COVID-19-004

SYSTEMIC ALLERGIC REACTIONS TO SARS-COV-2 VACCINATION

(SHORT TITLE: SARS VACCINATION)

v8.0/16 FEBRUARY 2022

IND# 27215

[National Clinical Trial (NCT)#] NCT04761822

IND SPONSOR: The National Institute of Allergy and Infectious Diseases (NIAID)

NIAID Funding Mechanism: *Grant 3UM2AI117870-07S1*

Investigational Agent(s)/Manufacturer(s): Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine

PROTOCOL CO-CHAIR
JAMES R. BAKER, JR., MD
[redacted]

PROTOCOL CO-CHAIR
REBECCA S. GRUCHALLA, MD, PHD
[redacted]

PROTOCOL CO-CHAIR
N. FRANKLIN ADKINSON, JR., MD
[redacted]

MEDICAL MONITOR
[redacted]

PROJECT MANAGER
[redacted]

REGULATORY OFFICER
[redacted]

RHO SCIENTIFIC LEAD
[redacted]

BIOSTATISTICIAN
[redacted]

PHARMACEUTICAL SPECIALIST
[redacted]

SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: COVID-19-004	**Version Number/Date:** 8.0/16 Feb 2022
Protocol Title: Systemic Allergic Reactions to SARS-CoV-2 Vaccination	
IND Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
Return Signed Form to: *The original signature page must be kept for your records. Return an electronic PDF copy of the signed signature page (*as described below) to the Division of Allergy, Immunology, and Transplantation (DAIT) Regulatory Management Center (RMC) via email to DAITRegulatory_SiteRegistration (SM) at DAITReg@ppd.com*	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) document titled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Further, I will conduct the study in keeping with local legal and regulatory requirements. As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.*

*[*The site Principal Investigator should sign and date at the indicated location below. A written signature/date is acceptable (e.g., scanned and sent via email as a PDF version). An electronic signature is also acceptable (e.g., sent via email as a PDF version).]*

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Systemic Allergic Reactions to SARS-CoV-2 Vaccination
Short Title	SARS Vaccination
Clinical Phase	Phase 2
Number of Sites	Approximately 30 clinical sites in the United States
IND Sponsor/Number	National Institute of Allergy and Infectious Diseases (NIAID) / IND# 27215
Study Objectives	The study is designed with two principal aims: First, to estimate the proportions of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and the Moderna COVID-19 Vaccine in a High-Allergy/Mast Cell Disorder (HA/MCD) population. Second, if the risk in the HA/MCD is demonstrable, to determine whether the proportions are higher in the HA/MCD versus a comparison population. Primary Objectives: • Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations Secondary Objectives: • Assess the proportion of participants with severe (Grade 3 or higher per Consortium for Food Allergy Research (CoFAR) Grading Scale for Systemic Allergic Reactions Version 3.0) systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0) systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with anaphylactic reactions (Levels 1-3) per Brighton Collaboration Criteria to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with anaphylactic reactions (Levels 1-3) per Brighton Collaboration Criteria to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations • Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD population by dose • Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD population by dose • Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD after adjusting for placebo • Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD after adjusting for placebo

	• Assess the difference in proportions of participants with systemic allergic reactions after the second Pfizer-BioNTech COVID-19 Vaccine dose (not placebo arm) versus the first vaccine dose within the placebo arm in the HA/MCD population • Assess the difference in proportion of participants with systemic allergic reactions after the second Moderna COVID-19 Vaccine dose (not placebo arm) versus the first vaccine dose within the placebo arm in the HA/MCD population • Assess the difference in proportion of HA/MCD participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine between the adult and child populations (for this analysis, the HA group will not include children who qualified for the study on the basis of uncontrolled asthma) • Assess the difference in proportion of HA/MCD participants with systemic allergic reactions to the Moderna COVID-19 Vaccine between the adult and child populations (for this analysis, the HA group will not include children who qualified for the study on the basis of uncontrolled asthma) Exploratory Objectives: • Assess the risk of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and independently to the Moderna COVID-19 Vaccine in the HA/MCD population by baseline covariates • Examine possible mechanisms of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and to the Moderna COVID-19 Vaccine • Identify genotypes associated with increased risk of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and to the Moderna COVID-19 Vaccine
Study Design	This is a multi-center, randomized, initially blinded, phase 2 trial to assess SARS-CoV-2 vaccination systemic allergic reactions in two populations: one population including individuals with a history of recent, severe allergic reactions (High-Allergy [HA]), poorly controlled allergic asthma, or mast cell disorders (MCDs) and one comparison population without severe allergies or mast cell disorders. Participants enrolled under protocol versions 1.0 - 4.0, were randomized 2:2:1:1 to receive the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, placebo + Pfizer-BioNTech COVID-19 Vaccine, or placebo + Moderna COVID-19 Vaccine. Participants enrolled under protocol versions 5.0 – 8.0 will be randomized 2:1 to receive the Pfizer-BioNTech COVID-19 vaccine or placebo + Pfizer-BioNTech COVID-19 vaccine. Active vaccine may be changed from Pfizer-BioNTech to Moderna, if enrollment is robust and sustained, Participants randomized to one of the placebo groups will receive placebo as a first dose and will receive two doses of their assigned active vaccine at subsequent visits.
Primary Endpoints	1. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Pfizer-BioNTech COVID-19 Vaccine 2. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Moderna COVID-19 Vaccine

Secondary Endpoints	1. The proportion of participants who experience a severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0) systemic allergic reactions within the 90-minute post-vaccination observation period to either dose of each vaccine 2. The proportion of participants who experience an anaphylactic reaction (Levels 1-3) per Brighton Collaboration Criteria within the 90-minute post-vaccination observation period to either dose of each vaccine 3. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the first dose 4. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the second dose conditional on no systemic allergic reaction to the first dose 5. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the first dose after adjusting for placebo administration 6. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above) within 48 hours of either dose of each vaccine
Exploratory Endpoints	1. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose 2. Prevalence of polyethylene glycol (PEG) antibodies in vaccine recipients before each vaccination 3. Changes in anti-PEG antibody levels 3-4 weeks after the first vaccine dose 4. Changes in biomarkers from pre- to post-vaccination and/or after onset of an allergic reaction (e.g., known mediators of systemic reactions due to mast cell activation, markers of inflammatory response, markers associated with activation of the classical and alternative complement pathways or the kinin system) 5. Changes in blood transcriptomics after vaccination, and plasma and urine proteomics from pre- to post-vaccination and/or after onset of an allergic reaction 6. Genetic variants identified by whole-genome sequencing (applicable only in protocol versions 1.0 - 4.0)
Accrual Objective	This study will enroll up to 3400 participants. Approximately 60% of participants will be in the High-Allergy/Mast Cell Disorder (HA/MCD) group, and 40% will be in the comparison group. Enrollment of participants who qualify only on the basis of reactions to multiple unrelated drugs will be limited to approximately 300. Enrollment of the Mast Cell Disorder group is anticipated to be at least 200, and not more than 300 participants. Approximately two-thirds of participants enrolled in each of the 2 groups will be female. Under protocol versions 1.0 - 4.0, participants were randomized 2:2:1:1 to receive either the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, placebo+ Pfizer-BioNTech COVID-19 Vaccine, or placebo + Moderna COVID-19 Vaccine. Under protocol versions 5.0 – 8.0, the study will only enroll children ages 5 through 17 years on the date of first study vaccination/placebo administration. Enrollment of participants aged 18 or older

	will be closed. Children will be randomized 2:1 to receive either the Pfizer-BioNTech COVID-19 Vaccine or placebo + Pfizer-BioNTech COVID-19 Vaccine. Active vaccine may be changed from Pfizer-BioNTech to Moderna if enrollment is robust and sustained. Participants randomized to one of the placebo groups will receive placebo as a first dose and will receive two doses of their assigned active vaccine at subsequent visits.
Study Duration	Participant Vaccination and Follow-up: Participants randomized under protocol versions 1.0 - 4.0: Randomized and vaccinated participants will complete study participation in approximately 29 days if vaccinated with the Pfizer-BioNTech COVID-19 Vaccine, 36 days if vaccinated with the Moderna COVID-19 Vaccine, and 50 or 64 days if administered placebo before receiving two doses of either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, respectively. Participants randomized under protocol versions 5.0 – 8.0: Randomized and vaccinated participants who receive both doses of vaccine will complete study participation in approximately 29 days if vaccinated with the Pfizer-BioNTech COVID-19 Vaccine, 36 days if vaccinated with the Moderna COVID-19 Vaccine, and 36 or 43 days if administered placebo before receiving two doses of either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, respectively.
Treatment Description	Each participant will receive 2 doses of either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine. Participants randomized to placebo, will receive a placebo dose before receiving 2 doses of either the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine.
Inclusion Criteria	Note criteria apply to all cohorts and protocol versions, unless otherwise stated. Individuals who meet all of the following criteria are eligible for enrollment as study participants: <u>Both groups:</u> 1. Participant and/or parent/legal guardian must be able to understand and provide informed consent and/or assent, as applicable 2. Male or non-pregnant female 12 years of age or older on the date of first study vaccination/placebo administration (protocol versions 1.0 - 4.0) **OR** male or non-pregnant female 5 to 17 years of age on the date of first study vaccination/placebo administration (protocol versions 5.0 – 8.0) 3. Females of childbearing potential must have a negative pregnancy test prior to the first vaccination and placebo administration, if applicable. If a participant becomes pregnant after receiving a placebo dose but prior to receiving study vaccination, she will be discontinued from the study. 4. Females of reproductive potential* and sexually active must agree to use Food and Drug Administration (FDA) approved methods of birth control for the duration of the study. These include hormonal contraceptives, intrauterine device, double barrier contraception (i.e., condom plus diaphragm), or male partner with documented vasectomy. *Menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone of ≥25 U/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception.

	<u>High-Allergy and Mast Cell Disorder (HA/MCD) group:</u> Individuals who meet at least one of the following criteria are eligible for enrollment in the HA/MCD group: 1. History of a severe allergic reaction to food(s), allergen immunotherapy, insect venom(s), or latex with use of epinephrine within the last 15 years 2. History of an Emergency Department visit with convincing evidence of a systemic allergic reaction (consistent with CoFAR Grade 3 or higher) to food(s), allergen immunotherapy, insect venom(s) or latex within the last 15 years 3. History of documented, immediate allergic reactions to 2 or more unrelated drugs within the last 15 years 4. A convincing clinical history, or a history that is accompanied by a positive skin test, of an immediate reaction to a drug, vaccine, or latex within the last 15 years 5. History of physician-diagnosed idiopathic anaphylaxis requiring epinephrine, or an Emergency Department visit in the last 15 years 6. History of a physician-diagnosed mast cell disorder (e.g., mastocytosis, mast cell activation syndrome (MCAS), or hereditary alpha-tryptasemia). MCAS must meet consensus criteria as defined below: • Criterion A: Typical clinical signs of severe, recurrent (episodic) systemic Mast Cell Activation are present (often in form of anaphylaxis) (definition of systemic: involving at least 2 organ systems) • Criterion B: Involvement of Mast Cell (MC) is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to plus 20% + 2 ng/ml • Criterion C: Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production or drugs blocking mediator release or effects of MC-derived mediators All 3 MCAS criteria (A + B + C) must be fulfilled to call a condition MCAS. 7. Poorly controlled allergic asthma as evidenced by one hospitalization or one or more systemic (oral or injectable) steroid burst(s) in the 24 months prior to enrollment and evidence of aeroallergen sensitization by blood work, skin test, or appropriate history. 8. A doctor diagnosis of food allergy with a convincing clinical history and a positive skin test or positive food challenge, with evidence of reactivity within the last 10 years. <u>Comparison group:</u> Individuals who meet all of the following criteria are eligible for enrollment in the comparison group: 1. No history of allergic asthma or atopic dermatitis within the last 10 years 2. No history of chronic spontaneous urticaria, or angioedema 3. No history of allergic reactions to foods or insect venoms 4. No history of allergic reactions to drugs or vaccines 5. No history of anaphylaxis 6. No history of a mast cell disorder (e.g., mastocytosis, MCAS, or hereditary alpha-tryptasemia)
Exclusion Criteria	Individuals who meet any of these criteria are not eligible for enrollment as study participants:

	1. Inability or unwillingness of a participant and/or parent/legal guardian to give written informed consent and/or assent, as applicable, or comply with study protocol 2. Weight less than 15 kg 3. Prior receipt of any doses of the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, or any other COVID-19 vaccine 4. History of a severe reaction to any component of the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine 5. History of contact dermatitis with confirmed patch test reaction to PEG 6. History of reaction to Doxil 7. Known exposure to SARS-CoV-2 and still within the quarantine window 8. Symptoms consistent with acute COVID-19 infection or known COVID-19 infection (positive PCR or antigen test) and still within the quarantine window 9. Have an acute illness, including body temperature greater than 100.4˚F, within 14 days of the first study vaccination/placebo administration or 3 days prior to each subsequent vaccination 10. History of autoimmune or other disorders requiring systemic immune modulators 11. History of acute urticaria within 28 days of randomization 12. Pregnant 13. Have received any vaccines within 14 days of the first study vaccination/placebo administration or plan to receive other vaccines during the study period 14. Had any allergen immunotherapy administration within 24 hours prior to vaccination/placebo administration or plan to receive within 24 hours after vaccination/placebo administration 15. Have received a biologic therapy within 6 months of randomization 16. Use of systemic steroids for any reason within 28 days of randomization 17. Use of Zileuton within 14 days of randomization 18. Use of any antibody agent for treatment or prevention of COVID-19 within 3 months of randomization 19. Coronary artery disease, peripheral or cerebral vascular disease, unstable angina, or cardiac arrhythmia other than supraventricular tachycardia (SVT) 20. Medically unstable hypertension 21. Current use of beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, monoamine oxidase (MAO) inhibitors, tricyclic anti-depressants or other agents that could interfere with the treatment of anaphylaxis, in the opinion of the investigator 22. Unstable asthma within 3 months of randomization or symptomatic asthma on the day of vaccination as assessed by the site investigator 23. Have past or current medical problems or findings from physical exam or laboratory testing not listed above, which in the opinion of the investigator, may pose additional risks from participation in the study or which may interfere with the ability to comply with study requirements. This includes individuals with underlying conditions or other medications that, in the opinion of the investigator, may increase risk in the event of an anaphylactic reaction or lead to complications following administration of epinephrine.

Premature Discontinuation of Investigational Agent	Vaccination will be prematurely discontinued for any participant for any of the following reasons: • Participant has a CoFAR Grade 2 or higher systemic allergic reaction regardless of tryptase, or a CoFAR Grade 1 reaction with elevated tryptase [1.2 x baseline plus 2 ng/ml] that is at least possibly related to the first dose of vaccine. If the systemic allergic reaction took place after the participant has left the vaccination clinic and no tryptase measurements are available, Grade 1 events will not constitute criteria for discontinuation, but counseling by a study physician will be required. • The investigator believes that it is no longer in the best interest of the participant to receive the second vaccination.
Study Stopping Rules	Study enrollment will be suspended and vaccinations will be put on hold pending Data and Safety Monitoring Board (DSMB) expedited review of all pertinent data in the event of any one of the following: 1. One Grade 4 or higher adverse event (AE) that is at least possibly related to the vaccine 2. Five participants in the first 100 HA/MCD participants vaccinated or 5% of HA/MCD participants thereafter experience a Grade 3 systemic allergic reaction at least possibly related to the vaccine

Table of Contents

Glossary of Abbreviations

AE	Adverse Event
ACE	Angiotensin Converting Enzyme
CARPA	Complement Activation-Related Pseudoallergy
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CoFAR	Consortium for Food Allergy Research
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HA	High-Allergy
ICH	International Conference on Harmonization
IND	Investigational New Drug
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MC	Mast Cell
MCAS	Mast Cell Activation Syndrome
MCD	Mast Cell Disorder
MAO	Monoamine Oxidase
modRNA	nucleoside-modified messenger RNA
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
PI	[Site] Principal Investigator
QC	Quality Control
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction

SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
SVT	Supraventricular Tachycardia
VAERS	Vaccine Adverse Event Reporting System

1. Background and Rationale

1.1. Background and Scientific Rationale

The SARS-CoV-2 virus has triggered a world-wide pandemic with nearly 25 million cases and more than 400,000 deaths in the United States as of January 20, 2021, a year after the first case was reported in this country. Vaccines are crucial in the effort to bring the pandemic to an end. The Food and Drug Administration (FDA) has given Emergency Use Authorization (EUA) to two vaccines, using mRNA in a lipid nanoparticle delivery system, that have been proven to be strikingly effective in preventing disease in large clinical trials. This platform is potentially paradigm changing in the development of vaccines, allowing an extremely rapid response to emerging infectious diseases.

Since introduction of these vaccines in a wider population, there have been reports of severe allergic reactions to vaccination with these products. The incidence rate of anaphylaxis for the Pfizer-BioNTech COVID-19 Vaccine, based on a Centers for Disease Control (CDC) publication, is estimated at 10/1,000,000 vaccine doses, which is approximately 10-fold higher than the rate typically seen with commonly used vaccines.[1, 2] In a recent publication by the CDC, the rate of anaphylaxis for the Moderna COVID-19 Vaccine has been reported as 2.5/1,000,000. The majority of these reactions have occurred in individuals with an allergic background and a large number in individuals with a history of anaphylaxis.[3] Although there have been no further official estimates of the rate, as of October 8, 2021 there were 1,027 reports of anaphylaxis in VAERS for the Pfizer-BioNTech Vaccine, and 651 reports for the Moderna Vaccine. As of October 21, 2021 per CDC, there have been 240,324,759 doses of Pfizer-BioNTech administered and 154,087,303 doses of Moderna, giving an approximate rate of 4.2-4.3 cases per million doses for each of the two vaccines.

In response to the cases of anaphylaxis in the United Kingdom, the Medical and Healthcare products Regulatory Agency initially issued a pause on vaccination with the Pfizer–BioNTech COVID-19 Vaccine, to exclude any person with a history of anaphylactic reaction to any food, drug, or vaccine, although this restriction has been withdrawn. The reports of anaphylactic reactions in allergic individuals who have received the lipid nanoparticle vaccines have alarmed people with allergies, and allergy physicians are being inundated with calls for advice. The CDC has recommended that individuals with a history of severe allergic reactions be monitored for at least 30 minutes after vaccination, rather than the 15 minutes advised for others, and has advised that appropriate treatment be immediately available.

The roll-out of COVID-19 vaccinations started with adults, and younger aged individuals have been included over time, starting with adolescents, and recently with EUA for children ≥5 years of age in early November 2021. Trials are in process for children down to age 6 months. As each age range has potentially different risk factors and responses to the vaccines, this trial has responded by lowering the age requirements to enable risk assessment across the population. As the rate of infection in children has risen, and children have returned to school, the trial has also been modified to limit the period after a placebo injection to 7 days to minimize the time children remain unprotected.

Both vaccines contain nucleoside modified mRNA encoding the SARS-CoV-2 spike protein, and both contain different polyethylene glycol (PEG) compounds with an approximate weight of 2000 among other lipids, including cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]) (Table 1.1). PEG compounds, of various molecular weights, are hydrophilic polymers widely used in medicinal, cosmetic, and household products. PEG compounds have been documented to induce IgE, IgG, and IgM antibodies which can cause both severe allergic and complement activation-related pseudoallergic (CARPA) reactions. Polysorbate compounds, which are structurally related to PEG compounds and are also used widely in medications, are known to induce immune responses that can lead to systemic allergic reactions. Although polysorbates are not components of these vaccines, cross-reactivity exists between PEG compounds and polysorbates.[4] IgE and CARPA-mediated reactions may involve different mitigation or treatment strategies. There are

no data to implicate PEG compounds in the reactions observed to date, and reactions mediated by other components of the vaccines need to be considered.

Table 1.1. Composition of Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine

	Pfizer-BioNTech COVID-19 Vaccine (12 years and older – Purple Cap)	Pfizer-BioNTech COVID-19 Vaccine (5-11 years old-Orange Cap)	Moderna COVID-19 Vaccine (18 years and older)
Active	Nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.	Nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.	Nucleoside-modified mRNA encoding the pre-fusion stabilized spike (S) glycoprotein of SARS-CoV-2
Inactive – lipids	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	SM-102 (Proprietary to Moderna)
	2[(polyethylene glycol [PEG])-2000]-N,N-ditetradecylacetamide	2[(polyethylene glycol [PEG])- 2000]-N,N-ditetradecylacetamide	Polyethylene glycol (PEG) 2000 dimyristoyl glycerol (DMG)
	1,2-distearoyl-sn-glycero-3-Phosphocholine	1,2-distearoyl-sn-glycero-3-Phosphocholine	1,2-distearoyl-sn-glycero-3-Phosphocholine
	Cholesterol	Cholesterol	Cholesterol
Inactive – salts, sugars, buffers	Potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dehydrate	Tromethamine, Tromethamine hydrochloride	Tromethamine, Tromethamine hydrochloride, acetic acid, sodium acetate
	Sugar (sucrose)	Sugar (sucrose)	Sugar (sucrose)
	Diluent (Sodium Chloride)	Diluent (Sodium Chloride)	Diluent (None)

This study is designed with two principal aims: First, to estimate the proportions of systemic allergic reactions to the Pfizer-BioNTech and the Moderna COVID-19 vaccines in individuals with a recent history of severe allergic reactions (High-Allergy [HA]), poorly controlled allergic asthma, or mast cell disorders (MCD). Second, if the risk in the HA/MCD is demonstrable, to determine whether the proportions are higher in the HA/MCD population compared to a comparison study population without severe allergy or mast cell disorders.

