.1).
- Analysis timing: Day 1 through 4 weeks after vaccination for AEs; Day 1 through 6 months after vaccination for SAEs, MAEs, and NDCMCs.
- Intercurrent events and missing data: All data collected are included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

Reporting results:

- The number of participants with AEs through 4 weeks after vaccination (n), the proportion (%), and the associated 2-sided Clopper-Pearson 95% CIs will be presented for each study intervention group.
- The number of participants with SAEs, MAEs, and NDCMCs through 6 months after vaccination (n), the proportion (%), and the associated 2-sided Clopper-Pearson 95% CIs will be presented for each study intervention group.
- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator used in the proportion calculation, and the 95% CIs for the percentage using the Clopper-Pearson method, will be presented for each SOC and each PT within each SOC for each study intervention group.

6.1.2.2. Sensitivity/Supplementary Analyses

To support the assessment of AEs, the endpoints below as specified in Section 3.1.3 will be summarized with the same analysis population using the same presentation as specified in the main analysis:

- Immediate AEs

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- Related AEs
- Severe AEs
- Life-threatening AEs
- AEs leading to study discontinuation/withdrawal
- AEs leading to death
- AESIs

All AEs/SAEs occurring after informed consent and prior to vaccination will not be included in the analyses but will be listed.

In addition, any AEs occurring up to 48 hours after blood draws will be listed.

6.2. Secondary Endpoint(s)

6.2.1. HAI Titers for the 2023-2024 Northern Hemisphere Seasonal Strains Recommended by WHO for CCI [redacted] Influenza Vaccines

6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.2).
- Analysis set: Evaluable immunogenicity population (HAI CCI [redacted]) (Section 4).
- Analysis methodology: Descriptive summary statistics (Section 5.2.1 and Section 5.2.2).
- Analysis timing: Day 1 prior to study intervention administration (HAI GMTs, HAI titers ≥1:40) and at 4 weeks after vaccination.
- Intercurrent events and missing data: All data collected after or at intercurrent events will be excluded (Section 2.2.2). Antibody titers below the LLOQ, denoted as BLQ, or below the LOD will be set to 0.5 × LLOQ for analysis (Section 5.3.2). Missing data will not be imputed. Immunogenicity data that are confirmed as not valid will not be used for analysis.

Reporting results:

- Descriptive statistics, including the sample size (n), HAI GMTs, HAI GMFRs, and 95% CIs for the HAI GMTs and HAI GMFRs, will be presented for each strain and each study intervention group (Section 5.2.2).

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- Descriptive statistics, ie, HAI GMRs of each tIRV (tIRV1, tIRV2 and tIRV3) group compared with each control group (QIV1, qIRV1) at 4 weeks after vaccination, and the 95% CIs for the HAI GMRs, will be presented for each strain (Section 5.2.2).

- The proportion of participants achieving HAI seroconversion for each strain at 4 weeks after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided by study intervention group.

- The proportion of participants with HAI titers ≥1:40 for each strain before vaccination and at 4 weeks after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided by study intervention group.

- Empirical RCDCs will be plotted by study intervention group.

- HAI GMTs for each strain, and the associated 95% CIs, will be plotted by study intervention group.

- HAI seroconversion rate for each strain, along with the associated 95% CIs, may be plotted by study intervention group.

6.2.1.2. Sensitivity/Supplementary Analysis

To support the assessment of immunogenicity, estimands as specified in Section 2.2.2 using the treatment policy strategy might be summarized with the mITT immunogenicity population (HAI [redacted] using the same presentation as specified in the main analysis.

6.3. Other Safety Summaries and Analyses Endpoint(s)

6.3.1. Data Collected on the Summary of Reactogenicity CRF Page

Data collected about reactogenicity events on the Summary of Reactogenicity CRF page will be summarized or listed.

The main reasons for noncompletion of the 7-day reactogenicity event reporting (including e-diary entries and the data on the Participant Reported Reactogenicity CRF page) will be listed.

Immediate reactogenicity events may be summarized by study intervention group.
The medically attended reactogenicity events will be listed.

6.3.2. Medical History

Each reported medical history term will be mapped to an SOC and PT according to MedDRA. The number and percentage of participants with an assigned vaccine having at least 1 diagnosis of medical history, overall and at each SOC and PT level, will be summarized by study intervention group and for all participants in total based on the safety population.

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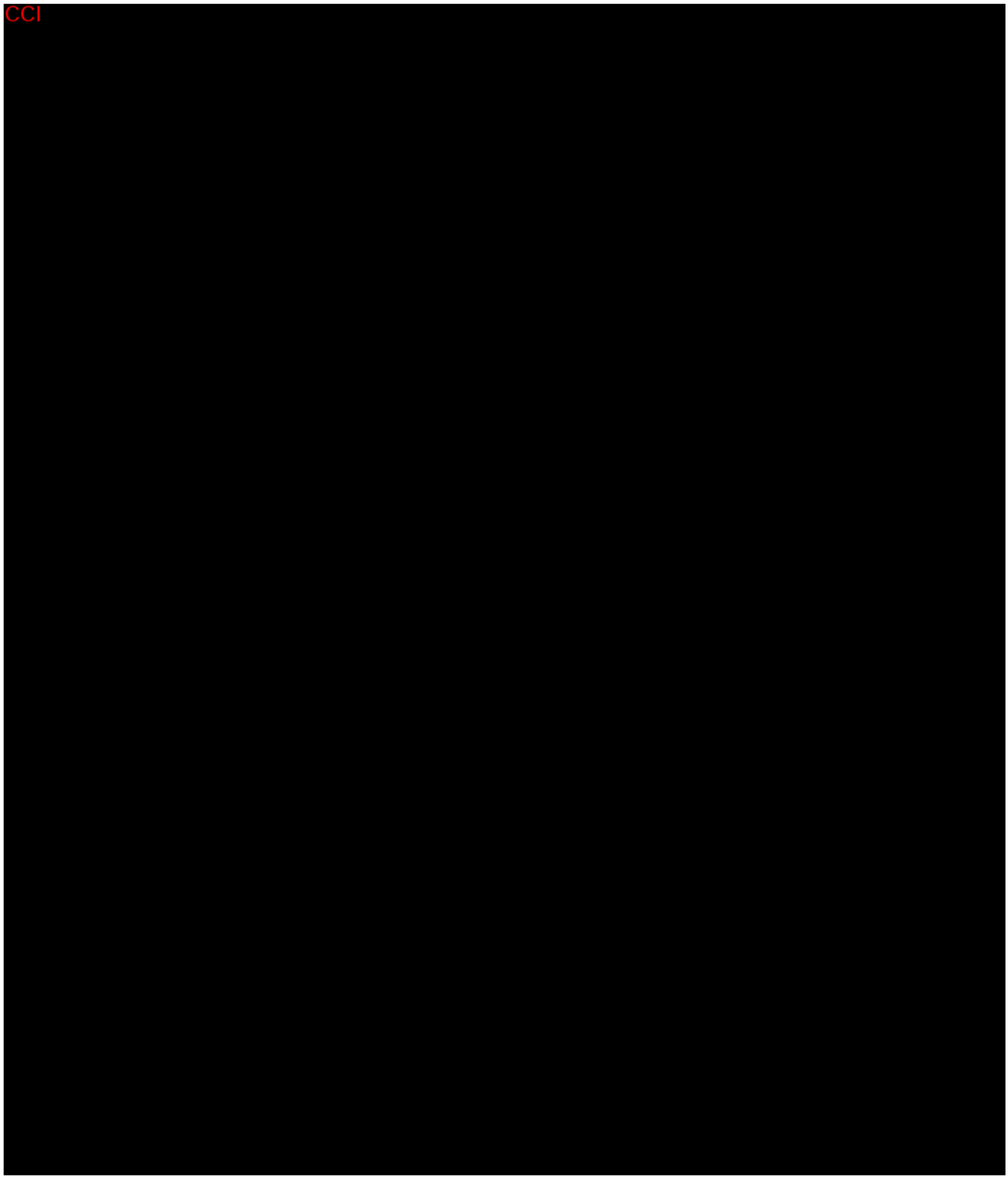
6.3.3. Electrocardiograms

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after a study vaccination (ECG, troponin I level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by vaccine group.

CCI



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CCI

[redacted]

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6.5. Subset Analyses

Subset analyses will be performed for safety primary endpoints and immunogenicity secondary endpoint by age subgroups (18-49 years; 50-64 years). The main analysis described for these endpoints in Section 6.1.1.1, Section 6.1.2.1, and Section 6.2.1.1 will be performed by the age subgroups.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, and ethnicity) will be generated by study intervention group and for all participants in total based on the safety population.

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Participant Disposition

All participants in the randomized population will be included in the disposition summaries. Summaries will be displayed by vaccine group separately.

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the number and percentage of participants who received vaccinations, completed the follow-up visits, and withdrew before the follow-up visit, along with the reasons for withdrawal, will be tabulated by study intervention group and the total sample. The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately by study intervention group, along with the reasons for exclusion by study intervention group.

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A listing of protocol deviations may also be provided.

6.6.2.2. Blood Samples for Assay

For each blood sampling time point, the number and percentage of randomized participants providing blood samples within the protocol-specified time frame, as well as before and after the protocol-specified time frame, will be tabulated separately by study intervention group.

6.6.2.3. E-Diaries

The participants who were vaccinated and who transmitted and completed e-diaries will be summarized according to the vaccine actually received. Besides the analysis described in Section 6.1.1, the summary will also include the number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary, and completing the e-diary for any day (based on the e-diary completion category as defined in Section 3.5.2) in the required reporting period after vaccination by assigned study intervention.

The number and percentage of participants transmitting and completing the e-diary for each day in the required reporting period, and overall, will be tabulated for each study intervention group.

The safety population will be used.

6.6.3. Study Intervention Exposure

6.6.3.1. Vaccination Administration

The relation of the randomized study intervention to the actual study intervention received will be presented as a cross-tabulation of the actual study intervention received versus the randomized study intervention.

A listing of participants showing the randomized study intervention and the study intervention actually received will be presented.

6.6.4. Concomitant Medications and Nondrug Treatments

Each prior/concomitant vaccine will be summarized according to the Anatomic Therapeutic Chemical fourth-level classification/WHODD, as appropriate. The prior/concomitant vaccines and medications as described in Section 3.5.3 will be listed. The number and percentage of participants receiving each prior (before vaccination) and concomitant vaccine (on or after vaccination) will be tabulated according to the assigned study intervention. The safety population will be used. Concomitant medications will be summarized similarly to concomitant vaccines.

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7. INTERIM ANALYSES

7.1. Introduction

As the study is sponsor-unblinded, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, dose selection, and/or supporting clinical development.

7.2. Interim Analyses

Not applicable.

8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

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Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
APE	analysis population exclusion
BLQ	below the limit of quantitation
CI	confidence interval
CORD	Clinical Oversight Review Dashboard
COVID-19	coronavirus disease 2019
CRF	case report form
ECG	electrocardiogram
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
ICD	informed consent document
IND	indeterminate
IPM	investigational product manual
IRT	interactive response technology
IV	intravenous(ly)
LLOQ	lower limit of quantitation
LOD	limit of detection
MAE	medically attended adverse event
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mIRV	monovalent influenza modRNA vaccine
mITT	modified intent-to-treat
CCI [redacted]	
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
PIPD	potential important protocol deviation
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QNS	quantity not sufficient

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Abbreviation	Term
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
tIRV	trivalent influenza modRNA vaccine
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

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Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
PPD	13-Jun-2024 14:08:40	Business Line Approver

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Protocol C4781013 – Substudy B

A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MODIFIED RNA VACCINES AGAINST INFLUENZA IN HEALTHY ADULTS

Statistical Analysis Plan
(SAP)

Version: 2

Date: 12 Jun 2024

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APPENDICES

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 18 Apr 2024	Original 12 Mar 2024	N/A	N/A
2 12 Jun 2024	1 26 Apr 2024	• To update the monitoring and collection period for myocarditis and pericarditis per protocol amendment 1. • To update the analysis population [redacted] for consistency with the protocol. • To make updates and clarifications on the reactogenicity events collected in the e-diary and CRF per regulatory comments. • To add a sensitivity analysis for the summary of reactogenicity events by maximum severity per regulatory comments.	• Section 3.1.3 and Section 6.3.3: Updated the monitoring and collection period for myocarditis and pericarditis from "14 days after vaccination" to "28 days after vaccination." • Section 2.2, Section 2.2.3, Section 4, Section 5.2, Section 6.4.1.1, Section 6.4.2.1, and Section 6.4.3.1: Updated the analysis population [redacted] for consistency with the protocol. • Section 2.3, Section 3.1.1, Section 3.1.2, Section 3.5.2, Section 5.3.1.1, Section 6.1.1.1, and Section 6.3.1: Clarified the reactogenicity data collected in the e-diary and CRF and the analysis of reactogenicity events. • Section 6.1.1.2: Added a sensitivity analysis for the summary of reactogenicity events by maximum severity.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4781013 – Substudy B. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

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2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
Primary safety	To define the safety and tolerability profile of tIRVs in participants ≥65 years of age	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs • MAEs • NDCMCs	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination
Secondary immunogenicity	To describe the immune response elicited by tIRVs in participants ≥65 years of age	• HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines	In participants complying with the key protocol criteria (evaluable immunogenicity population [HAI CCI]): • HAI GMTs at baseline and 4 weeks after vaccination • HAI GMFRs from before vaccination to 4 weeks after vaccination • The proportion of participants achieving HAI seroconversion[a] for each strain at 4 weeks after vaccination • The proportion of participants with HAI titers ≥1:40 for each strain at baseline and 4 weeks after vaccination
CCI			

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Type	Objective	Endpoint	Estimand
		CCI [redacted]	

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Type	Objective	Endpoint	Estimand
			CCI [redacted]

a. Seroconversion is defined as an HAI titer <1:10 prior to vaccination and ≥1:40 at the time point of interest, or an HAI titer ≥1:10 prior to vaccination with at least a 4-fold rise at the time point of interest.

2.2.1. Primary Estimand(s)

The primary estimands for the primary objective (safety) will use the treatment policy strategy and estimate the safety event rate (reactogenicity, AEs/SAEs/MAEs/NDCMCs) regardless of whether an intercurrent event occurs.

