A5404

SARS-CoV-2 Immune Responses after COVID-19 Therapy and Subsequent Vaccine

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

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ACTG
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A5404
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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teama5404@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teama5404@fstrf.org. A response should generally be received within 24 hours (Monday through Friday).

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5404 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the Clinical Management committee (CMC).

- Send an e-mail message to actg.cmca5404@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
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- Send an e-mail message to actg.teama5404@fstrf.org (ATTENTION: Scott Sieg, Immunologist; Jonathan Li, Virologist; Courtney Fletcher, Pharmacologist).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact [Sara Sieczkarski] directly.
- For other questions, send an e-mail message to actg.teama5404@fstrf.org (ATTENTION: Sara Sieczkarski).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/participant registration questions or problems and study identification number SID lists:

- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

- Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist.
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Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@dlhcorp.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
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For questions related to protocol activation at non-US sites contact the ACTG Site Coordination Group.
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Study Product
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Study Drug Orders
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

IND (Investigational New Drug) Number or Questions
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Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Telephone Calls
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Protocol-Specific Web Page

Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

Ab	antibody
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AE	adverse event
AESI	adverse event of special interest
COVID-19	coronavirus disease 2019
CRS	clinical research site
EAE	**expedited adverse event**
eCRF	electronic case report form
EUA	Emergency Use Authorization
FDA	US Food and Drug Administration
Investigational therapy	ACTIV-2/A5401 active treatment
LPC	lab processing chart
MOPS	Manual of Procedures
mRNA	messenger ribonucleic acid
NAb	neutralizing antibody
NP	nasopharyngeal
PBMC	peripheral blood mononuclear cell
PID	patient identification number
PSWP	protocol-specific web page
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
Select therapy	ACTIV-2/A5401 investigational therapy or corresponding placebo
SMC	Study Monitoring Committee
SOE	Schedule of Evaluations

SCHEMA

A5404
SARS-CoV-2 Immune Responses after COVID-19 Therapy and Subsequent Vaccine

DESIGN

A5404 is a phase IV, open-label study. The objective of A5404 is to evaluate how prior investigational therapy for COVID-19 versus comparator (placebo or active comparator) affects vaccine response.

Eligible A5404 participants include:

- **Cohort 1 (ACTIV-2/A5401 cohort):** Participants of ACTIV-2/A5401 who received an investigational therapy or its comparator (placebo or active comparator).
- **Cohort 2 (SARS-CoV-2-naïve cohort):** Persons without prior history of SARS-CoV-2 infection (non-A5401 participants).

Cohort 1 participants will be offered study-provided standard dosing of the Moderna mRNA-1273 vaccine, or will receive a community-provided mRNA-based COVID-19 vaccine (e.g., Moderna or Pfizer). **Cohort 1 participants** will receive their mRNA-based COVID-19 vaccine **30**-240 days after receiving their last dose of a select ACTIV-2/A5401 investigational therapy, or its comparator. **Cohort 2 p**articipants will receive study-provided standard dosing of the Moderna mRNA-1273 vaccine.

All participants will have blood collected and immune responses measured before first vaccine dose (if feasible), at second dose of vaccine (e.g., 28 days later**; if feasible**), and at 56 **(if feasible)**, 140, 365, and 730 days after **their first vaccine dose**.

DURATION

730 days.

SAMPLE SIZE

Cohort 1: 70 participants from each ACTIV-2/A5401 select therapy group (combining recipients in ACTIV-2/A5401 on a particular investigational therapy, corresponding active comparator, or placebo).

And

Cohort 2: Up to 70 participants without prior history of SARS-CoV-2 infection (SARS-CoV-2-naïve, non-A5401 participants) per select therapy group from ACTIV-2/A5401, based on vaccine supply at each A5404 site. For example, up to 350 SARS-CoV-2-naïve participants may enroll in A5404 if five A5401 select therapy groups are included.

The total sample size will depend on how many select therapy groups are evaluated from ACTIV-2/A5401.

If up to 70 Phase II participants in the A5401/ACTIV-2 trial from each therapy group are not able to be enrolled, then Phase III participants in the A5401/ACTIV-2 trial from that select therapy group can be enrolled until full enrollment is achieved. However, Phase II participants are preferred.

POPULATION

Cohort 1: ACTIV-2/A5401 trial participants who received an investigational therapy or its active comparator/placebo.

And

Cohort 2: Persons without prior history of SARS-CoV-2 infection.

REGIMEN

Cohort 1: ACTIV-2/A5401 participants
Participants will receive one of the following regimens:
Cohort 1a: Moderna mRNA-1273 COVID-19 vaccine, 100 µg **(0.5 mL) to be administered** intramuscularly **(IM) at Entry and Day 28**. **Both doses will be provided by the study.**

Or

Cohort 1b: Participants will receive a two-dose series of a community-provided mRNA-based COVID-19 vaccine that has received FDA EUA or FDA approval (e.g., Moderna or Pfizer). **Vaccine will not be provided by the study.**

NOTE: These participants may enter the study before their first vaccine dose, after their first vaccine dose, or after their second vaccine dose.

Or

Cohort 1c: Participants will receive their first Moderna mRNA-1273 COVID-19 vaccine dose in the community. Their second Moderna mRNA-1273 dose will be provided by the study (100 µg **[0.5 mL] to be administered IM 28 days after their first dose).**

NOTE: These participants may enter the study before or after their first vaccine dose.

Cohort 2: Participants without prior history of SARS-CoV-2 infection
Participants will receive the following study-provided regimen:
Moderna mRNA-1273 COVID-19 vaccine, 100 µg (0.5 mL) to be administered IM at Entry and Day 28.

1.0 STUDY OBJECTIVES

1.1 Primary Objective

1.1.1 To estimate the difference in neutralizing antibody (NAb) response to mRNA-based COVID-19 vaccine among participants with prior SARS-CoV-2 infection who received investigational therapy exposure compared to participants without prior investigational therapy exposure (placebo for investigational therapy or active comparator).

1.2 Secondary Objectives

To explore the safety of mRNA-based COVID-19 vaccines among participants with prior COVID-19 who received investigational therapy or its comparator for COVID-19 and persons who are SARS-CoV-2 naïve.

1.3 Other Objectives

1.3.1 To explore the difference in humoral and cellular immune responses to mRNA-based COVID-19 vaccines among participants with prior COVID-19 who received investigational therapy compared to participants without prior investigational therapy (placebo or corresponding active comparator) exposure and persons who are SARS-CoV-2 naïve.

1.3.2 To explore the difference in humoral and cellular immune responses, including NAb levels, B and T cell responses, and serologic responses to COVID-19 vaccination by duration of time of vaccination from prior investigational therapy versus active comparator/placebo exposure and compared to persons who are SARS-CoV-2 naïve.

1.3.3 To explore whether investigational therapy drug levels at time of first COVID-19 vaccination is associated with humoral and cellular responses in participants with prior COVID-19 who received investigational therapy or its comparator for COVID-19.

1.3.4 To explore B and T cell exhaustion before and after COVID-19 vaccination in persons with prior COVID-19 who received investigational therapy or corresponding comparator for COVID-19 and persons who are SARS-CoV-2 naïve.

1.3.5 To explore whether vaccine-associated symptoms are associated with immune responses to the vaccine.

1.3.6 To explore whether investigational therapy affects humoral and cellular responses to SARS-CoV-2 infection before first dose of vaccine is administered.

1.3.7 In participants with prior COVID-19, to explore whether COVID-19 disease severity affects humoral and cellular responses to SARS-CoV-2 infection.

1.3.8 In participants with prior COVID-19, to explore whether presence of viral resistance to the investigational therapy (measured in ACTIV-2/A5401) affects humoral and cellular responses to SARS-CoV-2 infection before and after vaccine.

1.3.9 In participants with prior COVID-19, to explore whether presence of SARS-CoV-2 IgG or IgM (measured in ACTIV-2/A5401) affects humoral and cellular responses to SARS-CoV-2 before and after vaccine administration.

1.3.10 To explore whether host characteristics (i.e., age, race, ethnicity, history of immunosuppression, body mass index **[**BMI**]**, co-morbidities) affect humoral and cellular responses to SARS-CoV-2 vaccination.

1.3.11 In participants with prior COVID-19, to explore whether duration of COVID-19 symptoms at time of ACTIV-2/A5401 enrollment affects humoral and cellular responses to SARS-CoV-2 vaccination.

1.3.12 In participants with prior COVID-19, to explore dynamics of humoral and cellular immune responses after first and second vaccine dose in relation to demographic, treatment and COVID-19 symptom progression, and vaccine-associated symptom covariates.

1.3.13 To explore whether baseline immune signatures (e.g., gene expression, proteomic) predict humoral and cellular responses to the vaccine.

1.3.14 **T**o explore differences in change in humoral and cellular immune responses after COVID-19 vaccination between people who previously had COVID-19 and people who previously did not have COVID-19.

1.3.15 To explore differences in change in humoral and cellular immune responses after COVID-19 vaccination between hospitalized (e.g., ACTIV-3) and non-hospitalized (e.g., ACTIV-2) people who previously had COVID-19 and who received investigational therapy or comparator.

1.3.16 In participants with prior COVID-19, to characterize and evaluate the role(s) of SARS-CoV-2 B and T cell adaptive immunity in protection versus pathogenesis in COVID-19 and subsequent vaccine response.

1.3.17 To determine the durability of SARS-CoV-2 specific B and T cell memory immunity and its correlation with disease severity and vaccine response.

1.3.18 To investigate the relationship between inflammatory markers measured just prior to COVID-19 vaccinations and immune responses to vaccine in participants

with prior COVID-19 who had received prior investigational therapy or active comparator or placebo for COVID-19.

1.3.19 In participants with prior COVID-19, to evaluate change in participant-reported symptoms of post-acute sequelae of SARS-CoV-2 (PASC) infection after COVID-19 vaccination.

2.0 INTRODUCTION

2.1 Background

Antibody and Non-Antibody-Based Therapies for COVID-19

COVID-19 has exacted a deadly toll on the US and the world. New treatments and vaccines are promising, but questions remain on how these biomedical interventions interact with each other. One of the first antiviral therapeutics to show promise has been antibody-based (Ab) therapies, **such as** monoclonal antibodies [1, 2]. Currently, a handful of monoclonal antibody therapies and vaccines have been granted emergency use authorization (EUA) by the FDA [3-6], and there are many more in development. Given their mechanism of action, such Ab therapies may impact the efficacy of subsequent SARS-CoV-2 vaccinations. Specifically, it remains unclear if treatment of COVID-19 with an Ab directed against SARS-CoV-2 proteins (e.g., Spike) impedes or blunts the development of humoral and cellular immune responses to a vaccine—responses that can augment and prolong immune responses produced by natural infection.

Other types of treatments (e.g., protease inhibitors, small molecule viral enzyme inhibitors, interferon) given during early COVID-19 may also impact immune responses to COVID-19 vaccination [7]. For example, abrogating a SARS-CoV-2 infection with a direct antiviral or modulating immune response with immunomodulatory drugs may have unexpected effects on future COVID-19 vaccine responses [8]. Therefore, we will examine the impact of vaccination after COVID-19 and treatment.

ACTIV-2/A5401

ACTIV-2/A5401 is a randomized, controlled adaptive platform trial to evaluate investigational therapies (Ab-therapies and non-Ab-therapies) for the treatment of outpatient COVID-19. The trial starts with a Phase II evaluation that transitions to a Phase III evaluation for therapies meeting safety and efficacy criteria in Phase II. The first therapy studied in this trial was a monoclonal antibody from Eli Lilly called bamlanivimab; 222 participants were enrolled in the Phase II portion of this trial. Half received bamlanivimab and half received placebo. Based on safety and efficacy data, this drug has received EUA for the treatment of outpatient COVID-19. Other Ab therapies being studied in the trial include those from Brii Biosciences, AstraZeneca, and SAB Biotherapeutics; in addition, non-Ab-therapies such as Camostat mesylate and SynAIRGen inhaled interferon beta (SNG001) are also being evaluated.

2.2 Rationale

Immune Responses

Early in the pandemic, it was unknown if natural infection with SARS-CoV-2 induced adaptive immune responses. Research by our collaborators found that people developed both viral-specific antibodies and T cell responses [9]. Further investigations found that multiple SARS-CoV-2 antigens were recognized by $CD4^+$ and $CD8^+$ T cells in these individuals [9]. The frequencies of viral antigen-specific T cells corresponded to predicted viral protein abundance in infected cells [9]. Analyses in persons followed from acute COVID-19 found that a coordinated adaptive immune response consisting of SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells and NAb was associated with less severe disease [10]. This study also defined how most people with COVID-19 had measurable antibody (IgG, IgA, IgM) to the viral Spike (S) protein, the receptor binding domain (RBD) of S, and Nucleocapsid (N) protein, as well as neutralizing antibody (NAb). Similarly, most participants also had SARS-CoV-2-specific $CD4^+$ T cells, $CD8^+$ T cells, and T follicular helper cells to viral S, matrix (M), N, and other viral epitopes. Interestingly, correlation analyses demonstrated that viral-specific T cell responses, but not NAbs, were associated with COVID-19 severity [10]. Further studies found that most participants had durable adaptive immunity to SARS-CoV-2, although heterogeneity was observed in the adaptive immune responses including half-lives of SARS-CoV-2 specific antibody titers and memory B and $CD4^+$ and $CD8^+$ T cell responses [11]. The same assays used in these studies and others will be used in this study [9-15]. This A5404 study will also evaluate persons without prior SARS-CoV-2 infection as a comparison group (i.e., SARS-CoV-2 naïve group) to evaluate vaccine-induced immune responses. Although persons ≥18 years old may enroll into the SARS-CoV-2 naïve group, the age eligibility for PBMC collection is limited to those persons ≥40 years old. This criteria has been added to avoid skewing of cellular based assays toward younger participants who have more robust immune responses, and less likely to match the ages of participants in ACTIV-2/A5401. Including this SARS-CoV-2 naïve group should also reduce waste of the Moderna mRNA-1273 COVID-19 vaccine, since doses must be delivered within a short timeframe after opening a multidose vial (see section 5.2.1 and Manual of Procedures [MOPS] for further description).

We imagine a number of people will be enrolled in the SARS-CoV-2 naïve group with prior asymptomatic SARS-CoV-2 infection. These people will still be able to obtain a**n** mRNA COVID-19 vaccine, as they would in the community, so they will not be pre-screened for our study. The A5404 study will assess baseline serology in the context of the trial to determine if such participants are evaluable for the sub-analyses of the SARS-CoV-2 naïve group, but these analyses will be conducted after the participant has enrolled in the trial and received their vaccination.