The first aim is independent of whether we can demonstrate a difference between the HA/MCD and the comparison groups. If the risk is low, this important information can be used to reassure highly allergic individuals that the vaccines are safe. Indeed, if no reactions are seen in the HA/MCD group, it would provide evidence that the reaction rate is less than approximately 1 in 275. Estimation of risk in the HA/MCD group, along with the corresponding confidence intervals, will be a key finding of this study regardless of the proportions of systemic allergic reactions observed. This information will be crucial to properly advise highly allergic individuals and those with poorly controlled allergic asthma or mast cell disorders, to maintain public trust in the safety of these vaccines, and to minimize vaccine hesitancy.

However, if the risk in the HA/MCD is demonstrable, we want to determine whether it is higher than that of the comparison population. We have set the 1% in the HA/MCD population as an arbitrary risk level for which we want to have the statistical power to compare the two populations. This protocol is powered to detect a difference of the

magnitude of 0.01 versus 0.0001 between the comparison and HA/MCD groups within each vaccine arm. If there are reactions in the HA/MCD population, but not enough to demonstrate a higher risk than in the other population, we will also have a corresponding confidence interval for the risk in the HA/MCD ruling out some particular risk level. We will also estimate the difference in vaccine reactions between the two populations.

In the event a significant number of immediate systemic allergic reactions to either or both vaccines are seen, a second focus of this study is to begin evaluating the mechanism(s) of allergic reactions to the COVID-19 vaccines, and to determine if specific risk factors can be identified by patient history or biomarker testing. The prospective design is important, because it will allow standardized collection of both clinical information and biospecimens before and after vaccination and, most importantly, at the time of immediate vaccine systemic allergic reactions, should such reactions occur. This information will be extremely helpful in improving the safety of this new and important vaccine platform.

The primary endpoint for this trial is the rate of systemic allergic reactions defined by the Consortium for Food Allergy Research (CoFAR) Grading Scale (Grade 2 or higher regardless of serum tryptase level or Grade 1 with elevated serum tryptase levels). This endpoint was chosen for several reasons: 1) The CoFAR Grading Scale was developed by specialists with extensive experience in systemic allergic reactions and in anaphylaxis and has proven to be a reliable system for assessing and recording reactions in multiple National Institute of Allergy and Infectious Diseases (NIAID) funded studies; 2) Because the study will be conducted under the supervision of an allergist at each site, it is unlikely that any participants will develop severe anaphylaxis, since they will be promptly treated to prevent such an outcome; and 3) Recognition, recording, and grading of all systemic allergic reactions is of importance as mild reactions induced by the first vaccine dose may constitute risk factors for more severe reactions after the second dose.

Epidemiologic studies, including the current CDC investigations into the anaphylactic responses to these vaccines, use the Brighton Collaboration Criteria.[5] These criteria will be used as a secondary endpoint in this study to allow comparisons with publications that rely on those criteria.

1.2. Rationale for Selection of Investigational Product

This trial will employ the two SARS-CoV-2 mRNA vaccines that have received FDA EUA and/or FDA approval for use to date.

1.3. Clinical Studies

Overall, 15,419 participants aged 18 years or older received at least one dose of the Moderna COVID-19 Vaccine in three clinical trials.[6-8] Adverse reactions reported in a clinical trial following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site.[9] A phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of the same 100 mcg dose of Moderna COVID-19 Vaccine used in adults is currently ongoing in approximately 3,000 healthy adolescents 12 to < 18 years of age (NCT04649151), as is a variable dose study in children 6 months to < 12 years (NCT04796896). [10]

The safety of the Pfizer-BioNTech COVID-19 Vaccine has been evaluated in three clinical studies.[11, 12] The BNT162-01 study (NCT04380701) was a phase 1/2 trial that enrolled 60 participants, 18 through 55 years of age. Study C459001 is an ongoing phase 1/2/3 study that has enrolled approximately 44,000 participants, 12 years of age or older.

Study C4591007 (Study 3) is a Phase 1/2/3 multicenter, randomized, dose-finding, open-label (Phase 1) and multinational, saline placebo-controlled, observer-blind, immunogenicity and efficacy (Phase 2/3) study that has enrolled 4,695 participants 5 through 11 years of age, of whom 3109 participants received Pfizer-BioNTech COVID-19

Vaccine (10 mcg modRNA) and 1538 participants received placebo in Phase 2/3. In an analysis of Study 3 Phase 2/3 data based on data up to the cutoff date of September 06, 2021, 2,268 participants [1,518 Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA); 750 placebo] were 5 through 11 years of age. Of these, 2,158 (95.1%) [1,444 Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA) and 714 placebo] participants have been followed for at least 2 months after the second dose. An analysis of Study 3 Phase 2/3 adverse event data also included another 2,379 participants [1,591 Pfizer-BioNTech COVID-19 Vaccine (10 mcg modRNA) and 788 placebo], of whom 71.2% had a follow-up period for at least 2 weeks after Dose 2 up to the cutoff date of October 8, 2021. The safety evaluation in Study 3 is ongoing.

Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy.[13]

2. Study Hypotheses/Objectives

2.1. Hypotheses

We hypothesize that vaccine administration will be safe in the large majority of highly allergic individuals and individuals with poorly controlled allergic asthma or MCD, but that there may be identifiable risk factors that can trigger a specific mechanism of reaction in some individuals.

2.2. Primary Objectives

This study is designed with two principal aims: First, to estimate the proportions of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and the Moderna COVID-19 Vaccine in a HA/MCD population. Second, if the risk in the HA/MCD is demonstrable, to determine whether the proportions are higher in the HA/MCD versus a comparison population without severe allergy or mast cell disorders.

- Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations
- Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations

2.3. Secondary Objectives

- Assess the proportion of participants with severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Allergic Reactions v3.0) systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations
- Assess the proportion of participants with severe (Grade 3 or higher per CoFAR Grading Scale) systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations
- Assess the proportion of participants with anaphylactic reactions (Levels 1-3) per Brighton Collaboration Criteria to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD and comparison populations
- Assess the proportion of participants with anaphylactic reactions (Levels 1-3) per Brighton Collaboration Criteria to the Moderna COVID-19 Vaccine in the HA/MCD and comparison populations
- Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD population by dose
- Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD population by dose

- Assess the proportion of participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine in the HA/MCD population after adjusting for placebo
- Assess the proportion of participants with systemic allergic reactions to the Moderna COVID-19 Vaccine in the HA/MCD population after adjusting for placebo
- Assess the difference in proportions of participants with systemic allergic reactions after the second Pfizer-BioNTech COVID-19 Vaccine dose (not placebo arm) versus the first vaccine dose within the placebo arm in the HA/MCD population
- Assess the difference in the proportions of participants with systemic allergic reactions after the second Moderna COVID-19 Vaccine dose (not placebo arm) versus the first vaccine dose within the placebo arm in the HA/MCD population
- Assess the difference in proportion of HA/MCD participants with systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine between the adult and child populations (for this analysis, the HA group will not include children who qualified for the study on the basis of uncontrolled asthma)
- Assess the difference in proportion of HA/MCD participants with systemic allergic reactions to the Moderna COVID-19 Vaccine between the adult and child populations (for this analysis, the HA group will not include children who qualified for the study on the basis of uncontrolled asthma)

2.4. Exploratory Objectives

- Assess the risk of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and independently to the Moderna COVID-19 Vaccine in the HA/MCD population by baseline covariates
- Examine possible mechanisms of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and to the Moderna COVID-19 Vaccine
- Identify genotypes associated with increased risk of systemic allergic reactions to the Pfizer-BioNTech COVID-19 Vaccine and to the Moderna COVID-19 Vaccine

3. Study Design

3.1. Description of Study Design

This is a multi-center, randomized, initially blinded, phase 2 trial to assess SARS-CoV-2 vaccination reactions in two populations: one population including individuals with a history of recent, severe allergic reactions, poorly controlled allergic asthma, or MCDs and one comparison population without severe allergies or mast cell disorders. The study aims at enrolling up to 2040 HA/MCD and 1360 comparison participants across approximately 30 US sites. Approximately two-thirds of participants enrolled in each of the 2 groups will be female. This is because the vast majority of cases of anaphylaxis to the COVID-19 vaccines have occurred in women. Enrollment of participants who qualify only on the basis of reactions to multiple unrelated drugs will be limited to approximately 300. Enrollment of the MCD group is anticipated to be at least 200 participants, and not more than 300 participants.

Participants enrolled under protocol versions 1.0 – 4.0 were randomized 2:2:1:1 to receive the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, placebo + Pfizer-BioNTech COVID-19 Vaccine, or placebo + Moderna COVID-19 Vaccine (Figure 1).

Participants enrolled under protocol versions 5.0 – 8.0 will be randomized 2:1 to receive the Pfizer-BioNTech COVID-19 Vaccine or placebo + Pfizer-BioNTech COVID-19 Vaccine. If enrollment is robust and sustained, active vaccine randomization may be changed to Moderna.

Participants randomized to one of the placebo groups will receive placebo as a first dose and will receive two doses of their assigned active vaccine at subsequent visits. During the first visit, all participants will be initially blinded to whether they are receiving placebo or vaccine (all protocol versions), and to which vaccine they are receiving (applicable to protocol versions 1.0 - 4.0 only). Parents/legal guardians of participants under the age of majority, will also be blinded to whether their child is receiving placebo or vaccine (all protocol versions), and to which vaccine they are receiving (applicable to protocol versions 1.0 - 4.0 only). For participants enrolled under protocol versions 1.0 - 4.0, the blind over placebo vs. vaccine will remain until after the second visit; during a follow-up call, scheduled 3 days after the second injection, participants will be unblinded as to whether they received placebo or active vaccine. Due to the different dosing schedules for the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine, it will become apparent to both the site staff, the study participant, and the parent/legal guardian which vaccine has been assigned, once the second injection visit is scheduled.

For participants enrolled under protocol versions 5.0 -8.0, at the call 3 days after the first injection visit, participants who received placebo as the first injection will be scheduled for a second injection visit to receive their first active vaccination for the vaccine to which they were assigned, as soon as 7 days after the placebo injection. For participants enrolled under versions 5.0 – 8.0, the participants and their parents/ legal guardians will know which company's vaccine they are receiving as the vaccines are anticipated to be used sequentially, and the vaccine will be noted in the consent form.

All participants will receive both recommended doses except if, after the first dose of either the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, a participant has, per CoFAR Grading Scale, a Grade 2 or higher systemic allergic reaction regardless of tryptase or a Grade 1 reaction with evidence of systemic mast cell activation as measured by serum tryptase that is at least possibly related to the first dose of vaccine; in that event, he/she will not receive the second dose.

If a participant has a Grade 1, per CoFAR Grading Scale, systemic allergic reaction with no evidence of systemic mast cell activation to the first dose of either the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine or if the Grade 1 systemic allergic reaction takes place after the participant has left the vaccination clinic and no tryptase measurements are available, he/she will receive counseling by a study physician and will be allowed to receive a second dose if he/she so chooses.

Because the placebo will consist of a normal saline injection, a reaction to placebo will not require termination from subsequent active vaccination, if the participant is willing to proceed following counseling.

If a participant becomes pregnant between the first and second doses of vaccine, she will receive counseling by a study physician and will be allowed to receive a second dose if she so chooses.

Vaccinated participants (placebo and active) will be followed for at least 7 days after their last dose.

Randomized and vaccinated participants will complete study participation in approximately 29 days if vaccinated with the Pfizer-BioNTech COVID-19 Vaccine or 36 days if vaccinated with the Moderna COVID-19 Vaccine. Participants enrolled under protocol versions 1.0 - 4.0 will complete participation in approximately 50 or 64 days if administered placebo before the two doses of Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, respectively, and participants enrolled under protocol versions 5.0 -8.0 will complete participation in approximately 36 or 43 days, respectively, if they receive placebo first.

Figure 1: Study Trial Design for Adults and Adolescents Enrolled Under Protocol Versions 1.0 - 4.0

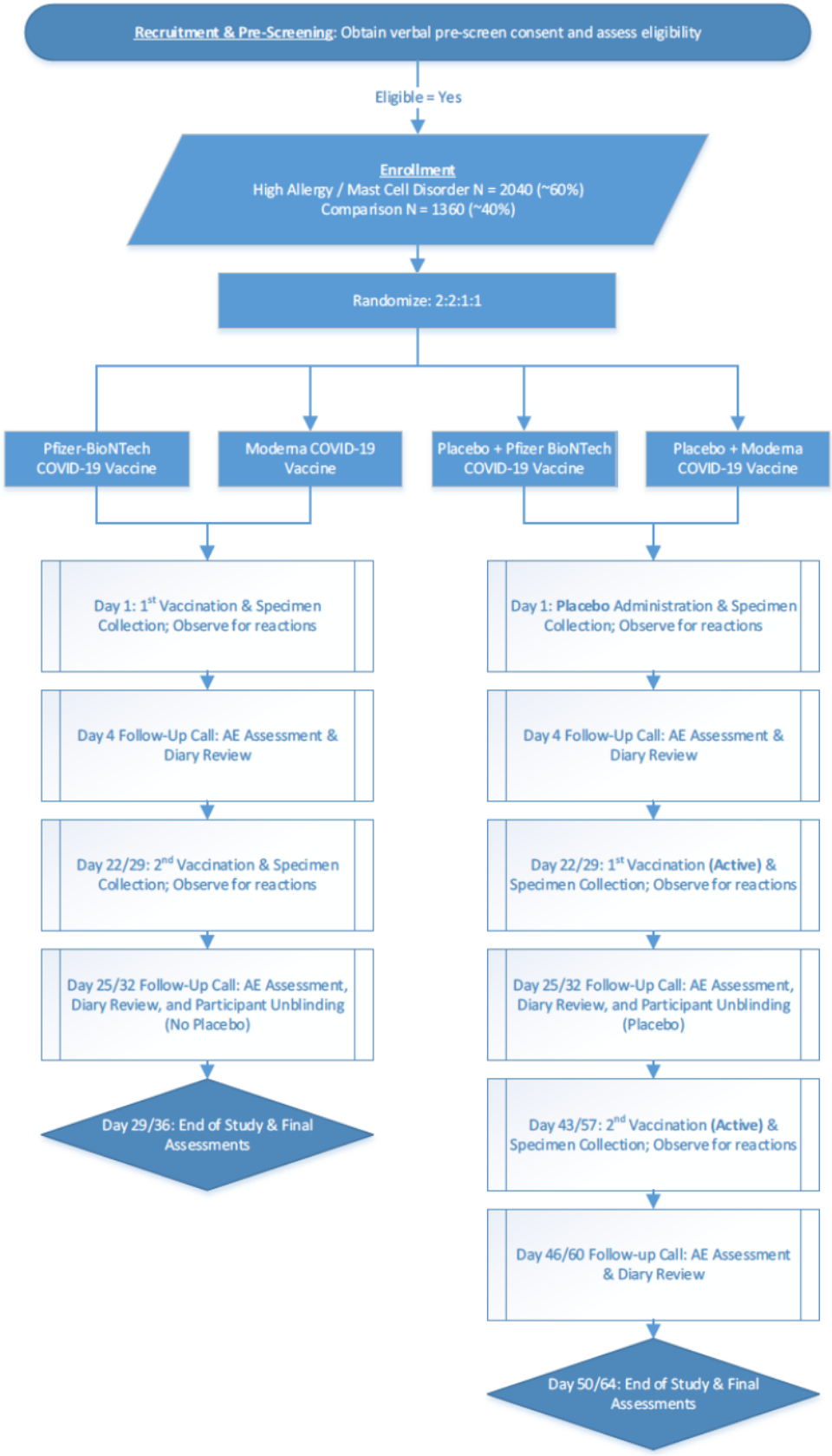
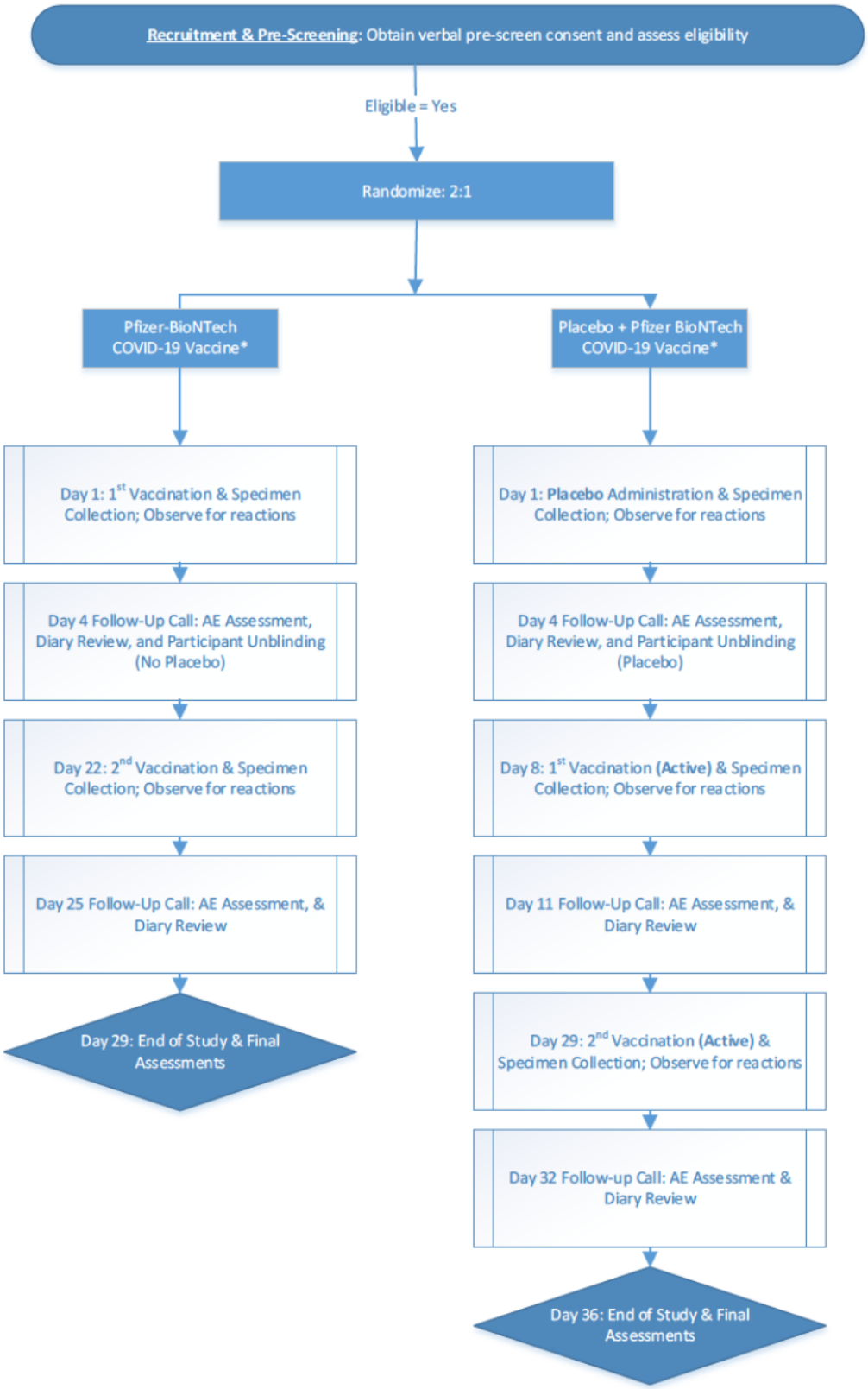


Figure 2: Study Trial Design for Children Enrolled Under Protocol Versions 5.0 – 8.0



*If the active vaccine arm is changed to Moderna, the 2nd Vaccination Visits will occur 28 days after the 1st Vaccination, and the visits there after will shift accordingly.

3.2. Primary Endpoints

The two primary endpoints are:

1. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Pfizer-BioNTech COVID-19 Vaccine
2. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Moderna COVID-19 Vaccine

A participant can have a reaction to either dose 1 or dose 2 (but not to both doses since a participant who has a reaction meeting qualifying criteria to dose 1 will not be able to receive the second dose) or to neither dose.

3.3. Secondary Endpoints

1. The proportion of participants who experience a severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0) systemic allergic reaction within the 90-minute post-vaccination observation period to either dose of each vaccine
2. The proportion of participants who experience an anaphylactic reaction (Levels 1-3) per Brighton Collaboration Criteria within the 90-minute post-vaccination observation period to either dose of each vaccine
3. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the first dose
4. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the second dose conditional on no systemic allergic reaction to the first dose
5. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to the first dose after adjusting for placebo administration
6. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above) within 48 hours of either dose of each vaccine

3.4. Exploratory Endpoints

1. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose
2. Prevalence of Polyethylene Glycol (PEG) antibodies in vaccine recipients before each vaccination
3. Changes in anti-PEG antibody levels 3-4 weeks after the first vaccine dose
4. Changes in biomarkers from pre- to post-vaccination and/or after onset of an allergic reaction (e.g., known mediators of systemic reactions due to mast cell activation, markers of inflammatory response, markers associated with activation of the classical and alternative complement pathways, or the kinin system)
5. Changes in blood transcriptomics after vaccination, and plasma and urine proteomics from pre- to post-vaccination and/or after onset of an allergic reaction
6. Genetic variants identified by whole-genome sequencing (applicable only in participants enrolled under protocol versions 1.0 - 4.0)

3.5. Stratification, Randomization, and Blinding/Masking

3.5.1. Stratification and Randomization

Randomization will be performed using a validated system configured by the Statistical and Clinical Coordinating Center (SACCC) that automates the random assignment of vaccine groups to study ID numbers. The randomization scheme will be generated by one statistician and reviewed and approved by another statistician at the SACCC.