- The reactogenicity estimands (local reactions and systemic events) have the following 5 attributes:
  - **Treatment condition:** Vaccination with 2 different formulations of tIRV (tIRV2 and tIRV3), QIV2 (CCI [redacted]), QIV3 (CCI [redacted], and qIRV2 as defined in Section 2.3.
  - **Population:** Participants ≥65 years of age who receive the study intervention.
  - **Variables:** Local reactions and systemic events from the e-diary up to 7 days following vaccination.
  - **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, use of rescue medication, missing e-diary entries on certain days, study discontinuation), if collected, will be included.
  - **Population-level summary:** The rates of reporting each prompted reactogenicity item, and the associated 2-sided 95% CIs, by study intervention group (in the tIRV2, tIRV3, QIV2, QIV3, and qIRV2 vaccine groups, separately).
- The AE, SAE, MAE and NDCMC estimands have the following 5 attributes:
  - **Treatment condition:** Vaccination with 2 different formulations of tIRV (tIRV2 and tIRV3), QIV2 CCI [redacted], QIV3 CCI [redacted], and qIRV2 as defined in Section 2.3.
  - **Population:** Participants ≥65 years of age who receive the study intervention.
  - **Variables:**
    - AEs reported through 4 weeks after vaccination.

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- SAEs reported through 6 months after vaccination.
- MAEs reported through 6 months after vaccination.
- NDCMCs reported through 6 months after vaccination.

- **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, use of rescue medication, study discontinuation), if collected, will be included.
- **Population-level summary:** The rates of AEs, SAEs, MAEs and NDCMCs, and the associated 2-sided 95% CIs, by study intervention group (in the tIRV2, tIRV3, QIV2, QIV3, and qIRV2 vaccine groups, separately).

2.2.2. Secondary Estimand(s)

The secondary estimands for the secondary objective (immunogenicity) will use the hypothetical strategy and estimate the vaccine immune response when an intercurrent event does not occur. In other words, the immune response is estimated in the hypothetical setting where participants follow the study schedule and protocol requirements as directed. It includes the following 5 attributes:

- **Treatment condition:** Vaccination with 2 different formulations of tIRV (tIRV2 and tIRV3), QIV2 (CCI [redacted], QIV3 (CCI [redacted], and qIRV2 as defined in Section 2.3.
- **Population:** Participants ≥65 years of age, as defined by the inclusion and exclusion criteria.
- **Variables:**

HAI CCI [redacted]

- HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines:
  - HAI titers at baseline and 4 weeks after vaccination.
  - HAI titer fold rise from before vaccination to 4 weeks after vaccination.
  - Presence of HAI seroconversion for each strain at 4 weeks after vaccination.
  - Presence of HAI titers ≥1:40 for each strain at baseline and 4 weeks after vaccination.

- **Intercurrent events:** The following intercurrent events could impact the interpretation or the measurement of the immune response:
  - Not meeting the study inclusion criteria or meeting the exclusion criteria.

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- Not receiving the study intervention as randomized.
- Blood for assay testing is taken outside of the defined window (<26 days or >35 days after vaccination).
- Having major protocol deviations (received prohibited vaccine or treatment that may alter the immune response and subsequently impact the vaccine protection).

All data after the above intercurrent events, if collected, will be excluded from analysis.

- **Population-level summary:** HAI GMTs, and the associated 2-sided 95% CIs, at baseline and 4 weeks after vaccination; HAI GMFRs, and the associated 2-sided 95% CIs, from before vaccination to 4 weeks after vaccination; the proportion of participants achieving HAI seroconversion for each strain at 4 weeks after vaccination, and the associated 2-sided 95% CIs; and the proportion of participants with HAI titers ≥1:40 for each strain at baseline and 4 weeks after vaccination, and the associated 2-sided 95% CIs, will be summarized by study intervention.

CCI

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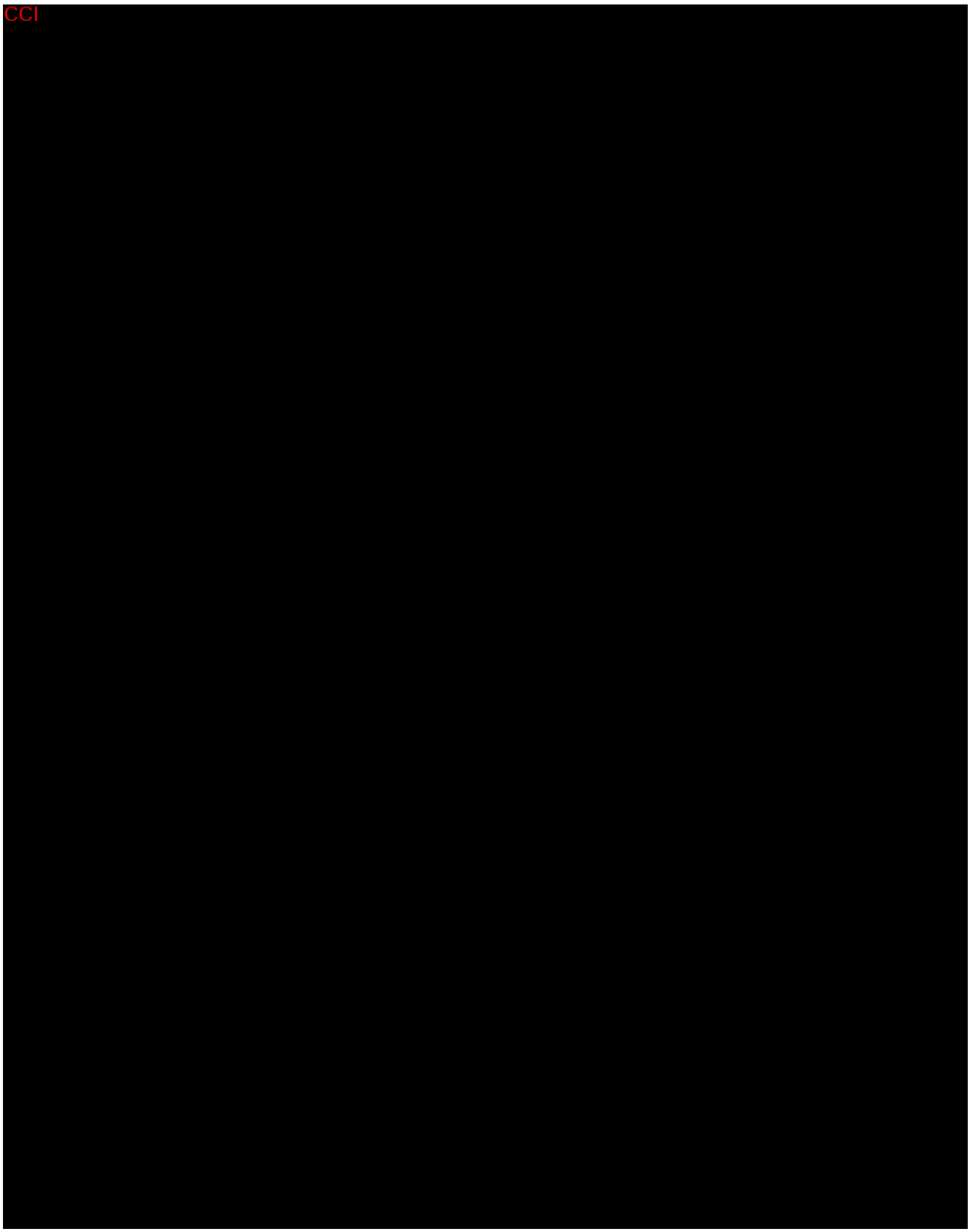
CCI



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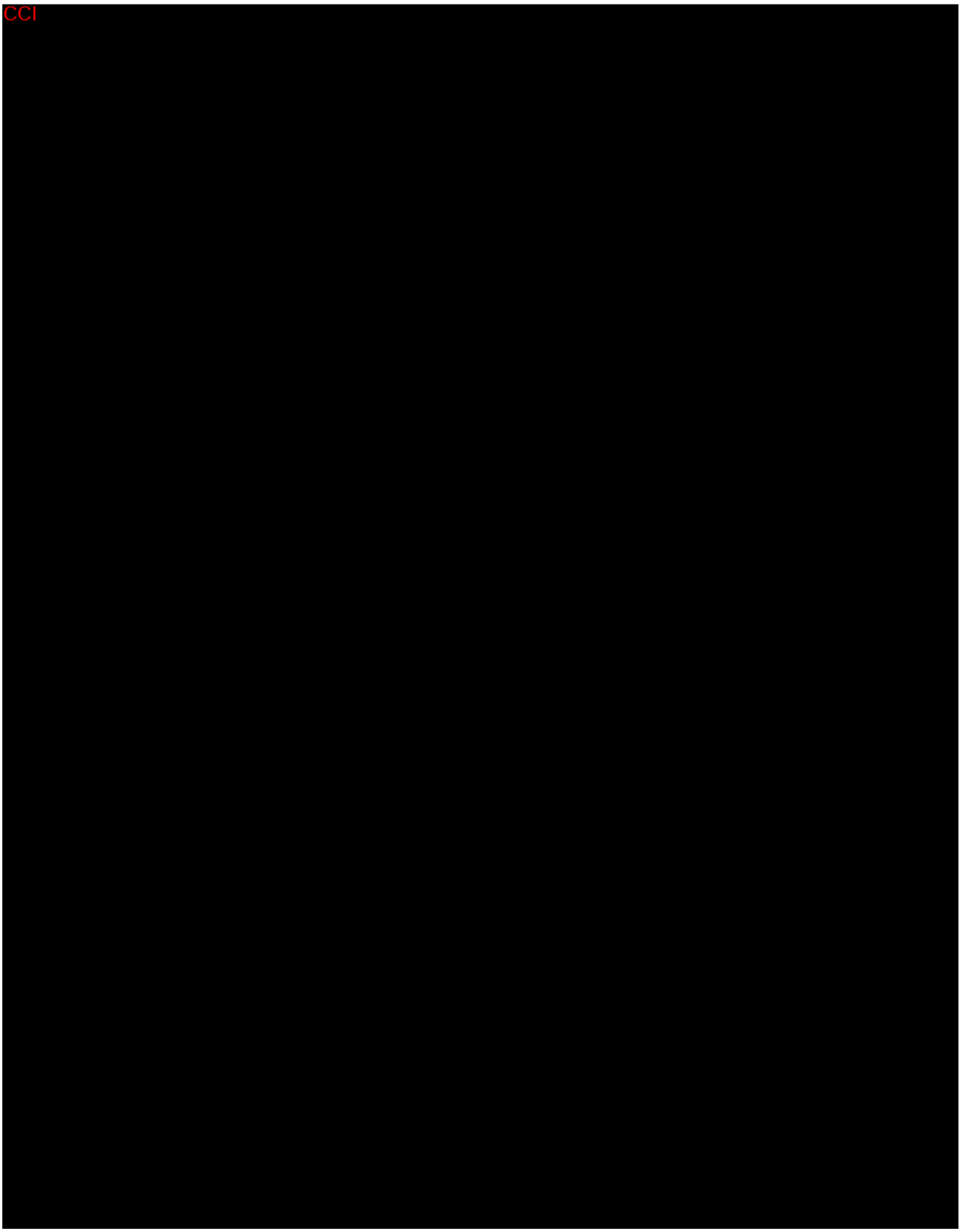
CCI



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CCI [redacted]

2.3. Study Design

This is a Phase 2, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, and immunogenicity of 2 different formulations of tIRV (tIRV2 and tIRV3) encoding HA for the targeted seasonal influenza strains compared to QIV2 (CCI [redacted]), QIV3 (CCI [redacted]), and qIRV2 (encoding HA for 2 A and 2 B seasonal influenza strains) in healthy adults ≥65 years of age.

Up to approximately 450 participants ≥65 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in Table 2.

Blood samples of approximately 30 mL will be collected CCI [redacted] prior to vaccination and at 4 weeks and 6 months after vaccination.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period after vaccination. Participants are required to complete the e-diary every evening (06:00 PM to 11:59 PM) for the 7 days following vaccination (including the day of vaccination). If participants are unable to complete the e-diary as expected on a particular day, they are allowed to retrospectively complete the missed entry within up to 3 days following the date of the missed entry (extended 72-hour e-diary reporting window).

For participants with ongoing symptoms after Day 7, subsequent e-diary entries will be followed only to monitor the duration of symptoms until resolution. The end date for the prespecified local reaction and systemic event beyond Day 7 will also be recorded on the Summary of Reactogenicity CRF page.

All AEs will be collected from informed consent signing through 4 weeks following vaccination. A subset of AEs (NDCMCs, MAEs, and SAEs) will be collected from informed consent signing through 6 months after vaccination. In addition, AEs occurring up to 48 hours after blood draws will be collected.

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Table 2. Number of Participants to Be Enrolled in Substudy B – Participants ≥65 Years of Age

Study Intervention	Preformulated[a]	Influenza Strains	CCI	Total modRNA Dose	Number of Participants
QIV2	Yes	2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines		N/A	90
QIV3	Yes	2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI influenza vaccines		N/A	90
tIRV2	No	A/H1N1		CCI	90
		A/H3N2			
		B/Victoria			
tIRV3	No	A/H1N1			90
		A/H3N2			
		B/Victoria			
qIRV2	Yes	A/H1N1			90
		A/H3N2			
		B/Victoria			
		B/Yamagata			

a. For tIRV2 and tIRV3 (which are not preformulated), mIRVs encoding HA for each A and B strain will be mixed at the site to generate these study interventions at the dose-level combination shown. Please see the IPM for further details.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- Local reactions (pain at the injection site, redness and swelling) through 7 days following vaccination.
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) through 7 days following vaccination.
- AEs through 4 weeks after vaccination.
- SAEs through 6 months after vaccination.
- MAEs through 6 months after vaccination.
- NDCMCs through 6 months after vaccination.

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3.1.1. Local Reactions

The local reactions reported in the e-diary are pain at the injection site, redness, and swelling, from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination.

If a local reaction persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and the corresponding resolution date. The investigator will enter this resolution date on the Summary of Reactogenicity CRF page.

For missing records on local reactions during the 7-day e-diary collection period, the data may be retrieved by the investigator via participant report and collected in the CRF. The local reactions collected on the Participant Reported Reactogenicity CRF page will be combined with the 7-day e-diary data and included for the below analysis (presence, maximum severity, onset day, and duration). The main reason for missing e-diary entries (missing when all reactogenicity entries are considered, including any recalled e-diary entries and data entered on the Participant Reported Reactogenicity CRF page) will be collected by the investigator on the Summary of Reactogenicity CRF page.

This section describes derivations with details for the assessment of local reactions: any presence, maximum severity, duration, and onset day of local reactions, in addition to any presence of severe local reactions.

Presence or Absence

For the data summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination, the following variables are required in order to compute the proportions:

- Presence (yes or no) of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7).
- Presence (yes or no) of each local reaction by maximum severity on any day (Day 1 through Day 7).

For each local reaction and any local reaction on any day, Table 3 and Table 4 details the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of vaccination.