The team recognizes the value in studying all COVID-19 vaccine types, but increasing the types of COVID-19 vaccines in A5404 will decrease the overall number of participants receiving the same type of vaccine. This heterogeneity could be an issue as there seems to be different NAb dynamics between mRNA versus adenoviral vaccines and therefore analyses would be carried out separately. Smaller sample sizes may lead to a decrease in precision on the estimated neutralizing antibody (NAb) levels post-vaccine. Since we will be providing the Moderna mRNA-1273 COVID-19 vaccine, we will only evaluate mRNA vaccines.

Reinfection

As described above, initial SARS-CoV-2 infection elicits human immune responses, and it is likely that these responses offer some level of protection from reinfection for some time. NAb seems to be an important immune correlate of protection and subsequent disease severity [16-18]. It is unclear how these reinfections impact vaccine development and long-term efficacy [19]. However, people who have had SARS-CoV-2 infection can **subsequently be reinfected [**20], and perhaps active viral infection generates a weaker immune response than what can be elicited by a COVID-19 vaccine [21]. Due to the lack of close molecular epidemiological surveillance, it remains unclear how frequently reinfection occurs [22]. Open questions that remain concerning initial infection include identifying exact correlates of immune protection, length of protection generated after initial SARS-CoV-2 infection, variability in protection, and whether a COVID-19 vaccine can improve a protective immune response generated from a previous SARS-CoV-2 infection. Additionally, the optimal time frame to immunize post COVID-19 infection has not been fully discerned nor is it known if predictors of immune responses to vaccination, such as baseline inflammation, are associated with immune responses to COVID-19 mRNA vaccination [23].

Currently, the CDC recommends that people with prior COVID-19 receive a currently authorized COVID-19 vaccine, even though recent data suggest that the risk of reinfection is low following initial infection [24]. It is noted, however, that the risk of reinfection may increase over time due to waning immunity [24]. The optimal timing of a vaccination to boost such waning immunity is unknown and is the rationale for the **30**-240-day window after receiving their last dose of ACTIV-2/A5401 select therapy (i.e., post-infection) for vaccination in the proposed study. Understanding how SARS-CoV-2 immune responses develop and then wane after vaccination may be important for developing future guidelines for re-vaccination.

Study Overview

We will recruit ACTIV-2/A5401 participants **(Cohort 1)** and persons without prior history of SARS-CoV-2 infection **(Cohort 2)** into the A5404 study. We will enroll participants who elect to receive mRNA vaccines outside of A5404 to maximize the number of ACTIV-2 participants **from** whom we can measure vaccine responses following investigational agent therapy for ACTIV-2 study participants. Participants will be offered open-label standard dosing of Moderna COVID-19 vaccine [21] or will obtain mRNA-based COVID-19 vaccination in the community outside of the study. **Cohort 2 participants will only be enrolled at sites enrolling Cohort 1 participants.** People who participate in the study will be followed longitudinally for humoral and cellular immune dynamics.

Closed to Accrual

Accrual closed on February 25, 2022, due to slow enrollment and difficulty enrolling new participants into the various study cohorts. Vaccine responses will be studied in the 43 participants who enrolled.

3.0 STUDY DESIGN

A5404 is a phase IV, open-label study. Eligible participants include:

- **Cohort 1:** Participants of ACTIV-2/A5401 who received selected investigational therapy or its comparator (active or placebo).
- **Cohort 2:** Persons without a prior history of SARS-CoV-2 infection (non-A5401 participants) who have not yet received a COVID-19 vaccine.

The objective of the study is to evaluate whether prior investigational therapy versus placebo or active comparator in ACTIV-2/A5401 affects vaccine response. **Cohort 1** participants will be offered the Moderna mRNA-1273 COVID-19 vaccine **(Cohorts 1a [full series to be administered through study] and 1c [first dose received in the community, second dose to be administered through the study])** or receive an mRNA-based COVID-19 vaccine in the community **(Cohort 1b [both doses received in the community] or Cohort 1c [first dose received in the community, second dose in the study]), with the first vaccine dose administered 30**-240 days after receiving their last dose of ACTIV-2/A5401 select therapy (investigational agent or active comparator or placebo). Community-provided mRNA-based COVID-19 vaccines must have received FDA EUA or FDA approval. **Cohort 2** participants will be offered standard dosing of the study-provided Moderna mRNA-1273 COVID-19 vaccine. Participants will have blood collected and immune responses measured before the first vaccine dose (if feasible), and before the second dose of vaccine (e.g., 28 days later for Moderna vaccine and 21 days later for Pfizer**-BioNTech BNT162b2 mRNA COVID-19** vaccine if given in the community) **(if feasible)**, and 56 **(if feasible)**, 140, 365, and 730 days after **their first vaccine dose** (Figure 3.0-1).

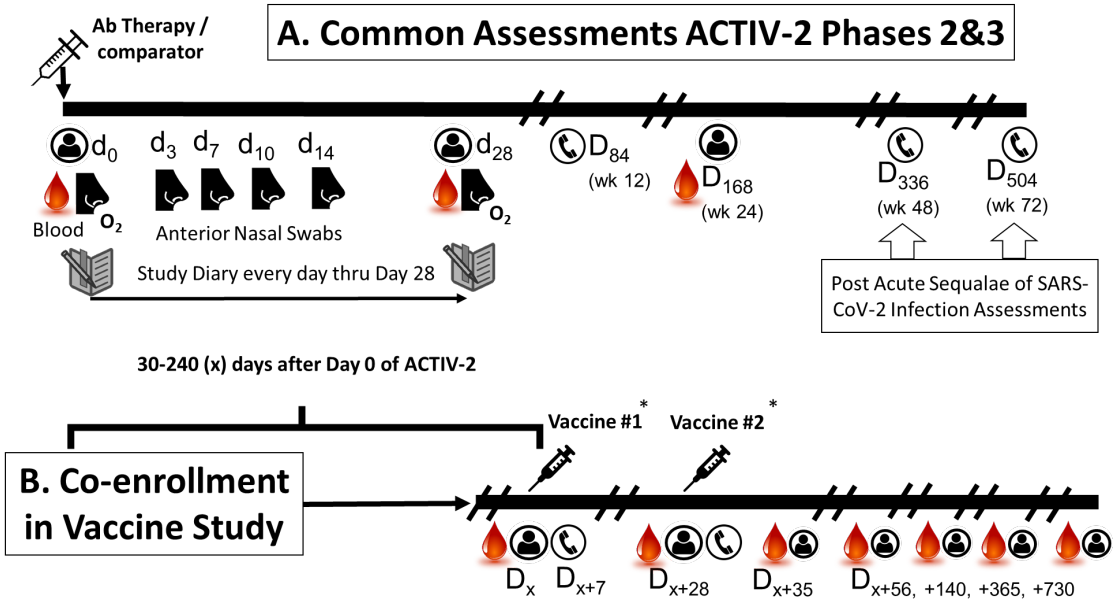

Figure 3.0-1: This schema includes common assessments for ACTIV-2/A5401 participants in both phases 2 and 3 (panel A). If possible, blood will be collected before

each vaccine dose is administered and 56, 140, 365, and 730 days after **their first vaccine dose** (panel B). If possible, participants will be contacted 7 days after each vaccine dose to grade vaccine-associated symptoms.

Up to **70 participants from Cohort 1** will be enrolled f**rom** each ACTIV-2/A5401 select therapy group **along with 350 participants from Cohort 2** without prior SARS-CoV-2 infection (**i.e.,** SARS-CoV-2-naïve, non-**ACTIV-2/**A5401 participants). The total sample size will depend on how many select therapy groups are evaluated in ACTIV-2**/A5401**.

If **a** sufficient **number of** Phase II participants in the A5401/ACTIV-2 trial from a select therapy group are not able to be enrolled, then Phase III participants in the A5401/ACTIV-2 trial from that select therapy group can be enrolled until full enrollment is achieved. However, Phase II participants are preferred.

As available, PBMC from days 0, 7, 28, and week 24 from **Cohort 1** participants will be used for this study. Plasma from each of the time points that blood for PBMC is collected will also be used for this study. Samples will be used to study the adaptive immune response to SARS**-**CoV-2 during acute and convalescent COVID-19 in the context of treatment versus active comparator/placebo receipt during acute COVID-19. This will also connect to the vaccination arm of the ACTIV-2/3 studies, as feasible.

The study will provide important information on the use of mRNA-based COVID-19 vaccines for persons after SARS-CoV-2 infection and for persons who received investigational therapy, including monoclonal antibodies, for COVID-19. Study outcome measures are provided in section 10.2 in line with the Study Objectives.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Ability and willingness of participant (or legally authorized representative) to provide informed consent prior to initiation of any study procedures.

4.1.2 Individuals ≥18 years of age

4.1.3 **Cohort 1:** Receipt of all selected investigational therapy or active comparator/placebo for that therapy.

NOTE**S**:

- Selected investigational therapies will be posted on the A5404 PSWP.
- **For participants who received camostat or the active comparator/placebo for camostat: Receipt of ≥50% of the doses indicated in ACTIV-2/A5401.**

4.1.4 **Cohort 1a:** Receipt of the last dose of investigational therapy or active comparator/placebo for that therapy ≥**30** days and ≤240 days prior to **study entry.**

4.1.5 **Cohorts 1b and 1c:** Receipt of the last dose of investigational therapy or active comparator/placebo for that therapy ≥**30** and ≤240 days prior to **receipt or** planned receipt of the first dose of community-provided vaccine.

4.2 Exclusion Criteria

4.2.1 **Cohort 1:** Self-report of prior receipt of a non-mRNA-based COVID-19 vaccine.

4.2.2 **Cohort 1:** Self-report of receipt of the **first** dose of an mRNA-based COVID-19 vaccine **140 days or more before A5404 enrollment**.

4.2.3 **Cohort 1:** Self-report of a second SARS-CoV-2 infection after the infection that qualified the participant for ACTIV-2/A5401.

4.2.4 **Cohort 2:** Self-report of receipt of any prior COVID-19 vaccine.

4.2.5 **Cohort 2:** Known prior history of any SARS-CoV-2-positive test (e.g., PCR test, Nucleic Acid Amplification Test **[**NAAT**]**, antigen test, serology test).

4.2.6 **Cohorts 1a and 1c and Cohort 2:** Known allergy to any component of the Moderna COVID-19 vaccine.

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s) WILL NOT be reviewed or approved by the DAIDS PRO. Sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete

registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant (or, when necessary, the legal representative if the participant is under guardianship) will be asked to read and sign the approved protocol consent form.

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the DMC Participant Enrollment System.

4.3.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.3.3 Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database. Participants who meet the enrollment criteria will be registered to the study according to standard ACTG DMC procedures.

4.4 Co-enrollment Guidelines

For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

5.1.1 Regimen and Duration

Cohort 1: ACTIV-2/A5401 participants
Participants will receive **one of** the following regimen**s**:

Cohort 1a: Moderna mRNA-1273 COVID-19 vaccine, 100 µg (0.5 mL) to be administered intramuscularly (IM) at **Entry** and Day 28. **Both doses will be provided by the study.**

Or

Cohort 1b: Participants will receive a two-dose series of a community-provided mRNA-based COVID-19 vaccine that has received FDA EUA or FDA approval **(e.g., Moderna or Pfizer). Vaccine will not be provided by the study.**

NOTE: **These participants may enter the study before their first vaccine dose, after their first vaccine dose, or after their second vaccine dose.**

Or

Cohort 1c: Participants will receive their first Moderna mRNA-1273 COVID-19 vaccine dose in the community. Their second Moderna mRNA-1273 dose will be provided by the study (100 µg [0.5 mL] to be administered IM 28 days after their first dose).

NOTE: These participants may enter the study before or after their first vaccine dose.

Or

<u>Cohort 2: Participants without prior history of SARS-CoV-2 infection</u>
Participants will receive the following study-provided regimen: Moderna mRNA-1273 COVID-19 vaccine, 100 µg (0.5 mL) to be administered IM at Entry and Day 28.

5.1.2 Administration of study-provided Moderna mRNA-1273:

Moderna mRNA-1273 COVID-19 vaccine will be administered IM in the deltoid, using standard IM injection technique.

Guidance for administration of the doses in each Moderna mRNA-1273 COVID-19 vial is provided in the MOPS.

5.2 Study Product Formulation and Preparation

5.2.1 Formulation and Storage

The Moderna mRNA-1273 COVID-19 vaccine is supplied as a frozen suspension, stored between **-50°C** to -15°C, in multi-dose vials, and does not contain a preservative. **Protect** from light. Do not store on dry ice or below **-50**°C. The Moderna mRNA-1273 COVID-19 vaccine is white to off-white suspension. It may contain white or translucent product-related particulates.

The Moderna mRNA-1273 COVID-19 vaccine must be thawed prior to administration. After thawing, a maximum of 10-11 doses (0.5 mL each) can be

withdrawn from each vial, dependent on the syringes and needles used. Vials can be stored refrigerated between 2° to 8°C for up to 30 days prior to first use. Do not refreeze once thawed. Unpunctured vials may be stored between 8° to 25°C for up to **24** hours. Do not refreeze. After the first dose has been withdrawn, the vial should be held between 2° to 25°C and discarded after **12** hours. Do not refreeze.

5.2.2 Preparation

Pharmacists must follow appropriate aseptic technique and consider sterile preparation procedures/guidance as outlined in USP. Pharmacists must also follow the requirements of their country, institution, and pharmacy regulatory authority regarding these procedures. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, face masks and safety glasses, must be followed.

Any empty vials or unused portion of entered vials of the Moderna mRNA-1273 COVID-19 vaccine should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

1. Remove one vial of the Moderna mRNA-1273 COVID-19 vaccine from the freezer and thaw either in the refrigerator or at room temperature. If thawed in the refrigerator, the vial must be kept between 2°C and 8°C for two hours and 30 minutes. If thawed at room temperature, the vial must be kept between 15°C and 25°C for one hour. Once thawed, the vial may be kept between 8°C and 25°C for up to **24** hours. Do NOT refreeze.
2. With the vial upright, gently swirl the vaccine. Do NOT shake. Do NOT dilute the vaccine.
3. Examine the vaccine. It should be white to off-white in color and may contain white or translucent product-related particulates. Do not use if liquid contains other particulate matter or is discolored.
4. Withdraw 0.5 mL of vaccine into an appropriately sized syringe. When the stopper of the vial is punctured to start preparation, record this as the vaccine preparation time. Assign a **12-**hour beyond use date and time from the preparation time.

The prepared vaccine should be administered immediately. If immediate administration is not possible, the **prepared** vaccine may be stored **and refrigerated at** 2°C **to 8**°C **or left at ambient (room) temperature at 15°C to 25°C** for up to **12** hours. **Keep out of direct sunlight.**

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

The Moderna mRNA-1273 COVID-19 vaccine will be provided through the US Government Response to COVID-19 and available through the NIAID Clinical

Research Products Management Center (CRPMC). The site pharmacist should obtain the study product(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. At US clinical research sites (CRSs), all unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.* At non-US CRSs, the site pharmacist must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused study products.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Required Medications

None.