Under protocol versions 1.0 – 4.0, participants were randomized 2:2:1:1 to receive either the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, placebo + Pfizer-BioNTech COVID-19 Vaccine, or placebo + Moderna COVID-19 Vaccine. Participants randomized to one of the placebo groups received placebo as a first dose and received two doses of their assigned active vaccine at subsequent visits.

Under protocol versions 5.0 – 8.0, participants will be initially randomized 2:1 to receive the Pfizer-BioNTech COVID-19 Vaccine or placebo + Pfizer-BioNTech COVID Vaccine. If enrollment is robust and sustained, the active vaccine may be changed to Moderna, and participants will then be randomized 2:1 to receive Moderna COVID-19 Vaccine or placebo + Moderna COVID-19 Vaccine.

Randomization will be stratified by site, sex, population (HA/MCD or comparison), and mast cell disorder/idiopathic anaphylaxis (yes or no) within the HA/MCD group. Randomization will occur in permuted blocks with varying block sizes randomly distributed. Randomization data will be kept strictly confidential, accessible only to authorized persons, until the time of unblinding. The clinical site's research pharmacy will dispense the study drug as per the randomly assigned treatments.

3.5.2. Blinding/Masking and Planned Unblinding

An unblinded pharmacist will prepare each vaccine, and an unblinded qualified medical professional will administer the vaccine in such a way that the participant cannot see the syringe. Unblinded staff may also schedule study visits and conduct procedures other than clinical endpoint assessments. Staff performing clinical assessments will not know whether a participant is receiving placebo or vaccine, or which vaccine a participant is receiving at the first visit. During a follow-up call, scheduled 3 days after the first vaccination/placebo dose, participants will be scheduled for their next dose.

Under protocol versions 1.0 - 4.0, participants and the staff were unblinded during the follow-up call 3 days after the second injection when a third appointment (for those who received a placebo injection first) was, or was not (active vaccinations only) scheduled. Due to the different dosing schedules for the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine, it became apparent to both the site staff and study participant which vaccine had been assigned, once their second injection was scheduled.

Under protocol versions 5.0 – 8.0, the participant, their parents/legal guardians, and staff will be aware of whether a participant received placebo at the phone call 3 days after the first injection when the participant is scheduled for the first active vaccine in approximately 7 days after placebo. Participants, their parents/legal guardians, and staff will not be blinded to vaccine assignment as only one active vaccine will be implemented at a given time.

Vaccination reports to the state and local authorities will be completed after a participant is unblinded.

3.6. Procedure for Unblinding/Unmasking due to a Life-Threatening Adverse Event, Early Termination of a Participant, or Determination of Whether a Participant Stopping Rule Has Been Met

If a CoFAR Grade 4 systemic allergic reaction or other life-threatening adverse event (AE) occurs and knowledge of the treatment assignment is required, the study treatment may be unblinded. Unblinding must be approved by the Division of Allergy, Immunology, and Transplantation (DAIT)/ NIAID Medical Monitor unless the DAIT/NIAID Medical Monitor is not accessible. In the event of an emergency, the investigator or designated qualified individual may obtain the participant's blinded treatment assignment via the validated system. Upon performance of a blind break, the system will send out a blinded notification to alert Statistical and Clinical Coordinating Center and NIAID staff. In the case of an accidental or emergency unblinding outside of the system, the site investigator will notify the DAIT/NIAID Medical Monitor and the SACCC team of the unblinding event by the next business day, following the unblinding. The unblinding will also be reported to the NIAID Asthma and Allergy Data and Safety Monitoring Board (DSMB).

In the event of early termination of a participant (Section 12.2), the request for non-emergent participant unblinding must be assessed and approved by the DAIT Medical Monitor. Unblinding approval may not be granted until data entry for the participant is complete. Once unblinded, a participant cannot re-enroll in the study and will be responsible for obtaining any subsequent doses of COVID-19 vaccine, if applicable. Refer to the MOP for additional details.

In the event a participant has had a reaction to the first injection or becomes pregnant following the first injection, it will be necessary to unblind the participant to determine whether the participant received placebo or vaccine and whether the participant has met a stopping rule or requires counseling prior to continuing in the study. The site should inform Rho and the DAIT Medical Monitor of the need for unblinding. The participant's assignment should be unblinded after the review of the diary on day 4, so that the participant may be informed if ineligible to continue, or counseled as to their options by an investigator if they remain eligible, and queried as to their wish to receive further injections.

A full account of each unblinding event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision, and the names of the Medical Monitor and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report.

Unblinding the study due to an approved interim analysis, final analysis, or study termination will require written approval from the DAIT/NIAID Medical Monitor.

All IND expedited safety reports will be reported to the FDA, IRBs, and DSMB in an unblinded fashion.

4. Selection of Participants

4.1. Rationale for Study Population

The occurrence of allergic reactions after administration of the new mRNA lipid nanoparticle vaccines has caused anxiety in the public, especially among those who have experienced severe allergic reactions to foods, insect stings, or medications. In the pediatric age group, most individuals with severe asthma are highly allergic as evidenced by multiple sensitivities to aeroallergens.[14] Currently, there are questions about the urgency for vaccination among those with severe allergic asthma as the data on risk is unclear. Pediatric onset asthma has been found to confer a decreased risk of COVID-19; however, poorly controlled pediatric asthma has been correlated to an increased risk of hospitalization.[15, 16] In addition to the highly allergic, there are individuals who have mast cell disorders which predispose them to life-threatening reactions to otherwise innocuous triggers. The mechanism of the vaccine reactions

is not known; the majority of people experiencing these reactions have had a history of "allergies" and a substantial number have reported a history of anaphylaxis, but careful evaluations of these individuals have not been conducted. Therefore, this study is designed to determine whether people with a recent history of severe allergic reactions to foods, allergen immunotherapy, insect stings, or allergic reactions to drugs or vaccines, or those with poorly controlled allergic asthma or mast cell disorders (HA/MCD group) are at increased risk for an allergic reaction compared to a comparison group without severe allergic disease or mast cell disorders. While it is possible that this HA/MCD group is not truly at the highest risk for allergic reactions to these SARS-CoV-2 vaccines, allergic and mast cell diseases that have the potential to produce serious allergic reactions are highly prevalent, and a study that reassures individuals with such conditions will positively impact the acceptability of the vaccine. Moreover, this will likely encompass individuals with milder allergic diseases who may also have second thoughts getting vaccinated.

In the event we do see a significant number of reactions, it would be important to be able to reliably ascertain relatedness to vaccination (hence exclusion of any allergen immunotherapy within the 24 hours prior to or after the vaccination, or other vaccination within 14 days). Similarly, we hope to begin to understand the mechanisms of reactions so have excluded medication use that would be expected to interfere with analysis in mechanistic studies. This includes medications such as immunomodulators including systemic steroids, biologics including type 2 inhibitors, as well as others such as rituximab, and the 5 LO inhibitor Zileuton. To minimize risks, we are excluding participants with underlying conditions or other medications that, in the opinion of the investigator, may increase risk in the event of an anaphylactic reaction or lead to complications following administration of epinephrine, including but not limited to, those with coronary artery disease, peripheral or cerebral vascular disease, unstable angina, cardiac arrhythmia other than supraventricular tachycardia (SVT), medically unstable hypertension, unstable asthma or symptomatic asthma on the day of vaccination, or with current use of beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, monoamine oxidase (MAO) inhibitors, tricyclic anti-depressants or other agents that could interfere with the treatment of anaphylaxis in the opinion of the investigator (Section 4.3). Finally, we do not anticipate many of the recruited individuals will meet current criteria for high risk for COVID-19, which are the only pregnant individuals the ACIP and CDC suggest should consider vaccination after a discussion with their physician, thus we are excluding pregnant women from enrolling, though they may elect to receive the second vaccination if they become pregnant during the 3 - 4 weeks between vaccinations.

As the pandemic has continued, the emergency use approvals have been expanded to younger ages over time. To date, the enrollment in DAIT-COVID-19-004 has been very largely adults. To ascertain if age is a risk factor for reaction, beginning under protocol version 5.0, children aged 5 to 17 years will be enrolled. The Pfizer-BioNTech COVID-19 Vaccine is currently approved for individuals 5 to 15 years of age under EUA and 16 years or older under full licensure. A phase 2/3 study is currently underway for the Moderna COVID-19 Vaccine in children from age 6 months to age 11 years (Section 1.3). Both because school aged children have not been assessed for the incidence of systemic allergic reactions to the mRNA vaccines and because they have a higher rate of food allergy-induced anaphylaxis than adults, it is important to include them in the assessment of reactions.

4.2. Inclusion Criteria

Note criteria apply to all cohorts and protocol versions, unless otherwise stated.

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

Both groups:

1. Participant and/or parent/legal guardian must be able to understand and provide informed consent and/or assent, as applicable

2. Male or non-pregnant female 12 years of age or older on the date of first study vaccination/placebo administration (protocol versions 1.0 – 4.0) **OR** male or non-pregnant female 5 -17 years of age on the date of first study vaccination/placebo administration (protocol versions 5.0 – 8.0)
3. Females of childbearing potential must have a negative pregnancy test prior to the first vaccination and placebo administration, if applicable. If a participant becomes pregnant after receiving a placebo dose but prior to receiving study vaccination, she will be discontinued from the study.
4. Females of reproductive potential* and sexually active must agree to use FDA approved methods of birth control for the duration of the study. These include hormonal contraceptives, intrauterine device, double barrier contraception (i.e., condom plus diaphragm), or male partner with documented vasectomy. *Menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone of ≥25 U/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception.

<u>High-Allergy and Mast Cell Disorder (HA/MCD) group:</u>

Individuals who meet at least one of the following criteria are eligible for enrollment in the HA/MCD group:

1. History of a severe allergic reaction to food(s), allergen immunotherapy, insect venom(s), or latex with use of epinephrine within the last 15 years
2. History of an Emergency Department visit with convincing evidence of a systemic allergic reaction (consistent with CoFAR Grade 3 or higher) to food(s), allergen immunotherapy, insect venom(s), or latex within the last 15 years
3. History of documented, immediate allergic reactions to 2 or more unrelated drugs within the last 15 years
4. A convincing clinical history, or a history that is accompanied by a positive skin test, of an immediate reaction to a drug, vaccine, or latex within the last 15 years
5. History of physician-diagnosed idiopathic anaphylaxis with use of epinephrine or an Emergency Department visit within the last 15 years
6. History of a physician-diagnosed mast cell disorder (e.g., mastocytosis, mast cell activation syndrome (MCAS), or hereditary alpha-tryptasemia). MCAS must meet consensus criteria[17], as defined below:
    - <u>Criterion A:</u> Typical clinical signs of severe, recurrent (episodic) systemic MCA are present (often in form of anaphylaxis) (definition of systemic: involving at least 2 organ systems)
    - <u>Criterion B: Involvement of MC is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to plus 20% + 2 ng/ml</u>
    - <u>Criterion C:</u> Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production or drugs blocking mediator release or effects of MC-derived mediators

    All 3 MCAS criteria (A + B + C) must be fulfilled to call a condition MCAS.
7. Poorly controlled asthma as evidenced by one hospitalization or one or more systemic (oral or injectable) steroid burst(s) in the 24 months prior to enrollment and evidence of aeroallergen sensitization by blood work, skin test, or appropriate history.
8. A doctor diagnosis of food allergy with a convincing clinical history and a positive skin test or positive food challenge, with evidence of reactivity in the last 10 years.

<u>Comparison group:</u>

Individuals who meet all of the following criteria are eligible for enrollment in the comparison group:

1. No history of allergic asthma or atopic dermatitis within the last 10 years
2. No history of chronic spontaneous urticaria or angioedema
3. No history of allergic reactions to foods or insect venoms
4. No history of allergic reactions to drugs or vaccines
5. No history of anaphylaxis
6. No history of a mast cell disorder (e.g., mastocytosis, MCAS, or hereditary alpha-tryptasemia)

4.3. Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant and/or parent/legal guardian to give written informed consent and/or assent, if applicable, or comply with study protocol
2. Weight less than 15 kg
3. Prior receipt of any doses of the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, or any other COVID-19 vaccine
4. History of a severe reaction to any component of the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine
5. History of contact dermatitis with confirmed patch test reaction to PEG
6. History of reaction to Doxil
7. Known exposure to SARS-CoV-2 and still within the quarantine window
8. Symptoms consistent with acute COVID-19 infection or known COVID-19 infection (positive PCR or antigen test) and still within the quarantine window
9. Have an acute illness, including body temperature greater than 100.4˚, within 14 days of the first study vaccination/placebo administration or 3 days prior to each subsequent vaccination
10. History of autoimmune or other disorders requiring systemic immune modulators
11. History of acute urticaria within 28 days of randomization
12. Pregnant
13. Have received any vaccines within 14 days of the first study vaccination/placebo administration or plan to receive other vaccines during the study period
14. Had any allergen immunotherapy administration within 24 hours prior to vaccination/placebo administration or plan to receive within 24 hours after vaccination/placebo administration
15. Have received a biologic therapy within 6 months of randomization
16. Use of systemic steroids for any reason within 28 days of randomization
17. Use of Zileuton within 14 days of randomization
18. Use of any antibody agent for treatment or prevention of COVID-19 within 3 months of randomization
19. Coronary artery disease, peripheral or cerebral vascular disease, unstable angina, or cardiac arrhythmia other than supraventricular tachycardia (SVT)
20. Medically unstable hypertension
21. Current use of beta-blockers, ACE inhibitors, MAO inhibitors, tricyclic anti-depressants or other agents that could interfere with the treatment of anaphylaxis, in the opinion of the investigator

22. Unstable asthma within 3 months of randomization or symptomatic asthma on the day of vaccination as assessed by the site investigator
23. Have past or current medical problems or findings from physical exam or laboratory testing not listed above, which in the opinion of the investigator, may pose additional risks from participation in the study or which may interfere with the ability to comply with study requirements. This includes individuals with underlying conditions or other medications that, in the opinion of the investigator, may increase risk in the event of an anaphylactic reaction or lead to complications following administration of epinephrine.

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Investigational Product as cited in the Full FDA EUA Prescribing Information and/or Package Insert

Adverse reactions following the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy.[13] Severe allergic reactions, including anaphylaxis, other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema), myocarditis, pericarditis, diarrhea, vomiting, and pain in extremity (arm) have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials.

In a clinical study in children 5 through 11 years of age who received Pfizer-BioNTech COVID-19 Vaccine containing 10 mcg of a nucleoside-modified messenger RNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 (10 mcg modRNA), adverse reactions following administration of any primary series dose included pain at the injection site (84.3%), fatigue (51.7%), headache (38.2%), injection site redness (26.4%), injection site swelling (20.4%), muscle pain (17.5%), chills (12.4%), fever (8.3%), joint pain (7.6%), lymphadenopathy (0.9%), nausea (0.4%), rash (0.3%), malaise (0.1%), and decreased appetite (0.1%).

Following FDA authorization of the Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years of age and older, severe allergic reactions, including anaphylaxis, have been reported outside of clinical trials. Myocarditis and pericarditis have also been reported.

Adverse reactions reported in a clinical trial following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site.[9] Severe allergic reactions, including anaphylaxis, myocarditis, and pericarditis have been reported during mass vaccination outside of clinical trials.

5.1.1. Allergic Reactions and Anaphylaxis

Allergic reactions have been reported to occur after vaccination with both the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine. Allergic reactions range from mild to severe and include life-threatening anaphylactic reactions, although no deaths have been reported with either vaccine.

Due to the risk of allergic reactions, participants with existing epinephrine prescriptions will be encouraged and reminded to bring their epinephrine auto-injectors with them to each clinic visit. The clinical team will provide prescriptions for epinephrine auto-injectors for those in the HA/MCD group as needed. If a HA/MCD participant does not bring his/her epinephrine auto-injectors or brings expired auto-injectors to clinic on the day of an injection, the site will provide the participant with an epinephrine auto-injector 2-pack.

In addition, participants will receive an Anaphylaxis Emergency Care Plan at each injection visit. The PI or designee will review the plan including symptoms of an allergic reaction and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant and/or parents/legal guardians prior to discharge.

If a participant has an allergic reaction, he/she may need oral, IM, or IV medications (Section 7.4 Rescue Medications). The site investigators for this trial are allergists, trained to recognize, and familiar with the treatment of anaphylaxis, and will be available within 60 seconds in the event of a reaction. Emergency medications, oxygen, and equipment will be available to treat any allergic reactions. Guidelines for the treatment of systemic allergic reactions are detailed in the Manual of Procedures (MOP).

5.2. Risks of Investigational Product or Intervention cited in Medical Literature

During December 14-23, 2020, monitoring by the Vaccine Adverse Event Reporting System (VAERS) detected 21 cases of anaphylaxis (corresponding to an estimated rate of 11.1 cases per million doses) and 83 cases of non-anaphylactic allergic reaction after administration of a reported 1,893,360 doses of the Pfizer-BioNTech COVID-19 Vaccine. Of the 21 individuals experiencing anaphylactic reactions, 17 (81%) had a documented history of allergies or allergic reactions, including to drugs or medical products, foods, or insect stings.[2]

Based on VAERS data for December 21, 2020-January 10, 2021, 10 cases of anaphylaxis were detected after reported administration of 4,041,396 doses of Moderna COVID-19 Vaccine (2.5 cases per million doses) and 47 cases of nonanaphylactic allergic reactions. Of the 10 cases of anaphylaxis, 9 were in persons with a documented history of allergies or allergic reactions, five of whom had a previous history of anaphylaxis.[3]

5.3. Risks of Other Protocol Specified Medications

Treatment of individual acute allergic reactions during the conduct of the study should be with epinephrine, IV fluids, β-adrenergic agonists (e.g., albuterol), oxygen, antihistamines, and steroids, as indicated for the severity of the reaction. Risks of these common medications are summarized below:

- Antihistamines: drowsiness, dizziness, constipation, stomach upset, blurred vision, or dry mouth/nose/throat
- Epinephrine: tachycardia, palpitations, nervousness, sweating, nausea, vomiting, trouble breathing, headache, dizziness, anxiety, tremors, or pale skin
- β-adrenergic agonists: nervousness, shaking (tremor), headache, or dizziness
- Steroids: nausea, vomiting, loss of appetite, heartburn, trouble sleeping, increased sweating, or acne

5.4. Risks of Study Procedures

5.4.1. Risks Associated with Physical Exam

There are no known risks associated with the physical exam.

5.4.2. Risks Associated with Medical History or Participant Diary

There is a possibility that participants may find questions about their medical history or questions asked on the participant diary to be too personal. Participants may refuse to answer any questions that make them feel uncomfortable. There is also a possibility that a participant's answers may be read by others; however, participants' records are carefully protected so this is very unlikely. See Section 18.3 Privacy and Confidentiality for more information.

5.4.3. Risks Associated with Blood Collection

Risks associated with drawing blood include possible pain when the needle is inserted, as well as bleeding, bruising and/or infection at the puncture site. Some people may experience lightheadedness, nausea, or fainting. National Institutes of Health (NIH) guidelines for blood collection (amount and frequency) will be followed.[18] Participants weighing less than 50 kg will not participate in PBMC sampling, and participants enrolled under protocol versions 5.0 – 8.0 will have a further modified set of bloods drawn such that they will not exceed the NIH pediatric limit of 5 ml/kg over any 8 week period.

5.4.4. Risks Associated with Nasal Swab Collection

Nasal swab collection may cause localized discomfort. Rarely, mild epistaxis may occur.

Nasal swab collection will not occur for participants enrolled under protocol version 8.0.

5.4.5. Risks Associated with Urine Collection

There are no risks associated with urine sample collection.

5.5. Potential Benefits

Participants will receive highly protective COVID-19 vaccines for the SARS-CoV-2 virus in an environment where the investigators and staff are experienced in the care of patients with anaphylactic reactions. The vaccines may not protect all vaccine recipients.

Information gained from this study will facilitate risk factor analysis to improve patient selection for these vaccines and potentially improve the design of future vaccines using this platform.

6. Investigational Agent

6.1. Investigational Agents

6.1.1. Investigational Agent #1: Moderna COVID-19 Vaccine

The Moderna COVID-19 Vaccine is authorized for use under EUA for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. In addition, a third primary series dose has been authorized for immunocompromised individuals 18 years of age and older. A single booster dose has been authorized for individuals 18 years and older.

6.1.1.1. Formulation, Packaging, and Storage

Moderna COVID-19 Vaccine is provided as a white to off-white suspension for intramuscular injection. Each 0.5 mL dose of Moderna COVID-19 Vaccine contains 100 mcg of nucleoside-modified messenger RNA (modRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus.

Each 0.5 mL dose of the Moderna COVID-19 Vaccine also contains the following ingredients: a total lipid content of 1.93 mg (SM-102, PEG 2000 dimyristoyl glycerol [DMG], cholesterol, and DSPC), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.20 mg sodium acetate trihydrate, and 43.5 mg sucrose. Each 0.25 mL dose of Moderna COVID-19 Vaccine contains half the amount of these ingredients.

Moderna COVID-19 Vaccine will be supplied to NIAID in cartons containing one multiple-dose vial per carton (two vial sizes: 10 doses per vial or 14 doses per vial); the vial stoppers are not made with natural rubber latex.

Moderna COVID-19 Vaccine multiple-dose vials should be stored frozen between -50° to -15° C (-58° to 5° F) in the original carton to protect from light. Product should not be stored on dry ice or below -50° C (-58° F). Vials may be stored refrigerated between 2° to 8° C (36° to 46° F) for up to 30 days prior to first use. Vials may be stored between 8° to 25° C (46° to 77° F) for a total of 24 hours. After the first dose has been withdrawn, the vial and/or prepared syringes should be held between 2° to 25° C (36° to 77° F) for up to twelve hours. Any remaining vaccine in the vial and/or prepared syringes should be discarded after 12 hours. Vials should not be refrozen.

