Protocol

SARS-CoV-2 Vaccination Strategies in Previously Hospitalized and Recovered COVID-19 Patients

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SARS-CoV-2 vaccination strategies in previously hospitalized and recovered COVID-19 patients

Short Title: Vaccination for Recovered Inpatients with COVID-19 (VATICO)

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GLOSSARY OF PROTOCOL-SPECIFIC TERMS

Ab	antibody
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AE	adverse event
BMI	body mass index
CDC	Centers for Disease Control and Prevention (US)
COVID-19	Coronavirus disease 2019
CRS	clinical research site
CTSN	Cardiothoracic Surgical Trials Network
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
EC	ethics committee
eCRF	electronic case report form
EMA	European Medicines Agency (EU)
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMR	geometric mean ratio
ICC	International Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IRB	institutional review board
LAR	legally authorized representative
mRNA	messenger ribonucleic acid
mL	milliliter
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
OHRP	Office for Human Research Protections (US)
PETAL	Prevention and Early Treatment of Acute Lung Injury
PHI	personal health information
PIM	Protocol Instruction Manual
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TICO	“Therapeutics for Inpatients with COVID-19” - a master protocol aka. ACTIV-3
UMN	University of Minnesota
UP	unanticipated problem
US	United States of America
VA	Veterans Affairs

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1. Protocol summary

INSIGHT 016
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RATIONALE

The optimal timing and number of vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the ACTIV-3/TICO population (hospitalized due to COVID-19) has not been determined, and is the subject of scientific and ethical equipoise. The vaccines to be investigated in this study have been administered in unprecedented numbers to a broad population, have been carefully investigated and monitored, and are currently considered to be both generally safe and effective. COVID-19 infection is known to generally confer a period of SARS-CoV-2 immunity in most individuals, which would presumably be protective during the study specified period of deferral. COVID-19 infection is also thought to provide an adequate priming effect in most individuals, making the single vaccination arms that are part of this study a scientifically sound avenue for investigation, and ethical from a risk perspective.

DESIGN

In this Phase 4, open-label trial, participants of the ACTIV-3/TICO clinical trial at selected sites who received certain pre-specified blinded investigational agents or placebo as part of that trial, and who have since achieved sustained recovery, and who are still [TICO assignment] blinded, and who are still within 28 to 90 days after initial TICO randomization, will be randomized in this 2x2 factorial design to one of four groups:

(i) immediate versus 12 week deferral of first dose administration and also
(ii) one dose only, versus two doses to be given 4 weeks apart

of the Moderna mRNA-1273 or the Pfizer BNT162b2 vaccine (mRNA vaccines).

The primary objectives of this 2x2 factorial design are (i) to estimate the difference in neutralizing antibody (NAb) response to the mRNA vaccine from baseline to Week 48 among participants vaccinated early versus deferred, and (ii) to estimate the difference in NAb response to this vaccine among participants vaccinated once versus twice. The primary analyses will be carried out in participants randomized to placebo in TICO. Analyses will also be carried out for those who receive the investigational agent(s) studied in TICO.

A key secondary objective is to ascertain the effect, if any, of SARS-CoV-2 monoclonal antibodies, and other interventions that have been studied in hospitalised COVID-19 subjects, on natural and vaccine-induced immunity.

	Participants will be offered enrollment between 28 and 90 days after receiving select ACTIV-3/TICO investigational agents or placebo. The primary endpoint, immune response specific to the vaccination received, will be assessed at Week 48. Participants will have blood collected at time of enrolment, and at Weeks 12, 24 and 48 after study entry.
DURATION	48 weeks.
SAMPLE SIZE	Approximately 640 participants. The total sample size will depend on how many select investigational agents/placebo are evaluated in ACTIV-3/TICO.
POPULATION	ACTIV-3/TICO trial participants at selected sites who received certain investigational agents or placebo 28 to 90 days previously, and have experienced sustained recovery for two or more weeks, and have not yet been vaccinated post COVID-19 illness.
REGIMEN	One or two (given approximately 4 weeks apart) injections of either the 100 µg Moderna mRNA-1273 vaccine or the 30 µg Pfizer BNT162b2 vaccine, given intramuscularly. Choice of vaccine is determined based on availability at the site. The choice is individual, although participants vaccinated twice should receive the same type of vaccines for both injections. The first vaccination is given either immediately after enrolment in this protocol or deferred for 12 weeks.
STRATIFICATION	Randomization to one of the 4 treatment groups will be stratified by study site pharmacy and investigational agent assignment in TICO.
MONITORING	An independent data and safety monitoring board (DSMB) will review interim safety data on a regular basis. The DSMB will be the same DSMB that reviews ACTIV-3/TICO agents.