5.4.2 Prohibited Medications

None.

5.4.3 Precautionary Medications

Antipyretic or analgesic medications (e.g., acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDS]) or antihistamines can be taken for the symptomatic treatment of post-vaccination local or systemic symptoms, but prophylactic administration of these medications to prevent post-vaccination symptoms is not currently recommended by the CDC [24]. If such medications are used before or after vaccination, then they should be recorded as concomitant medications (see section 6.3.**5**).

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1**:** Study-**p**rovided Moderna COVID-19 **V**accine **S**chedule of **E**valuations for ACTIV-2/A5401 **Participants** (**Cohort 1a)**

Evaluation	Screening	Study Entry See section 6.2.2	Post-Vaccination #1 Follow-up/Day 7	Day 28	Post-Vaccination #2 Follow-up/Day 35	Day 56	Day 140	Day 365 (1 Year)	Day 730 (2 Years)	Premature Study D/C	Event-Driven Evaluation: SARS-CoV-2 Infection
Visit Window (days)	**-28**		7-14 days post-vaccine	**+7**	7-14 days post-vaccine	+7	±7	±28			+14
Visit Type (P: In Person, R: Remote)	R/P	P	R	P	R	P	P	P	P	P	P
Documentation of ACTIV-2/A5401 participation and receipt of investigational therapy or active comparator/placebo for investigational therapy	X										
Medical/Medication History	X	X									
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing		X		X		If pregnancy suspected				X	X
Vaccine Administration ([1]See section 6.2.3.[2] See section 6.2.4)		X		X[1]						X[2]	

Evaluation	Screening	Study Entry See section 6.2.2	Post-Vaccination #1 Follow-up/Day 7	Day 28	Post-Vaccination #2 Follow-up/Day 35	Day 56	Day 140	Day 365 (1 Year)	Day 730 (2 Years)	Premature Study D/C	Event-Driven Evaluation: SARS-CoV-2 Infection
Visit Window (days)	**-28**		7-14 days post-vaccine	**+7**	7-14 days post-vaccine	+7	±7	±28			+14
Visit Type (P: In Person, R: Remote)	R/P	P	R	P	R	P	P	P	P	P	P
Vaccine Symptom Screen			X		X						
Stored Plasma		X		X		X	X	X	X	X	X
Stored Serum		X		X		X	X	X	X	X	X
Stored PBMCs		X		X		X	X	X	X	X	X
Stored PAXgene RNA Tube		X		X							
Documentation of New Active SARS-CoV-2 Infection by Antigen or Nucleic Acid Test											X
Nasopharyngeal (NP) Swab Collection (See section 6.3.11)											X
ACTIV-2/A5401 Investigational Therapy or Active Comparator/Placebo Questionnaire		X									

Table 6.1-2: Schedule of Evaluations for ACTIV-2/A5401 Participants Who Will Receive a Two-dose Series of a Community-provided mRNA-based COVID-19 Vaccine (Cohort 1b)

Evaluation	Screening See section 6.2.1	Study Entry See section 6.2.2	Post-Vaccination #1 Follow-up See section 6.2.3	Day of 2nd dose of vaccine	Post-Vaccination #2 Follow-up	56 Days Post-Vaccination #1 See section 6.2.3	140 Days Post-Vaccination #1 See section 6.2.3	365 Days (1 Year) Post-Vaccination #1	730 Days (2 Years) Post-Vaccination #1	Premature Study D/C	Event-Driven Evaluation: SARS-CoV-2 Infection
Visit Window (days)	-28		7-14 days post-1st dose of vaccine	-3	7-14 days post-2nd dose of vaccine	+7	±7	±28			+14
Visit Type (P: In Person, R: Remote)	R/P	P	R	P	R	P	P	P	P	P	P
Documentation of ACTIV-2/A5401 participation and receipt of investigational therapy or active comparator/placebo for investigational therapy	X										
Medical/Medication History	X	X									
Clinical Assessments	X	X		X[3]		X	X	X	X	X	X
Pregnancy Testing		X		X[3]		If pregnancy suspected				X	X
Documentation of Community-Provided COVID-19 Vaccination(s) (see section 6.3.7)		X[1]		X[2]		X[3]					
Vaccine Symptom Screen (see section 6.3.8)		X[1]	X[2]		X[3]						

Evaluation	Screening See section 6.2.1	Study Entry See section 6.2.2	Post-Vaccination #1 Follow-up See section 6.2.3	Day of 2nd dose of vaccine	Post-Vaccination #2 Follow-up	56 Days Post-Vaccination #1 See section 6.2.3	140 Days Post-Vaccination #1 See section 6.2.3	365 Days (1 Year) Post-Vaccination #1	730 Days (2 Years) Post-Vaccination #1	Premature Study D/C	Event-Driven Evaluation: SARS-CoV-2 Infection
Visit Window (days)	**-28**		**7-14 days post-1st dose of vaccine**	**-3**	**7-14 days post-2nd dose of vaccine**	**+7**	**±7**	**±28**			**+14**
Visit Type (P: In Person, R: Remote)	**R/P**	**P**	**R**	**P**	**R**	**P**	**P**	**P**	**P**	**P**	**P**
Stored Plasma		X				X	X	X	X	X	X
Stored Serum		X				X	X	X	X	X	X
Stored PBMCs		X				X	X	X	X	X	X
Stored PAXgene RNA Tube		X									
Documentation of New Active SARS-CoV-2 Infection by Antigen or Nucleic Acid Test											X
Nasopharyngeal (NP) Swab Collection (See section 6.3.11)											X
ACTIV-2/A5401 Investigational Therapy or Active Comparator/Placebo Questionnaire		X									

[1]If one or both vaccine doses administered prior to entry; [2]If vaccination #1 occurs after entry; [3]If vaccination #2 occurs after entry

Table 6.1-3: Schedule of **E**valuations for ACTIV-2/A5401 **P**articipants **Who Will Receive Their First Moderna mRNA-1273 COVID-19 Vaccine Dose in the Community and Their Second Moderna mRNA-1273 Dose Will Be Provided by the Study (Cohort 1c)**

Evaluation	Screening See section 6.2.1	Study Entry See section 6.2.2	Post-Vaccination #1 Follow-up See section 6.2.3	Day of 2nd dose of vaccine	Post-Vaccination #2 Follow-up	56 Days Post-Vaccination #1	140 Days Post-Vaccination #1	365 Days (1 Year) Post-Vaccination #1	730 Days (2 Years) Post-Vaccination #1	Premature Study D/C	Event-Driven Evaluation: SARS-CoV-2 Infection
Visit Window (days)	**-28**		7-14 days post-1st dose of vaccine	-3	7-14 days post-2nd dose of vaccine	+7	±7	±28			+14
Visit Type (P: In Person, R: Remote)	R/P	P	R	P	R	P	P	P	P	P	P
Documentation of ACTIV-2/A5401 participation and receipt of investigational therapy or active comparator/placebo for investigational therapy	X										
Medical/Medication History	X	X									
Clinical Assessments	X	X	X[1]	X	X	X	X	X	X	X	X
Pregnancy Testing		X		X		If pregnancy suspected				X	X
Documentation of **Community-Provided COVID-19** Vaccine Administration		X[2]		**X**[1]							
Vaccine Administration (See section 6.2.3)				X							
Vaccine Symptom Screen			X[1]		X						

Evaluation	Screening See section 6.2.1	Study Entry See section 6.2.2	Post-Vaccination #1 Follow-up See section 6.2.3	Day of 2nd dose of vaccine	Post-Vaccination #2 Follow-up	56 Days Post-Vaccination #1	140 Days Post-Vaccination #1	365 Days (1 Year) Post-Vaccination #1	730 Days (2 Years) Post-Vaccination #1	Premature Study D/C	Event-Driven Evaluation: SARS-CoV-2 Infection
Visit Window (days)	**-28**		7-14 days post-1st dose of vaccine	-3	7-14 days post-2nd dose of vaccine	+7	±7	±28			+14
Visit Type (P: In Person, R: Remote)	R/P	P	R	P	R	P	P	P	P	P	P
Stored Plasma		X		X		X	X	X	X	X	X
Stored Serum		X		X		X	X	X	X	X	X
Stored PBMCs		X		X		X	X	X	X	X	X
Stored PAXgene RNA Tube		X		X							
Documentation of New Active SARS-CoV-2 Infection by Antigen or Nucleic Acid Test											X
Nasopharyngeal (NP) Swab Collection (**s**ee section 6.3.11)											X
ACTIV-2/A5401 Investigational Therapy or Active Comparator/Placebo Questionnaire		X									

[1]If vaccination #1 occurs after entry; [2]If vaccination #1 occurs prior to entry

Table 6.1-**4:** Study-**p**rovided Moderna COVID-19 **V**accine **S**chedule of **E**valuations for **P**articipants **Wi**thout **P**rior **H**istory of SARS-CoV-2 **Infection (Cohort 2)**

Evaluation	Screening	Study Entry See section 6.2.2	Post-Vaccination #1 Follow-up/Day 7	Day 28	Post-Vaccination #2 Follow-up/Day 35	Day 56	Day 140	Day 365 (1 Year)	Day 730 (2 Years)	Premature Study D/C	Event-Driven Evaluation: SARS-CoV-2 Infection
Visit Window (days)	**-28**		7-14 days post-vaccine	**+7**	7-14 days post-vaccine	+7	±7	±28			+14
Visit Type (P: In Person, R: Remote)	R/P	P	R	P	R	P	P	P	P	P	P
Documentation of no prior history of SARS-CoV-2 infection by participant self-report	X										
Medical/Medication History	X	X									
Clinical Assessments	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing		X		X		If pregnancy suspected				X	X
Vaccine Administration ([1]See section 6.2.3.[2] See section 6.2.4)		X		X[1]						X[2]	
Vaccine Symptom Screen			X		X						
Stored Plasma		X		X		X	X	X	X	X	X
Stored Serum		X		X		X	X	X	X	X	X

Evaluation	Screening	Study Entry See section 6.2.2	Post-Vaccination #1 Follow-up/Day 7	Day 28	Post-Vaccination #2 Follow-up/Day 35	Day 56	Day 140	Day 365 (1 Year)	Day 730 (2 Years)	Premature Study D/C	Event-Driven Evaluation: SARS-CoV-2 Infection
Visit Window (days)	**-28**		7-14 days post-vaccine	**+7**	7-14 days post-vaccine	+7	±7	±28			+14
Visit Type (P: In Person, R: Remote)	R/P	P	R	P	R	P	P	P	P	P	P
Stored PBMCs for 35 total SARS-CoV-2-naïve participants (See section 6.3.9)		X				X		X	X		**X**
Documentation of New Active SARS-CoV-2 Infection by Antigen or Nucleic Acid Test											X
Nasopharyngeal (NP) Swab Collection (See section 6.3.11)											X

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

If the participant is **in Cohorts 1a or 1c or Cohort 2** (receiving study-provided Moderna COVID-19 vaccine), then screening evaluations must occur prior to the participant receiving first dose of study vaccine.

If the participant is **in Cohorts 1b or 1c (receiving community-provided mRNA COVID-19 vaccine),** it is preferred for these participants to have their screening evaluations before their first **or second community-provided** vaccine dose, if feasible.

For **all** participants, screening evaluations to determine eligibility must be completed within **28** days prior to study entry unless otherwise specified.

Screening and Entry can happen on the same day. The screening visit may be **conducted** remotely, over the phone, or via telemedicine systems approved for use at the site if necessary.

In addition to data being collected on participants who enroll into the study, demographic and clinical data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Entry Evaluations

For **all** participants, entry evaluations must occur ≤**28** days after screening evaluations unless otherwise specified.

Screening and Entry can happen on the same day.

Cohort 1 participants are expected to receive the first dose of study vaccine **30**-240 days after receiving the last dose of an investigational therapy or corresponding active comparator/placebo in ACTIV-2/A5401.

Entry Evaluations for **Cohort 1a and Cohort 2** Participants **(both vaccine doses provided by the study)**
Entry evaluations may be performed up to 72 hours before the first study-provided vaccine dose. Participants must have their blood collected before the first study-provided vaccine dose is administered. Entry pregnancy test results must be available before the study-provided vaccine dose is administered for participants of reproductive potential (see section 6.3.6 for definition of reproductive potential).

Entry Evaluations for **Cohort 1b (both vaccine doses received in the community)**
Participants who enroll prior to receiving a community-provided vaccine dose should have their Entry evaluations within 72 hours prior to the administration of the dose. Participants who enroll after receiving the second community-provided vaccine dose must have their blood collected within 14 days of the second community-provided dose.

Entry Evaluations for **Cohort 1c (first dose in the community, second dose through the study)**
Participants who enroll prior to receiving a community-provided Moderna mRNA-1273 vaccine dose should have their Entry evaluations within 72 hours prior to the administration of the dose. Participants who enroll after receiving their first community-provided Moderna mRNA-1273 vaccine dose must have their blood collected within 72 hours prior to the administration of the second study-provided dose.

6.2.3 Post-Entry Evaluations

On-Treatment and Post-Treatment Evaluations
Evaluations should occur in the visit windows described in section 6.1.

In-person visits will take place at the clinic, at the participant's home, or at another non-clinic location if the site is able to accomplish all of the scheduled study visit evaluations.

Remote visits can take place over the phone or via telemedicine systems approved for use at the site.

Community-Provided mRNA-based COVID-19 Vaccine, Post-Vaccination #1 Follow-up **(Cohorts 1b and 1c)**
This visit will only be performed if the participant enters the study ≤14 days after their first vaccine dose. **This visit may be combined with the entry visit.**

Study-Provided Moderna COVID-19 Vaccine: Second Vaccine Dose **(Cohorts 1a and 1c and Cohort 2)**
Evaluations may be performed up to 72 hours before the receipt of the second vaccine dose. Blood must be drawn before the second vaccine dose is administered. Pregnancy test results must be available before the study-provided vaccine dose is administered for participants of reproductive potential (see section 6.3.6 for definition of reproductive potential).

To be in the study window, the second dose of the study vaccine should be received at least 28 days and no later than 35 days after the first administration. Post-vaccination #1 follow-up should occur at least 7 days and no more than 14 days after the first vaccine dose, and post-vaccination #2 follow-up should occur at least 7 days and no more than 14 days after the second vaccine dose.

If the second vaccine dose window is missed, and a participant still wishes to receive it, then the second dose can be administered anytime between **36** days and 140 days after the first dose. Participants who receive their second vaccine between **36** and 140 days will have a post-vaccination visit between 7 and 14 days after second vaccine dose and then continue following the protocol schedule of evaluations. Documentation of timing of dose of second vaccine will be documented in the eCRF (see section 6.3.**7**).