6.1.1.2. Dosage, Preparation, and Administration

The Moderna COVID-19 Vaccine multiple-dose vial contains a frozen suspension that does not contain a preservative and must be thawed prior to administration, per the Full FDA EUA Prescribing Information.[9] Additional details are included in the Pharmacy Manual.

For participants 12 years of age or older, the Moderna COVID-19 Vaccine 100 mcg in **0.5 mL** will be administered intramuscularly in the deltoid. For participants aged 5 to 11 years, the Moderna COVID-19 vaccine 50 mcg in **0.25 mL** will be administered intramuscularly. Vaccine administration details will be recorded on the Vaccine Administration electronic case report form (eCRF).

The Moderna COVID-19 Vaccine is administered as a series of two doses 1 month (28 days) apart.

6.1.2. Investigational Agent #2: Pfizer-BioNTech COVID-19 Vaccine

The Pfizer-BioNTech COVID-19 (COMIRNATY®) Vaccine is FDA approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older and authorized for use under EUA for children ages 5 to 15 years. In addition, a third primary series dose has been authorized for immunocompromised individuals 12 years of age and older. A single booster dose has been authorized for individuals 12 years and older who have completed a primary series with the Pfizer-BioNTech COVID-19 (COMIRNATY®) Vaccine. A single booster has also been authorized for individuals 18 years and older who have completed primary vaccination with a different authorized COVID-19 vaccine.

6.1.2.1. Formulation, Packaging, and Storage for the Vaccine Approved for Individuals Aged 12-years and Older- Purple Cap

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple-dose vials. The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative and must be thawed per the Full FDA Prescribing Information prior to administration. Each vial must be diluted with 1.8 mL of sterile non-bacteriostatic 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 plus the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[PEG-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium

Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose. The vial stoppers are not made with natural rubber latex.

Pfizer-BioNTech COVID-19 Vaccine will be supplied in cartons containing 2 multiple-dose vials (up to 6 doses per vial after dilution), shipped in thermal insulated containers with dry ice. Once received, the vial cartons must be removed immediately from the thermal container and stored in an ultra-low temperature freezer between -90º C to -60º C (-130ºF to -76º F). Vials must be kept frozen between -90º C to -60º C (-130º F to -76º F) and protected from light until ready to use.

The diluent, 0.9% Sodium Chloride Injection, USP, 2 mL per vial is supplied in cartons containing 25 vials per carton and shipped under ambient conditions.

6.1.2.1.1. Dosage, Preparation, and Administration

The Pfizer-BioNTech COVID-19 Vaccine multiple-dose vial (up to 6 doses) with purple cap contains a volume of 0.45 mL supplied as a frozen suspension that does not contain preservative. Each vial must be thawed prior to dilution with 1.8 mL of sterile non-bacteriostatic 0.9% Sodium Chloride Injection, USP and vaccine administration, per the Full FDA EUA Prescribing Information.[13] Additional details are included in the Pharmacy Manual.

The Pfizer-BioNTech COVID-19 Vaccine 30 mcg in 0.3 mL will be administered intramuscularly in the deltoid. Vaccine administration details will be recorded on the Vaccine Administration eCRF.

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks (21 days) apart.

6.1.2.2. Formulation, Packaging, and Storage for the Vaccine Approved for Individuals Aged 5 through 11 Years – Orange Cap

The Pfizer-BioNTech COVID-19 Vaccine for individuals aged 5 through 11 years in multiple dose vials (up to 10 doses) **with orange caps and labels with orange borders** is supplied as a frozen suspension; each vial must be diluted with 1.3 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine.

Each 0.2 mL dose of the Pfizer-BioNTech COVID-19 Vaccine supplied in multiple dose vials with orange caps and labels with orange borders also includes the following ingredients: lipids (0.14 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.02 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.03 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.06 mg cholesterol), 10.3 mg sucrose, 0.02 mg tromethamine, and 0.13 mg tromethamine hydrochloride. The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes 0.9 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative.

The vial stoppers are not made with natural rubber latex.

6.1.2.2.1. Dosage, Preparation, and Administration

The Pfizer-BioNTech COVID-19 Vaccine for individuals aged 5 through 11 years multiple-dose vial (up to 10 doses) with orange cap contains a volume of 1.3 mL supplied as a frozen suspension that does not

contain preservative. Each vial must be thawed prior to dilution with 1.3 mL of sterile non-bacteriostatic 0.9% Sodium Chloride Injection, USP and vaccine administration, per the Full FDA EUA Prescribing Information.[13] Additional details are included in the Pharmacy Manual.

The Pfizer-BioNTech COVID-19 Vaccine 10 mcg in 0.2 mL will be administered intramuscularly. Vaccine administration details will be recorded on the Vaccine Administration eCRF.

The Pfizer-BioNTech COVID-19 Vaccine for individuals aged 5 through 11 years is administered intramuscularly as a series of two doses 10 mcg in 0.2 mL each 3 weeks (21 days) apart.

6.1.3. Placebo

6.1.3.1. Formulation, Packaging, and Storage

The placebo for Moderna and Pfizer-BioNTech COVID-19 vaccines will be commercially available sterile, preservative-free 0.9% Sodium Chloride Injection, USP in this study. Each mL contains sodium chloride 9 mg and water for injection, quantity sufficient. It contains no bacteriostat, antimicrobial agent, or added buffer. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment. Placebo will be provided by the clinical site pharmacies. The manufacturer, lot number(s), and expiration date will be documented.

Placebo should be stored at 20° C to 25°C (68° F to 77° F).

6.1.3.2. Dosage and Administration

Participants who are randomized to receive placebo prior to active vaccine will receive a single dose, either 0.2 mL, 0.25 mL, 0.3 mL or 0.5 mL. The dose to be administered intramuscularly will be consistent with the dose they will receive for their assigned active vaccine. The placebo dose will be followed by the two doses of active vaccine based on the appropriate dosing schedule for the assigned vaccine.

6.2. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62), the investigator will maintain adequate records of the disposition of the investigational agents, including the date and quantity of the vaccine product received, to whom the vaccine was dispensed (participant-by-participant accounting), and a detailed accounting of any vaccine accidentally or deliberately destroyed. Details of vaccine distribution to each participating clinical site will be maintained by the distributor (EMINENT). The investigator must delegate the investigational product accountability responsibility to a licensed/registered pharmacist at the registered investigational pharmacy at the clinical research site. Please refer to the DAIT Pharmacy Guidelines (https://www.niaid.nih.gov/sites/default/files/pharmacy.pdf).

All personnel involved in investigational product management and preparation must receive proper training based on DAIT and site requirements prior to study initiation. The Pharmacist of Record should be listed on the Delegation of Responsibility Log (DoR) and is responsible to ensure that any pharmacy personnel involved in any aspect of the investigational product management, preparation, and dispensing process have completed and documented all DAIT required trainings (GCP/HSP, protocol/pharmacy manual, DAIT Pharmacy Guidelines). Only individuals listed on the DoR log and/or 1572 may manage investigational products for this study. All disposition and dispensing (receipt, storage, use, return, and disposition) will be maintained by the study site using vaccine/placebo-accountability and participant-specific

dispensing logs that are approved by DAIT/NIAID and 21 CFR 11 compliant. This log will contain the identification of each participant and the date and quantity of vaccine/placebo dispensed.

The study clinical research associate (CRA) will conduct accountability of the investigational products by monitoring the main Accountability Records and Participant-Specific dispensing log. The study CRA will also review other pharmacy logs, as applicable. All records regarding the disposition of the investigational product will be available for monitoring and inspection. At the termination of the study, all unused product (expired or un-expired) will be returned to EMINENT. For more detailed information on handling of the vaccine/placebo, please refer to the Pharmacy Manual.

Clinical sites will establish plans to minimize waste of vaccine. However, priority will be placed on enrolling participants and minimizing the time for their vaccination.

6.3. Assessment of Participant Compliance with Investigational Agent

Participants in this study will receive all doses of the assigned vaccine/placebo under direct observation.

6.4. Toxicity Prevention and Management

Participants will receive investigational agents in facilities where the investigative team is familiar and practiced in the treatment of systemic allergic reactions. Standard therapeutic agents, oxygen, and equipment will be available on site to treat reactions. Refer to Section 5.1.1 Allergic Reactions and Anaphylaxis.

6.5. Premature Discontinuation of Investigational Agent

Vaccination will be prematurely discontinued for any participant for any of the following reasons:

- Participant has a CoFAR Grade 2 or higher systemic allergic reaction regardless of tryptase, or a CoFAR Grade 1 reaction with elevated tryptase [1.2 x baseline plus 2 ng/ml] that is at least possibly related to the first dose of the vaccine. If the systemic allergic reaction took place after the participant has left the vaccination clinic and no tryptase measurements are available, Grade 1 events will not constitute criteria for discontinuation, but counseling by a study physician will be required (see below).
- The investigator believes that it is no longer in the best interest of the participant to receive the second vaccination

In the above cases, the participant will be asked to return for his/her next in clinic study visit during which reactogenicity symptoms will be reviewed (electronic diary review or return and review of paper diary), adverse events (AEs) and concomitant medications will be recorded, and pre-vaccination biospecimens will be obtained per protocol.

Vaccination may be prematurely discontinued for any participant for any of the following reasons:

- If a participant has a Grade 1 (per CoFAR Grading Scale) systemic allergic reaction with no evidence of systemic mast cell activation to the first dose of either the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, he/she will receive counseling by a study physician and will be allowed to receive a second dose if he/she so chooses.
- Because the placebo will consist of a normal saline injection, a reaction to placebo will not require termination from subsequent active vaccination, if the participant is willing to proceed following counseling.
- If a participant becomes pregnant between the first and second doses of vaccine, she will receive counseling by a study physician and will be allowed to receive a second dose if she so chooses.

7. Other Medications

7.1. Concomitant Medications

7.1.1. Protocol-Mandated

Enrolled participants with existing epinephrine prescriptions will be encouraged to bring their epinephrine auto-injectors with them to each clinic visit. Expiration dates of prescribed epinephrine pens will be assessed during the collection of concomitant medications. If the epinephrine is expired, the study physician may offer to provide a prescription. If it is clear to the study team, that a participant does not have insurance coverage for epinephrine and/or cannot afford to purchase it, a study-provided pack of 2 pens may be dispensed. The decision of an individual to not carry epinephrine (for any reason) will not be exclusionary for study participation.

7.1.2. Other Permitted Concomitant Medications

Other than the prohibited medications listed in Section 7.3 Prohibited Medications, treatment with concomitant medications is permitted throughout study participation.

7.2. Prophylactic Medications

Female participants of child-bearing potential must use an effective method of contraception (e.g. total abstinence, oral contraceptives, IUDs, barrier method with spermicide, surgical sterilization or surgically sterilized partner, Depo-Provera, Norplant, NuvaRing, or hormonal implants) for the duration of study participation.

7.3. Prohibited Medications

The following medications are prohibited during participation in the study:

- Systemic immunomodulators including systemic steroids
- Biologic agents
- Any antibody agent for treatment or prevention of COVID-19
- Zileuton
- Vaccines administered outside of the study

If a participant takes a prohibited medication during the study, it should be recorded as a protocol deviation in the eCRF. The study physician will determine whether the second vaccination should be administered or not and whether vaccination should be delayed based on the medication(s) the participant used.

7.4. Rescue Medications

The following medications may be used to treat an allergic reaction:

- Epinephrine 1 mg/mL; 0.15 – 0.5 mg IM
- β-adrenergic agonist inhaler or nebulizer (e.g. albuterol)
- Antihistamines
- Steroids
- IV fluids
- Oxygen

Guidelines for the treatment of systemic allergic reactions are detailed in the MOP. Rescue medications should be recorded on the Concomitant Medications eCRF.

8. Study Procedures (Protocol versions 1.0 – 4.0)

A summary of complete study procedures is included in Tables A and B in Appendix 3: Schedule of Events.

8.1. Recruitment & Pre-Screening (Day -14 to Day 0)

Potential study participants may be identified by medical chart review or from a response to a study advertisement, and initially contacted by a member of the study team in person or over the phone. During this initial contact, the potential participant will be provided information on the study and asked to provide verbal permission for pre-screening. If a participant provides verbal permission for pre-screening, they may be pre-screened over the phone using a standardized form to confirm eligibility. Eligible pre-screened individuals interested in participating in the study will be consented either remotely or during a clinic visit.

If it is possible to provide a physical copy of the consent and/or assent (if applicable) and verify who is consenting/assenting, remote consenting may be conducted. In the event of a remote consent, the participant will need to return the signed consent and/or assent (if applicable) to the clinic, prior to the conduct of any study procedures. The signed consent and/or assent may be returned via an approved electronic platform, in person, and/or by mail. The process for remote consenting will be further defined in the MOP.

In the event a site does not have the ability to conduct a remote consent and/or the participant or parent/legal guardian does not have access to the methods required for remote consent, an in-person clinic visit may be scheduled to complete the consenting process. Based upon the site's policies and vaccination schedules, this may be a separate clinic visit and/or combined with the Enrollment Visit.

8.2. Enrollment Visit (Day 1)

The purpose of the Enrollment Visit is to obtain written informed consent and/or assent (if applicable), if not previously obtained remotely and/or during a separate clinic visit (prior to performing any other study procedures), confirm there are no changes in the participant's eligibility since pre-screening, and initiate vaccination or placebo administration.

The following procedures and assessments will be conducted during this visit:

Pre-Vaccination

- Obtain written informed consent and/or assent, if not obtained prior to visit
- Collect demographics
- Medical History and Physical Exam by a study physician or other qualified medical professional
- Urine pregnancy test for female participants of child-bearing potential who do not self-report as pregnant
- Assessment of concomitant medications
- Vital signs (temperature, pulse rate, respiratory rate, O_2 saturation, blood pressure), plus growth parameters (height and weight)
- Randomization
- Assessment of HA/MCD participant access to an epinephrine auto injector; distribution of epinephrine auto-injectors (2 pack) for participants in the HA/MCD group who did not bring auto-injectors with them or bring expired auto-injectors
- Blood, nasal swab, and urine sample collections for assessments defined in Appendix 3: Schedule of Events
- Assessment of AEs

- Diary Overview, Training, & Distribution: Participants will be provided access to an electronic 7-day diary to aid in recording solicited local and systemic reactions to the vaccine, as well as symptoms of a potential allergic reaction, unsolicited AEs, and concomitant medications, including start and stop dates. The diary will include instructions for participants on how to take an oral temperature and how to measure injection site reactions. A paper copy of the diary may be provided for participants who do not have a device to access the electronic diary or as a backup collection tool. A member of the study team will review the information in the diary with the participant, including how to use and access the electronic diary.

Following sample collection, participants will be randomized and will receive their initial vaccination or placebo dose. Following vaccination or placebo administration (as assigned), the study participant will be observed for 90 minutes for AEs, including examination of the injection site, and have vital sign measurements and additional urine and blood samples collected 1-hour post-vaccination and/or 30-60 minutes after the onset of an allergic reaction.

During the 90-minute observation period, all AEs will be recorded, and AEs judged by an investigator to constitute an allergic reaction, even if not severe, will be documented on the appropriate eCRFs. In the event of an allergic reaction occurring more than 1 hour post vaccination, urine and blood samples will be collected, per Appendix 3: Schedule of Events.

In the event of a systemic allergic reaction, participants will be treated with rescue medications (Section 7.4 Rescue Medications) and observed for a minimum of 2 hours after their symptoms resolve. Vital signs will be monitored during a systemic allergic reaction. Additional urine and blood samples will be obtained prior to discharge.

To assist study participants and/or their parents/legal guardians in the identification of and steps to take in the event of an allergic reaction after they leave the study site, each participant will be provided with an Anaphylaxis Emergency Care Plan. The PI or designee shall review the symptoms and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant and/or parents/legal guardians prior to discharge.

8.3. Follow-Up Call (Day 4 ± 1 Day)

Approximately 3 days following the participant's Enrollment Visit, the study team will call the participant to assess for AEs and review the participant diary. Any reported AEs and changes in concomitant medications will be recorded on the appropriate eCRF. Study staff will schedule the participant's next vaccination visit during the call.

8.4. Participants Randomized to Vaccine and No Placebo

8.4.1. Second Vaccination Visit (Day 22 or 29; -4 to +14 Days)

Participants randomized to vaccine (no placebo) will be asked to return to clinic for the second vaccination 21 days (Day 22) or 28 days (Day 29) after their first vaccination, based on their assignment to receive the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine.

The following procedures and assessments will be conducted during this visit:

Pre-Vaccination

- Abbreviated Medical History and Targeted Physical Exam by a study physician or other qualified medical professional
- Urine pregnancy test for female participants of child-bearing potential who do not self-report as pregnant

- Assessment of concomitant medications
- Vital signs
- Blood, nasal swab, and urine sample collections for assessments defined in Appendix 3: Schedule of Events
- Assessment of AEs
- Diary Review (Dose 1) and Distribution (Dose 2)
- Distribution of epinephrine auto-injectors (2 pack) for participants in the HA/MCD group who did not bring with them or bring expired auto-injectors

Following sample collections, participants will receive their second vaccination. Following vaccination, the study participant will be observed for AEs, including examination of the vaccination site, and have vital sign measurements and additional urine and blood samples collected 1-hour post-vaccination and/or 30-60 minutes after the onset of an allergic reaction.

During the 90-minute observation period, all AEs will be recorded, and AEs judged by an investigator to constitute an allergic reaction, even if not severe, will be documented on the appropriate eCRFs. In the event of an allergic reaction, occurring more than 1 hour post vaccination, urine and blood samples will be collected, per Appendix 3: Schedule of Events.

In the event of a systemic allergic reaction, participants will be treated with rescue medications (Section 7.4: Rescue Medications) and observed for a minimum of 2 hours after their symptoms resolve. Vital signs will be monitored during a systemic allergic reaction. Additional urine and blood samples will be obtained prior to discharge.

To assist study participants and/or their parents/legal guardians in the identification of and steps to take in the event of an allergic reaction after they leave the study site, each participant will be provided with an Anaphylaxis Emergency Care Plan. The PI or designee shall review the symptoms and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant and/or parents/legal guardians prior to discharge.

8.4.2. Follow-Up Call (Day 25 or 32 ± 1 Day)

Approximately 3 days following the participant's second vaccination visit, the study team will call the participant to assess for AEs and review the participant diary. Any reported AEs and changes in concomitant medications will be recorded on the appropriate eCRF. Participants will be told whether they were part of the group who received a placebo dose.

8.5. Participants Randomized to Receive Placebo

8.5.1. First Vaccination Visit (Day 22 or 29; -4 to + 14 Days)

Participants randomized to placebo will be asked to return to clinic to receive their first vaccine injection, approximately 21 or 28 days, per vaccine assignment, after they received the placebo. In addition to receiving the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, the participant will complete the same study procedures as those conducted during the Enrollment Visit, with the exception of growth parameters (Section 8.2 Enrollment Visit [Day 1]).

8.5.2. Follow-Up Call (Day 25 or 32 ± 1 Day)

Following their First Vaccination Visit, participants randomized to placebo, will have a follow-up call, approximately 3 days later. The study team will call the participant to assess for AEs and review the participant diary. Any reported AEs and changes in concomitant medications will be recorded on the appropriate eCRF. Participants will be told whether they were part of the group who received a placebo dose.

8.5.3. Second Vaccination Visit (Day 43 or 57; -4 to +14 Days)

Participants randomized to receive placebo during their Enrollment Visit, will complete a third clinic visit, during which they will receive their second injection of the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, as assigned. The procedures and assessments conducted during this visit will be the same as those conducted during the Second Vaccination Visit for participants not randomized to placebo. (Section 8.4.1 Second Vaccination Visit).

8.5.4. Follow-Up Call (Day 46 or Day 60 ± 1 Day)

Following their Second Vaccination Visit, participants randomized to placebo, will have a follow-up call, approximately 3 days later. The study team will call the participant to assess for AEs and review the participant diary. Any reported AEs and changes in concomitant medications will be recorded on the appropriate eCRF.

8.6. End of Study Call (Day 29 or 36 ± 1 Day [No Placebo] / Day 50 or 64 ± 1 Day [Placebo])

All participants who complete their assigned vaccination regimen will complete an End of Study Visit approximately 7 days after their last vaccination. This visit will be conducted over the phone, and participants will be asked to report any new AEs and review their final participant diary.

8.7. Unscheduled Visits

If a participant develops symptoms of a reaction post-visit or other concerns arise between regularly scheduled visits, participants will be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit. If the participant presents with symptoms for a suspected allergic reaction, the investigator – at his/her discretion, may elect to collect blood samples for the assessment of serum biomarkers and/or complement activation. Additional procedures, including the collection of samples for local labs, will follow the investigator's elected standard of care.

8.8. Visit Windows

Study visits should take place within the time limits specified above: the designated visit windows *(i.e. +/- n days)* for each scheduled visit are also indicated in Appendix 3: Schedule of Events. If study visits are not conducted within the visit windows, a protocol deviation will be recorded. In the rare event a vaccination window cannot be met, vaccination may be scheduled beyond the +14-day window. If a participant becomes infected with SARS-CoV-2 or another acute illness following his/her first dose of vaccine, the second vaccination will be delivered, with allowance for a delay up to 90 days following the first dose.

9. Study Procedures (Protocol versions 5.0 – 8.0)

A summary of complete study procedures is included in Tables C and D in Appendix 3: Schedule of Events.