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Table 3. Derived Variables for Presence of Each Local Reaction Within 7 Days After Vaccination

Variable[a]	Yes (1)	No (0)	Missing (.)[b]
Presence of each local reaction.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7)	Participant reports the reaction as "no" or "I don't recall" on all 7 days (Day 1 through Day 7) or as a combination of "no," "I don't recall," and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data on all 7 days (Day 1 through Day 7) for the reaction.

a. The variables will be derived for each of the local reactions (redness, swelling, and pain at the injection site) and for each of the severe local reactions within the interval from Day 1 through Day 7 after vaccination.
b. "Missing" means missing from both the e-diary and the Participant Reported Reactogenicity CRF page.

Table 4. Derived Variables for Presence of Any Local Reaction Within 7 Days After Vaccination

Variable[a]	Yes (1)	No (0)	Missing (.)[b]
Presence of any local reaction.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" or "I don't recall" on all 7 days (Day 1 through Day 7) or as a combination of "no," "I don't recall," and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

a. The variables will be derived for any of the local reactions (redness, swelling, and pain at the injection site) and for any of the severe local reactions within the interval from Day 1 through Day 7 after vaccination.
b. "Missing" means missing from both the e-diary and the Participant Reported Reactogenicity CRF page.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

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Table 5. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. A Grade 4 reaction that meets the definition of an SAE will be collected on the AE CRF.

For each local reaction reported, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration of Each Local Reaction (First to Last Day Reported)

For participants experiencing any local reaction (or those with a derived reaction as described in Table 3 and Table 4), the maximum duration (resolution date of reaction – start date of reaction + 1) will be derived for each study vaccination.

Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected in the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to "missing." Participants with no reported reactions have no duration.

Onset Day of Each Local Reaction

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, only the first day of reporting that specific local reaction will be counted, even if participants report a change in severity of the local reaction.

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In summary, the following variables will be derived for local reactions:

1. Presence or absence of each local reaction on each day (Day 1 through Day 7) after vaccination.

2. Presence or absence of each local reaction on any day (Day 1 through Day 7) after vaccination.

3. Presence or absence of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7) after vaccination.

4. Maximum severity of each local reaction on any day (Day 1 through Day 7) after vaccination.

5. Presence or absence of any local reaction on any day (Day 1 through Day 7) after vaccination.

6. Duration of each local reaction after vaccination.

7. Onset day of each local reaction after vaccination.

8. Onset day of any local reaction after vaccination.

3.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of vaccination.

If a systemic event persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and the corresponding resolution date. The investigator will enter this resolution date on the Summary of Reactogenicity CRF page.

The systemic events collected on the Participant Reported Reactogenicity CRF page will be combined with the 7-day e-diary data and be included for the below analysis (presence, maximum severity, onset day, and duration).

The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of the event, severity level, duration, and onset day.

The variables associated with the systemic events will be computed similarly to the way local reactions are computed (see Section 3.1.1).

1. Presence (yes or no) of each systemic event on each day (Day 1 through Day 7) after vaccination.

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2. Presence (yes or no) of each systemic event on any day (Day 1 through Day 7) after vaccination.

3. Presence or absence of each severe/Grade 4 systemic event on each day and any day (Day 1 through Day 7) after vaccination.

4. Maximum severity of each systemic event on any day (Day 1 through Day 7) after vaccination.

5. Presence or absence of any systemic event on any day (Day 1 through Day 7) after vaccination.

6. Duration of each systemic event after vaccination.

7. Onset day of each systemic event after vaccination.

8. Onset day of any systemic event after vaccination.

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6.

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain

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Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

a. Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. A Grade 4 event that meets the definition of an SAE will be collected on the AE CRF.

To record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary each evening during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection period, or longer following vaccination, when fever is suspected.

Fever is defined as an oral temperature ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 7 during analysis.

Table 7. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

3.1.3. Adverse Events

The time period for actively eliciting and collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 202 in Substudy B (approximately 4 weeks after vaccination).

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Additionally, MAEs, NDCMCs, and SAEs will be collected from the time the participant provides informed consent to Visit 203 in Substudy B (approximately 6 months after vaccination). In addition, AEs occurring up to 48 hours after blood draws must be recorded on the CRF.

Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer data standard rules.

The following derivations will be included for each participant:

- Any AE reported.
- Any related AE reported.
- Any immediate AE (assess acute reactions for at least 30 minutes after study intervention administration).
- Any SAE.
- Any MAE (an MAE is defined as a nonserious AE that results in an evaluation at a medical facility).
- Any NDCMC (an NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects [eg, asthma]).
- Any severe AE.
- Any life-threatening AE.
- Any AE leading to study withdrawal.
- Any AE leading to death.
- Any AESI.
    - Confirmed diagnosis of influenza (clinical signs/symptoms and positive laboratory testing) after Day 1 through 6 months after vaccination
    - Confirmed diagnosis of myocarditis or pericarditis occurring within 28 days after vaccination.

3.2. Secondary Endpoint(s)

- HAI titers for the 2023-2024 northern hemisphere seasonal strains recommended by WHO for CCI [redacted] influenza vaccines at baseline and 4 weeks after vaccination.

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3.3. Other Safety Endpoint(s)

3.3.1. Physical Examinations, Vital Signs, and Medical History

A physical examination may be performed at baseline (Visit 201 in Substudy B) prior to vaccination, if clinically indicated. Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

The participant's oral temperature will be measured prior to vaccination in Substudy B. Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

Medical history will be categorized according to MedDRA.

3.5. Baseline Variables

Measurements or samples collected prior to vaccination are considered the baseline data for the assessments. In this study, Day 1 is the baseline visit; the data from screening visit may be used as baseline only if the data on Day 1 are missing.

3.5.1. Demographics

The demographic variables are age at the first vaccination (in years), sex (male or female), race (Black/African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, not reported), and ethnicity (Hispanic/Latino/of Spanish origin, non-Hispanic/non-Latino/non-of Spanish origin, not reported), and racial designation (Japanese, other). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

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3.5.2. E-Diary Completion

An e-diary will be considered transmitted if any data for the 3 local reactions (redness, swelling, and pain at the injection site) and 8 systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain) are present on any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted.

An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

Note: Data entered as part of the 72-hour recall period will be counted for the e-diary completion/transmission.

The data from the Participant Reported Reactogenicity CRF page will not be included in the e-diary completion summary.

For transmitted e-diaries, the following variables will be defined: “Day 1,” “Day 2,” “Day 3,” “Day 4,” “Day 5,” “Day 6,” “and “Day 7.”

For completed e-diaries, the following variables will be defined: “Day 1,” “Day 2,” “Day 3,” “Day 4,” “Day 5,” “Day 6,” “Day 7,” and “Day 1-Day 7.”

“Day 1-Day 7” is the variable for participants who completed e-diaries on all 7 days.

For e-diaries that are incomplete, an indicator variable for the percentage of days without data will be derived as follows:

= 1, if data have been transmitted and are complete for 7 days (100%)

= 2, if data have been transmitted and are complete for 6 days (≥75% to <100%)

= 3, if data have been transmitted and are complete for 4 or 5 days (≥50% to <75%)

= 4, if data have been transmitted and are complete for 2 or 3 days (≥25% to <50%)

= 5, if data have been transmitted and are complete for 0 or 1 day (<25%)

3.5.3. Prior/Concomitant Vaccines and Concomitant Medications

The following concomitant medications and vaccinations will be recorded in the CRF:

- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 203).
- Last dose of licensed influenza vaccine, if received.

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- Prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine).
- Prohibited medications listed in Section 10.12.6.9.1 of the protocol, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

Nonstudy vaccines and concomitant medications will be coded using the WHODD.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per standard operating procedures.

Population	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
CCI	[redacted]
Safety	All participants who receive the study intervention.

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Important protocol deviations will be determined by clinical review. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication/treatment that might affect immune response or a medication error with a suspected decrease in potency of the vaccine. The sponsor's clinician will identify those participants with protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

The APE field will be included in the PIPD list from the CORD system and is used to help identify protocol deviations that may exclude participants from a particular population. For each reporting event, the most current endorsed version of the PIPD list must be used to generate the protocol deviation data set for analysis and reporting.

The APE flags for this study are as follows:

- YES-POP1 (participants excluded from the safety population)
- YES-POP2 (participants excluded from the evaluable immunogenicity population)
- YES-POP3 (participants identified as multiple enrollers)

Participants enrolling at multiple sites (multiple enroller): Any participant enrolling at more than 1 site in the study will be removed from the evaluable immunogenicity, mITT immunogenicity, and safety populations. These participants will be followed for safety and reported separately from the other participants.

Vaccinated but not randomized: These participants will be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received but will be excluded from the evaluable immunogenicity analyses or mITT immunogenicity analyses.

Randomized but not vaccinated: These participants will be included in the randomized population and excluded from any safety analyses and evaluable immunogenicity or mITT immunogenicity analyses.

Randomized but received incorrect vaccine: These participants will be included in the mITT populations for immunogenicity analyses if data are available and will be reported under the vaccine group based on the randomized vaccine. These participants will also be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The study is descriptive in nature, no formal statistical hypothesis testing will be performed. No decision rules will be applied.

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5.2. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Completely missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

For the immunogenicity endpoints, the main analysis will be based on the evaluable immunogenicity population. Antibody titers below the LLOQ, denoted as BLQ, will be set to 0.5 × LLOQ for GMT analysis. No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody titers that are below the LLOQ.

An additional analysis may be performed based on the mITT immunogenicity populations if there is a large enough difference (>10%) in sample size between the mITT immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

No formal multiplicity adjustments will be applied for the analyses in multiple endpoints or for multiple looks of the same endpoint due to the descriptive nature of this substudy.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics for binary variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson)[1] and implemented in SAS PROC FREQ.

5.2.2. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

5.2.2.1. Geometric Mean Titers

The GMTs will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI based on the Student t distribution, and then exponentiating the confidence limits.

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5.2.2.2. Geometric Mean Fold Rises

GMFRs are defined as the geometric mean of the fold rise in the assay results from before to a specified time point after vaccination. GMFRs are limited to participants with nonmissing values at both time points.

GMFRs will be calculated as the mean difference of logarithmically transformed assay results (later time point minus earlier time point) and exponentiating the mean difference. The associated 2-sided 95% CIs will be obtained by constructing CIs using the Student t distribution for the mean difference on the logarithm scale and exponentiating the confidence limits.

5.2.2.3. Geometric Mean Ratios

The GMR will be calculated as the mean of the difference of logarithmically transformed assay results and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using the Student t distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.

5.2.2.4. Reverse Cumulative Distribution Curves

Empirical RCDCs will plot proportions of participants with values equal to or exceeding a specified assay value versus the indicated assay value, for all observed assay values. Data points will be joined by a step function with the line first going down and then to the right to the next assay value.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms for handling missing AE dates, AE severity, laboratory test values, and ECG values will be applied according to the Pfizer safety rules. Missing data handling rules for safety data are described in detail in the corresponding endpoint sections.

5.3.1.1. Reactogenicity Data

Completely missing reactogenicity e-diary data (no data from both the 7-day e-diary and the Participant Reported Reactogenicity CRF page) will not be imputed. For derived variables based on reactogenicity data, if any day of the 7-day e-diary data are available, the “any day (Day 1 through Day 7)” data will be considered nonmissing.

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are nonmissing. For the “I do not recall” data in the e-diary, it will be imputed as “no” as described in Table 3 and Table 4 in Section 3.1.1. No missing reactogenicity data will be imputed other than what is described in Section 3.1.1 and Section 3.1.2.

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In summary, for any participant with all 7 days of the e-diary missing (no data from both the 7-day e-diary collection period and the Participant Reported Reactogenicity CRF page), this will not be included in the analysis (ie, assuming MCAR). If only 1 to 6 days of reactogenicity data are available, the reactogenicity data for the missing day(s) are considered as answering "no" for all reactions. This is based on the common assumption that no reports mean no events. See Table 3 and Table 4 for the derivation algorithms.

5.3.2. Immunogenicity Data

Any assay results above the LLOQ are considered accurate, and their quantitated values will be reported. Antibody titers below the LLOQ, denoted as BLQ, or below the LOD will be set to 0.5 × LLOQ for GMT analysis. No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

When calculating a fold rise, the assay results will be converted to 0.5 × LLOQ if assay results are < LLOQ, except when the prevaccination assay result is < LLOQ while the postvaccination result is ≥ LLOQ, in which case the prevaccination value will be set to LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.

If there are multiple batch assay results at baseline, the GMT will be calculated from the mean of the baseline assay results. GMFR and seroconversion will be calculated using paired baseline and postbaseline assay results from the same batch of assay data. If there is more than 1 assay value at baseline due to multiple assay result batches, the titer criterion ≥1:40 will be met if any of the assay values are ≥1:40.

Values for sera that are insufficient (QNS), IND results, or values recorded as "not done" will be set to "missing." Additionally, any time point with no blood draws will not be included in the analysis. No imputation will be done for these missing values, as MCAR is assumed for immunogenicity data.

LLOQ results for each assay used in this study will be included in the analysis specification once they are available.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Local Reactions and Systemic Events

6.1.1.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CI of the proportion of participants reporting each event, using the Clopper-Pearson method (Section 5.2.1).

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- Analysis timing: Day 1 through Day 7 after vaccination.

- Intercurrent events and missing data: All data collected after the intercurrent events will be included (Section 2.2.1). The participants without any e-diary data or reactogenicity event data on the Participant Reported Reactogenicity CRF page throughout the 7 days after vaccination will be excluded from the analysis; intermediate missing values will not be imputed. Partially missing e-diary data are imputed as "no" (Section 3.1.1, Section 3.1.2, and Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.

Reporting results:

- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for the percentage using the Clopper-Pearson method, will be presented for each study intervention group. The denominator will be the number of participants reporting at least 1 "yes" or "no" response for the local reaction after vaccination.

- Bar charts with the proportions of participants for each and any local reaction and each and any systemic event through the 7 days following vaccination will be plotted for each study intervention group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Sensitivity/Supplementary Analyses

A sensitivity analysis will be conducted for the above summary of reactogenicity events by maximum severity. A variable to indicate the time period from the planned e-diary day (11:59 PM on that calendar day) to the actual time of e-diary reporting will be derived based on FARFTDTC (reference time point, ie, the time of vaccination), FADTC (data collection time), and FATPT (time point of intended solicitation day) in the dataset. The period will be categorized in relation to the planned e-diary day, ie, within the planned day, 1 day out (1-24 hours), 2 days out (>24-48 hours), or 3 days out (>48-72 hours) from the planned e-diary day. The sensitivity analysis will exclude the participants with e-diary reports collected outside the intended solicitation (calendar) day or with data collected from the Participant Reported Reactogenicity CRF page.

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.1 and Section 3.1.2, will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction and each systemic event after vaccination.

- Onset day of each local reaction and each systemic event after vaccination.