Community-Provided Vaccine: Day of Second Dose of Vaccine **(Cohort 1b)**
This visit will only be performed if the participant enters the study before their second vaccine dose.

Evaluations may be performed up to 72 hours before the receipt of the second vaccine dose. Blood must be drawn before the second vaccine dose is administered.

Participants receiving a Moderna mRNA-1273 COVID-19 vaccine in the community may receive their second dose through the study **(Cohort 1c).** If the second vaccine dose window is missed, and a participant still wishes to receive it, then the second dose can be administered anytime between **36** days and 140 days after the first dose. Participants who receive their second vaccine between **36** and 140 days will have a post-vaccination visit between 7 and 14 days after the second vaccine dose and then continue following the protocol schedule of evaluations. Documentation of timing of dose of second vaccine will be documented in the eCRF (see section 6.3.7).

56 and 140 Days Post-Vaccination #1 for Cohort 1b Participants Who Received Both Vaccine Doses before Entry

- **56 days post-vaccination #1 time point:**
  - **This visit will not be conducted if the participant enrolls more than 56 days after their first vaccine dose.**
  - **This visit may be combined with the Entry visit if the participant enrolls between 56 and 63 days after their first mRNA COVID-19 vaccine dose. Evaluations indicated at both time points will be conducted only once.**
- **140 days post-vaccination #1 time point: This visit may be combined with the Entry visit if the participant enrolls between 133 and 139 days after their first mRNA COVID-19 vaccine dose. Evaluations indicated at both time points will be conducted only once.**

Study Completion Evaluations
Participants will be evaluated at Day **730**, as described in section 6.1.

Event-Driven Evaluation: SARS-CoV-2 Infection
Evaluations should occur within 14 days after the positive SARS-CoV-2 test (for new SARS-CoV-2 diagnoses after study enrollment only). Participants who report new COVID-19 symptoms should be tested or referred for testing with a PCR or

antigen-based FDA authorized test for SARS-CoV-2, and the results recorded. Should a new SARS-CoV-2 infection occur, participants are not discontinued from the study and will be asked to remain on the study until the final evaluation (Day 730). See section 8.6 for instructions for administering the second vaccine dose for participants who contract SARS-CoV-2 infection between their first and second scheduled vaccine dose.

6.2.4 Discontinuation Evaluations

Evaluations for Registered Participants Who Do Not Receive First Dose of Study- or Community-Provided Vaccine
All eCRFs must be keyed for the period up to and including the entry visit and participants will be discontinued from the study.

Evaluations for Participants Who Do Not Receive Second Dose of Study-Provided Vaccine **(Cohorts 1a and 1c and Cohort 2)**
Participants who do not receive the second dose of the Moderna mRNA-1273 vaccine within 140 days of study entry should remain on study. All evaluations should be performed, as described in section 6.1.

If the participant discontinues the study after 28 days and did not receive the second study-provided Moderna mRNA-1273 vaccine dose, they may receive it at their premature study discontinuation visit.

Evaluations for Participants Who Do Not Receive Second Dose of Community-Provided Vaccine **(Cohort 1b)**
Participants who do not receive the recommended second dose of the COVID-19 vaccine provided in the community should remain on study, and all evaluations should be performed, as described in section 6.1.

Cohort 1c participants may receive their second dose through the study at their premature study discontinuation visit.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue study participation should have premature study discontinuation evaluations, as outlined in section 6.1, prior to being taken off the study, unless the reason for premature study discontinuation was that the participant did not receive study vaccine or was lost to follow-up.

6.3 Instructions for Evaluations

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for Laboratories Performing Testing for DAIDS-Supported and/or Sponsored Clinical Trials, which is available at: https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf.

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the DAIDS Site Clinical Operations and Research

Essential (SCORE) Manual: Source Documentation on the DAIDS website for information about what must be included in the source documents: https://www.niaid.nih.gov/sites/default/files/score-source-documentation.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) and AE reporting of adverse events requirements.

6.3.1 Documentation of ACTIV-2/A5401 participation, including the Participant ID

ACTIV-2/A5401 Subject ID Number and receipt of investigational therapy or active comparator/placebo for investigational therapy for ACTIV-2/A5401 participants will be captured in the eligibility checklist. This information will not be recorded on the eCRF.

6.3.2 Documentation of no prior history of SARS-CoV-2 infection by participant self-report

Documentation of no prior history of SARS-CoV-2 infection will be captured for non-ACTIV-2/A5401 participants in the eligibility checklist. This information will not be recorded on the eCRF.

6.3.3 Medical History

At Screening and updated at Study Entry, a complete medical history for the preceding 120 days should be recorded. **Any signs or symptoms associated with an mRNA-based COVID-19 vaccine administration prior to study entry (including Grade 1 or higher allergic reactions and Grade 2 or higher injection site reactions) should be recorded, regardless of when the diagnosis was made.**

Additionally, the following diagnoses should be recorded regardless of when the diagnosis was made, except where noted:

- **A**utoimmune disease
- **P**ulmonary embolus
- **D**eep venous thrombosis
- HIV infection
- **C**ancer (exclusive of basal/squamous cell skin cancer)
- **A**cute viral respiratory infection (influenza, parainfluenza, respiratory syncytial virus, rhinovirus) within the previous 14 days (if known by participant)
- **C**hronic lung disease
- **A**sthma requiring daily inhaled medication
- **O**besity (BMI >35)
- **H**ypertension
- **C**ardiovascular disease
- **D**iabetes

- **C**hronic kidney disease
- **H**istory of cirrhosis
- **E**xogenous or endogenous immunosuppression

Any allergies to any medications and vaccines and their formulations must also be documented.

6.3.4 Medication History

A medication history must be present, including start and stop dates. Table 6.3.**4**-1 lists the medications that must be included in the history at screening and updated at entry.

Table 6.3.**4**-1: Medication History

Medication/Category	Timeframe
All prescription drugs	Last 7 days
Corticosteroids, anabolic steroids	Last 30 days
Non-steroidal anti-inflammatory drugs (NSAIDS)	Last 30 days
Acetaminophen, Paracetamol	Last 30 days
Prescription drugs for high blood pressure	Last 3 months
Prescription drugs for diabetes and pre-diabetes	Last 3 months
Prescription drugs for lung disease	Last 3 months
Prescription drugs for heart disease	Last 3 months
Prescription drugs for autoimmune disease	Last 3 months
Cancer chemotherapy	Last 3 months
Antiretroviral therapy	Last 3 months
Immune-based therapy	Last 3 months
Blinded investigational agent (including ACTIV-2/A5401 treatment)	Last 12 months
SARS-CoV-2 treatments	Complete history
Hydroxychloroquine	Complete history
Antibiotics	Last 3 months
Anti-parasitics	Last 3 months
Alternative therapies	Last 3 months
Dietary supplements (including zinc and vitamins C and D)	Last 3 months

6.3.5 Clinical Assessments

Targeted Physical Examination

A targeted physical examination should be conducted at all in-person visits, including vital signs and examinations driven by any previously identified or new adverse event (AE)/targeted condition (as described in section 7.2) that the participant has experienced since the last visit.

At Entry, a physical examination will include cardiac exam, pulmonary exam, weight, height, and vital signs (temperature, pulse, blood pressure, respiration rate, and resting peripheral oxygen saturation.

Post entry, see section 8.2 for collection requirements for pregnancy.

Assessment for Adverse Events
Beginning at entry, participants will be assessed at every visit (remote or in-person) for any new signs or symptoms and the relationship to study vaccine.

Refer to section 7.2 for AE collection requirements.

Concomitant Medications
Post-entry, the following new, modified, or discontinued concomitant medications must be recorded:

- **A**ll prescription drugs
- **C**orticosteroids, anabolic steroids
- **C**ancer chemotherapy
- **A**ntiretroviral therapy
- **I**mmune-based therapy
- **B**linded investigational agent
- SARS-CoV-2 treatments
- **Vaccines (experimental or standard of care, including COVID-19 booster vaccines); Note that 1st and 2nd doses of mRNA COVID-19 vaccines should be recorded per section 6.3.7.**
- **H**ydroxychloroquine
- **A**ntibiotics
- **A**nti-parasitics
- **A**lternative therapies
- **D**ietary supplements (including zinc and vitamins C and D)

6.3.6 Pregnancy Testing

For participants of reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of ≤25 mIU/mL.) Pregnancy testing should be performed per the SOE and section**s** 6.2.2 and 6.2.3.

NOTE: Reproductive potential is defined as:

- **P**articipants who have reached menarche
- **P**articipants who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available
- **P**articipants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)

- **P**articipants with no other clinical conditions (such as anorexia nervosa) that could induce amenorrhea
- **P**articipants not taking medications such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs) or chemotherapy that could induce amenorrhea
- For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied.

In the event of pregnancy occurring during the study, record pregnancy and pregnancy outcome per section 8.2.

6.3.7 Vaccine Administration

All first and second doses of mRNA COVID-19 vaccines, whether given by the study or outside of the study, will be recorded on the study treatment log eCRF.

Documentation of Community-Provided COVID-19 Vaccination **(Cohorts 1b and 1c)**
The date and type of vaccine administered to participants who received a community-provided COVID-19 vaccine will be recorded. Participants will be asked to bring their vaccine cards to the **Entry Visit (both cohorts, if Entry Visit occurs after administration of a community-provided dose)**, Day of 2nd Dose of Vaccination **(both cohorts, if not already provided at Entry Visit),** and 56 Days Post-Vaccination #1 **Visit (Cohort 1b only)** for verification of date of vaccine administration, type of vaccine, and vaccine lot number. Record any permanent vaccine discontinuation.

Study-Provided COVID-19 Vaccination Administration

- Pre-Medication: Pre-medication is not planned. However, if the participant has a medical history suggesting a potential benefit from pre-medication, the study investigator(s) should determine the appropriate pre-medication. Any pre-medications given will be documented as a concomitant medication.
- IM Administration**:** Each dose of the Moderna COVID-19 vaccine will be administered as one IM injection per the MOPS.
- Study Vaccine Modifications: Record all study vaccine modifications, including first and second doses, participant-initiated and/or protocol-mandated modifications. Record any permanent vaccine discontinuation.
- After Vaccine Administration: All participants should be monitored closely for 30 minutes following IM administration of the vaccine, as there is a risk of systemic reaction (including anaphylaxis) with any vaccine.

Symptoms and signs that may occur as part of an administration reaction include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

The severity of systemic reactions will be assessed and reported using the criteria for infusion-related reactions in the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The clinical site should have necessary equipment and medications for the management of any administration reaction, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen and antihistamine.

Investigators should determine the severity of the reaction and manage reactions based on standard of care and their clinical judgment. If an administration reaction occurs, then supportive care should be provided in accordance with the signs and symptoms.

Only AEs that meet AE reporting requirements will be recorded.

Participants may register with the CDC V-safe to report side effects after getting the vaccine. See the MOPS.

6.3.8 Vaccine Symptom Screen

For **Cohorts 1b and 1c** participants: If the participant enrolls >14 days after the first **or second** dose of their vaccine, then a Vaccine Symptom Screen is not collected **for the doses provided prior to enrollment**. Otherwise, 7 to 14 days after each vaccine, participants will be contacted and asked about their symptoms and signs post-vaccination. Symptoms should be recorded on the Adverse Events eCRF for symptoms meeting AE reporting criteria per section 7.2.

See the MOPS for further detail.

6.3.9 Stored Samples

Plasma, sera or PBMCs will be used to assess SARS-CoV-2 virologic and immunologic responses. Refer to the A5404 LPC for processing information. Entry samples must be collected for all participants. Entry samples must be collected before the first vaccine dose is administered, if the participant has not already received their first dose of vaccine through the community prior to entry. Samples for Day 28/Day of 2nd dose of vaccine must be collected as indicated in the SOE before the second vaccine dose is administered. All other blood samples must be collected as outlined in the SOE.

Stored Plasma

Blood plasma will be collected and stored for future testing, including:

- Total and antigen-specific SARS-CoV-2 IgA, IgG, and IgM levels
- Plasma protein, cytokine, and metabolomic analysis

Stored Serum
Blood sera will be collected and stored for future testing, including:
- Serologic responses to SARS-CoV-2 and other circulating coronavirus viral proteins
- Total and NAb assays

Stored PBMCs
PBMCs will be collected from all **Cohort 1** participants and 35 (in total) **Cohort 2** participants (see the MOPS). PBMCs for SARS-CoV-2-naïve participants should only be collected for those who are ≥40 years old on the day of collection. PBMC processing must be done in an IQA-approved lab. PBMCs will be stored for future testing, including:
- Antigen-specific, including Memory T cell assays
- Antigen-specific Memory B cell assays

Stored PAXgene Blood RNA Tube
Blood will be collected in a PAXgene tube and stored for future testing, including:
- To evaluate gene expression via RNASeq technology

6.3.10 Documentation of New Active SARS-CoV-2 Infection by Antigen or Nucleic Acid Test

In the case of new COVID-19 symptoms occurring at any time following vaccine administration while on study, participants should be tested or referred to testing with an antigen or nucleic acid test for SARS-CoV-2 infection. If a participant already received a new diagnosis of new SARS-CoV-2 infection by an antigen or nucleic acid test, then a test does not need to be repeated if a copy of the test result can be obtained. If a participant is found to have active SARS-CoV-2 infection, then additional blood samples should be collected. See section 6.1 and the LPC for further detail.

6.3.11 Nasopharyngeal (NP) Swab Collection

If feasible, NP swabs will be collected by staff after any documented new active SARS-CoV-2 infection within 14 days after onset of symptoms. Collection as early as possible after symptom onset is preferable. See the MOPS for further detail.

6.3.12 ACTIV-2/A5401 Investigational Therapy or Active Comparator/Placebo Questionnaire

Per the SOE, **Cohort 1** participants will be asked whether they believe they received the ACTIV-2/A5401 investigational therapy or the active comparator/placebo and whether this belief influenced their decision to join this study.

The questionnaire is posted on the DMC Portal in the Forms Management Utility.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study **after enrollment** REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the **pre-enrollment** baseline condition.

7.2 Adverse Event Collection Requirements for This Protocol

All AEs must be recorded on the eCRFs if any of the following criteria have been met:

- If any of the following targeted conditions occur, regardless of grade:
  - Allergic or hypersensitivity reactions to COVID-19 vaccine observed by study staff or reported by the participant. See section 6.3.7 for instructions for monitoring participants after vaccination.
  - **Myocarditis**
  - **Pericarditis**
  - Participant reported acute viral respiratory infection. If a diagnosis is known, then record on the eCRF
- Grade ≥2 AEs
- All AEs that led to a change in study treatment/intervention regardless of grade
- AEs meeting SAE definition or EAE reporting requirement

NOTE **A**: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

NOTE B: Participants reporting acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis within 4 to 6 weeks after vaccination must be referred to a cardiologist for evaluation and management. Cases should be followed until resolution of symptoms and abnormal test findings.

Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Suspected Unexpected Serious Adverse Events
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product).

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions, and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agent**s** for which expedited reporting is required **are** the Moderna mRNA-1273 COVID-19 vaccine **and the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine.**

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used, and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, *unexpected* serious adverse reactions (SUSARs), as defined in Version

2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

The protocol team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation, stored sample and data completeness, and AEs as described in the Study Progress, Data, and Safety Monitoring Plan (SPDSMP). These reports will be summarized among participants with no prior history of SARS-CoV-2 infection and pooled among **Cohort 1** participants.

The DAIDS Clinical Representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable. Additionally, the DAIDS clinical representative will **routinely** review aggregated AE summaries pooled across the blinded ACTIV-2/A5401 arms prepared by the Statistical and Data Analysis Center (SDAC) **on a schedule as defined in the SPDSMP**.

The study will undergo interim safety reviews by an ACTG-appointed Study Monitoring Committee (SMC) **at least annually**. The first interim review will occur when 10 participants have enrolled to one select therapy group**, received their first dose of vaccine after study entry,** and their data through study Day 7 (7 days after the first vaccine dose) are available, or 3 months after the first participant enrolls, whichever occurs first. Subsequent reviews will occur **annually** unless otherwise recommended by the SMC or requested by the study team. It is not intended that the SMC will review data on immunologic outcomes. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statistician in consultation with the team. Enrollment will pause and the SMC will review any death that occurs on study that is deemed related to study product as determined by the site investigator. A pause in enrollment will also occur and the SMC will review if two participants experience a Grade 4 AE that is deemed related to study product as determined by the site investigator. See section 10.0 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring are outlined in an SPDSMP developed by the SDMC prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

Only toxicities related to study medication provided through this study will be considered in the toxicity management section. Participants who receive community-provided COVID-19 vaccine should manage toxicity for that medication per SOC. The grading system for vaccine toxicities is located in the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

For the vaccine evaluated in this trial, if a participant develops a Grade 4 AE that is related to the study product as determined by the site investigator, no further doses of the study vaccine should be administered **by the site**.

It is possible that some participants will experience transient or prolonged AEs during the study. As some of the visits will be conducted remotely, AEs will often be assessed remotely and unplanned study visits scheduled if deemed necessary by the site investigator. For any concerning AEs that are felt to require clinical intervention, participants should be instructed to contact their health care provider or seek urgent or emergent care, or 911 should be called, as appropriate.

Vaccine may be discontinued without contacting the protocol team in advance, but the protocol team should be notified within 48 hours of vaccine discontinuation or interruption (follow the directions described in the Study Management section).

8.2 Pregnancy

There is limited data regarding the use of mRNA COVID-19 vaccines in participants who are pregnant. The American College of Obstetrics and Gynecology (ACOG) suggests offering vaccination to pregnant and breastfeeding individuals if they meet the criteria for vaccination based on the Advisory Committee on Immunization Practices (ACIP) recommending priority groups for vaccination [25, 26]. The Centers for Disease Control and Prevention (CDC) has recently classified pregnant and breastfeeding individuals at increased risk of severe illness or death from COVID-19 [27]. Therefore, pregnant individuals are eligible to participate in this study.

Participants who become pregnant after the first dose of the vaccine but prior to the second dose are eligible to receive the second dose of the vaccine. If pregnant participants choose not to receive the second dose of the vaccine, they will be encouraged to continue on study and complete the evaluations indicated in the Schedule of Evaluations. At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF.

If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact them regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

8.3 Breastfeeding

There are no data regarding the use of mRNA COVID-19 vaccines in participants who are breastfeeding. See section 8.2 for further rationale to allow individuals who are breastfeeding to participate in this study.

8.4 Allergic Reactions

All participants should be monitored closely, as there is a risk of systemic reaction (including anaphylaxis) with any vaccine.

Symptoms and signs that may occur as part of an administration reaction include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

The severity of systemic reactions will be assessed and reported using the criteria for infusion-related reactions in the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The clinical site should have necessary equipment and medications for the management of any administration reaction, which may include, but is not limited to, oxygen, IV fluid, epinephrine, acetaminophen, and antihistamine.

Investigators should determine the severity of the reaction and manage reactions based on standard of care and their clinical judgment. If an administration reaction occurs, then supportive care should be provided in accordance with the signs and symptoms.

8.5 Injection Site Reactions

Injection-site reactions (ISRs) will be differentiated from the above generalized allergic reactions by definition as localized pain/tenderness, induration, erythema, and/or formation of an ulceration or infection at the injection site. ISRs will be graded per the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

8.6 New SARS-CoV-2 Infection

Participants who are found to have new SARS-CoV-2 infection after study enrollment will have the measures detailed in section 6.2.3 (Post-Entry Evaluations), Event-Driven Evaluations.

If the new SARS-CoV-2 infection occurs after the first dose but before the second scheduled dose of the COVID-19 vaccine, then sites should follow CDC guidance which is available at https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html#CoV-19-vaccination when administering the second vaccine dose to participants who contract SARS-CoV-2 infection between their first and second scheduled vaccine dose. For such participants, the second vaccine dose should not be given until the participant has recovered from the acute phase of their infection and completed quarantine. Participants will have evaluations per section 6.2.3 and Schedule of Evaluations (section 6.1) and continue with the rest of planned evaluations. If the new SARS-CoV-2 infection happens after the second COVID-19 **vaccine** dose, then participants will continue with the planned Schedule of Evaluations.

8.7 **Myocarditis and Pericarditis**

Participants reporting acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis within 4 to 6 weeks after vaccination must be referred to a cardiologist for evaluation and management (see section 7.2). Cases of myocarditis and pericarditis should be followed until resolution of symptoms and abnormal test findings. Participants with events of myocarditis and/or pericarditis should be discontinued from the study and complete premature study discontinuation evalutations per section 6.1.

NOTE: The Centers for Disease Control and Prevention (CDC) provide guidelines on case definition and criteria for myocarditis and pericarditis (https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm)

9.0 CRITERIA FOR DISCONTINUATION

Participants may discontinue or withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep participants in the study. The reasons for participants discontinuing the vaccine series and/or withdrawing from the study will be recorded on the eCRF.

9.1 Permanent and Premature Vaccine Discontinuation for Participants **Receiving Study-Provided Vaccine**

- Vaccine-related toxicity (see section 8.1 Toxicity).
- Request by participant to terminate vaccine.
- Clinical reasons believed life-threatening by the physician, even if not addressed in section 8.1 Toxicity of the protocol.
- **Any clinically significant medical condition that, in the opinion of the investigator, poses an additional risk to the participant if they continue to participate in the study.**
- **Confirmed cases of myocarditis and/or pericarditis (see section 8.1 Toxicity).**

9.2 Premature Study Discontinuation **for Any Participant**

- Failure to receive the first dose of study- or community-provided mRNA vaccine.
- Request by the participant to withdraw.
- Request of the primary care provider if **they** think the study is no longer in the best interest of the participant.
- At the discretion of the IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.
- **Development of myocarditis or pericarditis.**

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

The aim of this study is to describe immunologic responses to mRNA-based SARS-CoV-2 vaccine among individuals who previously received investigational therapy in ACTIV-2/A5401 for SARS-CoV-2 infection in comparison to individuals who received a placebo. As ACTIV-2/A5401 is expected to change from using a placebo control to an active control, this study's aim will also evolve to describe immunologic responses to mRNA-based SARS-CoV-2 vaccine among individuals who previously received investigational therapy in ACTIV-2/A5401 for SARS-CoV-2 infection in comparison to individuals who received an active control. Results will need to be interpreted in the context of available information from outside the study when analyses are completed.

ACTIV-2/A5401 is evaluating multiple investigational agents with randomized comparison of a given investigational agent to a placebo control group which includes participants who were eligible to receive that investigational agent but who were concurrently randomized to receive the placebo for that specific agent or a placebo to another agent being evaluated at the same time. This combined placebo control group (or its equivalent combined active control group when ACTIV-2/A5401 changes to use an active control group) will be used in comparisons in this study. The randomization system in ACTIV-2/A5401 is designed so that the number of participants in the combined placebo group for evaluating a given investigational agent is approximately the same as the number of participants who received that investigational agent. Based on the select investigational agents likely to be included in this study, it is anticipated that the ratio of these numbers in this study will be close to 1:1. However, even if this is not achieved, the combined placebo group used in this study will still include participants who were eligible to receive the investigational agent and who were concurrently randomized to receive a placebo.

Although participants in this study were randomized to receive select therapy or corresponding active comparator/placebo in the ACTIV-2/A5401 study, the exposure comparison in this study is not a pure randomized comparison. Outcomes experienced in the ACTIV-2/A5401 study, including differential experiences by receipt of investigational therapy versus active comparator/placebo, may influence a participant's decision to enroll in this study (even though participants will still be blinded to their select therapy group assignment in ACTIV-2/A5401). Differences in mortality between the investigational therapy and active comparator/placebo exposures may also lead to differences in enrollment to this study. With the caveat of limited sample size, adjusted analyses and or analyses using propensity scores or other approaches for causal inference may be used to explore potential biases in exposure comparisons induced by selective enrollment.

Note that for the purposes of statistical analysis of this study, unblinded statisticians will have access to the treatment assignments from ACTIV-2/A5401 but the participants and other investigators in the study will not be unblinded.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to **https://**ClinicalTrials.gov. **Outcome measures will be analyzed as originally pre-specified if accrual is sufficiently high to provide meaningful estimates. Otherwise, analyses will instead be reported as descriptive estimates within participant groups rather than as comparisons between groups. Additional details are pre-specified in the primary Statistical Analysis Plan.**

10.2.1 Primary Outcome Measure

10.2.1.1 Neutralizing antibody (NAb) level at least **140** days after the first dose of the study- or community-provided vaccine.

10.2.2 **Secondary** Outcome Measures

10.2.2.1 Relative pre-vaccine to post-vaccine change in NAb response defined as the ratio of post-vaccine level/pre-vaccine level. The pre-vaccine NAb measurement will be obtained before the first dose of the vaccine, and the post-vaccine measurement will be obtained at least 56 days after the first dose of the vaccine.

10.2.2.2 New Grade 3 or higher AE, or SAE, or AE leading to change or discontinuation in vaccine receipt from first dose of the mRNA-based COVID-19 vaccine and through **140** days after the first dose of vaccine.

10.2.2.3 Grade 1 or higher allergic reaction from first dose of the mRNA-based COVID-19 vaccine through the visit 56 days after the first dose of the vaccine

10.2.2.4 Grade 2 or higher injection site reaction from first dose of the mRNA-based COVID-19 vaccine through the visit 56 days after the first dose of the vaccine.

10.2.2.5 Relative pre-vaccine to post-vaccine change in NAb response defined as the ratio of post-vaccine level/pre-vaccine level by received vaccine, i.e., Moderna versus Pfizer. The pre-vaccine NAb measurement will be obtained before the first dose of the vaccine, and the post-vaccine measurement will be obtained at least 56 days after the first dose of the vaccine.

10.2.3 **Other** Outcome Measures

10.2.3.1 CD4+ and CD8+ T cell responses to SARS-CoV-2 spike protein and IgG serologic responses to SARS-CoV-2 spike protein at receptor binding domain (RBD) and N terminal domain (NTD) at study entry/Day 0 and 56 days after the first vaccine dose.

10.2.3.2 Flow cytometry of PBMC for markers of exhaustion on B and T cells at study entry/Day 0, 56**, and 140** days after the first vaccine dose.

10.3 Randomization and Stratification

There is no randomization or stratification in this study.

10.4 Sample Size

The following considers sample size for a comparison of responses among participants who previously received an investigational agent versus among participants who previously received placebo. Similar considerations apply if instead the comparison is of responses among participants who previously received an investigational agent versus among participants who previously received an active control. **It was originally intended to consider the following sample sizes for each investigational therapy group separately. Due to lower than anticipated enrollment numbers, revisions to the protocol and SAP now consider combining the active arms from some investigational therapy groups together for comparisons against the pooled placebo group or active comparator.**

To inform sample size and precision of estimates, we use data from a recent study of outpatients with symptomatic COVID-19 followed longitudinally [8] to provide information about variability in NAb levels and changes in NAb levels (in the absence of both Ab therapy and vaccine). These data include samples taken up to 180 days after symptom onset. NAb levels in that study were measured using the pseudotyped virus reported from a single-round-of-infection neutralization assay (PsVNA or PSV), the same assay as will be used in this study. The standard deviation of log NAb levels was 0.48 among 54 participants with samples taken between 120 and 180 days after symptom onset. These data represent a similar time interval after select COVID-19 therapy or placebo to the post-vaccine NAb measurement in this study). The extended time interval up to 240 days in this study might result in reduced variability (lower standard deviation) and thus the estimate of 0.48 to inform our anticipated precision is conservative.

For the primary outcome measure of NAb levels **140** days after the first vaccine dose, we will calculate the ratio of geometric mean responses (GMRs) for participants with prior select investigational therapy exposure versus participants who received placebo. A ratio of GMRs (GMR for investigational therapy exposed divided by GMR for placebo) of one indicates no difference in NAb response. A ratio of less than 1 indicates lower NAb response among those who received prior select investigational therapy exposure compared to those who received placebo. The main analysis is descriptive: to provide an

estimate of the ratio of GMRs and associated confidence interval. **If the study does not enroll enough participants to provide meaningful estimates and/or precision, then NAb levels at 140 days after the first vaccine dose will be reported as separate descriptive results among participants exposed to ACTIV-2/A5401 active therapies, participants exposed to ACTIV-2/A5401 placebo, and participants exposed to ACTIV-2/A5401 active comparator.**

The statistical analysis will be undertaken on a log (base 10) scale as is conventional for NAb measurements (as the distribution of log responses is generally closer to a normal distribution). The estimate and confidence interval will be anti-logged to provide an estimate and confidence interval for the ratio of GMRs. For the purposes of evaluation of precision and sample size, we assume that the confidence intervals can be calculated using standard methods assuming that responses are approximately normally distributed on a log scale.