9.1. Recruitment & Pre-Screening (Day -14 to Day 0)

Potential study participants may be identified by medical chart review or from a response to a study advertisement, and initially contacted by a member of the study team in person or over the phone. During this initial contact, the potential

participant's parent/legal guardian will be provided information on the study and asked to provide verbal permission for pre-screening. If a participant's parent/legal guardian provides verbal permission for pre-screening, they may be pre-screened over the phone using a standardized form to confirm eligibility. Eligible pre-screened individuals interested in participating in the study will be consented either remotely or during a clinic visit.

If it is possible to provide a physical copy of the consent and/or assent (if applicable) and verify who is consenting/assenting, remote consenting may be conducted. In the event of a remote consent, the participant's parent/legal guardian will need to return the signed consent and/or assent (if applicable) to the clinic, prior to the conduct of any study procedures. The signed consent and/or assent may be returned via an approved electronic platform, in person, and/or by mail. The process for remote consenting will be further defined in the MOP.

In the event a site does not have the ability to conduct a remote consent and/or the participant or parent/legal guardian does not have access to the methods required for remote consent, an in-person clinic visit may be scheduled to complete the consenting process. Based upon the site's policies and vaccination schedules, this may be a separate clinic visit and/or combined with the Enrollment Visit.

9.2. Enrollment Visit (Day 1)

The purpose of the Enrollment Visit is to obtain written informed consent and assent (if applicable), if not previously obtained remotely and/or during a separate clinic visit (prior to performing any other study procedures), confirm there are no changes in the participant's eligibility since pre-screening, and initiate vaccination or placebo administration.

The following procedures and assessments will be conducted during this visit:

Pre-Vaccination

- Obtain written parent/legal guardian consent and participant assent (if applicable), if not obtained prior to visit
- Collect demographics
- Medical History and Physical Exam by a study physician or other qualified medical professional
- Urine pregnancy test for female participants of child-bearing potential who do not self-report as pregnant
- Assessment of concomitant medications
- Vital signs (temperature, pulse rate, respiratory rate, O_2 saturation, blood pressure), plus growth parameters (height and weight)
- Randomization
- Assessment of HA/MCD participant access to an epinephrine auto injector; distribution of epinephrine auto-injectors (2 pack) for participants in the HA/MCD group who did not bring auto-injectors with them or bring expired auto-injectors
- Blood, nasal swab (participants enrolled under protocol version 8.0 will not be required to provide a nasal swab), and urine sample collections for assessments defined in Appendix 3: Schedule of Events
- Assessment of AEs
- Diary Overview, Training, & Distribution: Participants will be provided access to an electronic 7-day diary to aid in recording solicited local and systemic reactions to the vaccine, as well as symptoms of a potential allergic reaction, unsolicited AEs, and concomitant medications, including start and stop dates. The diary will include instructions for participants and/or parent/legal guardian on how to take an oral temperature and how to measure injection site reactions. A paper copy of the diary may be provided for participants who do not have a device to access the electronic diary or as a backup collection tool. A member of the study team will review the

information in the diary with the participant and/or parent/legal guardian, including how to use and access the electronic diary. The parent and or legal guardian may need to assist their child or answer for their child.

Following sample collection, participants will be randomized and will receive their initial vaccination or placebo dose. Following vaccination or placebo administration (as assigned), the study participant will be observed for 90 minutes for AEs, including examination of the injection site, and have vital sign measurements. Participants will have blood collected 30-60 minutes after the onset of an allergic reaction. Samples will not be collected 1 hour post vaccination under protocol versions 5.0 – 8.0. Sample collections post vaccination will be based on participant weight, detailed further in the MOP.

During the 90-minute observation period, all AEs will be recorded, and AEs judged by an investigator to constitute an allergic reaction, even if not severe, will be documented on the appropriate eCRFs.

In the event of a systemic allergic reaction, participants will be treated with rescue medications (Section 7.4 Rescue Medications) and observed for a minimum of 2 hours after their symptoms resolve. Vital signs will be monitored during a systemic allergic reaction.

To assist study participants and/or their parents/legal guardians in the identification of and steps to take in the event of an allergic reaction after they leave the study site, each participant will be provided with an Anaphylaxis Emergency Care Plan. The PI or designee shall review the symptoms and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant and/or parents/legal guardians prior to discharge.

9.3. Follow-Up Call (Day 4 ± 1 Day)

Approximately 3 days following the participant's Enrollment Visit, the study team will call the participant to assess for AEs and review the participant diary. Any reported AEs and changes in concomitant medications will be recorded on the appropriate eCRF. Study staff will schedule the participant's next vaccination visit during the call.

During this call, the participant will be informed if they received placebo at their first injection visit (Day 1). If so, their next vaccination visit will occur within 7 days of Day 1. For participants who received vaccine on Day 1, the next vaccination visit will be scheduled to occur on Day 22 (for Pfizer) or 29 (for Moderna).

9.4. Participants Randomized to Receive Vaccine and No Placebo Under Protocol Versions 5.0 – 8.0

9.4.1. Second Vaccination Visit (Day 22 or 29; -4 to +14 Days)

Participants randomized to vaccine (no placebo) will be asked to return to clinic for the second vaccination 21 days (Day 22) or 28 days (Day 29) after their first vaccination, based on their assignment to receive the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine.

The following procedures and assessments will be conducted during this visit:

Pre-Vaccination

- Abbreviated Medical History and Targeted Physical Exam by a study physician or other qualified medical professional
- Urine pregnancy test for female participants of child-bearing potential who do not self-report as pregnant
- Assessment of concomitant medications

- Vital signs
- Nasal swab (participants enrolled under protocol version 8.0 will not be required to provide a nasal swab) and urine sample collections for assessments defined in Appendix 3 : Schedule of Events
- Assessment of AEs
- Diary Review (Dose 1) and Distribution (Dose 2)
- Distribution of epinephrine auto-injectors (2 pack) for participants in the HA/MCD group who did not bring with them or bring expired auto-injectors

Following sample collections, participants will receive their second vaccination. Following vaccination, the study participant will be observed for AEs, including examination of the vaccination site, and have vital sign measurements and additional urine and blood samples collected 1-hour post-vaccination and/or 30-60 minutes after the onset of an allergic reaction. Sample collections post vaccination will be based on participant weight, detailed further in the MOP.

During the 90-minute observation period, all AEs will be recorded, and AEs judged by an investigator to constitute an allergic reaction, even if not severe, will be documented on the appropriate eCRFs. In the event of an allergic reaction, occurring more than 1 hour post vaccination, urine and blood samples will be collected, per Appendix 3: Schedule of Events. Sample collections post vaccination will be based on participant weight, detailed further in the MOP.

In the event of a systemic allergic reaction, participants will be treated with rescue medications (Section 7.4: Rescue Medications) and observed for a minimum of 2 hours after their symptoms resolve. Vital signs will be monitored during a systemic allergic reaction.

To assist study participants and/or their parents/legal guardians in the identification of and steps to take in the event of an allergic reaction after they leave the study site, each participant will be provided with an Anaphylaxis Emergency Care Plan. The PI or designee shall review the symptoms and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant and/or parents/legal guardians prior to discharge.

9.4.2. Follow-Up Call (Day 25 or 32 ± 1 Day)

Approximately 3 days following the participant's second vaccination visit, the study team will call the participant to assess for AEs and review the participant diary. Any reported AEs and changes in concomitant medications will be recorded on the appropriate eCRF.

9.5. Participants Randomized to Receive Placebo Under Protocol Versions 5.0 – 8.0

9.5.1. First Vaccination Visit (Day 8; + 14 Days)

Participants randomized to placebo will be asked to return to clinic to receive their first vaccine injection, approximately 7 days, after they received the placebo. In addition to receiving the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, the participant will complete the same study procedures as those conducted during the Enrollment Visit, with the exception of growth parameters and pre-vaccination blood sample collections. (Section 9.2 Enrollment Visit [Day 1]). Following vaccination, the study participant will be observed for 90 minutes for AEs, including examination of the injection site, and have vital sign measurements. Participants will have blood collected 30-60 minutes after the onset of an allergic reaction. Sample collections post vaccination will be based on participant weight, detailed further in the MOP.

In addition, the study team will complete a review of the participant's diary and distribute an additional diary, as needed.

9.5.2. Follow-Up Call (Day 11 ± 1 Day)

Following their First Vaccination Visit, participants randomized to placebo, will have a follow-up call, approximately 3 days later. The study team will call the participant to assess for AEs and review the participant diary. Any reported AEs and changes in concomitant medications will be recorded on the appropriate eCRF.

9.5.3. Second Vaccination Visit (Day 29 or 36; -4 to +14 Days)

Participants randomized to receive placebo during their Enrollment Visit, will complete a third clinic visit, during which they will receive their second injection of the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine, as assigned.

The following procedures and assessments will be conducted during this visit:

Pre-Vaccination

- Abbreviated Medical History and Targeted Physical Exam by a study physician or other qualified medical professional
- Urine pregnancy test for female participants of child-bearing potential who do not self-report as pregnant
- Assessment of concomitant medications
- Vital signs
- Nasal swab (participants enrolled under protocol version 7.0 and 8.0 will not be required to provide a nasal swab) and urine sample collections for assessments defined in Appendix 3: Schedule of Events; no blood will be collected pre-vaccination
- Assessment of AEs
- Diary Review (Dose 1) and Distribution (Dose 2)
- Distribution of epinephrine auto-injectors (2 pack) for participants in the HA/MCD group who did not bring with them or bring expired auto-injectors

Following urine sample collections, participants will receive their second vaccination. Following vaccination, the study participant will be observed for AEs, including examination of the vaccination site, and have vital sign measurements and additional urine and blood samples collected 1-hour post-vaccination and/or 30-60 minutes after the onset of an allergic reaction. Sample collections post vaccination will be based on participant weight, detailed further in the MOP.

During the 90-minute observation period, all AEs will be recorded, and AEs judged by an investigator to constitute an allergic reaction, even if not severe, will be documented on the appropriate eCRFs. In the event of an allergic reaction, occurring more than 1 hour post vaccination, urine and blood samples will be collected, per Appendix 3: Schedule of Events. Sample collections post vaccination will be based on participant weight, detailed further in the MOP.

In the event of a systemic allergic reaction, participants will be treated with rescue medications (Section 7.4: Rescue Medications) and observed for a minimum of 2 hours after their symptoms resolve. Vital signs will be monitored during a systemic allergic reaction.

To assist study participants and/or their parents/legal guardians in the identification of and steps to take in the event of an allergic reaction after they leave the study site, each participant will be provided with an Anaphylaxis Emergency Care Plan. The PI or designee shall review the symptoms and steps to take in the event of an allergic reaction, including training on how to use the epinephrine auto-injector, with the participant and/or parents/legal guardians prior to discharge

9.5.4. Follow-Up Call (Day 32 or 39 ± 1 Day)

Following their Second Vaccination Visit, participants randomized to placebo, will have a follow-up call, approximately 3 days later. The study team will call the participant to assess for AEs and review the participant diary. Any reported AEs and changes in concomitant medications will be recorded on the appropriate eCRF.

9.6. End of Study Call (Day 29/36 ± 1 Day [No Placebo] or Day 36/43± 1 Day [Placebo]

All participants who complete their assigned vaccination regimen will complete an End of Study Visit approximately 7 days after their last vaccination. This visit will be conducted over the phone, and participants will be asked to report any new AEs and review their final participant diary.

9.7. Unscheduled Visits

If a participant develops symptoms of a reaction post-visit or other concerns arise between regularly scheduled visits, participants will be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit. If the participant presents with symptoms for a suspected allergic reaction, the investigator – at his/her discretion, may elect to collect blood samples for the assessment of serum biomarkers and/or complement activation. Additional procedures, including the collection of samples for local labs, will follow the investigator's elected standard of care.

9.8. Visit Windows

Study visits should take place within the time limits specified above; the designated visit windows *(i.e. +/- n days)* for each scheduled visit are also indicated in Appendix 3: Schedule of Events. If study visits are not conducted within the visit windows, a protocol deviation will be recorded. In the rare event a vaccination window cannot be met, vaccination may be scheduled beyond the +14-day window. If a participant becomes infected with SARS-CoV-2 or another acute illness following his/her first dose of vaccine, the second vaccination will be delivered, with allowance for a delay up to 90 days following the first dose.

10. Mechanistic Assays

The need for, and extent of, laboratory analysis of systemic allergic reactions will be determined based on the number and character of reactions seen within the trial. Samples will be collected prospectively and stored at a sample repository, with the exception of serum tryptase samples which will be analyzed in "real-time" for those who experience systemic allergic reactions. Specimen collection will be focused on:

- Overall atopic status
- Pre-existing antibodies to polyethylene glycols (Sample analysis will not be completed prior to vaccination; therefore, results will not be used to assess eligibility.)
- Known mediators of systemic reactions due to mast cell activation (e.g., serum tryptase and urinary leukotrienes)
- General markers of an acute inflammatory response (e.g., serum IL-6)

- Activation of the classical and alternative complement pathways
- Contact activation of the kinin system
- Genetic analysis (protocol versions 1.0 – 4.0 only)
- Unsupervised proteomics (blood and urine) and whole blood transcriptomics
- Analysis of peripheral blood mononuclear cells (PBMCs) may also be explored to assess for new mechanisms (e.g., Cellular Indexing of Transcriptomes and Epitopes by Sequencing [CITE-seq] or B cell studies)

Specific anticipated laboratory studies may include, but will not be limited to, those listed below. Specific assays may be removed or added based on the number and character of reactions seen within the trial. In addition, the timepoints for the conduct of specific laboratory studies may change from what is specified below, although the timepoints for sample collection are not anticipated to change.

10.1. Anticipated laboratory studies, protocol versions 1.0 -4.0:

- Whole blood for genetic analysis: Visit 1, pre-vaccination
- Total IgE: Visit 1, pre-vaccination
- Allergen-specific IgE: Visit 1, pre-vaccination
- Anti-Polyethylene glycol (PEG) IgE, IgG, and IgM antibody measurements: all Visits, pre-vaccination
- Anti-SARS-CoV-2 spike antibodies: all Visits, pre-vaccination
- Serum tryptase: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour blood draw, and at time of discharge after an allergic reaction
- Serum IL-6: all visits pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction including if this occurs after the 1-hour blood draw, and at time of discharge after an allergic reaction
- Complement activation testing: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction including if this occurs after the 1-hour blood draw, and at time of discharge after an allergic reaction
- Urinary LTE_4: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour specimen, and at time of discharge after an allergic reaction
- CBC with differential: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour blood draw, and at time of discharge after an allergic reaction
- Whole blood transcriptomics: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour blood draw, and at time of discharge after an allergic reaction
- Plasma proteomics: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour blood draw, and at time of discharge after an allergic reaction
- Urine proteomics: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour blood draw, and at time of discharge after an allergic reaction
- PBMC separation and storage (only at a sub-set of sites): all Visits, pre-vaccination, and 30-60 minutes after the onset of an allergic reaction, including if this occurs after the 1-hour blood draw. PBMCs will be collected on a sub-set of participants who don't have allergic reactions at the 1-hour time point post-vaccination to serve as controls.) Participants weighing less than 50 kg will not participate in PBMC collections.
- Plasma kallikrein: 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour blood draw, and at time of discharge after an allergic reaction

Details of the laboratory processes are described in Standard Operating Procedures (SOPs) maintained by each laboratory.

10.2. Anticipated laboratory studies protocol version 5.0 – 8.0:

- Total IgE (Visit 1, pre-vaccination)
- Allergen-specific IgE (Visit 1, pre-vaccination)
- Anti-Polyethylene glycol (PEG) IgE, IgG, and IgM antibody measurements: Pre-vaccination at Visit 1 and post-vaccination 1 hour and/or 30-60 minutes after onset of an allergic reaction at each participant's second active vaccination visit
- Anti-SARS-CoV-2 spike antibodies: pre-vaccination at Visit 1 and post-vaccination 1 hour and/or 30-60 minutes after onset of an allergic reaction at each participant's second active vaccination visit
- Serum tryptase: pre-vaccination at Visit 1, all visits post-vaccination 30-60 minutes after onset of an allergic reaction, and 1 hour post-vaccination at each participant's second active vaccination visit
- Serum IL-6: pre-vaccination at Visit 1, all visits post-vaccination 30-60 minutes after onset of an allergic reaction, and 1 hour post-vaccination at each participant's second active vaccination visit
- Complement activation testing: pre-vaccination at Visit 1, all visits post-vaccination 30-60 minutes after onset of an allergic reaction, and 1 hour post-vaccination at each participant's second active vaccination visit
- Urinary LTE4: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour specimen
- CBC with differential: pre-vaccination at Visit 1, all visits post-vaccination 30-60 minutes after onset of an allergic reaction, and 1 hour post-vaccination at each participant's second active vaccination visit
- Whole blood transcriptomics: pre-vaccination at Visit 1, all visits post-vaccination 30-60 minutes after onset of an allergic reaction, and 1 hour post-vaccination at each participant's second active vaccination visit
- Plasma proteomics: pre-vaccination at Visit 1, all visits post-vaccination 30-60 minutes after onset of an allergic reaction, and 1 hour post-vaccination at each participant's second active vaccination visit
- Urine proteomics: all Visits, pre- and post-vaccination at 1 hour and/or 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour blood draw
- PBMC separation and storage (only at a sub-set of sites for participants weighing greater than 50 kg): pre-vaccination at Visit 1, all visits post-vaccination 30-60 minutes after onset of an allergic reaction, and 1 hour post-vaccination at each participant's second active vaccination visit
- Plasma kallikrein: 30-60 minutes after onset of an allergic reaction, including if this occurs after the 1-hour blood draw after an allergic reaction and 1 hour post-vaccination at each participant's second active vaccination visit

Details of the laboratory processes are described in Standard Operating Procedures (SOPs) maintained by each laboratory.

11. Biospecimen Storage

During the consent process, participants will be asked to give permission for long-term storage and future use of samples for research related to vaccine reactions or allergy research. The following biospecimens and any derivatives will be stored:

- Whole blood (DNA and RNA)
- Serum
- Plasma

- Urine
- PBMCs

Instructions for sample preparation, handling, storage, and shipping are included in the MOP. Site investigators will be responsible for being aware of and observing all the regulations for classification, packaging and labeling, permits or authorizations, and personnel training for shipment of biological and hazardous materials required for the conduct of this study.

12. Criteria for Participant and Study Completion and Premature Study Termination

12.1. Participant Completion

Participation will be considered to be complete when the 7-day follow up after the last vaccination is complete.

12.2. Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant and/or parent/legal guardian elects to withdraw consent/assent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. Participants for whom vaccinations are terminated early (refer to Section 6.5 Premature Discontinuation of Investigational Agent).
5. The Investigator no longer believes participation is in the best interest of the participant.

12.3. Participant Replacement

Participants who withdraw or are withdrawn will not be replaced if they have received at least one vaccine (or placebo) dose. If a participant is randomized but does not receive the first dose of vaccine (or placebo), the participant will be withdrawn and will not be counted toward the total enrollment goal. Additional participants will be randomized to achieve enrollment goals.

12.4. Follow-up After Early Study Withdrawal

Participants who prematurely withdraw (without withdrawing consent) or who are withdrawn may be asked to complete a final phone visit to assess any AEs and concomitant medications as applicable depending on when they are withdrawn relative to the visit schedule. This visit will occur 7 days after the participant received their last vaccine dose. Participants who are withdrawn due to early vaccine termination will be asked to complete study procedures as noted in Section 6.5 Premature Discontinuation of Investigational Agent prior to being withdrawn from the study. Participants who are withdrawn from the study prior to receipt of study treatment will not be followed after their last completed study visit. Monitoring of a pregnant participant will continue until the conclusion of the pregnancy.

12.5. Study Stopping Rules

Study enrollment will be suspended and vaccinations will be put on hold pending DSMB expedited review of all pertinent data in the event of any one of the following:

1. One Grade 4 or higher AE that is at least possibly related to the vaccine

2. Five participants in the first 100 HA/MCD participants vaccinated or 5% of HA/MCD participants thereafter experience a Grade 3 systemic allergic reaction at least possibly related to the vaccine

Following their unblinded review, the DSMB will determine whether modifications should be made to study conduct and whether and when enrollment and vaccinations can resume.

The study may be suspended or terminated by DAIT/NIAID or the DSMB upon review of any observations, events, or new information that merits such action. In the case of suspension or premature termination, DAIT/NIAID will promptly inform the investigators and regulatory authorities as appropriate of the suspension or termination and the reason for suspension/termination.

13. Safety Monitoring and Reporting

13.1. Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. AEs that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5.1. Reporting of Serious Adverse Events to DAIT/NIAID). Appropriate notifications will also be made to site investigators, Institutional Review Boards (IRBs), and the FDA.

Information in this section complies with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). Refer to Appendix 4: Tables for Clinical and Laboratory Abnormalities.

13.2. Definitions

13.2.1. Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32(a)).[19]

The investigator must report adverse events regardless of relationship to study therapy regimen or study mandated procedures.

For this study, an adverse event will include the following associated with the vaccinations/placebo administration or procedures:

- **Vaccine or placebo administration**:
  - All AEs occurring after vaccination/placebo administration and within 7 days after the last dose of vaccine or placebo
  - All solicited local reactions, with the exception of injection site reactions of erythema/redness and induration/swelling measuring <2.5 cm, will be reported as AEs.

- **Study mandated procedures:**
  Events related to the following procedures will be considered AEs, with the exception of:

  Blood Draw
  - Bruising at the puncture site less than 2 cm diameter
  - Bleeding from the puncture site lasting less than 30 minutes
  - Induration/swelling at the puncture site less than 2 cm diameter

  Nasal Swab Collection
  - Bleeding of the nose lasting less than 5 minutes

13.2.1.1 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the SARS-CoV-2 vaccine caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the vaccine and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

13.2.2. Solicited and Unsolicited Adverse Events

For the purposes of this study, the following specific local and systemic reactogenicity events, as well as symptoms of a potential allergic reaction, will be solicited from the participant for 7 days post-vaccination, inclusive of the vaccination/placebo administration day. Refer to Section 8.2 Enrollment Visit (Day 1) and Section 9.2 Enrollment Visit (Day 1).