2. Introduction

2.1. Study Rationale

2.1.1. Immune Responses after Natural Infection

Natural infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces innate and adaptive immune responses, comprising of humoral immunity and cell mediated immunity. Both viral-specific neutralizing antibodies and T cell responses develop post-infection, creating immunological memory [1-4]; the response is more profound in persons with severe/ critical infection including those in intensive care than in patients with milder disease. Further investigations found that multiple SARS-CoV-2 antigens were recognized by $CD4^+$ and $CD8^+$ T cells in these individuals. The frequencies of viral antigen-specific T cells corresponded to predicted viral protein abundance in infected cells [5]. 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 [6-8].

2.1.2. Reinfection

As described above, initial SARS-CoV-2 infection elicits immune memory, and it is likely that these immune responses offer some level of protection from re-infection for some time. Neutralizing antibodies are an important immune correlate of protection and a potential modifier of disease severity should infection occur. Though rare, post-infection cases of reinfection have been reported [9-14]. For example, a large prospective study in healthcare workers followed up for 7 months, suggested that the risk of SARS-CoV-2 re-infection was reduced by 89% in those seropositive for SARS-CoV-2 anti-spike IgG at baseline compared to seronegative individuals [15]. The timing of the study coincided with the second epidemic surge in the United Kingdom, approximately 4-7 months post the end of the first surge.

Therefore, the risk of reinfection, although present, is greatly reduced for several months after the initial infection, and appears to be comparable to the reduced risk seen with vaccination of immunologically-naïve individuals (see section below). However, detailed comparisons of the strength and durability of immune protection post infection (natural immunity) compared to vaccine-induced immunity is lacking.

Open questions that remain concerning initial infection include:

- what exactly are the correlates of immune protection?
- what is the durability of protection generated after initial SARS-CoV-2 infection?
- what is the degree of heterogeneity of responses across the population?
- what is the impact of circulating escape variant(s) on re-infection risk?

2.1.3. SARS-CoV-2 Vaccination

A number of SARS-CoV-2 vaccines have been developed [16]. Several of them have undergone Phase 3 testing, demonstrating vaccine efficacy for symptomatic COVID-19 that is between 60-95% and marked protection against severe COVID-19 [17-19].

This evidence was derived from studies of populations without a prior history of COVID-19 illness. The follow-up period remains short (up to 4-6 months), thus the duration of protective response remains uncertain. The vaccines, except for one, were administered twice in the Phase 3 trials. The interval between the administration of the two doses has typically been 3-6 weeks apart. However, the pre-specified pooled analysis of trials of ChAdOx1 nCoV-19 (AZD1222) showed that those with a longer prime-boost interval (12 weeks or more) have a higher vaccine efficacy compared to those with an interval of less than 6 weeks. [20]. Such observations would suggest that the boosting of the immune response, intended by the second dose, may be more profound (and hence likely last longer) if the initial priming of the immune response from the first dose is allowed to mature.

Among persons with prior COVID-19 illness, the optimal timing and dosing of vaccination remains uncertain, and is not informed by robust clinical evidence from properly powered randomized trials. It is possible that reactogenic adverse events (AEs) may be different compared to what was seen in immunologically naïve persons, due to pre-existing natural immunity.

A recent smaller observational study showed that a single dose of mRNA vaccine in previously infected seropositive participants elicited equivalent or higher antibody responses compared to seronegative individuals who received two doses. This suggests one vaccine dose may suffice in those who have recently recovered from COVID-19 [21, 22]. Further, AEs were higher in the seropositive group.

It is also plausible that deferring the initiation of post-infection vaccination (while the person is at low risk of reinfection) may lead to a better, more robust, and more durable immune response, similar to observations made with increased prime-to-boost spacing in immunologically naïve persons [23].

Hence, emerging data suggest that protective immune function matures gradually, as seen in natural immunity post COVID-19 illness, and as also seen in response to first dose of SARS-CoV-2 vaccine in those who are immunologically-naïve. It is plausible that provision of vaccine at a later time than the currently recommended period [e.g. initiation at around 90 days pos COVID-19 illness] may induce better long-term protection.