- Presence of each and any severe local reaction and each and any severe systemic event on each of the 7 days and for "any day (Day 1 through Day 7)."

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The presentation of the results will include a basic descriptive summary without 95% CIs (Section 5.2).

These continuous endpoints will be summarized by displaying the n, mean, median, standard deviation, minimum, and maximum for each study intervention group.

In addition, the proportions of participants reporting prompted local reactions, by maximum severity level, with any e-diary errors will be included as a supplemental summary.

6.1.2. AEs, SAEs, MAEs, and NDCMCs

6.1.2.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CI of the proportion of participants reporting such events, using the Clopper-Pearson method (Section 5.2.1).
- Analysis timing: Day 1 through 4 weeks after vaccination for AEs; Day 1 through 6 months after vaccination for SAEs, MAEs, and NDCMCs.
- Intercurrent events and missing data: All data collected are included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

Reporting results:

- The number of participants with AEs through 4 weeks after vaccination (n), the proportion (%), and the associated 2-sided Clopper-Pearson 95% CIs will be presented for each study intervention group.
- The number of participants with SAEs, MAEs, and NDCMCs through 6 months after vaccination (n), the proportion (%), and the associated 2-sided Clopper-Pearson 95% CIs will be presented for each study intervention group.
- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator used in the proportion calculation, and the 95% CIs for the percentage using the Clopper-Pearson method, will be presented for each SOC and each PT within each SOC for each study intervention group.

6.1.2.2. Sensitivity/Supplementary Analyses

To support the assessment of AEs, the endpoints below as specified in Section 3.1.3 will be summarized with the same analysis population using the same presentation as specified in the main analysis:

- Immediate AEs

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- Related AEs
- Severe AEs
- Life-threatening AEs
- AEs leading to study discontinuation/withdrawal
- AEs leading to death
- AESIs

All AEs/SAEs occurring after informed consent and prior to vaccination will not be included in the analyses but will be listed.

In addition, any AEs occurring up to 48 hours after blood draws will be listed.

6.2. Secondary Endpoint(s)

6.2.1. HAI Titers for the 2023-2024 Northern Hemisphere Seasonal Strains Recommended by WHO for [redacted] Influenza Vaccines

6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical approach (Section 2.2.2).
- Analysis set: Evaluable immunogenicity population (HAI [redacted]) (Section 4).
- Analysis methodology: Descriptive summary statistics (Section 5.2.1 and Section 5.2.2).
- Analysis timing: Day 1 prior to study intervention administration (HAI GMTs, HAI titers ≥1:40) and at 4 weeks after vaccination.
- Intercurrent events and missing data: All data collected after or at intercurrent events will be excluded (Section 2.2.2). Antibody titers below the LLOQ, denoted as BLQ, or below the LOD will be set to 0.5 × LLOQ for analysis (Section 5.3.2). Missing data will not be imputed. Immunogenicity data that are confirmed as not valid will not be used for analysis.

  Reporting results:

- Descriptive statistics, including the sample size (n), HAI GMTs, HAI GMFRs, and 95% CIs for the HAI GMTs and HAI GMFRs, will be presented for each strain and each study intervention group (Section 5.2.2).

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- Descriptive statistics, ie, HAI GMRs of each tIRV (tIRV2 and tIRV3) group compared with each control group (QIV2, QIV3, and qIRV2) at 4 weeks after vaccination, and the 95% CIs for the HAI GMRs, will be presented for each strain (Section 5.2.2).

- The proportion of participants achieving HAI seroconversion for each strain at 4 weeks after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided by study intervention group.

- The proportion of participants with HAI titers ≥1:40 for each strain before vaccination and at 4 weeks after vaccination, and the associated 2-sided Clopper-Pearson 95% CIs, will be provided by study intervention group.

- Empirical RCDCs will be plotted by study intervention group.

- HAI GMTs for each strain, and the associated 95% CIs, will be plotted by study intervention group.

- HAI seroconversion rate for each strain, along with the associated 95% CIs, may be plotted by study intervention group.

6.2.1.2. Sensitivity/Supplementary Analysis

To support the assessment of immunogenicity, estimands as specified in Section 2.2.2 using the treatment policy strategy might be summarized with the mITT immunogenicity population (HAI[CCI]) using the same presentation as specified in the main analysis.

6.3. Other Safety Summaries and Analyses Endpoint(s)

6.3.1. Data Collected on the Summary of Reactogenicity CRF Page

Data collected about reactogenicity events on the Summary of Reactogenicity CRF page will be summarized or listed.

The main reasons for noncompletion of the 7-day reactogenicity event reporting (including e-diary entries and the data on the Participant Reported Reactogenicity CRF page) will be listed.

Immediate reactogenicity events may be summarized by study intervention group. The medically attended reactogenicity events will be listed.

6.3.2. Medical History

Each reported medical history term will be mapped to an SOC and PT according to MedDRA. The number and percentage of participants with an assigned vaccine having at least 1 diagnosis of medical history, overall and at each SOC and PT level, will be summarized by study intervention group and for all participants in total based on the safety population.

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6.3.3. Electrocardiograms

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after a study vaccination (ECG, troponin I level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by vaccine group.

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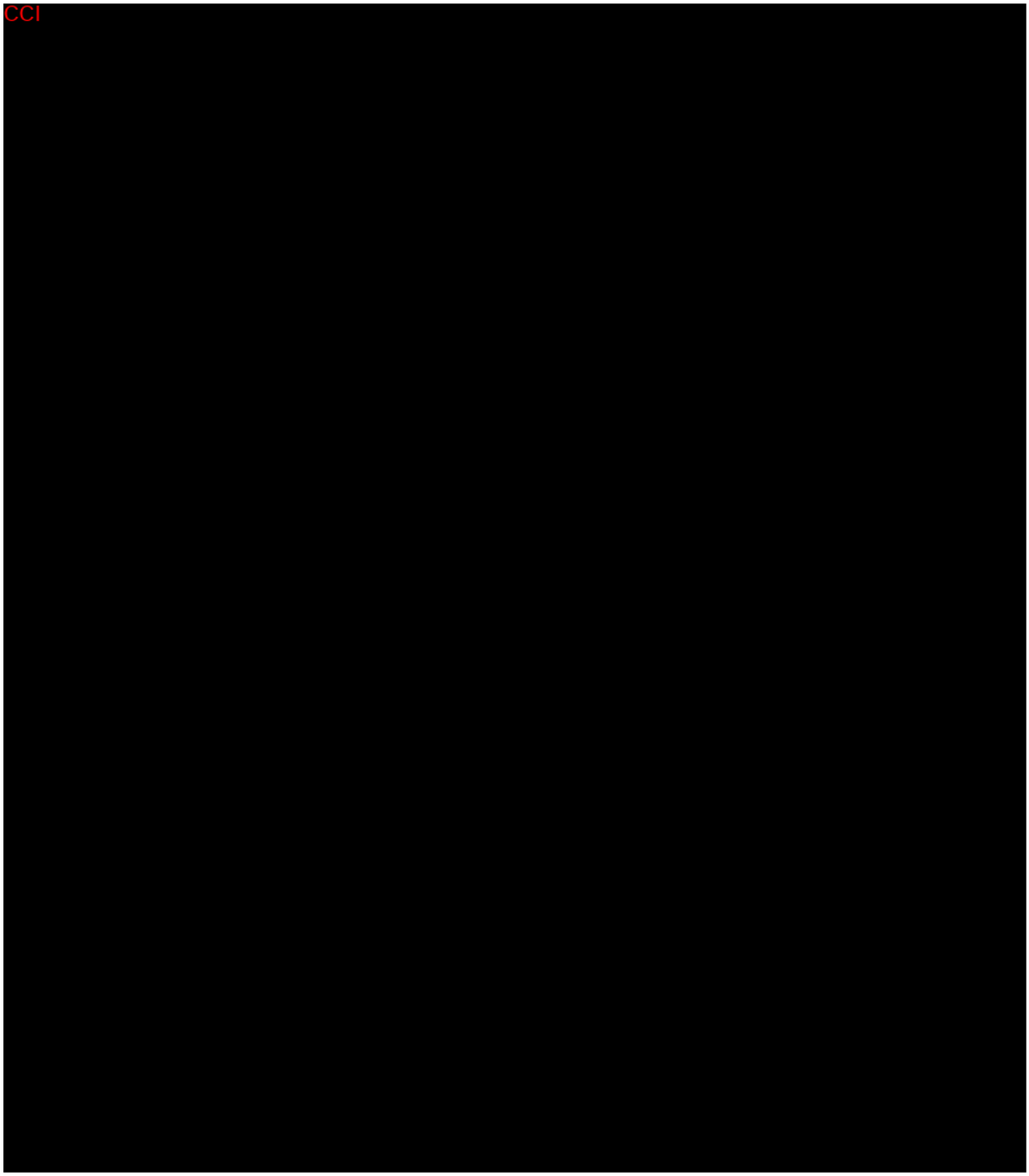

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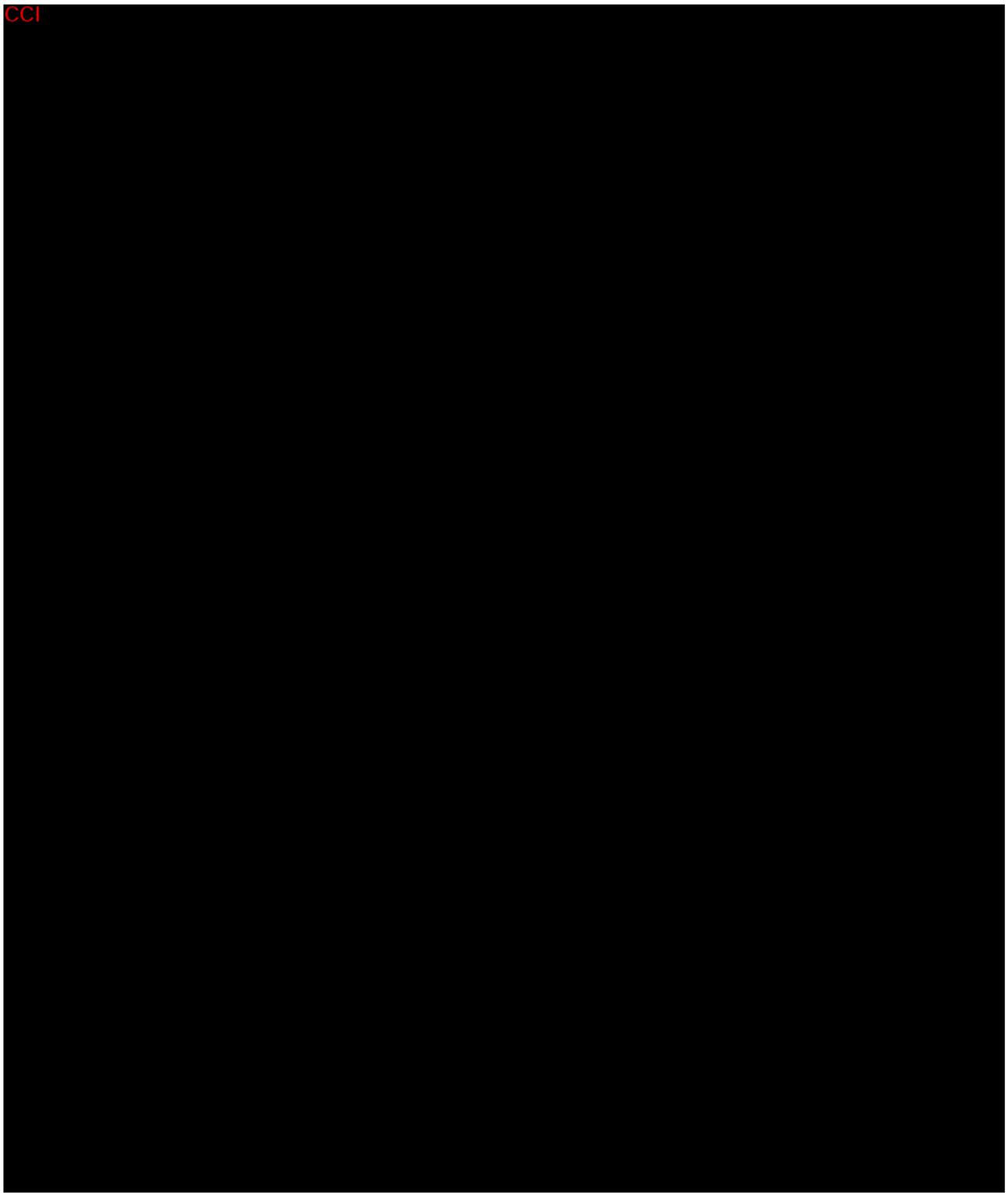

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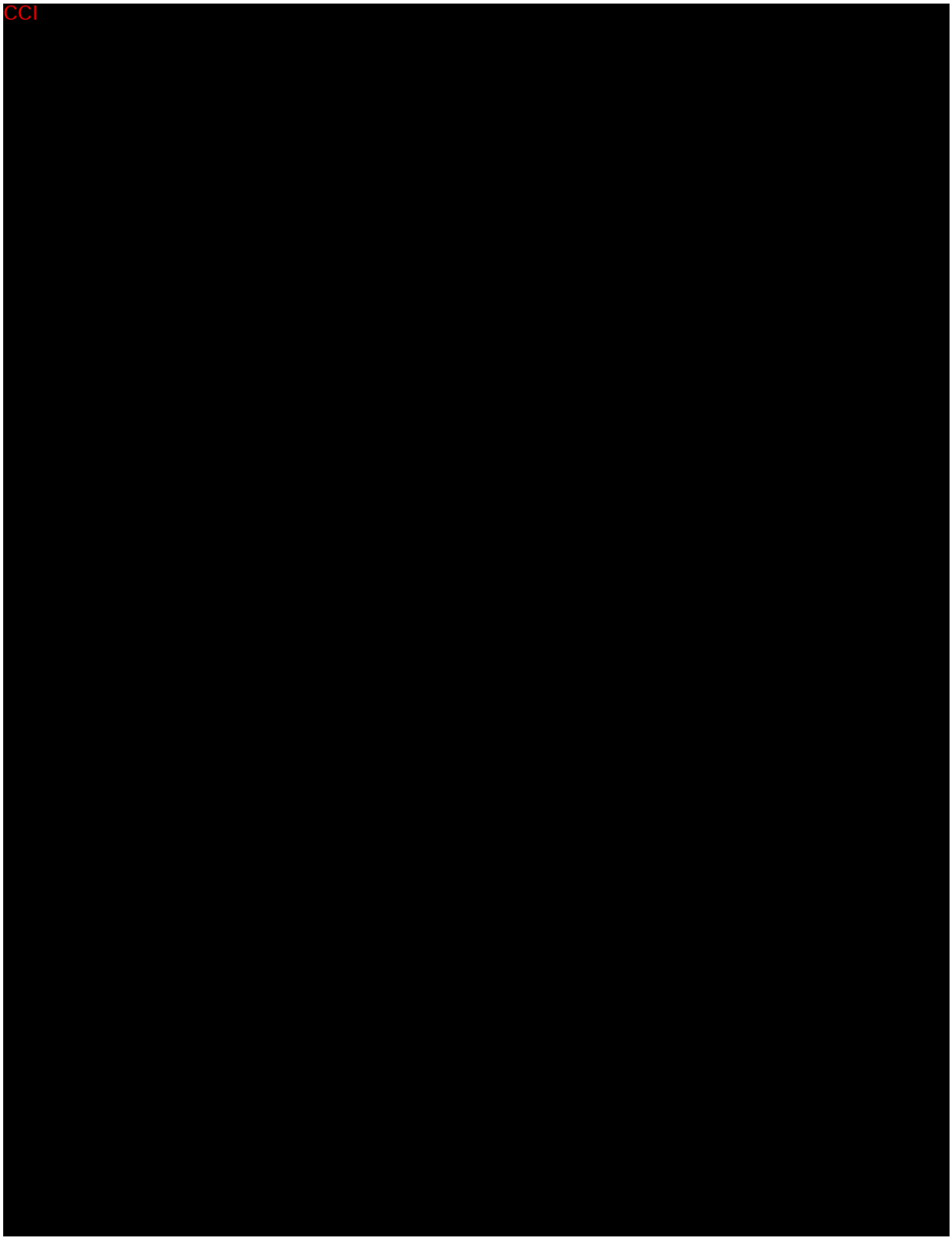

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6.5. Subset Analyses

Not applicable.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, and ethnicity) will be generated by study intervention group and for all participants in total based on the safety population.