- Solicited local reactions at the injection site will include erythema/redness, swelling/induration (hardness), and pain.
- Solicited systemic reactions will include fever (assessed as daily oral temperature), myalgia, arthralgia, fatigue, headache, nausea, vomiting, diarrhea, and chills.
- Solicited symptoms related to a potential allergic reaction will include the following:
  - Skin: hives, swelling other than injection site, itching, redness other than injection site, rash
  - Respiratory: wheezing, shortness of breath, coughing, tightness in the throat or chest, sneezing, nasal stuffiness or congestion
  - Gastrointestinal: trouble swallowing, abdominal cramps, diarrhea, nausea, vomiting
  - Dizziness or lightheadedness

All other AEs reported by the participant during the study will be defined as unsolicited AEs.

13.2.3. Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Pfizer-BioNTech COVID-19 Vaccine Full FDA EUA Prescribing Information or Moderna COVID-19 Vaccine Full FDA EUA Prescribing Information or is not listed at the specificity, severity or rate of occurrence that has been observed.[9, 13]

13.2.4. Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or DAIT/NIAID Medical Monitor, it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT/NIAID Medical Monitor, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations are not to be reported as an SAE unless hospitalization is prolonged due to complications.

13.3. Grading and Attribution of Adverse Events

13.3.1. Grading Criteria

13.3.1.1. Grading of Adverse Events Other than Systemic Allergic Reactions

The study sites will grade the severity of non-allergic adverse events experienced by the study participants according to the criteria set forth in the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007); hereafter, referred to as the FDA Toxicity Grading Scale.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the FDA Toxicity Grading Scale (Appendix 4: Tables for Clinical and Laboratory Abnormalities):

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Life-threatening
Grade 5 = Death

Events grade 1 or higher will be recorded on the appropriate AE eCRF for this study.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to administration of the first dose of vaccine/placebo will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the FDA Toxicity Grading Scale, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

13.3.1.2. Grading of Systemic Allergic Reactions

The investigator will grade severity of systemic allergic reactions on a scale of 1 to 5 according to criteria set forth in the CoFAR Grading Scale modified for use in adults only (Appendix 1: CoFAR Grading Scale).

13.3.2. Attribution Definitions

The relationship, or attribution, of an adverse event to the vaccine/placebo or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE eCRF. Final determination of attribution for safety reporting will be determined by the DAIT/NIAID Medical Monitor. The relationship of an adverse event to the vaccine/placebo or study procedures will be determined using the descriptors and definitions provided in Table 13.3.2.

Table 13.3.2. Attribution of Adverse Events

Code	Descriptor	Relationship (to vaccine/placebo or study procedures: blood draw or nasal swab collection)
NOT RELATED CATEGORY		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

13.4. Collection and Recording of Adverse Events

13.4.1. Collection Period

Adverse events will be collected from the time of consent, until a participant completes study participation or until 7 days after their last vaccine dose after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study if the participant received study treatment (vaccine or placebo).

AEs will be recorded during the periods defined below.

- Solicited AEs: Those occurring within 7 days of each injection (vaccine or placebo), inclusive of the injection day
- Unsolicited AEs: Those occurring from the time of consent through study participation

13.4.2. Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.]
- Receiving an unsolicited complaint from the participant

- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 13.3 Grading and Attribution of Adverse Events.

13.4.3. Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2 Definitions) on the appropriate AE/SAE eCRF regardless of the relationship to study vaccine/placebo or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or the AE/SAE stabilizes, or until the end of study participation, or until 7 days after the participant's last vaccine dose if the participant prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first. Monitoring of a pregnant participant shall continue until the conclusion of the pregnancy.

13.5. Reporting of Serious Adverse Events and Adverse Events

13.5.1. Reporting of Serious Adverse Events to DAIT/NIAID

This section describes the responsibilities of the site investigator to report serious adverse events to DAIT/NIAID and the SACCC via the SAE eCRF. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all serious adverse events (see Section 13.2.4 Serious Adverse Event (SAE)), regardless of relationship or expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. Initial SAE eCRFs should include as much information as possible, but at a minimum must include the following:

- AE term
- Relationship to study vaccination (or placebo)
- Relationship to study procedure
- Reason why the event is serious
- Supplementary eCRF pages that are current at the time of the SAE reporting: medical history, concomitant medications, demographics, vaccine/placebo administration

As additional details become available, the AE/SAE eCRF will be updated and submitted. Every time the SAE eCRF is submitted, it should be electronically signed by the investigator or sub-investigator.

For additional information regarding SAE reporting, contact Rho Product Safety:

13.5.2. Reporting to Health Authority

After an adverse event requiring 24-hour reporting (per Section 13.5.1 Reporting of Serious Adverse Events to DAIT/NIAID) is submitted by the site investigator and assessed by the DAIT/NIAID Medical Monitor, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities:

13.5.2.1. Annual Reporting

Per 21 CFR 312.33, DAIT/NIAID will include in the Investigational New Drug (IND) Annual Report to FDA all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 13.2.1.1 Suspected Adverse Reaction (SAR) and Section 13.2.3 Unexpected Adverse Event).
- Serious and not a suspected adverse reaction (see Section 13.2.1.1 Suspected Adverse Reaction (SAR)).
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the IND Annual Report.

13.5.2.2. Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious and unexpected suspected adverse reaction [SUSAR]** (see Section 13.2.1.1 Suspected Adverse Reaction (SAR), Section 13.2.3 Unexpected Adverse Event, Section 13.4 Serious Adverse Event (SAE), and 21 CFR 312.32(c)(1)i)).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with vaccine exposure (e.g., angioedema, Stevens-Johnson Syndrome, Guillain-Barré syndrome);
2. One or more occurrences of an event that is not commonly associated with vaccine exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of treatment) that indicates those events occur more frequently in the treatment group than in a concurrent or historical control group.

Category 2: Any findings from studies that suggests a significant human risk

The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the FDA and all participating investigators of expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

13.5.3. Mandatory reporting to Vaccine Adverse Event Reporting System

Per the FDA EUA for the Pfizer-BioNTech COVID-19 Vaccine and the FDA EUA for the Moderna COVID-19 Vaccine, the site investigator, or designee, is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):[9, 13]

- vaccine administration errors whether or not associated with an adverse event,
- serious adverse events (irrespective of attribution to vaccination),
- cases of Multisystem Inflammatory Syndrome in adults, and
- cases of COVID-19 that result in hospitalization or death.

The site investigator, or designee, is also responsible for recording vaccination information in the state/local jurisdiction's Immunization Surveillance System or other designated system.

13.5.4. Reporting of Adverse Events to IRBs/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs and central IRB in accordance with applicable regulations and guidelines. All safety reports to the FDA shall be distributed by the Sponsor (DAIT/NIAID) or designee to all participating institutions for site IRB submission.

13.6. Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study participant. Vaccinations may be discontinued for the pregnant participant after consultation with the site investigator. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to the SACCC all pregnancies within 1 business day of becoming aware of the event using the Pregnancy eCRF. The SACCC will report all pregnancies to DAIT/NIAID. All pregnancies identified during the study shall be followed to conclusion, and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to the SACCC, when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender

- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

Should pregnancy complications result in a congenital abnormality, birth defect, miscarriage, or medically indicated abortion – an SAE must be submitted to the SACCC, using the SAE reporting procedures described above.

13.7. Reporting of Other Safety Information

An investigator shall promptly notify their local and central IRB, in accordance with applicable regulations and guidelines, as well as the SACCC and DAIT/NIAID via email when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

13.8. Review of Safety Information

13.8.1. Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive reports (approximately every two weeks) from the SACCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

In addition, the DAIT/NIAID Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the SACCC (See Section 13.5.1 Reporting of Serious Adverse Events to DAIT/NIAID and Section 12.6 Pregnancy Reporting).

13.8.2. DSMB Review

13.8.2.1. Planned DSMB Reviews

The NIAID Allergy and Asthma Data and Safety Monitoring Board (DSMB) shall review unblinded outcome and safety data after approximately every 500 participants complete their vaccination schedule. Unblinded data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs by vaccine arm/placebo and population. Outcome data will show the counts, proportions (with corresponding 95% CI), and difference in proportions between the HA/MCD and comparison group within each vaccine (with corresponding 95% CI) of the primary and key secondary endpoints. Interim p-values will be available upon request. Data may be reviewed and discussed via email or by teleconference. The DSMB may recommend continuing the study, modifying the study, stopping the study, and/or announcing information will the study is still ongoing.

The DSMB will also review results of the planned interim analysis of the primary endpoint (Refer to Section 14.5.1 Interim Analysis of Primary Endpoint). In addition to reviewing interim analysis results, the DSMB will be asked to consider the nature and severity of the reactions, the rate of reactions in the placebo arm, and the adequacy of information obtained that will allow in-depth characterization of the risk and nature of systemic allergic reactions in the HA/MCD population. The DSMB may recommend continuing the study, modifying the study, or stopping the study. DAIT/NIAID, as sponsor, will determine whether any changes to study conduct will be implemented.

13.8.2.2. *Ad hoc* DSMB Safety Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request

of the protocol chair or DAIT/NIAID Medical Monitor. The DAIT/NIAID Medical Monitor will inform the DSMB of an Expedited Safety Report within 24-48 hours.

In addition, an *ad hoc* comprehensive DSMB Safety Review will be triggered in the event that a study stopping rule is met (Section 12.5 Study Stopping Rules).

After review of the unblinded data, the DSMB will make recommendations regarding study conduct, including modifications and/or continuation. The DSMB will recommend and DAIT/NIAID, as Sponsor, will determine whether protocol changes should be implemented and/or whether and when enrollment and vaccinations can resume.

13.8.2.2.1. Temporary Suspension of Enrollment and Vaccinations for *ad hoc* DSMB Safety Review

A temporary halt in enrollment will be implemented by the Sponsor if an *ad hoc* DSMB safety review is required. New participants will not be consented for study participation during the enrollment halt. All vaccinations will be placed on hold. Participants screened but not yet randomized will not be allowed to continue with the Enrollment Visit. All participants not randomized within 7 days of screening must be rescreened.

14. Statistical Considerations and Analytical Plan

14.1. Overview

The primary research question of this study is to assess the proportion of participants who experience a systemic allergic reaction to either dose of the Pfizer-BioNTech COVID-19 Vaccine, and, independently, of Moderna COVID-19 Vaccine in HA/MCD and comparison populations. This objective will be addressed using a multi-center, randomized, initially-blinded (to the first injection), phase 2 trial in these two populations.

For adults, if no systemic allergic reactions are observed, the within vaccine sample size will be sufficient to rule out a rate as high as 1/275 in the HA/MCD population. If systemic allergic reactions are observed, the within vaccine sample size of 1700 participants was determined to detect a minimum proportion difference between these two populations of ~0.01 with at least 80% power. This translates to a true proportion of 1/100 vs. 1/10,000 in the HA/MCD and comparison populations, respectively.

For children, if no systemic allergic reactions are observed, the within vaccine sample size will be sufficient to rule out a rate as high as 1/50 in the HA/MCD population. If systemic allergic reactions are observed, the within vaccine sample size of 300 participants will detect a minimum proportion difference between the HA/MCD and comparison populations of ~0.05 with approximately 80% power. This translates to a true proportion of 1/20 vs. 1/10,000 in the HA/MCD and comparison populations, respectively.

14.2. Endpoints/Outcomes

The two primary endpoints are:

1. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose* of the Pfizer-BioNTech COVID-19 Vaccine

2. The proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose* of the Moderna COVID-19 Vaccine

*A participant can have a reaction to either dose 1 or dose 2 (but not to both doses since a participant who has a reaction meeting qualifying criteria to dose 1 will not be able to receive the second dose) or to neither dose.

14.3. Measures to Minimize Bias

To minimize bias, a randomization schedule will be generated by the SACCC and implemented in a validated system that will be used by site personnel to automate the random assignment. For protocol versions 1.0 - 4.0, participants were randomized 2:2:1:1 to receive either the Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, placebo + Pfizer-BioNTech COVID-19 Vaccine, or placebo + Moderna COVID-19 Vaccine. For protocol versions 5.0 – 8.0, participants will be randomized 2:1 to receive active vaccine alone or placebo + active vaccine. The Pfizer-BioNTech COVID-19 Vaccine will be the active vaccine distributed initially.

The randomization scheme will be reviewed and approved by a statistician at the SACCC and will not be modified thereafter except to accommodate any changes required by amendments to the protocol. Furthermore, all first doses of active and placebo vaccine will be blinded to the participant, and all site staff except the unblinded pharmacist and any unblinded personnel administering vaccine and/or scheduling visits. All laboratory assays will be performed by laboratory technicians who do not know the participants' group assignments.

14.4. Analysis Plan

14.4.1. Analysis Populations.

As-treated sample: All participants who are randomized and receive at least one active vaccination. Participants will be analyzed according to the vaccine they received.

Per-Protocol sample: All participants who are randomized and receive all assigned vaccination doses. Participants who do not receive a second active vaccination due to experiencing an allergic reaction will be included in the analysis. Participants will be analyzed according to the vaccine they received.

Safety sample: All participants who consent and undergo screening procedures. Participants will be analyzed according to the vaccine they actually received, regardless of the treatment arm to which they were randomized. Non-treatment emergent adverse events (e.g., any adverse event that occurs before the first injection) will be summarized in all participants in the safety sample, while treatment-emergent adverse events (e.g., any adverse event that occurs on or after the first injection) will be summarized in the subset of participants who receive any injection (placebo or active).

14.4.2. Primary Analysis of Primary Endpoints

The primary analyses will estimate the proportion of participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Pfizer-BioNTech COVID-19 Vaccine and independently the Moderna COVID-19 Vaccine for both the HA/MCD and comparison populations. These four proportions will be accompanied by their 95% exact confidence intervals.

If systemic allergic reactions are observed, we will compare the proportions of participants experiencing a systemic allergic reaction to the Pfizer-BioNTech COVID-19 Vaccine and independently to the Moderna COVID-

19 Vaccine between the HA/MCD and comparison populations. The point estimate of the differences in proportions between populations within vaccines will be reported, together with their corresponding 95% exact unconditional confidence intervals. Exact p-values will be calculated using an unconditional test, as some cell counts are likely to have an expected value less than 5. No multiplicity adjustment will be applied for these two primary endpoints. Details of the implementation of the exact unconditional confidence intervals and p-value calculations will be included in the statistical analysis plan.

14.4.3. Analyses of Secondary and Other Endpoints

Similarly, the secondary analyses will estimate the proportion of participants with severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Adverse Reactions Version 3.0) systemic allergic reactions within 90 minutes, Grade 2 or higher (per CoFAR Grading Scale for Systemic Adverse Reactions Version 3.0) within 48 hours, and anaphylactic reactions (Levels 1-3) per Brighton Collaboration Criteria within 90 minutes to either dose of the Pfizer-BioNTech COVID-19 Vaccine and independently to the Moderna COVID-19 Vaccine between the HA/MCD and comparison populations. Again, these estimates will be presented with their 95% exact confidence intervals. Due to the likelihood of these events to be extremely rare, no inferential analyses are planned.

An estimate of the proportion of participants with systemic allergic reactions to the first dose of the Pfizer-BioNTech COVID-19 Vaccine and independently the Moderna COVID-19 Vaccine in the HA/MCD population will be conducted. These estimates will be presented together with their 95% exact confidence intervals. Likewise, the estimate of the proportion and 95% exact confidence interval will be reported for the second dose conditional on no systemic allergic reaction to the first dose to each vaccine.

Another secondary analysis will be conducted to estimate the placebo-adjusted proportion of participants experiencing systemic allergic reactions to the first dose of either the Pfizer-BioNTech COVID-19 Vaccine and independently the Moderna COVID-19 Vaccine in the HA/MCD population. The placebo-adjusted proportions will be estimated as the differences in proportions between the first active vaccine dose versus the corresponding placebo vaccine arm. These estimates will be reported together with their corresponding 95% exact unconditional confidence intervals. Exact p-values will be calculated using an unconditional test. Details for implementation of the secondary analyses will be included in the statistical analysis plan.

Additionally, we will estimate the proportions of participants with systemic allergic reactions to the second vaccine dose (no placebo arm), first vaccine dose within the placebo arm, and their difference for the Pfizer-BioNTech COVID-19 Vaccine and independently the Moderna COVID-19 Vaccine in the HA/MCD population. These estimates will be presented together with their 95% exact confidence intervals.

Finally, we will compare the proportion of HA/MCD participants who experience a systemic allergic reaction (CoFAR Grade 2 and above regardless of tryptase, or CoFAR Grade 1 with elevated tryptase [1.2 x baseline plus 2 ng/ml]) within the 90-minute post-vaccination observation period to either dose of the Pfizer-BioNTech COVID-19 Vaccine (and independently the Moderna COVID-19 Vaccine, if child data are obtained) for both the adult and children populations. For this analysis, children who qualified on the basis of poorly controlled asthma will be excluded. These proportions will be accompanied by their 95% exact confidence intervals. The point estimate of the differences in proportions between the adult and child populations within vaccines will be reported, together with their corresponding 95% exact unconditional confidence intervals. This same analysis will be performed comparing the proportion of HA/MCD participants who experience a severe (Grade 3 or higher per CoFAR Grading Scale for Systemic Adverse Reactions Version 3.0) systemic allergic reactions within 90 minutes,

Grade 2 or higher (per CoFAR Grading Scale for Systemic Adverse Reactions Version 3.0) within 48 hours, and anaphylactic reactions (Levels 1-3) per Brighton Collaboration Criteria within 90 minutes to either dose of the Pfizer-BioNTech COVID-19 Vaccine (and independently the Moderna COVID-19 Vaccine, if child data are obtained) between the adult and child populations.

14.4.4. Analyses of Exploratory Endpoints

An estimate of the proportion of participants with systemic allergic reactions to either dose of the Pfizer-BioNTech COVID-19 Vaccine and independently the Moderna COVID-19 Vaccine in the HA/MCD population by baseline covariates will be conducted. For example, demographic, clinical and other measures at baseline will be examined as covariates in order to explore possible heterogeneity in the assessment of risk of systemic allergic reactions.

If the proportions of participants with systemic allergic reactions for either dose of the Pfizer-BioNTech COVID-19 Vaccine and the Moderna COVID-19 Vaccine are similar in the HA/MCD population, a pooled analysis will be conducted. This combined vaccine analysis will have a significant increase in power (>95%) and will provide a more precise estimate of the proportion difference and exact unconditional 95% confidence interval between the comparison and HA/MCD populations. As described earlier, the p-value will be calculated using an unconditional exact test.

Likewise, if the proportions of participants with systemic allergic reactions for adults and children are similar in the HA/MCD population, a pooled analysis will be conducted.

Additionally, an exploratory analysis evaluating risk factors associated with systemic allergic reactions to either dose of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine will be conducted if sufficient allergic reactions are observed. The details of such analysis will be described in the statistical analysis plan.

Statistical analysis is not specified here for exploratory objectives (e.g. transcriptomics), which will only be undertaken if systemic allergic reactions occur in a substantial number of participants.

14.4.5. Descriptive Analyses

Descriptive analyses will be reported separately for each vaccine and population. Continuous baseline measures will be reported using: (1) means (or geometric means) with 95% confidence intervals or (2) median with first and third quartiles, as appropriate. Categorical baseline and demographic characteristics and study disposition will be reported as frequencies and proportions. These descriptive analyses may be further stratified by gender, HA/MCD inclusion criteria, and other demographics/clinical baseline characteristics.

14.5. Interim Analyses

14.5.1. Interim Analysis of Primary Endpoint

After fifty percent of participants have completed their vaccination schedule (approximately 1700 participants), a test of the primary analysis will be conducted using a two-sided alpha level of 0.001, without adjustment of the final analysis (i.e. using a Haybittle–Peto boundary). Interim analysis results will be reviewed by the DSMB. Refer to Section 13.8.2.1 Planned DSMB Reviews.

14.5.2. Interim Analysis of Safety Data

The DSMB will receive periodic safety reports on enrolled participants. However, no formal interim analysis of safety data will be conducted.

14.5.3. Futility Analysis

No formal futility analysis will be performed for this study.

14.6. Statistical Hypotheses

All primary and secondary objectives will be based on two-sided superiority tests. For instance, the null and alternative hypotheses for the primary objectives are:

- H_0: The proportion of participants with systemic allergic reactions in the comparison population is equal to the proportion of participants with systemic allergic reactions in the HA/MCD population
- H_A: The proportion of participants with systemic allergic reactions in the comparison population is different from the proportion of participants with systemic allergic reactions in the HA/MCD population

14.7. Sample Size Considerations

The within vaccine sample size of 1700 participants, 1020 in the HA/MCD population and 680 in the comparison population was determined to detect a minimum proportion difference between the two populations of approximately 0.01 with at least 80% power, assuming a two-sided unconditional exact test. The proportion is assumed to be 0.0001 (1/10,000) in the comparison group and 0.01 (1/100) in the HA/MCD group (see Table 14.7). Power was calculated using an unconditional exact test, with the significance level of the test targeted at 0.05.