In this study, participants will be offered open-label vaccination with either the Moderna mRNA-1273 or the Pfizer BNT162b2 SARS-CoV-2 vaccine, dosed either once or twice, and initiated either immediately upon recruitment 28-90 days after randomization to TICO, or deferred. People who participate in the study will be followed longitudinally for humoral immune dynamics in order to determine vaccine responses (assessed 12 weeks after first vaccination) and durability of these responses (after 48 weeks after enrolment into the study).

2.2. Background

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

COVID-19 has exacted a deadly toll on the United States of America (US) and the world. During 2020, dexamethasone [24] and remdesivir [25] have been introduced in many places as part of standard of care (SOC) for patients hospitalized with COVID-19 illness.

New treatments and vaccines are promising, but questions remain how these biomedical interventions interact with each other.

One of the first antiviral therapeutics to show promise have been antibody (Ab) based therapies, like monoclonal antibodies [26, 27]. At least three monoclonal antibody therapies (i.e. bamlanivimab; casirivimab and imdevimab; bamlanivimab and etesevimab), as well as three vaccines, have been granted emergency use authorization by the US Food and Drug Administration (FDA), 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 immune responses to a vaccine or natural infection.

Other types of treatments (e.g., protease inhibitors, small molecule viral enzyme inhibitors, interferon, etc.) given during early COVID-19 may also impact immune responses to COVID-19 vaccination [28]. 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 response. This may be different from people who completed their SARS-CoV-2 infection without treatment [29].

2.2.2. The TICO Trial

TICO (Therapeutics for Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or aimed at directly enhancing viral control in order to limit disease progression [30, 31].

TICO is a Phase 3 randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the course of the study for efficient testing of new agents against control (i.e., placebo + SOC) within the same trial infrastructure. When more than one agent is being tested concurrently, participants are randomly allocated across agents (as well as between the agent and its placebo) so the same control group will be used for multiple agents, when feasible. Randomization is stratified by study site pharmacy and disease severity.

Follow-up in TICO is for 18 months after randomization. The study team and participants remain blinded to individual allocation to the investigational agent or matching placebo during this period. The present vaccine protocol will hence be offered to participants during their blinded follow-up in TICO.

The present vaccine protocol overlaps in some of its design features with those of a vaccine substudy to the ACTIV-2 trial. ACTIV-2 is a master protocol that examines interventions similar to TICO, but in an outpatient setting [32, 33]. As the two vaccine protocols are complementary in some aspects, the intention is ultimately to merge the results, in order to provide a comprehensive picture of best use of vaccines during recovery from COVID-19 across the spectrum of its disease severities.

3. Risk/Benefit Assessment

3.1. Known Potential Risks

Vaccination after recovery from COVID-19 is provided in order to reduce the risk of reinfection. Whether vaccines in general, developed against SARS-CoV-2, provides such an effect is presently unknown, as the Phase 3 pivotal vaccine trials intentionally excluded persons with a history of COVID-19. Natural immunity, acquired from past infection, provides robust protection against reinfection for several months of follow-up [11, 15]. The number of reported cases of infection after recovery is low, especially if persons had prior severe disease. Patients with more severe COVID-19, such as those included in TICO, mount a more robust natural immunity response than persons with milder COVID-19 [4].

Risk of deferring vaccination for up to 4-6 months after initial COVID-19 (of the severity required for enrolment in TICO) is considered minimal.

Potential risks of participating in this trial are those associated with the product, and these are described in the sample informed consent. Other risks include having blood drawn, breach of confidentiality, and other potential and theoretical risks related to the length/level of immunity in the single-dose arms of the trial. This is an unavoidable component of the research, being a key question to be addressed.

Should conclusive data emerge, through VATICO or other efforts, that a second vaccination is beneficial in this post-severe-covid population, participants randomized to one dose will be notified and can be boosted.

3.1.1. Risks of Reactogenicity and Anaphylaxis

Potential risks of vaccination include reactogenic AEs [34], which either are localized at the site of injection or generalized. Local reactions include pain, swelling and reddening of the skin, and tenderness and swelling of the lymph nodes in the same arm. Generalized reactions include headache, fatigue, muscle aches, joint pain, chills, nausea and vomiting, and fever. Onset of such reactions are typically seen 12-24 hours after vaccination, and are typically self-limited with symptoms waning over the next 1-4 days. Their intensity is more frequent after the second than the first injection, at least among persons not previously infected with SARS-CoV-2. Symptoms may be reduced in intensity by use of paracetamol (1 gram up to 4 times daily).