Table 10.4-1 shows the anticipated precision in this study of estimates of the ratio of GMRs (after anti-logging) for participants with versus without prior exposure to investigational agent**s** and assuming that the observed ratio of GMRs is one (i.e., under the null hypothesis of no difference between groups), for a range of standard deviations encompassing the value of 0.5. For a standard deviation of 0.5 and a sample size of 70 participants who receive vaccine (35 with prior investigational therapy and 35 who received active comparator/placebo [a 1:1 ratio]), the 90% confidence interval for the ratio of GMRs is (0.63, 1.58) and the 95% confidence interval is (0.58, 1.73). These confidence intervals suggest reasonable precision to rule out reductions in response associated with prior investigational therapy of about 40% or more or increases of about 60% or more. If there are investigational agents included in ACTIV-2/A5401 but not in this study, it is possible that the ratio of number of participants with prior exposure to a given agent to the number of participants in the combined placebo group will differ from 1:1. Table 10.4-1 shows confidence intervals for various ratios of participants in this study with prior investigational therapy versus placebo. There is some loss of precision (wider confidence intervals) as the ratio increases from 1:1 to 4:1 for fixed sample size but the precision is still reasonable (note 4:1 is likely a very extreme ratio based on the select investigational agents likely to be included in this study). There is also some loss of precision for standard deviations larger than 0.5 and some gain in precision for smaller standard deviations. **In protocol version 3.0, we revised the scenarios shown in Table 10.4-1 to show precision for expected sample sizes of 10, 20, 30, 50, and 70 to reflect lower than anticipated observed enrollment numbers. With a total sample size less than 30, expected precision on the GMR ratio is low, and therefore if total enrollment numbers do not exceed this level, descriptive analyses may be preferred.**

Table 10.4-1: Confidence Intervals for an Observed Ratio of GMRs Comparing Participants With Versus Without Prior Investigational Therapy for a Range of Sample Sizes and Standard Deviations (SDs: for log base 10 values)

			90% CI for a true ratio of GMR of 1				95% CI for a true ratio of GMR of 1			
Allocation Ratio	Total N	n Ab, n Placebo	SD=0.3	SD=0.4	SD=0.5	SD=0.6	SD=0.3	SD=0.4	SD=0.5	SD=0.6
1 to 1	10	5, 5	(0.44, 2.25)	(0.34, 2.95)	(0.26, 3.87)	(0.20, 5.08)	(0.36, 2.74)	(0.26, 3.83)	(0.19, 5.36)	(0.13, 7.50)
	20	10, 10	(0.58, 1.71)	(0.49, 2.04)	(0.41, 2.44)	(0.34, 2.92)	(0.52, 1.91)	(0.42, 2.38)	(0.34, 2.95)	(0.27, 3.66)
	30	15, 15	(0.65, 1.53)	(0.56, 1.77)	(0.49, 2.05)	(0.42, 2.36)	(0.60, 1.67)	(0.50, 1.99)	(0.42, 2.37)	(0.36, 2.81)
	50	25, 25	(0.72, 1.39)	(0.65, 1.55)	(0.58, 1.73)	(0.52, 1.93)	(0.67, 1.48)	(0.59, 1.69)	(0.52, 1.92)	(0.46, 2.19)
	70	35, 35	(0.76, 1.32)	(0.69, 1.44)	(0.63, 1.58)	(0.58, 1.73)	(0.72, 1.39)	(0.64, 1.55)	(0.58, 1.73)	(0.52, 1.93)
2 to 1	10	7, 3	(0.41, 2.43)	(0.31, 3.26)	(0.23, 4.39)	(0.17, 5.89)	(0.33, 3.00)	(0.23, 4.34)	(0.16, 6.25)	(0.11, 9.02)
	20	13, 7	(0.57, 1.75)	(0.47, 2.11)	(0.39, 2.55)	(0.33, 3.08)	(0.51, 1.97)	(0.40, 2.48)	(0.32, 3.10)	(0.26, 3.90)
	30	20, 10	(0.63, 1.58)	(0.54, 1.84)	(0.47, 2.13)	(0.40, 2.48)	(0.58, 1.73)	(0.48, 2.07)	(0.40, 2.49)	(0.33, 2.99)
	50	34, 16	(0.70, 1.42)	(0.63, 1.60)	(0.56, 1.79)	(0.50, 2.02)	(0.66, 1.52)	(0.57, 1.75)	(0.50, 2.02)	(0.43, 2.32)
	70	47, 23	(0.75, 1.34)	(0.68, 1.48)	(0.61, 1.63)	(0.56, 1.80)	(0.70, 1.42)	(0.63, 1.60)	(0.56, 1.80)	(0.50, 2.02)
3 to 1	10	8, 2	(0.36, 2.76)	(0.26, 3.87)	(0.18, 5.43)	(0.13, 7.62)	(0.28, 3.52)	(0.19, 5.36)	(0.12, 8.17)	(0.08, 12.42)
	20	15, 5	(0.54, 1.86)	(0.44, 2.28)	(0.36, 2.81)	(0.29, 3.44)	(0.47, 2.11)	(0.37, 2.72)	(0.29, 3.48)	(0.22, 4.48)
	30	23, 7	(0.60, 1.66)	(0.51, 1.97)	(0.43, 2.33)	(0.36, 2.76)	(0.54, 1.84)	(0.44, 2.26)	(0.36, 2.77)	(0.29, 3.40)
	50	38, 12	(0.68, 1.47)	(0.60, 1.67)	(0.53, 1.90)	(0.46, 2.15)	(0.63, 1.58)	(0.54, 1.85)	(0.47, 2.15)	(0.40, 2.51)
	70	53, 17	(0.73, 1.38)	(0.65, 1.53)	(0.59, 1.71)	(0.53, 1.90)	(0.68, 1.47)	(0.60, 1.67)	(0.53, 1.90)	(0.46, 2.16)
4 to 1	10	8, 2	(0.36, 2.76)	(0.26, 3.87)	(0.18, 5.43)	(0.13, 7.62)	(0.28, 3.52)	(0.19, 5.36)	(0.12, 8.17)	(0.08, 12.42)
	20	16, 4	(0.51, 1.95)	(0.41, 2.44)	(0.33, 3.05)	(0.26, 3.82)	(0.44, 2.25)	(0.34, 2.95)	(0.26, 3.86)	(0.20, 5.07)
	30	24, 6	(0.58, 1.71)	(0.49, 2.05)	(0.41, 2.44)	(0.34, 2.92)	(0.52, 1.91)	(0.42, 2.37)	(0.34, 2.93)	(0.27, 3.64)
	50	40, 10	(0.66, 1.51)	(0.58, 1.73)	(0.51, 1.98)	(0.44, 2.27)	(0.61, 1.63)	(0.52, 1.92)	(0.44, 2.26)	(0.37, 2.67)
	70	56, 14	(0.71, 1.41)	(0.63, 1.58)	(0.56, 1.77)	(0.50, 1.99)	(0.66, 1.51)	(0.58, 1.73)	(0.50, 1.99)	(0.44, 2.28)

A **key secondary** outcome measure evaluates relative change in NAb level pre-vaccine to post-vaccine. The statistical analysis for this outcome measure will use change in log (base 10) NAb level pre-vaccine to post-vaccine. The outpatient study provides information about the variability in change in log NAb level over time. Forty-three of the participants in that study had an additional measurement earlier in follow-up. The median time of the first measurement was 63 days after onset of symptoms and the median time of the second measurement was 159 days after onset of symptoms. The median duration of time between measurements was 96 days (similar to the time interval between the pre-vaccine and post-vaccine measurements in this study). The standard deviation of changes in log NAb level among these 43 participants was 0.35. Assuming that the variability of changes in this study is similar (standard deviation of 0.4 and recognizing that the vaccine should alter the mean change), then Table 10.4-1 shows that with a sample size of 70 participants receiving vaccine with equal numbers with versus without prior investigational therapy, the 90% confidence interval is (0.69, 1.44) and the 95% confidence interval is (0.64, 1.55) when the observed ratio of GMRs comparing participants with versus without prior select therapy is 1. Similar considerations as noted above for the primary outcome measure apply if the ratio of

participants with versus without prior investigational select therapy increases from 1:1, or if the standard deviation increases from 0.4. **If total enrolment numbers are low, we may consider reporting descriptive analyses of change in NAb level without the comparisons of investigational therapy exposure to placebo/active comparator.**

10.5 Data and Safety Monitoring

The study will undergo safety reviews by an ACTG-appointed SMC as described in section 7.4. There are no formal statistical stopping guidelines for these planned safety reviews. It is not intended that the SMC review immunologic outcome data or that the study be stopped early based on the magnitude of immune responses.

10.6 Analyses

Statistical analysis plans will be developed describing analyses to address the primary and **secondary** objective of the study.

The primary outcome analysis is descriptive and **was originally intended to** be carried out separately for each investigational therapy and associated combined placebo group or investigational agent and associated active comparator group. **Due to lower than anticipated enrollment into the study, the primary outcome analysis may be amended to be carried out in a combined group of participants exposed to particular ACTIV-2/A5401 investigational agents. Additional details are described in the Statistical Analysis Plan.** The analysis will combine **participants regardless of which** mRNA-based COVID-19 vaccine **they received.** An exploratory analysis **may** be carried out separately for each mRNA-based COVID-19 vaccine **if sample size permits.**

The following description focuses on the comparison of outcomes among participants who received a**n** investigational agent in ACTIV-2/A5401 compared with participants in the combined placebo control group. Similar analyses will be undertaken if the comparison is to parti**c**ipants in an active control group.

For the primary outcome measure, we will evaluate the ratio of GMRs for participants with prior investigational therapy versus participants who received placebo. A ratio of GMRs (GMR for investigational therapy exposed divided by GMR for placebo) of one indicates no difference in NAb response. A ratio less than 1 indicates lower NAb response among those who received prior investigational therapy exposure compared to those who received placebo. **If the study does not enroll enough participants to provide meaningful estimates and/or precision, then NAb levels at 140 days after the first vaccine dose will be reported as separate descriptive results among participants exposed to ACTIV-2/A5401 active therapies, participants exposed to ACTIV-2/A5401 placebo, and participants exposed to ACTIV-2/A5401 active comparator.**

The primary analysis population will include all participants who received at least one vaccine dose and provided NAb responses at least **140** days after the first vaccine dose.

Participants reinfected with SARS-CoV-2 after receiving the first dose of the vaccine will be excluded from the primary analysis. **Similarly, participants reinfected with SARS-CoV-2 between receipt of the second dose of vaccine and 140 days after the first vaccine dose will be excluded from the primary analysis.** The primary analysis is descriptive: to provide estimate**s of NAb and if sample size allows,** the ratio of GMRs and associated confidence interval. No formal statistical tests will be performed. Estimates and confidence intervals will be obtained from linear regression with an indicator variable for prior investigational therapy exposure versus placebo using standard methods assuming that NAb responses are approximately normally distributed on a log (base 10) scale. To allow for the possibility that the distribution of time from receipt of investigational therapy or placebo to the first dose of vaccine may vary, an analysis adjusted for this time will also be undertaken. A supplemental analysis will be conducted among participants who received both doses of the vaccine. An exploratory analysis will be conducted by mRNA-based COVID-19 vaccine.

The analysis population for the **secondary** outcome measure exploring change in NAb levels from pre- to post-vaccine will include all participants who received at least one vaccine dose and provided NAb responses within 7 days prior to the first dose of the vaccine and at least **56** days after the first vaccine dose. Participants reinfected with SARS-CoV-2 after receiving the first dose of the vaccine will be excluded from this analysis. **Similarly, participants reinfected with SARS-CoV-2 between receipt of the second dose of vaccine and 140 days after the first vaccine dose will be excluded.** The analysis is descriptive: To provide estimate**s of change in NAb and if sample size allows**, the ratio of GMRs and associated confidence interval. No formal statistical tests will be performed. Estimates and confidence intervals will be obtained from linear regression with an indicator variable for prior investigational therapy exposure versus placebo using standard methods assuming that NAb responses are approximately normally distributed on a log (base 10) scale. To allow for the possibility that the distribution of time from receipt of investigational therapy or placebo to the first dose of vaccine may vary, an analysis adjusted for this time **may** also be undertaken. A sensitivity analysis will be conducted among participants who received both doses of the vaccine. An exploratory analysis will be conducted by mRNA-based COVID-19 vaccine **if sample size allows.**

Outcomes among participants without prior COVID-19 will be analyzed in the same way as for participants with prior COVID-19 and is intended to be descriptive. In the event that there are differences in outcomes between participants with prior COVID-19 (including taking account of exposure to ACTIV-2/A5401 investigational agent, placebo, or active control) and participants without prior COVID-19, which are considered large, exploratory analyses may be undertaken taking account of information available at the time of analysis about participant char**a**cteristics that might affect the magnitude of vaccine response.

The safety analysis population will include all participants who receive at least the first vaccine dose. The analysis of safety outcome measures will be descriptive by whether participants had been exposed to investigational therapy or active comparator/placebo in ACTIV-2/A5401, and separately for participants without prior COVID-19. We will

summarize each safety outcome measure (estimate of proportion and corresponding 95% confidence interval) at the pre-specified time points detailed in section 10.2.2.

Outcomes experienced in the ACTIV-2/A5401 study, including differential experiences by receipt of investigational therapy versus active comparator/placebo, may influence a participant's decision to enroll in this study even though participants will still be blinded to their assignment in ACTIV-2/A5401. If sample size permits, adjusted analyses or analyses using propensity scores or other causal inference methods may be used to explore potential biases in exposure comparisons induced by selective enrollment.

11.0 PHARMACOLOGY PLAN

Not applicable.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration.

12.2 Role of Data Management

12.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to ensure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

12.3.1 Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity [28]. The site **must** make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. **The Data Management Center will configure Medidata Remote Source Review (RSR) and make it available to all sites. We encourage Sites to use the DMC provided Medidata RSR platform but other** potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution**s**. Other secure platforms that are 21 CFR Part 11

compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

12.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, the industry supporter or designee, other local, US, and international regulatory entities for confirmation of the study data.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (**INFORMED CONSENT FORM**) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, parent, or legal guardian, and this fact will be documented in the participant's record.

13.2 Participant Information and Consent

Informed consent in compliance with US Title 21 CFR Part 50 and US Title 45 CFR Part 46 shall be obtained from each participant before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant.

Before recruitment and enrollment, each prospective participant or their legal guardian will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the investigator is assured that the participant/legal guardian understands the implications of participating in the study, the participant/legal guardian will be asked to give consent to participate in the study. A witness may be used for the informed consent process if remote consent is performed and it is not possible to obtain a copy of the signed consent form from the participant (or legal guardian or person with power of attorney for participants who cannot consent for themselves).

The **I**nformed **C**onsent **F**orm will include a description of the risks and benefits of the COVID-19 vaccine. There is increasing evidence that COVID-19 vaccination has the potential of direct benefit whether participants have been infected previously or not, because it offers high levels of protection against future SARS-CoV-2 infection.

13.3 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other local, US, and international regulatory entities as part of their duties, or the industry supporter or designee.