Table 14.7. Expected Rates, Number of Systemic Allergic Reactions, and Sample Size

Rate (Number) ***Sample Size***	**Pfizer-BioNTech COVID-19 Vaccine**	**Moderna COVID-19 Vaccine**	**Total (Sample)**
Comparison (40%)	0.0001 (0) *680*	0.0001 (0) *680*	1360
HA/MCD (60%)	0.01 (10) *1020*	0.01 (10) *1020*	2040
Total	0.006 (10) *1700*	0.006 (10) *1700*	0.006 (20) ***3400***

Under the scenario described in Table 14.7, the proportion difference within a vaccine between the two populations is estimated at 0.01 with an unconditional exact 95% confidence interval (0.003, 0.018) and unconditional exact test p-value < 0.05. This illustration shows the expected precision of the estimated proportion difference under the assumed scenario.

This sample size also allows the following precision for estimation of risk in the HA/MCD group within each vaccine sample. If no reactions are observed out of 1020, the corresponding exact 95% confidence interval is (0, 0.0036), which rules out a risk as high as 1/275. If instead, the observed proportion is 10/1020 (i.e., about 0.01), then the 95% confidence interval is (0.005, 0.018).

For children, the within vaccine sample size of 300 participants was chosen. Under this scenario, we expect 180 in the HA/MCD population and 120 in the comparison population. This will detect a minimum proportion difference between

the two populations of approximately 0.05 with approximately 80% power, assuming a two-sided unconditional exact test. The proportion is assumed to be 0.0001 (1/10,000) in the comparison group and 0.05 (1/20) in the HA/MCD group.

Furthermore, a sample size goal of 300 children into the Pfizer-BioNTech COVID-19 vaccine allows for the following precision for the estimation of risk in the HA/MCD group. If no reactions are observed out of the 180 HA/MCD participants, the corresponding exact 95% confidence interval is (0, 0.020), which rules out a risk as high as 1/50. If instead the observed proportion is 2/180 (i.e., about 0.01), then the 95% confidence interval is (0.001, 0.039).

The sample size calculations do not account for dropouts since we expect that number to be extremely low. Although vaccine is widely available, there are difficulties getting into the registration systems and few individuals who receive an initial dose do not return for the second dose.

15. Identification and Access to Source Data

15.1. Source Data

Source documents and source data are considered to be the original documentation where participant information, visit consultations, examinations, and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

The investigator should retain all documentation relating to the study (including but not limited to ICFs, source documentation, study vaccine records, eCRFs, and essential documents) for a period of at least 2 years after the last marketing application approval or, if no application will be filed or if the application is not approved, 2 years following the discontinuation of the investigation.

If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

At study closure, the investigator must inform DAIT/NIAID, or the SACCC as designee, of the long-term storage location of the study's records and must inform DAIT/NIAID if that location changes subsequently.

No study records should be destroyed without prior authorization from DAIT/NIAID.

15.2. Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID and authorized representatives of DAIT/NIAID, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

16. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data, and biological specimen collection, documentation, and completion. An individualized quality management plan may be reviewed by the clinical monitor during review of institutional SOPs.

The eCRFs will be completed online via a web-based EDC system that has been validated and is compliant with Part 11 Title 21 of the CFR. Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. All elements of data entry (i.e., time, date, verbatim text, and the name of the

person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained in accordance with federal regulations.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), or FDA Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), and applicable regulatory requirements (e.g., Good Laboratory Practices [GLP], Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related facilities, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

17. Protocol Deviations

17.1. Protocol Deviation Definitions

- **Protocol Deviation** – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.
- **Major Protocol Deviation (Protocol Violation)** - A Protocol Violation is a deviation from the IRB approved protocol that may affect the participants' rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures. Examples of Major Protocol Deviations are described in the MOP.
- **Non-Major Protocol Deviation** - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participants' rights, safety or well-being, or the completeness, accuracy, and reliability of the study data.

17.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by DAIT/NIAID. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

Upon determination that a protocol deviation has occurred, the study staff will: (a) notify the site principal investigator (PI), (b) notify the SACCC (as Sponsor designee), and (c) will complete a Protocol Deviation form. The protocol deviation form will document at minimum the date the deviation occurred, the date it was identified, a description of the event, whether the deviation resulted in an AE/SAE, PI signature, IRB report requirement, and documentation of a corrective action plan. DAIT/NIAID may request discussion with the site PI to determine the effect of the protocol deviation on the study participant and his/her further participation, the effect of the protocol deviation on the overall study, and corrective actions. The DAIT/NIAID Medical Monitor will make the decision as to whether each deviation is major or not.

The PI will sign the paper source Protocol Deviation, electronically sign Major Deviations in the EDC, and submit the deviation to the central IRB, and local IRB/IEC per IRB regulations. Major protocol deviations will be reported to the DSMB by the DAIT/NIAID Medical Monitor at the medical monitor's discretion.

18. Ethical Considerations and Compliance with Good Clinical Practice

18.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in FDA *Guidance for Industry:* E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the central IRB. Any amendments to the protocol or to the consent materials will also be approved by the central IRB before they are implemented.

18.2. Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator listed on the FDA 1572 or designee will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. The participant will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in the participant's primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

18.3. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number, and these numbers rather than names will be used to collect, store, and report participant information. All biospecimens will be labeled with unique identification numbers. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

Data reported in medical journals or scientific meetings will be presented in aggregate for participants as a whole. No individual participant will be identified in any way.

19. Publication Policy

DAIT/NIAID will be responsible for organizing publication activities related to the multisite aggregate data and will work with the investigators to define the manuscript/presentation development process, the number and order of authors, the publication/scientific meeting to which it will be submitted, and related issues. DAIT/NIAID has final approval authority over all such issues. Single site data may be published by the site investigator(s) after the primary publication, or if the multisite aggregate data has not been published 24 months after database lock.

The National Institutes of Health (NIH) Public Access Policy will apply to this study. [20]

20. References

1. *Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020*, in *Morbidity and Mortality Weekly Report*, CDC, Editor.
2. Shimabukuro, T. and N. Nair, *Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine*. JAMA, 2021.
3. *Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine — United States, December 21, 2020–January 10, 2021*, in *Morbidity and Mortality Weekly Report*, CDC, Editor.
4. Stone, C.A., Jr., et al., *Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized.* J Allergy Clin Immunol Pract, 2019. **7**(5): p. 1533-1540 e8.
5. Ruggeberg, J.U., et al., *Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data.* Vaccine, 2007. **25**(31): p. 5675-84.
6. *Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis of SARS-CoV-2 Infection (COVID-19)*. 2020, National Library of Medicine (US): https://clinicaltrials.gov/ct2/show/NCT04283461.
7. *Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 COVID-19 Vaccine in Adults Aged 18 Years and Older*. 2020, National Library of Medicine (US): https://clinicaltrials.gov/ct2/show/NCT04405076.
8. *A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19*. 2020, National Library of Medicine (US): https://www.clinicaltrials.gov/ct2/show/NCT04470427.
9. *Full FDA EUA Prescribing Information: Moderna COVID-19 Vaccine.*, FDA, Editor. 2020.
10. clinicaltrials.gov. *A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19 (TeenCove)*. [cited 2021 April 19]; Available from: https://clinicaltrials.gov/ct2/show/NCT04649151.
11. *A Trial Investigating the Safety and Effects of Four BNT162 Vaccines Against COVID-2019 in Healthy Adults*. 2020, National Library of Medicine (US): https://clinicaltrials.gov/ct2/show/NCT04380701.
12. *Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates against COVID-19 in Healthy Individuals*. 2020, National Library of Medicine (US): https://clinicaltrials.gov/ct2/show/NCT04368728.
13. *Full FDA EUA Prescribing Information: Pfizer-BioNTech COVID-19 Vaccine*, FDA, Editor. 2020.
14. Zoratti, E.M., et al., *Asthma phenotypes in inner-city children.* J Allergy Clin Immunol, 2016. **138**(4): p. 1016-1029.
15. Shi, T., et al., *Risk of COVID-19 hospital admission among children aged 5-17 years with asthma in Scotland: a national incident cohort study.* Lancet Respir Med, 2021.
16. Lodge, C.J., et al., *Is asthma associated with COVID-19 infection? A UK Biobank analysis.* ERJ Open Res, 2021. **7**(4).
17. Valent, P., et al., *Proposed Diagnostic Algorithm for Patients with Suspected Mast Cell Activation Syndrome.* J Allergy Clin Immunol Pract, 2019. **7**(4): p. 1125-1133 e1.
18. *Policy M95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center*, in *Policy and Communications Bulletin – The Clinical Center/Medical Administrative Series*, NIH, Editor. 2009.
19. *Unanticipated Problems Involving Risks & Adverse Events Guidance (2007)*, OHRP, Editor. 2007.
20. *Public Access Policy [updated 2014 Mar18; cited 2017 May30]*, NIH, Editor.

Appendix 1. CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Reaction involving **one of the following organ systems in which the symptoms are mild**: <u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (no change in activity level), single episode of vomiting and/or single episode of diarrhea	Reaction involving **two or more of the following organ systems in which the symptoms are mild**: <u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (no change in activity level), single episode of vomiting, and/or single episode of diarrhea **OR** Reaction involving **at least one of the following organ systems in which the symptoms are moderate:** <u>Cutaneous</u> Generalized pruritus, generalized urticaria, flushing, angioedema <u>Upper respiratory</u> Rhinitis, cough unrelated to laryngeal edema or bronchospasm <u>Conjunctival</u> Injection/redness, itching, tearing <u>GI</u> Nausea, abdominal pain (with change in activity level), two episodes of vomiting and/or diarrhea	Reaction involving **one or more of the following organ systems**: <u>Lower respiratory</u> Throat tightness, wheezing, chest tightness, dyspnea, cough that respond to short-acting bronchodilator treatment (including IM epinephrine) with or without supplemental oxygen <u>GI</u> Severe abdominal pain, more than two episodes of vomiting and/or diarrhea	**Life-threatening reaction** involving **one or more of the following organ systems** with or without other symptoms listed in Grades 1 to 3: <u>Lower respiratory</u> Throat tightness with stridor, wheezing, chest tightness, dyspnea, or cough associated with a requirement for supplemental oxygen and refractoriness to short-acting bronchodilator treatment (including IM epinephrine)[1] **OR** Respiratory compromise requiring mechanical support <u>Cardiovascular</u> Reduced BP with associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope) defined as: • Children: low systolic BP (age specific[2]) or >30% decrease in systolic BP • Adults: systolic BP of less than 90 mmHg or >30% decrease from baseline	Death

1. Examples of refractoriness could include continuous albuterol nebulizer or epinephrine IV infusion or more than three IM epinephrine injections.
2. Low systolic BP for children is defined as: less than 70 mmHg from 1 month to 1 year of age, less than (70 mmHg + [2 x age]) from 1 to 10 years of age, and less than 90 mmHg from 11 to 17 years of age.

Appendix 2: Brighton Collaboration Criteria

Case Definition of Anaphylaxis

For all levels of diagnostic certainty	Level 1 of diagnostic certainty	Level 2 of diagnostic certainty	Level 3 of diagnostic certainty
Anaphylaxis is a clinical syndrome characterized by • sudden onset AND • rapid progression of signs and symptoms AND • involving multiple (≥2) organ systems, as follows →	• ≥1 major dermatological AND • ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion	•≥1 major cardiovascular AND ≥1 major respiratory criterion OR • ≥1 major cardiovascular OR respiratory criterion AND • ≥1 minor criterion involving ≥1 different system (*other than* cardiovascular or respiratory systems) OR • (≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion)	• ≥1 minor cardiovascular OR respiratory criterion AND • ≥1 minor criterion from each of ≥2 different systems/ categories

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Major and minor criteria used in the case definition of anaphylaxis

	Major Criteria	Minor Criteria
Dermatologic or mucosal	• generalized urticaria (hives) or generalized erythema • angioedema*, localized or generalized • generalized pruritus with skin rash	• generalized pruritus without skin rash • generalized prickle sensation • localized injection site urticaria • red and itchy eyes

Cardiovascular	• measured hypotension
	• clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:
	  • tachycardia
	  • capillary refill time >3 s
	  • reduced central pulse volume
	  • decreased level of consciousness or loss of consciousness
		• reduced peripheral circulation as indicated by the combination of at least 2 of
		  • tachycardia and
		  • a capillary refill time of >3 s without hypotension
		  • a decreased level of consciousness

Respiratory	• bilateral wheeze (bronchospasm)
	• stridor
	• upper airway swelling (lip, tongue, throat, uvula, or larynx)
	• respiratory distress—2 or more of the following:
	  • tachypnoea
	  • increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)
	  • recession
	  • cyanosis
	  • grunting
		• persistent dry cough
		• hoarse voice
		• difficulty breathing without wheeze or stridor
		• sensation of throat closure
		• sneezing, rhinorrhea

Gastrointestinal		• diarrhoea • abdominal pain • nausea • vomiting
Laboratory		Mast cell tryptase elevation > upper normal limit

* Not hereditary angioedema

Appendix 3: Schedule of Events

Table A: Schedule of Events for Participants Randomized to Receive Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine (No Placebo dose) Protocol versions 1.0-4.0

Visit	Recruitment & Pre-Screening[1]	Enrollment[2]				FU Call	Second Vaccination				FU Call	End of Study Call	UV
Day (Pfizer-BioNTech COVID-19 Vaccine)	Day -14 to 0	Day 1				Day 4	Day 22				Day 25	Day 29	As Needed
Day (Moderna COVID-19 Vaccine)							Day 29				Day 32	Day 36	
Visit Window	N/A	N/A				±1 Day	-4 to + 14 Days				±1 Day	±1 Day	N/A
Time, in relation to vaccination		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)			
Study Evaluations, Assessments, & Procedures													
Informed Consent and/or Assent, as applicable	X[5]	X[6]											
Eligibility Questionnaire	X	X					X[7]						
Demographics		X											
Medical History	X	X[8]				X[8]	X[8]				X[8]	X[8]	
Physical Assessment		X					X						
Vital Signs[9]		X	X	X	X		X	X	X	X			X
Growth Parameters (height and weight)		X											
Pregnancy Test[10]		X					X						
Concomitant Medications	X	X	X[11]	X[11]	X[11]	X	X	X[11]	X[11]	X[11]	X	X	X
Randomization		X											
Assess Epinephrine Access and Distribute as needed for HA/MCD Participants		X					X						
Blood Sample Collections													
CBC with Differential (~3 mL)		X	X	X	X		X	X	X	X			
Whole Blood for Genetic Analysis (~2.5 mL)		X											
Whole Blood: RNA for Transcriptomics (~2.5 mL)		X	X	X	X		X	X	X	X			
Blood for Serum Collection: Biomarkers & Antibodies[12] (~20-30 mL)		X	X	X	X		X	X	X	X			X[13]
Blood for Plasma Collection: Proteomics and Complement Activation Testing (~12 mL)		X	X	X	X		X	X	X	X			X[13]
Blood for Plasma Collection: Kallikrein (~3 mL)				X	X				X	X			
Blood for PBMC Isolation and Plasma Collection (~48 mL)[14]		X	X[15]	X			X	X[15]	X				
Nasal Swab Collection: SARS-CoV-2 by PCR		X					X						
Urine Collection: LTE_4 and Proteomics		X	X	X	X		X	X	X	X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Diary Distribution		X					X						
Diary Review						X	X				X	X	
Distribute Anaphylaxis Care Plan		X					X						

Visit	Recruitment & Pre-Screening[1]	Enrollment[2]				FU Call	Second Vaccination				FU Call	End of Study Call	UV
Day (Pfizer-BioNTech COVID-19 Vaccine)	Day -14 to 0	Day 1				Day 4	Day 22				Day 25	Day 29	As Needed
Day (Moderna COVID-19 Vaccine)							Day 29				Day 32	Day 36	
Visit Window	N/A	N/A				±1 Day	-4 to + 14 Days				±1 Day	±1 Day	N/A
Time, in relation to vaccination		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)			
Study Evaluations, Assessments, & Procedures													
Vaccine Administration[16]		X					X						

FU = Follow-Up, UV = Unscheduled Visit, Hr = Hour, RX = Reaction

1. Participants may be pre-screened over the phone or in person.
2. Participants who complete pre-screening or consenting in-person and are found eligible may complete the Enrollment Visit on the same day as pre-screening or consenting.
3. If a participant has a systemic allergic reaction prior to the 1-hour post-vaccination time point, samples will be collected 30-60 minutes after onset of the reaction, and additional samples will not need to be collected at the 1-hour post timepoint. Detailed instructions for sample processing are defined in the MOP.
4. After the 1-hour sample collection, additional samples will be collected 30-60 minutes after the onset of a systemic allergic reaction, as applicable. Detailed instructions for sample processing are defined in the MOP.
5. Individuals pre-screened over the phone may provide verbal consent for pre-screening. Per institutional policies, after pre-screening is complete, remote consenting may be performed. In the event of a remote consent, the participant will need to return the signed consent and/or assent (if applicable) to the clinic, prior to the conduct of any study procedures. Eligible individuals pre-screened in person and/or unable to complete remote consenting will be asked to sign the written informed consent during a separate clinic visit or during their Enrollment Visit, prior to the conduct of any study procedures.
6. Written informed consent and assent as applicable will be obtained prior to conducting any study procedures.
7. Participant eligibility will be reviewed to assess if a change in concomitant medications or an acute illness may delay the timing of the participant's second dose.
8. An interim medical history will be collected.
9. Vital sign measurements include temperature, pulse rate, respiratory rate, O_2 saturation, and blood pressure. Vital signs will be measured before blood is collected. Blood pressure will be measured after participant is sitting for at least 5 minutes. Vital signs will be taken both pre-vaccination and 1-hour post-vaccination. In addition, vital signs will be monitored during a systemic allergic reaction and prior to discharge.
10. Female participants of child-bearing potential who do not self-report as pregnant will complete a urine pregnancy test.
11. In the event of a reaction, use of rescue medications will be recorded on the Concomitant Medications eCRF.
12. Serum (approximately 30 mL pre-vaccination and 20 mL post) will be collected for the measurement of biomarkers and antibodies, including but not limited to, tryptase, IL-6, anti-PEG antibodies (IgE, IgG, and IgM), and anti-SARS-CoV-2 spike antibodies, as defined in the MOP.
13. Participants who return for an Unscheduled Visit may have serum and plasma collected for assessment of an allergic reaction at the discretion of the investigator.
14. PBMC isolation and plasma collection will occur at a sub-set of the clinical sites. Participants weighing less than 50 kg will not participate in PBMC collections.
15. PBMCs will be collected on a sub-set of participants who don't have allergic reactions at the 1-hour time point post-vaccination to serve as controls.
16. Following vaccine administration, participants will be observed for 90 minutes during which the study staff will examine the vaccination site for erythema/redness, induration/swelling, and monitor for pain.

Table B: Schedule of Events for Participants Randomized to Receive Placebo prior to Vaccination with Either the Pfizer-BioNTech COVID-19 or Moderna COVID-19 Vaccine Protocol Versions 1.0 - 4.0

Visit	**Recruitment & Pre-Screening[1]**	**Enrollment[2]**				**FU Call**	**First Vaccination**				**FU Call**	**Second Vaccination**				**FU Call**	**End of Study Call**	**UV**
Day (Pfizer-BioNTech COVID-19 Vaccine)	Day -14 to 0	Day 1				Day 4	Day 22				Day 25	Day 43				Day 46	Day 50	As Need-ed
Day (Moderna COVID-19 Vaccine)							Day 29				Day 32	Day 57				Day 60	Day 64	
Visit Window	N/A	N/A				±1 Day	-4 to +14 Days				±1 Day	-4 to + 14 Days				±1 Day	±1 Day	N/A
Time, in relation to vaccination		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)			
Study Evaluations, Assessments, & Procedures																		
Informed Consent and/or Assent, as applicable	X[5]	X[6]																
Eligibility Questionnaire	X	X					X[7]					X[7]						
Demographics		X																
Medical History	X	X[8]				X[8]	X[8]				X[8]	X[8]				X[8]	X[8]	
Physical Assessment		X					X					X						
Vital Signs[9]		X	X	X	X		X	X	X	X		X	X	X	X			X
Growth Parameters (height and weight)		X																
Pregnancy Test[10]		X					X					X						
Concomitant Medications	X	X	X	X	X	X	X	X[11]	X[11]	X[11]	X	X	X[11]	X[11]	X[11]	X	X	X
Randomization		X																
Assess Epinephrine Access and Distribute as needed for HA/MCD Participants		X					X					X						
Blood Sample Collections																		
CBC with Differential (~3 mL)		X	X	X	X		X	X	X	X		X	X	X	X			
Whole Blood for Genetic Analysis (~2.5 mL)		X																
Whole Blood: RNA for Transcriptomics (~2.5 mL)		X	X	X	X		X	X	X	X		X	X	X	X			
Blood for Serum Collection: Biomarkers & Antibodies[12] (~ 20-30 mL)		X	X	X	X		X	X	X	X		X	X	X	X			X[13]
Blood for Plasma Collection: Proteomics & Complement Activation Testing (~12 mL)		X	X	X	X		X	X	X	X		X	X	X	X			X[13]
Blood for Plasma Collection: Kallikrein (~3 mL)				X	X				X	X				X	X			

Visit	Recruitment & Pre-Screening[1]	Enrollment[2]				FU Call	First Vaccination				FU Call	Second Vaccination				FU Call	End of Study Call	UV
Day (Pfizer-BioNTech COVID-19 Vaccine)	Day -14 to 0	Day 1				Day 4	Day 22				Day 25	Day 43				Day 46	Day 50	As Need-ed
Day (Moderna COVID-19 Vaccine)							Day 29				Day 32	Day 57				Day 60	Day 64	
Visit Window	N/A	N/A				±1 Day	-4 to +14 Days				±1 Day	-4 to + 14 Days				±1 Day	±1 Day	N/A
Time, in relation to vaccination		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)		Pre	1 Hr Post[3]	Rx Post 1 Hr[4]	Discharge (If Rx)			
Study Evaluations, Assessments, & Procedures																		
Blood for PBMC Isolation and Plasma Collection (~48 mL)[14]		X	X[15]	X			X	X[15]	X			X	X[15]	X				
Nasal Swab Collection: SARS-CoV-2 by PCR		X					X					X						
Urine Collection: LTE_4 and Proteomics		X	X	X	X		X	X	X	X		X	X	X	X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary Distribution		X					X					X						
Diary Review						X	X				X	X				X	X	
Distribute Anaphylaxis Care Plan		X					X					X						
Placebo/Vaccine Administration[16]		X[17]					X[17]					X[17]						

FU = Follow-Up, UV = Unscheduled Visit, Hr = Hour, RX = Reaction

1. Participants may be pre-screened over the phone or in person.
2. Participants who complete pre-screening or consenting in-person and are found eligible may complete the Enrollment Visit on the same day as pre-screening or consenting.
3. If a participant has a systemic allergic reaction prior to the 1-hour post-vaccination time point, samples will be collected 30-60 minutes after onset of the reaction, and additional samples will not need to be collected at the 1-hour post timepoint. Detailed instructions for sample processing are defined in the MOP.
4. After the 1-hour sample collection, additional samples will be collected 30-60 minutes after the onset of a systemic allergic reaction, as applicable. Detailed instructions for sample processing are defined in the MOP.
5. Individuals pre-screened over the phone may provide verbal consent for pre-screening. Per institutional policies, after pre-screening is complete, remote consenting may be performed. In the event of a remote consent, the participant will need to return the signed consent and/or assent (if applicable) to the clinic, prior to the conduct of any study procedures. Eligible individuals pre-screened in person and/or unable to complete remote consenting will be asked to sign the written informed consent during a separate clinic visit or during their Enrollment Visit, prior to the conduct of any study procedures.
6. Written informed consent and assent as applicable will be obtained prior to conducting any study procedures.
7. Participant eligibility will be reviewed to assess if a change in concomitant medications or an acute illness may delay the timing of the participant's vaccine dose.
8. An interim medical history will be collected.
9. Vital sign measurements include temperature, pulse rate, respiratory rate, O_2 saturation, and blood pressure. Vital signs will be measured before blood is collected. Blood pressure will be measured after participant is sitting for at least 5 minutes. Vital signs will be taken both pre-vaccination and 1-hour post-vaccination. In addition, vital signs will be monitored during a systemic allergic reaction and prior to discharge.
10. Female participants of child-bearing potential who do not self-report as pregnant will complete a urine pregnancy test.