Anaphylactic reactions are seen, but occur rarely (< 2/100.000) [35, 36]. If they develop, the onset is typically within minutes of the injection. Persons without signs of anaphylaxis 15 minutes after vaccination will not develop this reaction. Anaphylactic reactions require immediate injection of epinephrine (0.01 mg/kg (up to a maximum dose of 0.5 mg) per single dose) injected intramuscularly. Symptomatic treatment includes ensuring a secured airway, intravenous fluid (normal saline) administration (125 milliliter [mL]/hour or higher in case of hypotension), and monitoring of pulse, blood pressure and oxygen saturation.

3.1.2. Risks of Drawing Blood

Drawing blood may cause transient discomfort and, rarely, fainting. Fainting is usually transient and managed by having the participant lie down and elevate his/her legs. Bruising at the blood

collection site may occur but can be prevented or lessened by applying pressure to the venipuncture site immediately after blood draw.

3.1.3. Risks to Privacy

Participants will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the participant's PHI. All source records including electronic data will be stored in secured systems in accordance with institutional policies and government regulations.

All study data that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a participant through a code key maintained at the clinical site. Names or readily identifying information will not be released. Electronic files will be password protected.

Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publication from this trial will not use information that will identify study participants. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the study monitor, other authorized representatives of the institutional review board (IRB), National Institutes of Health (NIH), and applicable regulatory agencies (e.g. FDA, European Medicines Agency [EMA]).

3.1.4. Risks Due to Perceived Inadequacy of Single-Dose Vaccine Regimen

Some public health agencies currently define "fully vaccinated" with an mRNA vaccine as having received both doses of the two-dose regimen, whereas others may consider prior infection and a single dose as sufficient. In settings with a more conservative approach to defining "fully vaccinated," the inability to provide evidence of full vaccination may limit one's ability to travel to certain countries, or to work at particular employers or attend certain functions.

3.2. Potential Benefits

As discussed above, while routine administration of two vaccine doses to some participants would offer adequate protection against reinfection, delayed administration, after natural infection, may theoretically offer an equal or perhaps greater and/or more durable level of protection to those so randomized. Furthermore, while two doses will, again, presumably offer adequate protection to those so randomized, those assigned to receive one dose after natural infection may benefit from a level and duration of immunity that is at least as good as the standard regimen, without any of the risks that might accompany a standard second dose of vaccine.

Answering these critical questions, negatively or positively, will offer significant and immediate societal benefits in the face ot the global COVID-19 pandemic.

4. Outcomes

Primary and secondary outcome measures listed below will be addressed in the study's 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 ClinicalTrials.gov.

4.1. Primary Outcome Measures

The primary outcome measure is neutralizing antibody levels specific to the Moderna or Pfizer vaccine at Week 48 after randomization.

Comparisons will be evaluated using the ratio of geometric mean responses. Antibody levels will be $\log_{10}$ transformed and summarized with stratified analysis of covariance (see section 11.2).

4.1.1. Justification for this Endpoint

Neutralizing antibody levels are likely the best surrogate for protection against reinfection, and vaccines are able to increase their level. A minimal protective titer is, however, not yet defined. Additionally, emerging viral variants of concern have selected for mutations rendering the variants less susceptible to neutralization by serum from vaccinated persons [38, 39]. As such, the concept of minimal protective titer will not be one number, but rather will differ depending on viral variant that induced the immunity relative to the variant the vaccinated person is exposed to.

The primary analysis of this outcome will focus on level of neutralizing antibodies against the virus variant whose mRNA is part of the vaccine. However, neutralization against other viral variants will be assessed to broaden applicability of the findings depending on the type of viral variant in circulation.

Rate of reinfection would have been a more optimal primary outcome, but is not feasible given the requirement for a substantially larger sample size and the need for continued intense viral surveillance of the population to capture reinfections including those with minimal or no symptoms.

During follow-up, there may be residual levels of the investigational agent assessed in TICO that are detectable in blood. Several although not all of the trials in the TICO platform investigate neutralizing monoclonal antibodies, designed to extend half lives in circulation. As this protocol focuses on the host ability to produce neutralizing antibodies in response to vaccination, the levels of the investigational monoclonal antibody agent(s) are not reflecting this response. Hence, assays to assess NAb levels must be able to differentiate between the person's own produced antibodies versus those infused.

This trial will be able to compare vaccine responses depending on randomization to the investigational agent(s) studied in TICO or placebo.