13.4 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, other government agencies as part of their duties to ensure that research participants are protected, or the industry supporter.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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INFORMED CONSENT **FORM**

Sponsor / Study Title:	National Institute of Allergy and Infectious Diseases / "SARS-CoV-2 Immune Responses after COVID-19 Therapy and Subsequent Vaccine"
Protocol Number:	A5404
Principal Investigator: (Study Doctor)	«PiFullName»
Telephone:	«IcfPhoneNumber»
Address:	«PiLocations»

This form is for use in a research study that may involve participants who may or may not have the capacity to consent to take part in the study. When the participant cannot legally consent to take part, pronouns "you" and "your" should be read as referring to the participant rather than the person (legally authorized representative) who is signing and dating this form for the participant. In cases where the participant's representative gives consent, the participant should be informed about the study to the extent possible given his/her understanding. During the course of the study, if the participant regains the capacity to consent, informed consent will be obtained from the participant, and the participant offered the ability to leave the study if desired.

SUMMARY

PURPOSE

This is a research study and your participation in this study is voluntary. The purpose of this study is to evaluate the safety and efficacy of mRNA COVID-19 vaccines in:

- People with prior COVID-19 (SARS-CoV-2 infection) who were in the ACTIV-2/A5401 study.
  And
- People who have never had COVID-19 (SARS-CoV-2 infection).

VACCINE

Study-provided Moderna mRNA-1273 COVID-19 vaccine, or

Community-provided mRNA COVID-19 vaccine (from a local clinic or vaccination site, for example).

NUMBER OF PARTICIPANTS

This study **planned to** enroll 70 people who were in ACTIV-2/A5401 from each ACTIV-2/A5401 study treatment group, and up to 70 people who have never had COVID-19 per each ACTIV-2/A5401 study treatment group. **Enrollment into this study closed on February 25, 2022, due to slow enrollment. A total of 43 participants were enrolled.**

LENGTH OF STUDY

You will be on this study for up to 730 days, which is about 2 years.

REQUIRED ACTIVITIES

If you enter the study before you have the first **vaccination**, you will have blood drawn from a vein in your arm before your first **and second** mRNA COVID-19 **vaccinations**. **If you enter the study before you have the second vaccination, you** will have blood drawn before your second mRNA COVID-19 **vaccination**. **If you enter the study after you have two doses of vaccine, you will have blood drawn on the day you enroll in the study.** This blood will be used to measure immune and genetic (determined by inherited factors) responses to your initial SARS-CoV-2 (the virus that causes COVID-19) infection and to the mRNA COVID-19 vaccine.

If you are receiving study-provided Moderna mRNA-1273 COVID-19 vaccine, the study vaccine will be given by needle into the muscle of your arm on study days 0 and 28.

Phone Visits 7 to 14 Days after Vaccinations

If you enter the study before your first or second mRNA COVID-19 vaccination, you will be contacted by phone by the study team **between 7 and 14 days after each vaccine** to see whether or not you have had any new symptoms or medical events. If you **enter the study** more than 14 days after your first **vaccination**, you will only be contacted after the second vaccine. **If you enter the study more than 14 days after your second vaccination, you will not have a scheduled phone visit.**

Study Visits 2 Months, 5 Months, 1 Year, and 2 Years After Your First mRNA COVID-19 Vaccine

You will have blood drawn. This blood will be used to measure immune responses to your study-provided or community-provided mRNA COVID-19 vaccine.

RISKS

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

If You Are Receiving **the** Study-Provided Moderna mRNA-1273 COVID-19 Vaccine

Side effects that have been reported with the Moderna mRNA-1273 COVID-19 vaccine include:

- Injection site reactions: pain, itching, tenderness and swelling of the lymph nodes in the same arm of the injection, swelling and hardness around the injected area, and redness.
- General side effects: fatigue (tiredness), headache, muscle pain, joint pain, chills, nausea and vomiting, fever, and mild abdominal pain.
- Other: facial flushing (redness), generalized itching, tingling of face or extremities, runny nose, sneezing, hypotension (low blood pressure), hives, and pruritus (itching).

- **There is increased risk of myocarditis and pericarditis. Myocarditis is inflammation of the heart muscle, and pericarditis is inflammation of the lining outside the heart.**

There is a very small chance that the study-provided Moderna mRNA-1273 COVID-19 vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to one hour after being vaccinated. For this reason, you will be asked to stay at the study site for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing or swallowing
- Chest tightness
- Shortness of breath
- Coughing
- Wheezing
- Swelling of your face and throat
- A fast heartbeat
- A bad rash all over your body
- Vomiting
- Abdominal pain
- Dizziness and weakness
- Fainting (loss of consciousness), convulsions (like a seizure)

<u>If You are Receiving Community-Provided mRNA COVID-19 Vaccine</u>
This is an observational study of the community-provided mRNA COVID-19 vaccine that you are receiving locally, so the risks of taking those vaccines are not part of this study. Your medical provider or vaccine administrator should give you that information.

<u>BENEFITS</u> There is increasing evidence that COVID-19 vaccination has the potential of direct benefit because it offers high levels of protection against future COVID-19 (SARS-CoV-2 infection), whether you have been infected previously or not.

<u>OTHER CHOICES</u> Instead of being in this study, you have the choice of obtaining a COVID-19 vaccine **in the community**, obtaining an experimental COVID-19 vaccine in another study, if you qualify, or no vaccination.

INTRODUCTION

You are being asked to take part in this research study because you**:**

1. Have previously had COVID-19 (SARS-CoV-2 infection) and received an experimental treatment, placebo (a look-alike product that has no active substance), or a standard of care

COVID-19 treatment (the usual care for COVID-19 at the time) in a clinical trial known as ACTIV-2/A5401.

Or

2. You have not previously been diagnosed with a COVID-19 (SARS-CoV-2 infection) infection and have not previously been vaccinated for COVID-19.

The current study is sponsored by the National Institutes of Health (NIH). The study doctor in charge of this study at this site is listed on the first page of this form. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign and date this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

SARS-CoV-2 is a recently identified virus that has caused a widespread outbreak of an illness called COVID-19. New treatments and vaccines are being developed for this virus. Some of these treatments and vaccineshave received Emergency Use Authorization (EUA) from the FDA. This means that they became available for use more quickly than usual. **The Moderna mRNA-1273 vaccine received full FDA approval.** Some of these treatments and vaccines are being evaluated in clinical trials, **such as** ACTIV-2/A5401 and this study (A5404).

People who have previously experienced SARS-CoV-2 infection can get it again, and it is not known if active viral infection generates a weaker immune response than what can be elicited by a COVID-19 vaccine.

This study is for people who had COVID-19 and participated in ACTIV-2/A5401 and received either experimental treatment, a standard of care COVID-19 treatment, or placebo. This study is also for people who have not previously had a COVID-19 infection. The study is designed to evaluate how the immune system responds to mRNA-COVID-19 vaccines in these participants. The safety of mRNA COVID-19 vaccines in persons with prior COVID-19 who did and did not receive prior experimental treatment for COVID-19 will be explored. Prior infection with or without treatment could increase, decrease, or have no significant effect on the response to mRNA COVID-19 vaccines, as well as the risk of side effects from these vaccines. Immune responses of participants who have not previously been infected with COVID-19 will be compared to those who have previously had COVID-19.

Enrollment for this study closed on February 25, 2022, due to slow enrollment. Vaccine responses will be studied in the 43 participants enrolled. Your continued participation is appreciated.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Location of Study Visits

Your study visits will take place in person or remotely. You and the **study** staff at your **study** site will discuss the location for each visit.

- In-person visits will take place at the clinic, at your home, or at another non-clinic location.
- Remote visits will take place over the phone or via telemedicine systems approved for use at your **study** site.

Information Collected at Screening

There is some information that we collect on everyone who is screened for an AIDS Clinical Trials Group (ACTG, part of the National Institute of Allergy and Infectious Diseases, an institute of the NIH) study. As part of your screening visit, some demographic (for example, age, gender, race) and clinical (for example, disease condition, diagnosis) information will be collected from you. We also collect information on whether you use (or have used) injection drugs.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may determine whether there are patterns and/or common reasons why people do not join a study.

Blood Drawn

The study site staff can tell you how much blood will be collected at any particular visit.

Screening Visit

If you would like to be in this study, after you have read, signed, and dated this consent form, you will have a screening visit to make sure you meet the requirements for joining the study. This visit will take about 1 hour. You may come to the clinic, or if it is possible or necessary, this visit might be done remotely (for example, by telephone).

At this visit:

- Study staff will tell you more about the study.
- If you will receive **the** study-provided Moderna mRNA-1273 COVID-19 vaccine, then study staff will tell you about that **study** vaccine.
- If you are receiving **a** community-provided mRNA COVID-19 vaccine, then study staff will ask you which vaccine (for example, Pfizer or Moderna) you are getting and when you received or are scheduled to receive your first **and (if applicable) second** vaccine dose**s**.
- If you were a participant in the A5401/ACTIV-2 study: Study staff will review your history and confirm your participation in ACTIV-2/A5401.
- You will be asked about any symptoms you are experiencing.
- Study staff will ask you about your allergy history, any health conditions you have, and questions about your health in general.
- Study staff will ask you about your medication history and any medications you are taking.
- You may have a brief physical exam if your screening visit takes place at the clinic.

Entry Visit

If you qualify for the study, you will have an entry visit. This visit might occur on the same day as your screening visit.

- You will have a physical exam and answer questions about your medical and allergy history and any medications you are taking or have taken in the past.
- **If you have already received a community-provided mRNA COVID-19 vaccine dose before the Entry visit, you will be asked to bring your vaccine card to this visit.**
- **If you have already received a community-provided mRNA COVID-19 vaccine dose before the Entry visit, you will be asked to bring your vaccine card to this visit.**
- If you were a participant in the A5401/ACTIV-2 study, your information collected from A5401/ACTIV-2 will also be used in this trial.
- If you were a participant in the A5401/ACTIV-2 study, you will be asked some questions about ACTIV-2/A5401 experimental treatment and about your interest in this study.
- You will be asked about symptoms you are experiencing.
- You will have a pregnancy test, if applicable.
- You will have blood collected. This blood will be tested to measure any responses that your genes and immune system have had to your previous SARS-CoV-2 infection.
- If you are receiving **the** study-provided Moderna mRNA-1273 COVID-19 vaccine, you will receive the first dose of the vaccine. You will be asked to remain at the clinic for approximately 30 minutes for monitoring after you receive the Moderna mRNA-1273 COVID-19 vaccine.
- If you are receiving **both** COVID-19 vaccine **doses outside of the study ("in the community") and enroll prior to receiving the first or second dose, you should have your entry visit within 72 hours prior to receiving the dose. If you enroll after receiving the second dose, you must have blood collected within 14 days of that second dose.**
- **If you are receiving the first vaccine dose outside of the study, and the second dose through the study (this is for people who receive Moderna mRNA-1273 vaccine only), and enroll prior to receiving the first dose, you should have your entry visit within 72 hours prior to receiving that first dose. If you enroll after receiving the first vaccine dose, you must have blood collected within 72 hours prior to the second dose you receive through the study.**

<u>Phone Visits 7 to 14 Days after Vaccinations</u>

If you enter the study before your first or second mRNA COVID-19 vaccination, between 7 and 14 days after **the** vaccine**(s)**, you will be contacted by phone by the study team to see whether or not you have had any new symptoms or medical events. If you **enter the study** more than 14 days after your first **vaccination**, then you will only be contacted after the second vaccine. **If you enter the study more than 14 days after your second vaccination, then you will not be contacted.**

<u>Study Visit on Day of 2nd Dose of Vaccine</u>

- If you are receiving **the** study-provided Moderna mRNA-1273 COVID-19 vaccine, you will return to the clinic a**round** 28 days (about 4 weeks, or 1 month) after your first vaccine dose to receive your second dose. You will be asked to remain at the clinic for approximately 30 minutes for monitoring after you receive the vaccine. If you do not receive the second dose of the vaccine at this time (and you still want to receive it), you may still get the second dose

through the study up to 140 days after your first vaccine dose. You will still be contacted by phone 7 to 14 days after you receive the vaccine.

- If you are receiving **the** community-provided mRNA COVID-19 vaccine **and enter the study before receiving your second dose**:
  - If you received the Moderna mRNA-1273 COVID-19 vaccine, **you will receive your second dose** about 28 days after your first dose. If you received the Pfizer-BioNTech **BNT162b2** mRNA COVID-19 vaccine, **you will receive your second dose** about 21 days after your first dose. You will be asked to bring your vaccine card to this visit.
  - If you received the Moderna mRNA-1273 COVID-19 vaccine for your first dose, you may be able to get the second dose of the Moderna mRNA-1273 COVID-19 vaccine through the study, if you want to.
- If you do not receive your 2nd dose of **the** vaccine, you may still remain on the study and have the remaining study visits performed.
- **If you enter the study after receiving both doses of mRNA COVID-19 vaccine in the community, then you will not have this visit.**
- **If your first community-provided mRNA-based COVID-19 vaccine dose occurred after entry, you will be asked to bring your vaccine card to this visit.**

At this visit:

- You will have a physical exam and answer questions about current medications you are taking.
- You will have a pregnancy test, if applicable.
- You will be asked about symptoms you are experiencing.
- You will have blood collected. This blood will be tested to measure any responses that your genes and immune system have had to your previous SARS-CoV-2 infection.

<u>Study Visit 8 Weeks (56 days, or about 2 months) after Your First mRNA COVID-19 Vaccine Dose</u>

You will have a physical exam and answer questions about medications you are currently taking. You will have blood drawn. This blood will be used to measure immune responses to the vaccine you took. If you think you may be pregnant, you will have a pregnancy test. If you **received the second** community-provided mRNA COVID-19 vaccine **dose after entering the study**, you will be asked to bring your vaccine card to this visit. **If you enroll more than 56 days after your first mRNA COVID-19 vaccine dose, you will not have this visit. If you enroll between 56 and 63 days after your first mRNA COVID-19 vaccine dose, then this study visit may be combined with your entry visit.**

<u>Study Visit 20 Weeks (140 days, or about 5 months) after Your First mRNA COVID-19 Vaccine Dose</u>

You will have a physical exam and answer questions about medications you are currently taking. You will have blood collected. This blood will be tested to measure immune responses to the vaccine you took. If you think you may be pregnant, you will have a pregnancy test.

If you enroll between 133 and 139 days after your first mRNA COVID-19 vaccine dose, then this study visit may be combined with your entry visit.

Study Visit 1 Year (365 days) after Your First mRNA COVID-19 Vaccine Dose
You will have a physical exam and answer questions about medications you are currently taking. You will have blood collected. This blood will be tested to measure immune responses to the vaccine you took. If you think you may be pregnant, you will have a pregnancy test.