11. In the event of a reaction, use of rescue medications will be recorded on the Concomitant Medications eCRF.
12. Serum (approximately 30 mL pre-vaccination and 20 mL post) will be collected for the measurement of biomarkers and antibodies, including but not limited to, tryptase, IL-6, anti-PEG antibodies (IgE, IgG, and IgM), and anti-SARS-CoV-2 spike antibodies, as defined in the MOP.
13. Participants who return for an Unscheduled Visit may have serum and plasma collected for assessment of an allergic reaction at the discretion of the investigator.
14. PBMC isolation and plasma collection will occur at a sub-set of the clinical sites. Participants weighing less than 50 kg will not participate in PBMC collections.
15. PBMCs will be collected on a sub-set of participants who don't have allergic reactions at the 1-hour time point post-vaccination to serve as controls.
16. Following placebo/vaccine administration, participants will be observed for 90 minutes during which the study staff will examine the vaccination site for erythema/redness, induration/swelling, and monitor for pain.
17. Participants will receive an injection of placebo during their Enrollment Visit, followed by the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine at their First Vaccination and Second Vaccination Visits.

Table C: Schedule of Events for Participants Randomized to receive Pfizer-BioNTech COVID-19 or Moderna COVID-19 Vaccine (No Placebo dose) Under Protocol Version 5.0-8.0

Visit	**Recruitment & Pre-Screening[1]**	**Enrollment[2]**			**FU Call**	**Second Vaccination**			**FU Call**	**End of Study Call**	**UV**
Day (Pfizer-BioNTech COVID-19 Vaccine)	Day -14 to 0	Day 1			Day 4	Day 22			Day 25	Day 29	As Needed
Day (Moderna COVID-19 Vaccine)						Day 29			Day 32	Day 36	
Visit Window	N/A	N/A			±1 Day	-4 to + 14 Days			±1 Day	±1 Day	N/A
Time, in relation to vaccination		Pre	1 Hr Post[3]	Rx Post Vacc[4]		Pre	1 Hr Post[3]	Rx Post Vacc[4]			
Study Evaluations, Assessments, & Procedures											
Informed Consent and/or Assent, as applicable	X[5]	X[6]									
Eligibility Questionnaire	X	X				X[7]					
Demographics		X									
Medical History	X	X[8]			X[8]	X[8]			X[8]	X[8]	
Physical Assessment		X				X					
Vital Signs[9]		X	X	X		X	X	X			X
Growth Parameters (height and weight)		X									
Pregnancy Test[10]		X				X					
Concomitant Medications	X	X	X	X	X	X	X[11]	X[11]	X	X	X
Randomization		X									
Assess Epinephrine Access and Distribute as needed for HA/MCD Participants		X				X					
Blood Sample Collections											
CBC with Differential (~3 mL)		X		X			X	X			
Whole Blood: RNA for Transcriptomics (~2.5 mL)		X		X			X	X			
Blood for Serum Collection: Biomarkers & Antibodies[12] (~10 mL)		X		X			X	X			X[13]
Blood for Plasma Collection: Proteomics & Complement Activation Testing (~6 mL)		X		X			X	X			X[13]
Blood for Plasma Collection: Kallikrein (~3 mL)				X			X	X			
Blood for PBMC Isolation and Plasma Collection (~48 mL)[14]		X		X			X[15]	X			
Nasal Swab Collection: SARS-CoV-2 by PCR[16]		X				X					
Urine Collection: LTE_4 and Proteomics		X	X	X		X	X	X			
Adverse Events		X	X	X	X	X	X	X	X	X	X
Diary Distribution		X				X					
Diary Review					X	X			X	X	
Distribute Anaphylaxis Care Plan		X				X					
Vaccine Administration[17]		X				X					

FU = Follow-Up, UV = Unscheduled Visit, Hr = Hour, RX = Reaction

1. Participants may be pre-screened over the phone or in person.
2. Participants who complete pre-screening or consenting in-person and are found eligible may complete the Enrollment Visit on the same day as pre-screening or consenting.
3. If a participant has a systemic allergic reaction prior to the 1-hour post-vaccination time point, samples will be collected 30-60 minutes after onset of the reaction, and additional samples will not need to be collected at the 1-hour post timepoint. All collections will be based upon the participant's weight. Detailed instructions for sample processing are defined in the MOP.
4. After the 1-hour sample collection, additional samples will be collected 30-60 minutes after the onset of a systemic allergic reaction, as applicable. All collections will be based upon the participant's weight. Detailed instructions for sample processing are defined in the MOP.
5. Individuals pre-screened over the phone may provide verbal consent for pre-screening. Per institutional policies, after pre-screening is complete, remote consenting may be performed. In the event of a remote consent, the participant will need to return the signed consent and/or assent (if applicable) to the clinic, prior to the conduct of any study procedures. Eligible individuals pre-screened in person and/or unable to complete remote consenting will be asked to sign the written informed consent during a separate clinic visit or during their Enrollment Visit, prior to the conduct of any study procedures.
6. Written informed consent and assent as applicable will be obtained prior to conducting any study procedures.
7. Participant eligibility will be reviewed to assess if a change in concomitant medications or an acute illness may delay the timing of the participant's vaccine dose.
8. An interim medical history will be collected.
9. Vital sign measurements include temperature, pulse rate, respiratory rate, O_2 saturation, and blood pressure. Vital signs will be measured before blood is collected. Blood pressure will be measured after participant is sitting for at least 5 minutes. Vital signs will be taken both pre-vaccination and 1-hour post-vaccination. In addition, vital signs will be monitored during a systemic allergic reaction and prior to discharge.
10. Female participants of child-bearing potential who do not self-report as pregnant will complete a urine pregnancy test.
11. In the event of a reaction, use of rescue medications will be recorded on the Concomitant Medications eCRF.
12. Serum (approximately 10 mL pre-vaccination and post) will be collected for the measurement of biomarkers and antibodies, including but not limited to, tryptase, IL-6, anti-PEG antibodies (IgE, IgG, and IgM), and anti-SARS-CoV-2 spike antibodies, as defined in the MOP.
13. Participants who return for an Unscheduled Visit may have serum and plasma collected for assessment of an allergic reaction at the discretion of the investigator.
14. PBMC isolation and plasma collection will occur at a sub-set of the clinical sites. Participants weighing less than 50 kg will not participate in PBMC collections.
15. PBMCs will be collected on a sub-set of participants who don't have allergic reactions at the 1-hour time point post-vaccination to serve as controls.
16. Participants enrolled under protocol version 7.0 and 8.0 will not be required to provide a nasal swab sample.
17. Following vaccine administration, participants will be observed for 90 minutes during which the study staff will examine the vaccination site for erythema/redness, induration/swelling, and monitor for pain.

Table D: Schedule of Events for Participants Randomized to Receive Placebo prior to Vaccination with Either the Pfizer-BioNTech COVID-19 or Moderna COVID-19 Vaccine Under Protocol Version 5.0 -7.0

Visit	**Recruitment & Pre-Screening[1]**	**Enrollment[2]**			**FU Call**	**First Vaccination**			**FU Call**	**Second Vaccination**			**FU Call**	**End of Study Call**	**UV**
Day (Pfizer-BioNTech COVID-19 Vaccine)	Day -14 to 0	Day 1			Day 4	Day 8			Day 11	Day 29			Day 32	Day 36	As Need-ed
Day (Moderna COVID-19 Vaccine)										Day 36			Day 39	Day 43	
Visit Window	N/A	N/A			±1 Day	-4 to +14 Days			±1 Day	-4 to + 14 Days			±1 Day	±1 Day	N/A
Time, in relation to vaccination		Pre	1 Hr Post[3]	Rx Post Vacc[4]		Pre	1 Hr Post[3]	Rx Post Vacc[4]		Pre	1 Hr Post[3]	Rx Post Vacc[4]			
Study Evaluations, Assessments, & Procedures															
Informed Consent and/or Assent, as applicable	X[5]	X[6]													
Eligibility Questionnaire	X	X				X[7]				X[7]					
Demographics		X													
Medical History	X	X[8]			X[8]	X[8]			X[8]	X[8]			X[8]	X[8]	
Physical Assessment		X				X				X					
Vital Signs[9]		X	X	X		X	X	X		X	X	X			X
Growth Parameters (height and weight)		X													
Pregnancy Test[10]		X				X				X					
Concomitant Medications	X	X	X	X	X	X	X[11]	X[11]	X	X	X[11]	X[11]	X	X	X
Randomization		X													
Assess Epinephrine Access and Distribute as needed for HA/MCD Participants		X				X				X					
Blood Sample Collections															
CBC with Differential (~3 mL)		X		X				X			X	X			
Whole Blood: RNA for Transcriptomics (~2.5 mL)		X		X				X			X	X			
Blood for Serum Collection: Biomarkers & Antibodies[12] (~10 mL)		X		X				X			X	X			X[13]
Blood for Plasma Collection: Proteomics & Complement Activation Testing (~6 mL)		X		X				X			X	X			X[13]
Blood for Plasma Collection: Kallikrein (~3 mL)				X				X			X	X			
Blood for PBMC Isolation and Plasma Collection (~48 mL)[14]		X		X				X			X[15]	X			
Nasal Swab Collection: SARS-CoV-2 by PCR[16]		X				X				X					

Visit	Recruitment & Pre-Screening[1]	Enrollment[2]			FU Call	First Vaccination			FU Call	Second Vaccination			FU Call	End of Study Call	UV
Day (Pfizer-BioNTech COVID-19 Vaccine)	Day -14 to 0	Day 1			Day 4	Day 8			Day 11	Day 29			Day 32	Day 36	As Need-ed
Day (Moderna COVID-19 Vaccine)										Day 36			Day 39	Day 43	
Visit Window	N/A	N/A			±1 Day	-4 to +14 Days			±1 Day	-4 to + 14 Days			±1 Day	±1 Day	N/A
Time, in relation to vaccination		Pre	1 Hr Post[3]	Rx Post Vacc[4]		Pre	1 Hr Post[3]	Rx Post Vacc[4]		Pre	1 Hr Post[3]	Rx Post Vacc[4]			
Study Evaluations, Assessments, & Procedures															
Urine Collection: LTE_4 and Proteomics		X	X	X		X	X	X		X	X	X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary Distribution		X				X				X					
Diary Review					X	X			X	X			X	X	
Distribute Anaphylaxis Care Plan		X				X				X					
Placebo/Vaccine Administration[17]		X[18]				X[18]				X[18]					

FU = Follow-Up, UV = Unscheduled Visit, Hr = Hour, RX = Reaction

1. Participants may be pre-screened over the phone or in person.
2. Participants who complete pre-screening or consenting in-person and are found eligible may complete the Enrollment Visit on the same day as pre-screening or consenting.
3. If a participant has a systemic allergic reaction prior to the 1-hour post-vaccination time point, samples will be collected 30-60 minutes after onset of the reaction, and additional samples will not need to be collected at the 1-hour post timepoint. All collections will be based upon the participant's weight. Detailed instructions for sample processing are defined in the MOP.
4. After the 1-hour sample collection, additional samples will be collected 30-60 minutes after the onset of a systemic allergic reaction, as applicable. All collections will be based upon the participant's weight. Detailed instructions for sample processing are defined in the MOP.
5. Individuals pre-screened over the phone may provide verbal consent for pre-screening. Per institutional policies, after pre-screening is complete, remote consenting may be performed. In the event of a remote consent, the participant will need to return the signed consent and/or assent (if applicable) to the clinic, prior to the conduct of any study procedures. Eligible individuals pre-screened in person and/or unable to complete remote consenting will be asked to sign the written informed consent during a separate clinic visit or during their Enrollment Visit, prior to the conduct of any study procedures.
6. Written informed consent and assent as applicable will be obtained prior to conducting any study procedures.
7. Participant eligibility will be reviewed to assess if a change in concomitant medications or an acute illness may delay the timing of the participant's vaccine dose.
8. An interim medical history will be collected.
9. Vital sign measurements include temperature, pulse rate, respiratory rate, O_2 saturation, and blood pressure. Vital signs will be measured before blood is collected. Blood pressure will be measured after participant is sitting for at least 5 minutes. Vital signs will be taken both pre-vaccination and 1-hour post-vaccination. In addition, vital signs will be monitored during a systemic allergic reaction and prior to discharge.
10. Female participants of child-bearing potential who do not self-report as pregnant will complete a urine pregnancy test.
11. In the event of a reaction, use of rescue medications will be recorded on the Concomitant Medications eCRF.
12. Serum (approximately 10 mL pre-vaccination and post) will be collected for the measurement of biomarkers and antibodies, including but not limited to, tryptase, IL-6, anti-PEG antibodies (IgE, IgG, and IgM), and anti-SARS-CoV-2 spike antibodies, as defined in the MOP.
13. Participants who return for an Unscheduled Visit may have serum and plasma collected for assessment of an allergic reaction at the discretion of the investigator.
14. PBMC isolation and plasma collection will occur at a sub-set of the clinical sites. Participants weighing less than 50 kg will not participate in PBMC collections.

15. PBMCs will be collected on a sub-set of participants who don't have allergic reactions at the 1-hour time point post-vaccination to serve as controls.
16. Participants enrolled under protocol version 7.0 and 8.0 will not be required to provide a nasal swab sample.
17. Following placebo/vaccine administration, participants will be observed for 90 minutes during which the study staff will examine the vaccination site for erythema/redness, induration/swelling, and monitor for pain.
18. Participants will receive an injection of placebo during their Enrollment Visit, followed by the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine at their First Vaccination and Second Vaccination Visits.

Appendix 4: Tables for Clinical and Laboratory Abnormalities

The tables for clinical and laboratory abnormalities are presented in Tables A and B, respectively, according to the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007).*

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration or swelling[b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration (underlying hardening of tissue associated with inflammation) or swelling (localized tissue distension) should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[b] (°F)[b]	38.0-38.4 100.4-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	>40 >104
Tachycardia – beats per minute (12-17 years)	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Tachycardia – beats per minute (5-11 years)	115-125	126-140	>140	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute[c] (12-17 years)	50-54	45-49	<45	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute[d] (5-11 years)	67-74	52-66	<52	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mm Hg (12-17 years)	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (systolic) – mm Hg (5-11 years)	120-129	130-139	>140	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mm Hg (12-17 years)	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hypertension (diastolic) – mm Hg (5-11 years)	80-84	85-89	>90	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg (12-17 years)	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock
Hypotension (systolic) – mm Hg (5-11 years)	<70 without symptoms	<70 with symptoms	<70 requiring medications or fluids	ER visit or hospitalization for hypotensive shock
Respiratory rate – breaths per minute (12-17 years)	17-20	21-25	>25	Intubation
Respiratory rate – breaths per minute (5-11 years)	22-24	25-27	>27	Intubation

ER = emergency room

[a] Subject should be at rest for all vital sign measurements.

[b] Oral temperature; no recent hot or cold beverages or smoking.

[c] Heart rate should be measured while the subjects is awake. BPM based on resting heart rate between 60 to 100 beats per minute for adolescents. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 g/24 hours	4-5 stools or 400-800 g/24 hours	6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

ER = emergency room; IV = intravenous

B. Tables for Laboratory Abnormalities

Serum[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
Sodium – hyponatremia mEq/L	132-134	130-131	125-129	<125
Sodium – hypernatremia mEq/L	144-145	146-147	148-150	>150
Potassium – hyperkalemia mEq/L	5.1-5.2	5.3-5.4	5.5-5.6	>5.6
Potassium – hypokalemia mEq/L	3.5-3.6	3.3-3.4	3.1-3.2	<3.1
Glucose – hypoglycemia mg/dL	65-69	55-64	45-54	<45
Glucose – hyperglycemia Fasting - mg/dL Random - mg/dL	 100-110 110-125	 111-125 126-200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood urea nitrogen mg/dL	23-26	27-31	>31	Requires dialysis
Creatinine mg/dL	1.5-1.7	1.8-2.0	2.1-2.5	>2.5 or requires dialysis
Calcium-hypocalcemia mg/dL	8.0-8.4	7.5-7.9	7.0-7.4	<7.0
Calcium-hypercalcemia mg/dL	10.5-11.0	11.1-11.5	11.6-12.0	>12.0
Magnesium-hypomagnesemia mg/dL	1.3-1.5	1.1-1.2	0.9-1.0	<0.9
Phosphorus – hypophosphatemia mg/dL	2.3-2.5	2.0-2.2	1.6-1.9	<1.6
CPK - mg/dL	1.25-1.5 × ULN	1.6-3.0 × ULN	3.1-10 × ULN	>10 × ULN
Albumin – hypoalbuminemia g/dL	2.8-3.1	2.5-2.7	<2.5	–
Total protein – hypoproteinemia g/dL	5.5-6.0	5.0-5.4	<5.0	–
Alkaline phosphate – increase by factor	1.1-2.0 × ULN	2.1-3.0 × ULN	3.1-10 × ULN	>10 × ULN
Liver function tests – ALT, AST increase by factor	1.1-2.5 × ULN	2.6-5.0 × ULN	5.1-10 × ULN	>10 × ULN
Bilirubin – when accompanied by any increase in liver function test increase by factor	1.1-1.25 × ULN	1.26-1.5 × ULN	1.51-1.75 × ULN	>1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1-1.5 × ULN	1.6-2.0 × ULN	2.0-3.0 × ULN	>3.0 × ULN
Cholesterol mg/dL	201-210	211-225	>226	-
Pancreatic enzymes – amylase, lipase	1.1-1.5 × ULN	1.6-2.0 × ULN	2.1-5.0 × ULN	>5.0 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; ULN = upper limit of normal.

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[b] The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter

(125-129 mEq/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

Hematology[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (female) – g/dL	11.0-12.0	9.5-10.9	8.0-9.4	<8.0
Hemoglobin (female) change from baseline value	Any decrease – 1.5	1.6-2.0	2.1-5.0	>5.0
Hemoglobin (male) – g/dL	12.5-13.5	10.5-12.4	8.5-10.4	<8.5
Hemoglobin (male) change from baseline value – g/dL	Any decrease – 1.5	1.6-2.0	2.1-5.0	>5.0
WBC increase – cell/mm^3	10,800-15,000	15,001-20,000	20,001-25,000	>25,000
WBC decrease – cell/mm^3	2,500-3,500	1,500-2,499	1,000-1,499	<1,000
Lymphocytes decrease – cell/mm^3	750-1 000	500-749	250-499	<250
Neutrophils decrease – cell/mm^3	1,500-2,000	1,000-1,499	500-999	<500
Eosinophils – cell/mm^3	650-1 500	1501-5 000	>5 000	Hypereosinophilic
Platelets decrease – cell/mm^3	125,000-140,000	100,000-124,000	25,000-99,000	<25,000
PT – increase by factor	1.0-1.10 × ULN	1.11-1.20 × ULN	1.21-1.25 × ULN	>1.25 x ULN
PTT – increase by factor	1.0-1.2 × ULN	1.21-1.4 × ULN	1.41-1.5 × ULN	>1.5 x ULN

PPT = partial thromboplastin time; PT = prothrombin time; ULN = upper limit of normal; WBC = white blood cell.

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Urine[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization or hyperglycemia
Blood (microscopic) – red blood cells per high power field	1-10	11-50	>50 and/or gross blood	Hospitalization or packed red blood cells transfusion

[a] The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.