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Participant Disposition

All participants in the randomized population will be included in the disposition summaries. Summaries will be displayed by vaccine group separately.

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the number and percentage of participants who received vaccinations, completed the follow-up visits, and withdrew before the follow-up visit, along with the reasons for withdrawal, will be tabulated by study intervention group and the total sample. The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately by study intervention group, along with the reasons for exclusion by study intervention group.

A listing of protocol deviations may also be provided.

6.6.2.2. Blood Samples for Assay

For each blood sampling time point, the number and percentage of randomized participants providing blood samples within the protocol-specified time frame, as well as before and after the protocol-specified time frame, will be tabulated separately by study intervention group.

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6.6.2.3. E-Diaries

The participants who were vaccinated and who transmitted and completed e-diaries will be summarized according to the vaccine actually received. Besides the analysis described in Section 6.1.1, the summary will also include the number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary, and completing the e-diary for any day (based on the e-diary completion category as defined in Section 3.5.2) in the required reporting period after vaccination by assigned study intervention.

The number and percentage of participants transmitting and completing the e-diary for each day in the required reporting period, and overall, will be tabulated for each study intervention group.

The safety population will be used.

6.6.3. Study Intervention Exposure

6.6.3.1. Vaccination Administration

The relation of the randomized study intervention to the actual study intervention received will be presented as a cross-tabulation of the actual study intervention received versus the randomized study intervention.

A listing of participants showing the randomized study intervention and the study intervention actually received will be presented.

6.6.4. Concomitant Medications and Nondrug Treatments

Each prior/concomitant vaccine will be summarized according to the Anatomic Therapeutic Chemical fourth-level classification/WHODD, as appropriate. The prior/concomitant vaccines and medications as described in Section 3.5.3 will be listed. The number and percentage of participants receiving each prior (before vaccination) and concomitant vaccine (on or after vaccination) will be tabulated according to the assigned study intervention. The safety population will be used. Concomitant medications will be summarized similarly to concomitant vaccines.

7. INTERIM ANALYSES

7.1. Introduction

As the study is sponsor-unblinded, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, dose selection, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

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8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

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Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
APE	analysis population exclusion
BLQ	below the limit of quantitation
CI	confidence interval
CORD	Clinical Oversight Review Dashboard
COVID-19	coronavirus disease 2019
CRF	case report form
ECG	electrocardiogram
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
ICD	informed consent document
IND	indeterminate
IPM	investigational product manual
IRT	interactive response technology
IV	intravenous(ly)
LLOQ	lower limit of quantitation
LOD	limit of detection
MAE	medically attended adverse event
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mIRV	monovalent influenza modRNA vaccine
mITT	modified intent-to-treat
CCI	[redacted]
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
PIPD	potential important protocol deviation
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event

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Abbreviation	Term
SAP	statistical analysis plan
SOC	system organ class
tIRV	trivalent influenza modRNA vaccine
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

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Document Approval Record

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Document Title:	A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MODIFIED RNA VACCINES AGAINST INFLUENZA IN HEALTHY ADULTS

Signed By:	Date(GMT)	Signing Capacity
PPD	13-Jun-2024 14:09:54	Business Line Approver

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Protocol C4781013 – Substudy C

A STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MODIFIED RNA VACCINES AGAINST INFLUENZA IN HEALTHY ADULTS

Statistical Analysis Plan (SAP)

Version: 2

Date: 12 Jun 2024

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APPENDICES

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 18 Apr 2024	Original 12 Mar 2024	N/A	N/A
2 12 Jun 2024	1 26 Apr 2024	• To update the monitoring and collection period for myocarditis and pericarditis per protocol amendment 1. • To update the analysis population CCI [redacted] for consistency with the protocol. • To make updates and clarifications on the reactogenicity events collected in the e-diary and CRF per regulatory comments. • To add a sensitivity analysis for the summary of reactogenicity events by maximum severity per regulatory comments. • To delete the analysis for CCI [redacted]	• Section 3.1.3, Section 3.3.2, and Section 6.3.3: Updated the monitoring and collection period for myocarditis and pericarditis from "14 days after vaccination" to "28 days after vaccination." • Section 2.2, Section 2.2.2, Section 4, Section 5.2, Section 6.4.3.1, Section 6.4.4.1, and Section 6.4.5.1: Updated the analysis population CCI [redacted] for consistency with the protocol. • Section 2.3, Section 3.1.1, Section 3.1.2, Section 3.5.2, Section 5.3.1.1, Section 6.1.1.1, and Section 6.3.1: Clarified the reactogenicity data collected in the e-diary and CRF and the analysis of reactogenicity events. • Section 6.1.1.2: Added a sensitivity analysis for the summary of reactogenicity events by maximum severity. • Section 6.4.2: Deleted the analysis for CCI [redacted]

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4781013 – Substudy C. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

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2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
Primary safety	To define the safety and tolerability profile of tIRVs and qIRV in participants ≥65 years of age	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs • MAEs • NDCMCs	In participants receiving study intervention (safety population), the percentage of participants reporting: • Local reactions for up to 7 days following vaccination • Systemic events for up to 7 days following vaccination • AEs through 4 weeks after vaccination • MAEs through 6 months after vaccination • NDCMCs through 6 months after vaccination • SAEs through 6 months after vaccination
CCI			

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Type	Objective	Endpoint	Estimand
CCI			

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Type	Objective	Endpoint	Estimand
CCI			

2.2.1. Primary Estimand(s)

The primary estimands for the primary objective (safety) will use the treatment policy strategy and estimate the safety event rate (reactogenicity, AEs/SAEs/MAEs/NDCMCs) regardless of whether an intercurrent event occurs.

- The reactogenicity estimands (local reactions and systemic events) have the following 5 attributes:
  - **Treatment condition:** Vaccination with 6 different formulations of tIRV (tIRV3 through tIRV8), QIV2 (CCI), QIV3 (CCI, and qIRV3 as defined in Section 2.3.
  - **Population:** Participants ≥65 years of age who receive the study intervention.
  - **Variables:** Local reactions and systemic events from the e-diary up to 7 days following vaccination.

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- **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, use of rescue medication, missing e-diary entries on certain days, study discontinuation), if collected, will be included.
- **Population-level summary:** The rates of reporting each prompted reactogenicity item, and the associated 2-sided 95% CIs, by study intervention group (in the tIRV3 through tIRV8, QIV2, QIV3, and qIRV3 vaccine groups, separately).

- The AE, SAE, MAE, and NDCMC estimands have the following 5 attributes:
  - **Treatment condition:** Vaccination with 6 different formulations of tIRV (tIRV3 through tIRV8), QIV2 (CCI), QIV3 (CCI , and qIRV3 as defined in Section 2.3.
  - **Population:** Participants ≥65 years of age who receive the study intervention.
  - **Variables:**
    - AEs reported through 4 weeks after vaccination.
    - SAEs reported through 6 months after vaccination.
    - MAEs reported through 6 months after vaccination.
    - NDCMCs reported through 6 months after vaccination.
  - **Intercurrent events:** All data after an intercurrent event (receiving prohibited vaccine or concomitant therapy, receiving the vaccine not as randomized, use of rescue medication, study discontinuation), if collected, will be included.
  - **Population-level summary:** The rates of AEs, SAEs, MAEs, and NDCMCs, and the associated 2-sided 95% CIs, by study intervention group (in the tIRV3 through tIRV8, QIV2, QIV3, and qIRV3 vaccine groups, separately).

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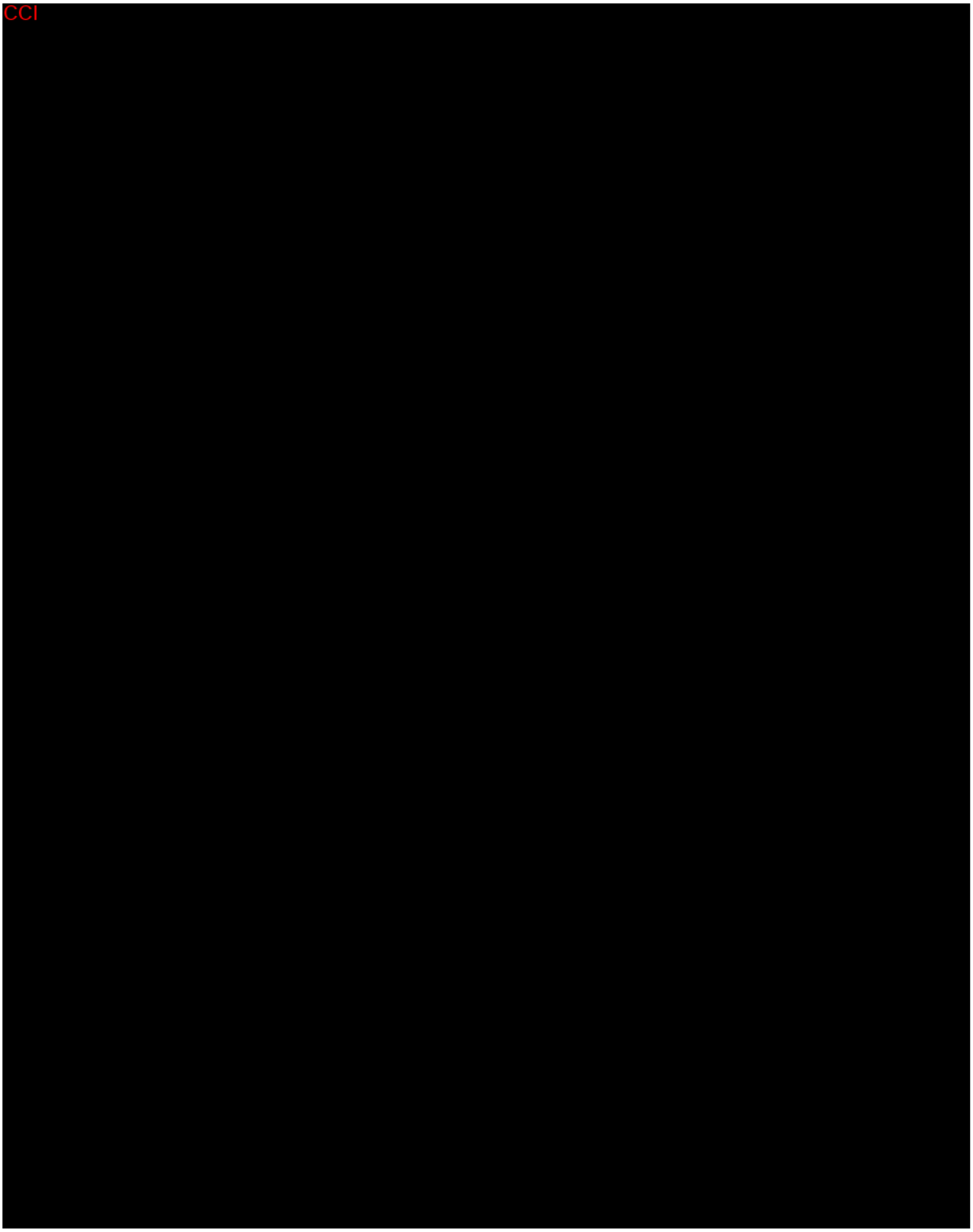