Study Visit 2 Years (730 days) after Your First mRNA COVID-19 Vaccine Dose – FINAL VISIT
You will have a physical exam and answer questions about medications you are currently taking. You will have blood collected. This blood will be tested to measure immune responses to the vaccine you took. If you think you may be pregnant, you will have a pregnancy test.

Additional Study Visit
If you think you have contracted COVID-19, you will be asked to come in for an extra study visit.

At this visit:
- You will have a physical exam.
- Diagnosis and documentation of new active SARS-CoV-2 infection with an antigen or nucleic acid test (these tests that can detect active SARS-CoV-2 infection from your nose or throat) will be done or you will be referred to a site that can do this testing
- If you are found to have an active SARS-CoV-2 infection, you may have nasopharyngeal swabs (**for example,** deep nasal swabs) collected by a study staff person as early as possible within 14 days after your symptoms begin. Your current medications will also be reviewed.
- You will be asked about symptoms you are experiencing.
- You will have blood drawn. This blood will be stored for future study-required testing.
- You will have a pregnancy test, if applicable.

Genetic Testing
Your body, like all living things, is made up of cells. Cells contain deoxyribonucleic acid, also known as “DNA.” DNA is like a string of information put together in a certain order. Parts of the string make up “genes.” Genes contain instructions on how to make your body work and fight disease. These genes direct the cells to make particular sequences or types of ribonucleic acid, also known as “RNA.” Differences or changes in DNA and RNA explain some of the physical differences among people. These differences partly explain why some people get diseases **such as** cancer or diabetes while others do not. Genetic testing looks at the differences in people’s DNA and RNA. This testing also looks at how differences affect health and the body’s response to disease, treatment, and vaccination.

If you agree, some of your blood that is collected will be used to study whether there are genetic differences in how people respond to study drugs. This genetic testing might include whole genome sequencing (WGS) for DNA and gene expression for RNA. “Sequencing” is looking at the order of a person’s genes to see how this order is different from the order of other people to see if these differences are associated with different disease states or immune responses. You must agree to participate in this genetic testing in order to participate in this study.

Please put your initials below to indicate your choice:

_____ (initials) I understand and I agree to this use of my samples.

OR
_____ (initials) I understand but I do not agree to this use of my samples**,** and I understand that this means I cannot participate in this study.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Your information and samples from ACTIV-2/A5401 and data generated from your information and samples from ACTIV-2/A5401 will be used for this study. Some of your blood will be stored and used for study-required testing.

Your samples and any private information that has been collected about you **will be coded**. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study. Your samples may be used for commercial profit and you will not share in this commercial profit.

Please refer to **the separate consent at the end of this document** to consent for use of your samples in other studies.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

This study **planned to** enroll 70 people who were in ACTIV-2/A5401 from each ACTIV-2/A5401 study treatment group, and up to 70 people who have never had a COVID-19 infection per each ACTIV-2/A5401 study treatment group. **In total, the study enrolled 43 participants.**

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 730 days.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- The study is stopped or cancelled.
- You are not able to attend the study visits as required by the study.
- You do not receive the first dose of mRNA COVID-19 vaccine, or other community–provided mRNA vaccine**, such as** the Pfizer BioNTech **BNT162b2 mRNA** COVID-19 vaccine.

If you received **the** study- or community-provided Moderna mRNA-1273 COVID-19 vaccine for your first dose:

- You may still be able to get the second dose of the Moderna mRNA-1273 COVID-19 vaccine through the study (up to 140 days after your first dose) at the premature study discontinuation visit if you are taken off of the study early.

If you are receiving **the** study-provided Moderna mRNA-1273 COVID-19 vaccine, the study doctor may need to take you off the Moderna mRNA-1273 COVID-19 vaccine without your permission if:

- Continuing the Moderna mRNA-1273 COVID-19 vaccine may be harmful to you.
- You are not able to take the Moderna mRNA-1273 COVID-19 vaccine as required by the study.

If you must stop taking the Moderna mRNA-1273 COVID-19 vaccine before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

If you leave the study early, you will have a physical exam, pregnancy test (if applicable), and blood collection.

<u>If I have to permanently stop taking study-provided Moderna mRNA-1273 COVID-19 vaccine, or once I leave the study, how would the Moderna mRNA-1273 COVID-19 vaccine be provided?</u>

During the study:
If you must permanently stop receiving study-provided Moderna mRNA-1273 COVID-19 vaccine before your study participation is over, the study staff will discuss other options that may be of benefit to you.

WHAT ARE THE RISKS OF THE STUDY?

The study-provided Moderna mRNA-1273 COVID-19 vaccine used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this vaccine. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional Moderna mRNA-1273 COVID-19 vaccine side effects please ask the medical study staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the Moderna mRNA-1273 COVID-19 vaccine. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Since we do not fully understand the Moderna mRNA-1273 COVID-19 vaccine's effectiveness in participants who have previously had COVID-19, it is recommended that you continue to take general precautions (**for example**, physical distancing, wearing a mask) to reduce the risk of infection.

Risks of **the** Study-provided Moderna mRNA-1273 COVID-19 Vaccine
There are risks to taking part in any research study.

There is a risk that the study-provided Moderna mRNA-1273 COVID-19 vaccine may not stop you from acquiring COVID-19.

Additionally, if you have previously had COVID-19 and received an experimental treatment, placebo, or a standard of care COVID-19 treatment in the ACTIV-2/A5401 study:

- The study-provided Moderna mRNA-1273 COVID-19 vaccine has received **full FDA approval. It** has been shown in a clinical trial to be effective in preventing COVID-19 following two doses given at least 1 month apart, but it is not known if it is effective in people who have had COVID-19 previously and if being treated with experimental treatment has any effect.

Side effects that have been reported with the study-provided Moderna mRNA-1273 COVID-19 vaccine include:

- Injection site reactions: pain, itching, tenderness and swelling of the lymph nodes in the same arm of the injection, swelling (hardness) redness, and formation of an ulceration (a break in the skin) or infection.
- General side effects: fatigue (tiredness), headache, muscle pain, joint pain, chills, nausea, vomiting, fever, and mild abdominal pain.
- Other: facial flushing (redness), generalized itching, tingling of face or extremities, runny nose, sneezing, hypotension (low blood pressure), hives, and pruritus (itching).

There is a very small chance that the study-provided Moderna mRNA-1273 COVID-19 vaccine could cause a severe allergic reaction. A severe allergic reaction would usually occur within a few minutes to 1 hour after getting a dose of the study-provided Moderna mRNA-1273 COVID-19 vaccine. For this reason, you will be asked to stay at the study site where you received your vaccine for about 30 minutes after vaccination. Signs of a severe allergic reaction can include:

- Difficulty breathing or swallowing
- Chest tightness
- Shortness of breath
- Coughing
- Wheezing
- Swelling of your face and throat
- A fast heartbeat
- A bad rash all over your body
- Vomiting
- Abdominal pain
- Dizziness and weakness
- Fainting (loss of consciousness), convulsions (like a seizure)

There is an increased risk of myocarditis and pericarditis after getting the study-provided Moderna mRNA-1273 COVID-19 vaccine. Myocarditis is inflammation of the heart muscle, and pericarditis is inflammation of the lining around the heart. In both cases, the body's immune system is causing inflammation in response to the vaccine. Symptoms can include chest pain, shortness of breath, or palpitations. Symptoms usually start within a

few days after receipt of the Moderna mRNA-1273 COVID-19 vaccine. Most individuals who have sought medical care have responded well to medications and rest, and symptoms have resolved for most persons who experienced this side effect. It is not known if either myocarditis or pericarditis from the vaccine causes long-term health effects.

Myocarditis and pericarditis have been reported in greatest numbers in males under the age of 40 years following a second dose of mRNA vaccines (including the COVID-19 vaccine), but cases have been reported in older males and in females as well, and also following other doses. Risk for myocarditis and pericarditis has been observed to be highest in males between 12 to 17 years of age. While some cases required intensive care support, data suggests that symptoms got better in most people with some management. Information is not yet available about the potential long-term affects of myocarditis and pericarditis in these people. While there is limited data on the risk of myocarditis and pericarditis in children younger than 12 years old (especially compared to the risk data that is available in adolescents and adults), it is an area of science that is currently being studied.

Please let a member of the study staff know if you experience any of the following symptoms of myocarditis or pericarditis, following vaccination provided through the study:

- **Chest pain**
- **Shortness of breath**
- **A fast heartbeat, fluttering, or pounding heart**

Study staff will provide you with appropriate contact information so that you can reach out should you experience any of these symptoms.

You should not get the study-provided Moderna mRNA-1273 COVID-19 vaccine if you:

- Had a severe allergic reaction after a previous dose of this vaccine.
- Had a severe allergic reaction to any ingredient of this vaccine.

Serious and unexpected side effects may also occur.

Risks of Blood Collection

Having blood collected may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, and in rare cases it may result in fainting. There is a small risk of infection.

ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING?

Pregnancy

If at any point during the study you think you may be pregnant, you should let the staff at your site know so that a pregnancy test can be done.

If you become pregnant after the first dose of the mRNA COVID-19 vaccine but prior to the second dose, you are eligible to receive the second dose. If you choose not to receive the

second dose of the vaccine, you will be encouraged to continue on study and complete the study.

At the end of the pregnancy, study staff will contact you to ask about the pregnancy outcome.

If you have completed the study or choose to discontinue from the study before the end of the pregnancy, then **study** staff will request permission to contact you regarding pregnancy outcomes at the end of pregnancy.

<u>If you are receiving **the** study-provided Moderna mRNA-1273 COVID-19 vaccine:</u>
There is limited data regarding the use of mRNA COVID-19 vaccines in people who are pregnant. The American College of Obstetrics and Gynecology (ACOG suggests offering vaccination in pregnant and breastfeeding individuals if they are at risk for COVID-19 if they meet the criteria for vaccination based on the Advisory Committee on Immunization Practices (ACIP) recommending priority groups for vaccination. The Centers for Disease Control and Prevention (CDC) has recently classified pregnant and breastfeeding individuals at increased risk of severe illness or death from COVID-19. Therefore, pregnant individuals are eligible to participate in this study.

The study-provided Moderna mRNA-1273 COVID-19 vaccine may involve risks to you (or to the embryo or fetus, if you or your partner become pregnant), which are currently unforeseen.

<u>Breastfeeding</u>
If you are receiving **the** study-provided Moderna mRNA-1273 COVID-19 vaccine: It is not known if the Moderna mRNA-1273 COVID-19 vaccine is safe to use in people who are breastfeeding; however, you are eligible to receive this vaccine if you are breastfeeding.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There is increasing evidence that COVID-19 vaccination has the potential of direct benefit because it offers high levels of protection against future COVID-19 (SARS-CoV-2 infection), whether you have been infected previously or not.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- Obtaining a COVID-19 vaccine **in the community**.
- Obtaining an experimental COVID-19 vaccine, if you qualify.
- No vaccination.

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

For sites in the US

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally. **Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.**

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, Advarra IRB institutional review board (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

All information collected about you as part of the study will be sent securely to the ACTG Statistical and Data Management Center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations, and policies of your country and research site.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

For sites outside the US

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will

not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations, and policies of your country and research site.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:

- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ *["following each completed visit," "monthly," "quarterly," "at the end of your participation in the research study," "following each completed visit or at the end of your participation in the research study, whichever you prefer"]*.

If you have any questions regarding your compensation for participation, please contact the study staff.

[OR]

You will not receive any monetary compensation for your participation in this study.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The US National Institutes of Health (NIH) does not have a mechanism to provide direct compensation for research-related injury.

[For sites outside the US: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry CTI, this must be indicated in the informed consent.

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study. OR*
- *The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH].*

The US federal government has a program that may provide compensation to you or your family if you experience serious physical injuries or death and these costs are not covered by other payors. To find out more about this "Countermeasures Injury Compensation Program" go to https://www.hrsa.gov/cicp/about/index.html or call 1-855-266-2427.

For sites in the US: To pay medical expenses, the sponsor will need to know some information about you such as your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

Due to the coronavirus public health crisis, the US federal government has issued an order that may limit your right to sue and recover for losses if you are injured or harmed while participating in this COVID-19 clinical study. If the order applies, it limits your right to sue and recover for losses from the researchers, healthcare providers, any study sponsor, or manufacturer or distributor involved with the study. However, the order does not limit your right to seek compensation for injuries that result from conduct or activities of the researchers, health care providers, study sponsors, manufacturers, and distributors that is unrelated to the study. Review the Public Readiness and Emergency Preparedness Act (PREP): https://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx.
You will not be giving up any of your legal rights by signing and dating this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know. Clinically relevant research results, including individual research results, will not be provided to you. If applicable, pregnancy test results will be provided to you.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns, or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document.

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants.

[Sites: Select the contact information of your IRB below.]

If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- **O**r call toll free: 877-992-4724
- **O**r by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00050357.

[OR]

If you have any questions about **your rights as a research participant, and/or concerns or complaints regarding this research study, contact:**

- **Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site.**
- **T**elephone number of above.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below and date it.

Printed Name of Participant

Signature of Participant **Date**

Printed Name of Legally Authorized Representative (As Appropriate)

Signature of Legally Authorized Representative **Date**

Printed Name of Study Staff Conducting Consent Discussion (print)

Signature of Study Staff Conducting Consent Discussion **Date**

Printed Name of Witness (As Appropriate)

Signature of Witness **Date**

CONSENT FOR **OPTIONAL** USE OF **EXTRA** SAMPLES IN OTHER STUDIES

Everything in the main study consent you signed and dated above still applies to your participation unless otherwise noted below.

When samples are no longer needed for this study, the AIDS CLINICAL TRIALS GROUP (ACTG) may want to use them in other studies and share them with other researchers. These samples are called "extra samples." The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored. ***[Site: Revise the previous sentence to insert limits, if your regulatory authority imposes them.]***

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher's **I**nstitutional **R**eview **B**oard (IRB) **or ethics committee (EC) will review their plan.** ***[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]*** IRBs **and ECs** protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher's location. This means that researchers who are not part of the study team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you.

You may withdraw your consent for research on your extra samples at any time, and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the study staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (as described above) and used for ACTG-approved research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples.

OR

____ (initials) I understand but I do not agree to this storage and possible use of my samples.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below and date it.

_____
Printed Name of Participant

_____ _____
Signature of Participant **Date**

_____
Printed Name of Legally Authorized Representative (As Appropriate)

_____ _____
Signature of Legally Authorized Representative **Date**

_____
Printed Name of Study Staff Conducting Consent Discussion

_____ _____
Signature of Study Staff Conducting Consent Discussion **Date**

_____
Printed Name of Witness (As Appropriate)

_____ _____
Signature of Witness **Date**