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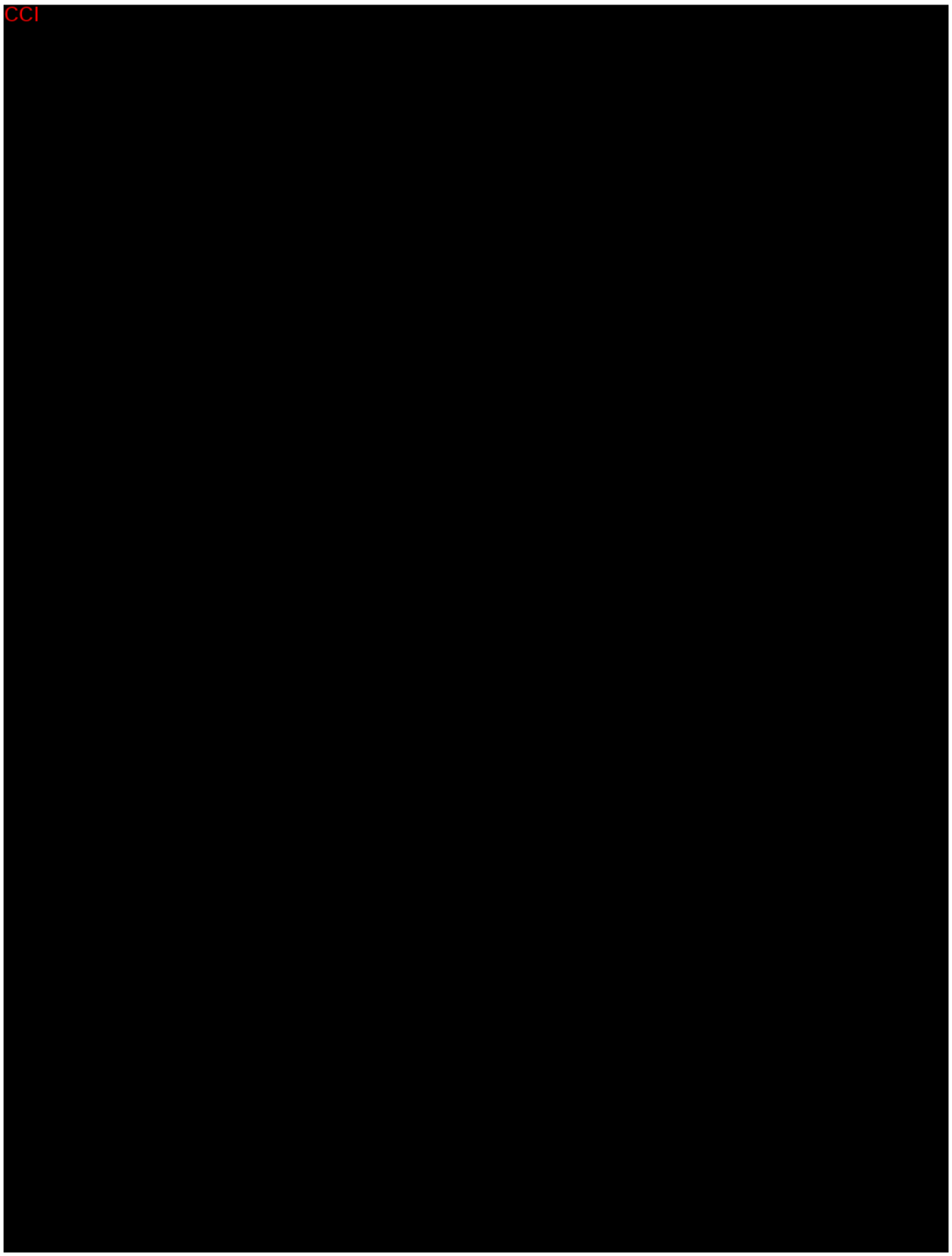

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2.3. Study Design

This is a Phase 1, randomized, observer-blinded (sponsor-unblinded) substudy to evaluate the safety, tolerability, CCI of various formulations of tIRV (encoding HA CCI for the targeted seasonal strains [tIRV3 through tIRV8]) and qIRV3 (CCI CCI compared to QIVs (CCI in healthy adults ≥65 years of age.

Up to approximately 270 participants ≥65 years of age will be enrolled and randomized to receive 1 dose of study intervention as shown in Table 2.

Blood samples of approximately 30 mL will be collected CCI prior to vaccination and at 4 weeks and 6 months after vaccination. Additional blood samples will be collected as summarized below:

- Approximately CCI mL of blood will be collected from participants (approximately 20 participants per group) who consent to this at the time points specified in the Schedule of Activities for Substudy C (Section 10.13.1 of the protocol) CCI [redacted]
- Approximately 2.5 mL of blood will be collected from all participants at screening for assessment of troponin I.

Local reaction and systemic event data will be collected in an e-diary during the 7-day follow-up period after vaccination. Participants are required to complete the e-diary every evening (06:00 PM to 11:59 PM) for the 7 days following vaccination (including the day of vaccination). If participants are unable to complete the e-diary as expected on a particular day, they are allowed to retrospectively complete the missed entry within up to 3 days following the date of the missed entry (extended 72-hour e-diary reporting window).

For participants with ongoing symptoms after Day 7, subsequent e-diary entries will be followed only to monitor the duration of symptoms until resolution. The end date for the prespecified local reaction and systemic event beyond Day 7 will also be recorded on the Summary of Reactogenicity CRF page.

All AEs will be collected from informed consent signing through 4 weeks following vaccination. A subset of AEs (NDCMCs, MAEs, and SAEs) will be collected from informed consent signing through 6 months after vaccination. In addition, AEs occurring up to 48 hours after blood draws will be collected.

Table 2. Number of Participants to Be Enrolled in Substudy C – Participants ≥65 Years of Age

Study Intervention	Preformulated	Influenza Strains	CCI [redacted]	Total modRNA Dose	Number of Participants
QIV2	Yes	2023-2024 northern hemisphere seasonal strains Recommended by WHO for CCI influenza vaccines		N/A	30
QIV3	Yes	2023-2024 northern hemisphere seasonal strains Recommended by WHO for CCI influenza vaccines		N/A	30

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Table 2. Number of Participants to Be Enrolled in Substudy C – Participants ≥65 Years of Age

Study Intervention	Preformulated	Influenza Strains	CCI	Total modRNA Dose	Number of Participants
tIRV3	No	A/H1N1		CCI	30
		A/H3N2			
		B/Victoria			
tIRV4	No	A/H1N1			30
		A/H3N2			
		B/Victoria			
qIRV3	No	CCI			30
tIRV5	No	A/H1N1			30
		A/H3N2			
		B/Victoria			
tIRV6	No	A/H1N1			30
		A/H3N2			
		B/Victoria			
tIRV7	No	A/H1N1			30
		A/H3N2			
		B/Victoria			
tIRV8	No	A/H1N1			30
		A/H3N2			
		B/Victoria			

a. CCI

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- Local reactions (pain at the injection site, redness and swelling) through 7 days following vaccination.
- Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) through 7 days following vaccination.
- AEs through 4 weeks after vaccination.

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- SAEs through 6 months after vaccination.
- MAEs through 6 months after vaccination.
- NDCMCs through 6 months after vaccination.

3.1.1. Local Reactions

The local reactions reported in the e-diary are pain at the injection site, redness, and swelling, from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination.

If a local reaction persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and the corresponding resolution date. The investigator will enter this resolution date on the Summary of Reactogenicity CRF page.

For missing records on the local reactions during the 7-day e-diary collection period, the data may be retrieved by the investigator via participant report and collected in the CRF. The local reactions collected on the Participant Reported Reactogenicity CRF page will be combined with the 7-day e-diary data and be included for the below analysis (presence, maximum severity, onset day, and duration). The main reason for missing e-diary entries (missing when all reactogenicity entries are considered, including any recalled e-diary entries and data entered on the Participant Reported Reactogenicity CRF page) will be collected by the investigator on the Summary of Reactogenicity CRF page.

This section describes derivations with details for the assessment of local reactions: any presence, maximum severity, duration, and onset day of local reactions, in addition to any presence of severe local reactions on each day.

Presence or Absence

For the data summary of the presence (yes or no) of a local reaction during the interval from Day 1 through Day 7 after vaccination, where Day 1 is the day of vaccination, the following variables are required in order to compute the proportions:

- Presence (yes or no) of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7).
- Presence (yes or no) of each local reaction by maximum severity on any day (Day 1 through Day 7).

For each local reaction and any local reaction on any day, Table 3 and Table 4 details the algorithm to derive the presence of a reaction (yes or no) during the interval from Day 1 through Day 7, where Day 1 is the day of vaccination.

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Table 3. Derived Variables for Presence of Each Local Reaction Within 7 Days After Vaccination

Variable[a]	Yes (1)	No (0)	Missing (.)[b]
Presence of each local reaction.	Participant reports the reaction as "yes" on any day (Day 1 through Day 7)	Participant reports the reaction as "no" or "I don't recall" on all 7 days (Day 1 through Day 7) or as a combination of "no," "I don't recall," and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data on all 7 days (Day 1 through Day 7) for the reaction.

a. The variables will be derived for each of the local reactions (redness, swelling, and pain at the injection site) and for each of the severe local reactions within the interval from Day 1 through Day 7 after vaccination.
b. "Missing" means missing from both the e-diary and the Participant Reported Reactogenicity CRF page.

Table 4. Derived Variables for Presence of Any Local Reaction Within 7 Days After Vaccination

Variable[a]	Yes (1)	No (0)	Missing (.)[b]
Presence of any local reaction.	Participant reports any local reaction as "yes" on any day (Day 1 through Day 7).	For all 3 local reactions, participant reports "no" or "I don't recall" on all 7 days (Day 1 through Day 7) or as a combination of "no," "I don't recall," and missing on all 7 days (Day 1 through Day 7).	Participant does not report any data for all 3 local reactions on all 7 days (Day 1 through Day 7).

a. The variables will be derived for any of the local reactions (redness, swelling, and pain at the injection site) and for any of the severe local reactions within the interval from Day 1 through Day 7 after vaccination.
b. "Missing" means missing from both the e-diary and the Participant Reported Reactogenicity CRF page.

Severity and Maximum Severity

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 5. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 5.

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Table 5. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

a. Only an investigator or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. A Grade 4 reaction that meets the definition of an SAE will be collected on the AE CRF.

For each local reaction reported, the maximum severity grade will be derived for the e-diary collection period (Day 1 through Day 7, where Day 1 is the day of vaccination) as follows:

> Maximum severity grade = highest grade (maximum severity) within 7 days after vaccination (Day 1 through Day 7) among severity grades where the answers are neither "no" nor missing for at least 1 day during the interval from Day 1 through Day 7.

Duration of Each Local Reaction (First to Last Day Reported)

For participants experiencing any local reaction (or those with a derived reaction as described in Table 3 and Table 4), the maximum duration (resolution date of reaction – start date of reaction + 1) will be derived for each study vaccination.

Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant e-diary recording period (end date collected in the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to "missing." Participants with no reported reactions have no duration.

Onset Day of Each Local Reaction

The onset day of each local reaction will be derived. Onset day is defined as the first day of reporting any severity.

For the onset day of each local reaction, only the first day of reporting that specific local reaction will be counted, even if participants report a change in severity pf the local reaction.

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In summary, the following variables will be derived for local reactions:

1. Presence or absence of each local reaction on each day (Day 1 through Day 7) after vaccination.

2. Presence or absence of each local reaction on any day (Day 1 through Day 7) after vaccination.

3. Presence or absence of each severe/Grade 4 local reaction on each day and any day (Day 1 through Day 7) after vaccination.

4. Maximum severity of each local reaction on any day (Day 1 through Day 7) after vaccination.

5. Presence or absence of any local reaction on any day (Day 1 through Day 7) after vaccination.

6. Duration of each local reaction after vaccination.

7. Onset day of each local reaction after vaccination.

8. Onset day of any local reaction after vaccination.

3.1.2. Systemic Events

The systemic events assessed and recorded in the e-diary are fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain from Day 1 through Day 7, where Day 1 is the day of vaccination.

If a systemic event persists beyond the end of the 7-day e-diary collection period following vaccination, the participant will be requested to report that information and the corresponding resolution date. The investigator will enter this resolution date on the Summary of Reactogenicity CRF page.

The systemic events collected on the Participant Reported Reactogenicity CRF page will be combined with the 7-day e-diary data and be included for the below analysis (presence, maximum severity, onset day, and duration).

The derivations for systemic events will be handled similarly to the way local reactions are handled for presence of the event, severity level, duration, and onset day.

The variables associated with the systemic events will be computed similarly to the way local reactions are computed (see Section 3.1.1).

1. Presence (yes or no) of each systemic event on each day (Day 1 through Day 7) after vaccination.

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2. Presence (yes or no) of each systemic event on any day (Day 1 through Day 7) after vaccination.

3. Presence or absence of each severe/Grade 4 systemic event on each day and any day (Day 1 through Day 7) after vaccination.

4. Maximum severity of each systemic event on any day (Day 1 through Day 7) after vaccination.

5. Presence or absence of any systemic event on any day (Day 1-7) after vaccination.

6. Duration of each systemic event after vaccination.

7. Onset day of each systemic event after vaccination.

8. Onset day of any systemic event after vaccination.

The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 6.

Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain

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Table 6. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4[a])
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

a. Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. A Grade 4 event that meets the definition of an SAE will be collected on the AE CRF.

To record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary each evening during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection period, or longer following vaccination, when fever is suspected.

Fever is defined as an oral temperature ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place. Temperatures recorded in degrees Fahrenheit will be programmatically converted to degrees Celsius and then categorized according to the scale shown in Table 7 during analysis.

Table 7. Scale for Fever

≥38.0-38.4°C (100.4-101.1°F)
>38.4-38.9°C (101.2-102.0°F)
>38.9-40.0°C (102.1-104.0°F)
>40.0°C (>104.0°F)

3.1.3. Adverse Events

The time period for actively eliciting and collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 303 in Substudy C (approximately 4 weeks after vaccination).

Additionally, MAEs, NDCMCs, and SAEs will be collected from the time the participant provides informed consent to Visit 304 in Substudy C (approximately 6 months after vaccination). In addition, AEs occurring up to 48 hours after blood draws must be recorded on the CRF.

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Standard algorithms for handling missing AE dates and missing AE severity will be applied as described in the Pfizer data standard rules.

The following derivations will be included for each participant:

- Any AE reported.
- Any related AE reported.
- Any immediate AE (assess acute reactions for at least 30 minutes after study intervention administration).
- Any SAE.
- Any MAE (an MAE is defined as a nonserious AE that results in an evaluation at a medical facility).
- Any NDCMC (an NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects [eg, asthma])
- Any severe AE.
- Any life-threatening AE.
- Any AE leading to study withdrawal.
- Any AE leading to death.
- Any AESI.
    - Confirmed diagnosis of influenza (clinical signs/symptoms and positive laboratory testing) after Day 1 through 6 months after vaccination.
    - Confirmed diagnosis of myocarditis or pericarditis occurring within 28 days after vaccination.

3.2. Secondary Endpoint(s)

Not applicable.

3.3. Other Safety Endpoint(s)

3.3.1. Physical Examinations, Vital Signs, and Medical History

A physical examination will be performed at screening in Substudy C. Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are

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identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

In Substudy C, the participant's body temperature will be measured at screening and prior to vaccination at Visit 301. Additionally, weight and height (at screening), pulse rate, and seated BP will be measured prior to the participants' first vaccination in Substudy C.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded in the CRF.

Medical history will be categorized according to MedDRA.

3.3.2. Laboratory Troponin I and ECG

Laboratory troponin I levels and ECGs will be collected at screening in Substudy C.

And for participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after a study vaccination, ECG and troponin I testing will be performed via central laboratory. If myocarditis or pericarditis is suspected based upon the initial evaluation, cardiac echocardiogram, and/or cardiac magnetic resonance study will also be performed.

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3.5. Baseline Variables

Measurements or samples collected prior to vaccination are considered the baseline data for the assessments. In this study, Day 1 is the baseline visit; the data from screening visit may be used as baseline only if the data on Day 1 are missing.

3.5.1. Demographics

The demographic variables are age at the first vaccination (in years), sex (male or female), race (Black/African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, not reported), and ethnicity (Hispanic/Latino/of Spanish origin, non-Hispanic/non-Latino/non-of Spanish origin, not reported), and racial designation (Japanese, other). In cases where more than 1 category is selected for race, the participant would be counted under the category "multiracial" for analysis.

3.5.2. E-Diary Completion

An e-diary will be considered transmitted if any data for the 3 local reactions (redness, swelling, and pain at the injection site) and 8 systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain) are present on any day. If all data are missing for all items on the e-diary for all 7 days after vaccination, then the e-diary will be considered not transmitted.

An e-diary will be considered completed if all expected data for all 7 days are available (ie, not missing). Otherwise, the e-diary will be considered incomplete. For any given day, an e-diary will be considered complete if all expected data are available.

Note: Data entered as part of the 72-hour recall period will be counted for the e-diary completion/transmission.

The data from the Participant Reported Reactogenicity CRF page will not be included in the e-diary completion/transmission summary.

For transmitted e-diaries, the following variables will be defined: "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," "and "Day 7."

For completed e-diaries, the following variables will be defined: "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," "Day 7," and "Day 1-Day 7."

"Day 1-Day 7" is the variable for participants who completed e-diaries on all 7 days.

For e-diaries that are incomplete, an indicator variable for the percentage of days without data will be derived as follows:

= 1, if data have been transmitted and are complete for 7 days (100%)

= 2, if data have been transmitted and are complete for 6 days (≥75% to <100%)

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= 3, if data have been transmitted and are complete for 4 or 5 days (≥50% to <75%)

= 4, if data have been transmitted and are complete for 2 or 3 days (≥25% to <50%)

= 5, if data have been transmitted and are complete for 0 or 1 day (<25%)

3.5.3. Prior/Concomitant Vaccines and Concomitant Medications

The following concomitant medications and vaccinations will be recorded in the CRF:

- Any vaccinations received from 28 days prior to study enrollment until the last visit (Visit 304).
- Last dose of licensed influenza vaccine.
- Prior receipt of any mRNA vaccine (eg, mRNA-based COVID-19 vaccine).
- Prohibited medications listed in Section 10.13.6.9.1 of the protocol, if taken, will be recorded and include start and stop dates, name of the medication, dose, unit, route, and frequency.

Nonstudy vaccines and concomitant medications will be coded using the WHODD.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per standard operating procedures.

Population	Description
Screened	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IRT system.
CCI	[redacted]

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Population	Description
CCI [redacted]	
Safety	All participants who receive the study intervention.

Important protocol deviations will be determined by clinical review. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's clinician, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication/treatment that might affect immune response or a medication error with a suspected decrease in potency of the vaccine. The sponsor's clinician will identify

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those participants with protocol deviations that result in exclusion from analysis populations before any unblinded analysis is carried out.

The APE field will be included in the PIPD list from the CORD system and is used to help identify protocol deviations that may exclude participants from a particular population. For each reporting event, the most current endorsed version of the PIPD list must be used to generate the protocol deviation data set for analysis and reporting.

The APE flags for this study are as follows:

- YES-POP1 (participants excluded from the safety population)
- YES-POP2 (participants excluded from the evaluable immunogenicity population)
- YES-POP3 (participants identified as multiple enrollers)

Participants enrolling at multiple sites (multiple enroller): Any participant enrolling at more than 1 site in the study will be removed from the evaluable, mITT, and safety populations. These participants will be followed for safety and reported separately from the other participants.

Vaccinated but not randomized: These participants will be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received but will be excluded from the evaluable immunogenicity analyses or mITT immunogenicity analyses.

Randomized but not vaccinated: These participants will be included in the randomized population and excluded from any safety analyses and evaluable immunogenicity or mITT immunogenicity analyses.

Randomized but received incorrect vaccine: These participants will be included in the mITT populations for immunogenicity analyses if data are available and will be reported under the vaccine group based on the randomized vaccine. These participants will also be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The study is descriptive in nature, no formal statistical hypothesis testing will be performed. No decision rules will be applied.

5.2. General Methods

CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level unless specified otherwise.

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The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the study interventions they actually received. Completely missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.

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[redacted]

No formal multiplicity adjustments will be applied for the analyses in multiple endpoints or for multiple looks of the same endpoint due to the descriptive nature of this substudy.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics for binary variables (eg, proportions) are the percentage (%), the numerator (n) and the denominator (N) used in the percentage calculation, and the 95% CIs where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson)[1] and implemented in SAS PROC FREQ.

5.2.2. Analyses for Continuous Endpoints

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

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5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms for handling missing AE dates, AE severity, laboratory test values, and ECG values will be applied according to the Pfizer safety rules. Missing data handling rules for safety data are described in detail in the corresponding endpoint sections.

5.3.1.1. Reactogenicity Data

Completely missing reactogenicity e-diary data (no data from both the 7-day e-diary and the Participant Reported Reactogenicity CRF page) will not be imputed. For derived variables based on reactogenicity data, if any day of the 7-day e-diary data are available, the "any day (Day 1 through Day 7)" data will be considered nonmissing.

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are nonmissing. For the "I do not recall" data in the e-diary, it will be imputed as "no" as described in Table 3

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and Table 4 in Section 3.1.1. No missing reactogenicity data will be imputed other than what is described in Section 3.1.1 and Section 3.1.2.

In summary, for any participant with all 7 days of the e-diary missing (no data from both the 7-day e-diary collection period and the Participant Reported Reactogenicity CRF page), this will not be included in the analysis (ie, assuming MCAR). If only 1 to 6 days of reactogenicity data are available, the reactogenicity data for the missing day(s) are considered as answering "no" for all reactions. This is based on the common assumption that no reports mean no events. See Table 3 and Table 4 for the derivation algorithms.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Local Reactions and Systemic Events

6.1.1.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).

- Analysis methodology: 95% CI of the proportion of participants reporting each event, using the Clopper-Pearson method (Section 5.2.1).

- Analysis timing: Day 1 through Day 7 after vaccination.

- Intercurrent events and missing data: All data collected after the intercurrent events will be included (Section 2.2.1). The participants without any e-diary data or reactogenicity event data on the Participant Reported Reactogenicity CRF page throughout the 7 days after vaccination will be excluded from the analysis; intermediate missing values will not be imputed. Partially missing e-diary data are imputed as "no" (Section 3.1.1, Section 3.1.2, and Section 5.3.1.1); e-diary data that are confirmed as errors will not be used for analysis.

  Reporting results:

- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for the percentage using the Clopper-Pearson method, will be presented for each study intervention group. The denominator will be the number of participants reporting at least 1 "yes" or "no" response for the local reaction after vaccination.

- Bar charts with the proportions of participants for each and any local reaction and each and any systemic event through the 7 days following vaccination will be plotted for each study intervention group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.1.2. Sensitivity/Supplementary Analyses

A sensitivity analysis will be conducted for the above summary of reactogenicity events by maximum severity. A variable to indicate the time period from the planned e-diary day (11:59 PM on that calendar day) to the actual time of e-diary reporting will be derived based on FARFTDTC (reference time point, ie, the time of vaccination), FADTC (data collection time), and FATPT (time point of intended solicitation day) in the dataset. The period will be categorized in relation to the planned e-diary day, ie, within the planned day, 1 day out (1-24 hours), 2 days out (>24-48 hours), or 3 days out (>48-72 hours) from the planned e-diary day. The sensitivity analysis will exclude the participants with e-diary reports collected outside the intended solicitation (calendar) day or with data collected from the Participant Reported Reactogenicity CRF page.

To support the assessment of reactogenicity, the endpoints below, as specified in Section 3.1.1 and Section 3.1.2, will be summarized with the same analysis time point and analysis population:

- Duration (days) of each local reaction and each systemic event after vaccination.

- Onset day of each local reaction and each systemic event after vaccination.

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- Presence of each and any severe local reaction and each and any severe systemic event on each of the 7 days and for "any day (Day 1 through Day 7)."

The presentation of the results will include a basic descriptive summary without 95% CIs (Section 5.2).

These continuous endpoints will be summarized by displaying the n, mean, median, standard deviation, minimum, and maximum for each study intervention group.

In addition, the proportions of participants reporting prompted local reactions, by maximum severity level, with any e-diary errors will be included as a supplemental summary.

6.1.2. AEs, SAEs, MAEs, and NDCMCs

6.1.2.1. Main Analysis

- Estimand strategy: Treatment policy (Section 2.2.1).
- Analysis set: Safety population (Section 4).
- Analysis methodology: 95% CI of the proportion of participants reporting those events, using the Clopper-Pearson method (Section 5.2.1).
- Analysis timing: Day 1 through 4 weeks after vaccination for AEs; Day 1 through 6 months after vaccination for SAEs, MAEs, and NDCMCs.
- Intercurrent events and missing data: All data collected are included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

Reporting results:

- The number of participants with AEs through 4 weeks after vaccination (n), the proportion (%), and the associated 2-sided Clopper-Pearson 95% CIs will be presented for each study intervention group.
- The number of participants with SAEs, MAEs, and NDCMCs through 6 months after vaccination (n), the proportion (%), and the associated 2-sided Clopper-Pearson 95% CIs will be presented for each study intervention group.
- Descriptive statistics, including the proportion (%), the numerator (n) and the denominator used in the proportion calculation, and the 95% CIs for the percentage using the Clopper-Pearson method, will be presented for each SOC and each PT within each SOC for each study intervention group.

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6.1.2.2. Sensitivity/Supplementary Analyses

To support the assessment of AEs, the endpoints below as specified in Section 3.1.3 will be summarized with the same analysis population using the same presentation as specified in the main analysis:

- Immediate AEs
- Related AEs
- Severe AEs
- Life-threatening AEs
- AEs leading to study discontinuation/withdrawal
- AEs leading to death
- AESIs

All AEs/SAEs occurring after informed consent and prior to vaccination will not be included in the analyses but will be listed.

In addition, any AEs occurring up to 48 hours after blood draws will be listed.

6.2. Secondary Endpoint(s)

Not applicable.

6.3. Other Safety Summaries and Analyses Endpoint(s)

6.3.1. Data Collected on the Summary of Reactogenicity CRF Page

Data collected about reactogenicity events on the Summary of Reactogenicity CRF page will be summarized or listed.

The main reasons for noncompletion of the 7-day reactogenicity event reporting (including e-diary entries and the data on the Participant Reported Reactogenicity CRF page) will be listed.

Immediate reactogenicity events may be summarized by study intervention. The medically attended reactogenicity events will be listed.

6.3.2. Medical History

Each reported medical history term will be mapped to an SOC and PT according to MedDRA. The number and percentage of participants with an assigned vaccine having at least 1 diagnosis of medical history, overall and at each SOC and PT level, will be

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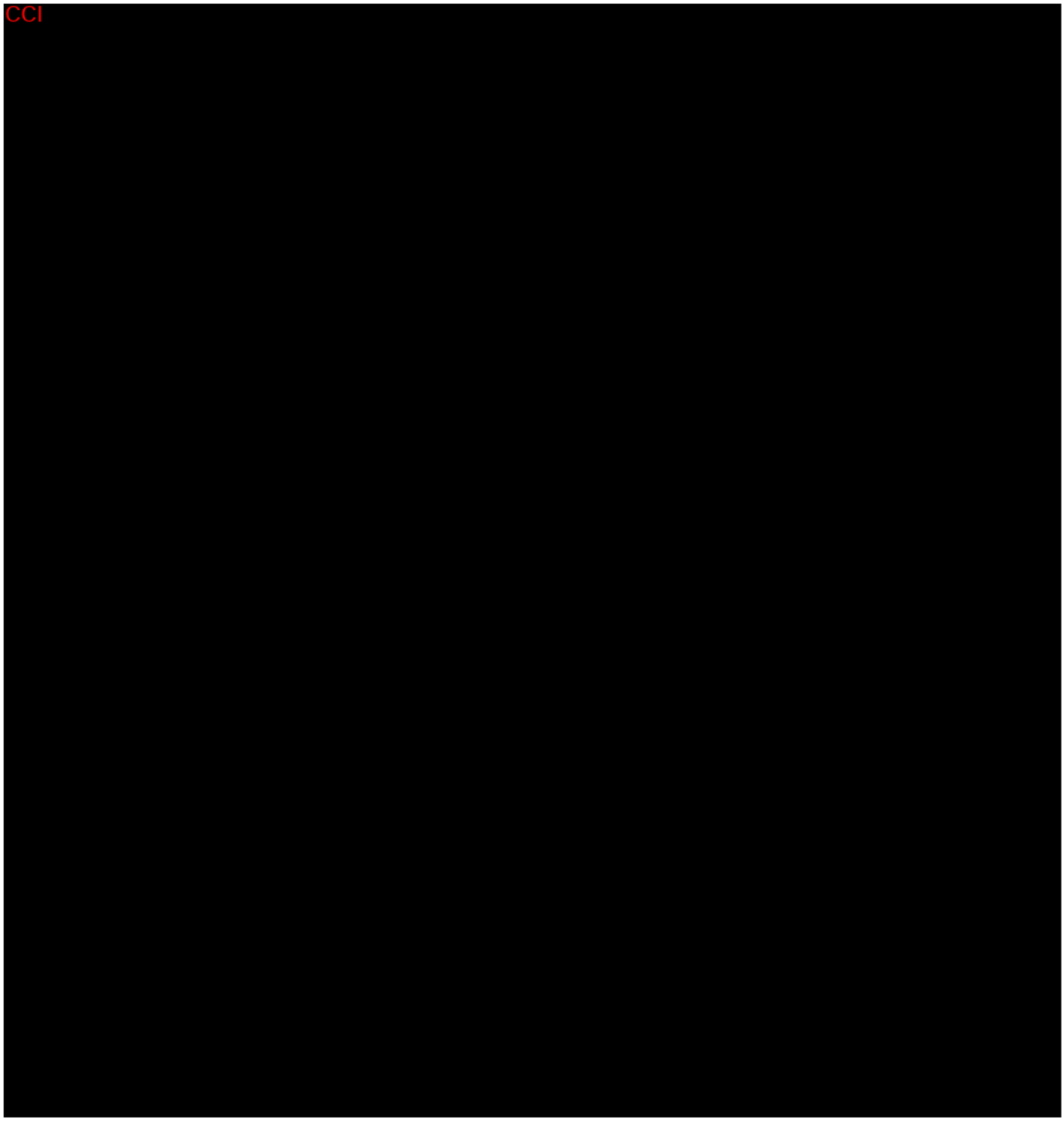
summarized by study intervention group and for all participants in total based on the safety population.

6.3.3. Electrocardiograms

The data collected for study participants who report any symptom(s) that might be indicative of myocarditis or pericarditis within 28 days after a study vaccination (ECG, troponin I level, cardiac echocardiogram, and/or cardiac magnetic resonance study) will be summarized and listed by vaccine group.



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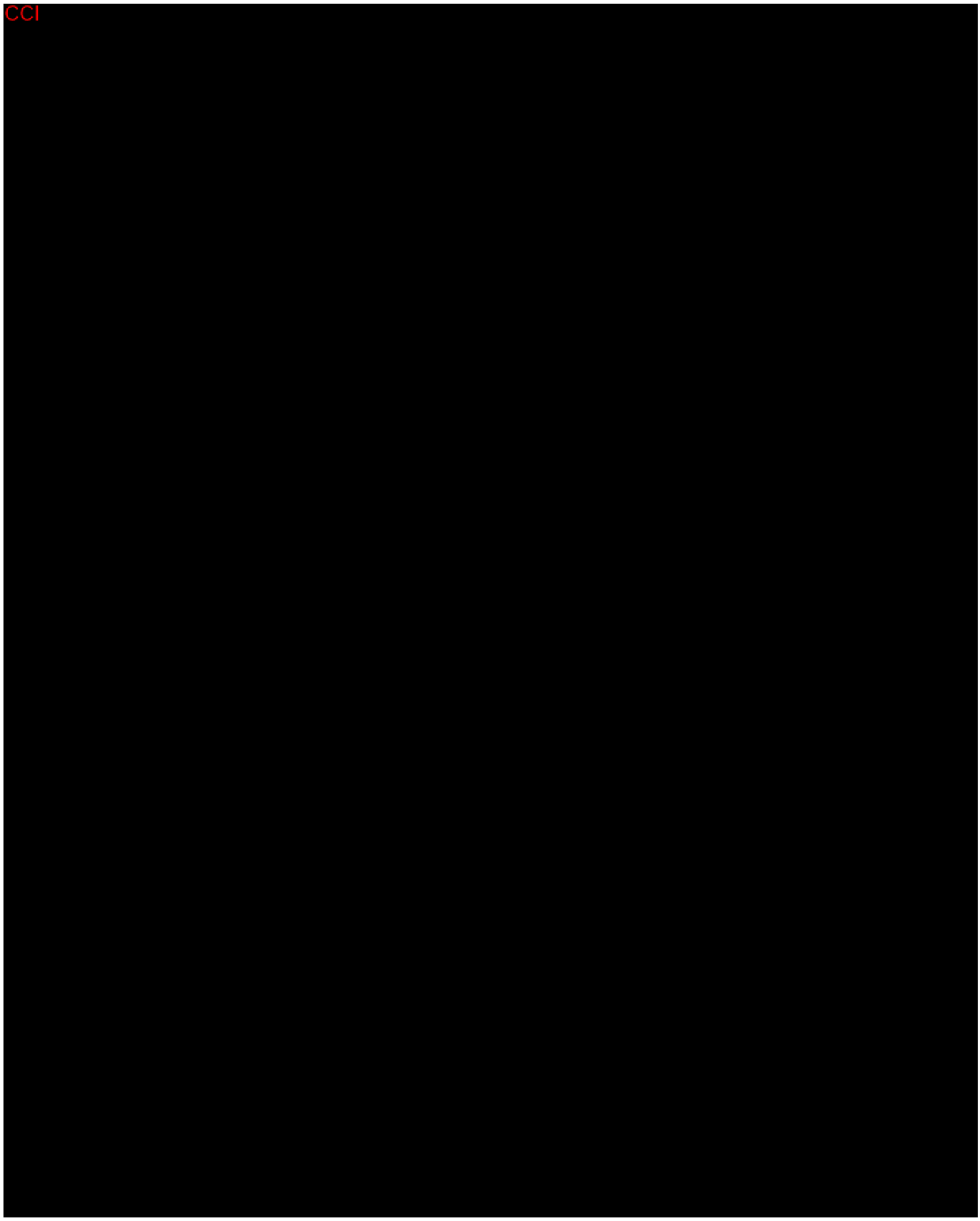

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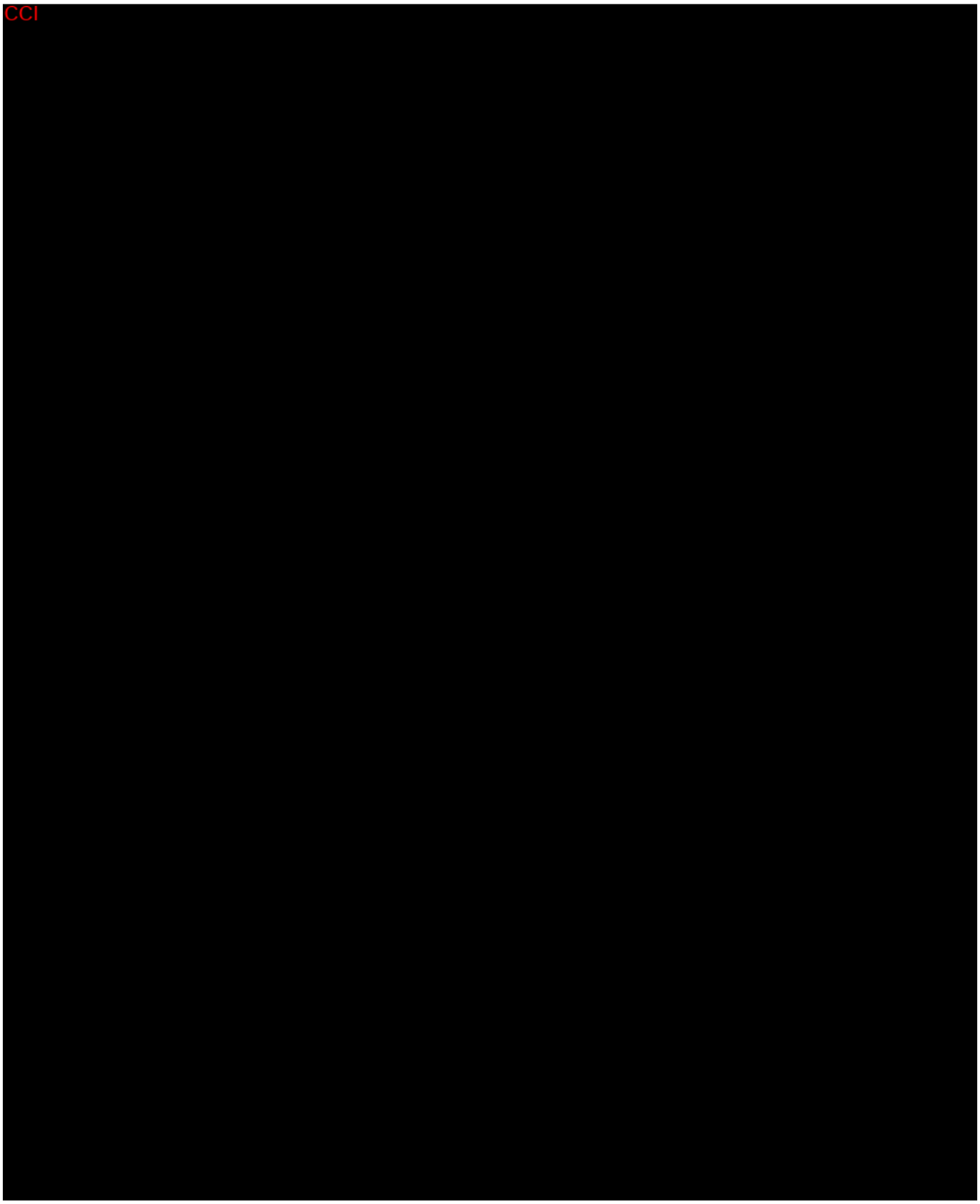

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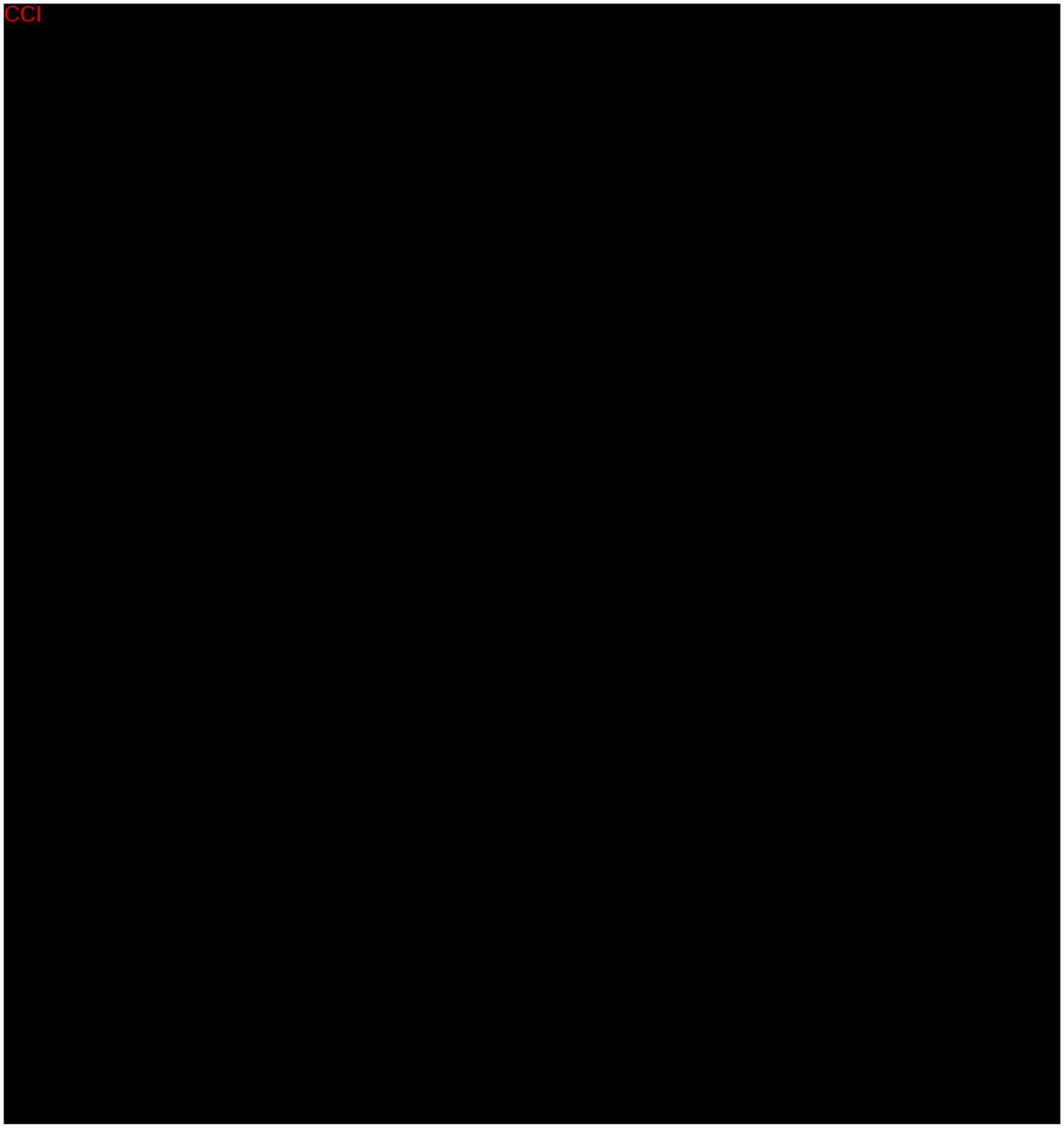

6.5. Subset Analyses

Not applicable.

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6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, ethnicity, and BMI) will be generated by study intervention group and for all participants in total based on the safety population.

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Participant Disposition

All participants in the randomized population will be included in the disposition summaries. Summaries will be displayed by vaccine group separately.

The number and percentage of randomized participants will be included in the participant disposition summary. In addition, the number and percentage of participants who received vaccinations, completed the follow-up visits, and withdrew before the follow-up visit, along with the reasons for withdrawal, will be tabulated by study intervention group and the total sample. The reasons for withdrawal will be those as specified in the database.

Participants excluded from each analysis population will also be summarized separately by study intervention group, along with the reasons for exclusion by study intervention group.

A listing of protocol deviations may also be provided.

6.6.2.2. Blood Samples for Assay

For each blood sampling time point, the number and percentage of randomized participants providing blood samples within the protocol-specified time frame, as well as before and after the protocol-specified time frame, will be tabulated separately by study intervention group.

6.6.2.3. E-Diaries

The participants who were vaccinated and who transmitted and completed e-diaries will be summarized according to the vaccine actually received. Besides the analysis described in Section 6.1.1, the summary will also include the number and percentage of vaccinated participants not transmitting the e-diary, transmitting the e-diary, and completing the e-diary for any day (based on the e-diary completion category as defined in Section 3.5.2) in the required reporting period after vaccination by assigned study intervention.

The number and percentage of participants transmitting and completing the e-diary for each day in the required reporting period, and overall, will be tabulated for each study intervention group.

The safety population will be used.

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6.6.3. Study Intervention Exposure

6.6.3.1. Vaccination Administration

The relation of the randomized study intervention to the actual study intervention received will be presented as a cross-tabulation of the actual study intervention received versus the randomized study intervention.

A listing of participants showing the randomized study intervention and the study intervention actually received will be presented.

6.6.4. Concomitant Medications and Nondrug Treatments

Each prior/concomitant vaccine will be summarized according to the Anatomic Therapeutic Chemical fourth-level classification/WHODD, as appropriate. The prior/concomitant vaccines and medications as described in Section 3.5.3 will be listed. The number and percentage of participants receiving each prior (before vaccination) and concomitant vaccine (on or after vaccination) will be tabulated according to the assigned study intervention. The safety population will be used. Concomitant medications will be summarized similarly to concomitant vaccines.

7. INTERIM ANALYSES

7.1. Introduction

As the study is sponsor-unblinded, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, dose selection, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

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Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
CCI	
APE	analysis population exclusion
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
CI	confidence interval
CORD	Clinical Oversight Review Dashboard
COVID-19	coronavirus disease 2019
CRF	case report form
ECG	electrocardiogram
CCI	
HA	hemagglutinin
CCI	
ICD	informed consent document
CCI	
IRT	interactive response technology
IV	intravenous(iy)
CCI	
MAE	medically attended adverse event
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
CCI	
modRNA	nucleoside-modified messenger ribonucleic acid
mRNA	messenger ribonucleic acid
CCI	
N/A	not applicable
CCI	
NDCMC	newly diagnosed chronic medical condition
CCI	
PIPD	potential important protocol deviation
PT	preferred term
qIRV	quadrivalent influenza modRNA vaccine
QIV	quadrivalent influenza vaccine
CCI	
RNA	ribonucleic acid
SAE	serious adverse event

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Abbreviation	Term
SAP	statistical analysis plan
SOC	system organ class
tIRV	trivalent influenza modRNA vaccine
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

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PPD	13-Jun-2024 14:07:22	Business Line Approver

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