The two strategic questions addressed using this factorial design aim to define the most optimal vaccination strategy among persons recovered from COVID-19. Risk of reinfection shortly after the initial infection is minimal, and hence durability of protective response is of key relevance. It is assumed that NAb titers have stabilized at Week 48 in follow-up for all randomized groups in the trial, and thus we have chosen this timepoint for determining the primary outcome in this trial.

4.2. Secondary Outcome Measures

1. Antibody levels 12 weeks after the first vaccination (i.e. at Weeks 12 and 24 depending on randomization to vaccinate immediately or deferred).

2. Estimated percentage of participants in each of the four vaccination groups with > 16, 8-16, 4-8, 2-4, and < 2-fold differences in NAbs from baseline to Week 48 and from just before vaccination to 12 weeks thereafter.

3. Relative pre-vaccine to post-vaccine change in NAb response defined as the ratio, post-vaccine level/pre-vaccine level. The pre-vaccine NAb measurement will be obtained immediately before the first dose of the vaccine (i.e. at Week 0 or 12) and the post-vaccine measurement will be obtained at Week 12 or at Week 24, depending on whether the vaccine was administered immediately or deferred.

4. Composite outcome of death, serious adverse event (SAE), grade 3 AEs, and grade 4 AEs within 12 weeks following randomization for the immediate group and from Week 12 to Week 24 in the deferred group.

5. Deaths or SAEs through Week 24.

6. The percentage of participants assigned to 2nd dose who do not receive it: a) for any reason and b) due to an AE following the 1st dose.

7. Non-adherence to the assigned treatment strategy.

4.2.1. Justification of the Various Secondary Outcomes

Re 1): Vaccine-induced NAb levels peak around 8 weeks post vaccination. If the immune system thereafter is no longer exposed to relevant antigens, levels start to decline. Hence, analyses assessing a vaccine's ability to induce peak levels and slope of declining levels are both relevant.

Re 2): This outcome supports the primary outcome and is often used in vaccine trials. Given the sample size, power to assess this outcome will be limited, and hence it is a secondary outcome.

Re 3): There is large interindividual variation in NAb levels after recovering from COVID-19. The ratio between post- and pre-vaccination levels is an alternative and possibly more sensitive marker for the effect of vaccination, both short-term (i.e. after 12 weeks) and long-term.

Re 4): Reactogenic adverse effects from vaccination are typically seen in the first few days after the vaccination, but may be protracted in a few persons. These AEs are well described in immunologically naïve populations, but poorly described in the population in this study. A 12-week period after initiation of vaccination (i.e. from Weeks 0 to 12 in those randomized to immediate vaccination and from Weeks 12 to 24 in those randomized to deferred vaccination) appears justifiable for adequately describing these AEs in this study population.

Re 5): SAEs and deaths are ascertained through Week 24 for all participants. This allows for

randomized comparisons for participants randomized to immediate or deferred vaccination. Deaths are reported via the TICO protocol and will not be separately reported in VATICO.

Re 6): For participants assigned to receive two doses of the vaccine, but for whom the second dose was not administered, separating reasons for this into these two broad categories will assist in understanding participants' tolerance and acceptance of a two-dose vaccination.

Re 7): Ascertaining reasons for non-adherence to the assigned regimen may shed light on vaccine desirability, tolerability and acceptance.

5. Objectives

5.1. Primary Objectives

1. Among participants in TICO who were randomized to placebo, to estimate the difference in NAb levels at Week 48 to the Moderna mRNA-1273 vaccine or the Pfizer BNT162b2 vaccine among participants who are vaccinated early (i.e. at time of enrolment into this protocol, within 28 to 90 days of enrolment in TICO) versus deferred (i.e. 12 weeks after enrolment into this protocol).

   There are limited data to guide the timing of vaccination in persons who have recovered from SARS-CoV-2 infection. It is possible that deferral may lead to a more durable immune response. Thus, to address this objective, the following hypothesis was formulated: deferral of vaccination will lead to a better vaccination response as the immune system has had more time to mature after the primary infection. Any treatment difference(s) observed in this study, together with immune correlates of protection, will further inform dosing practices in the future.

2. Among participants in TICO who were randomized to placebo, to estimate the difference in neutralizing antibody levels at Week 48 to the Moderna mRNA-1273 vaccine or the Pfizer BNT162b2 vaccine among participants who are vaccinated once versus twice.

   There are limited data to guide vaccine dosing requirements in persons who have recovered from SARS-CoV-2 infection. Studies in uninfected individuals show that that two doses of mRNA vaccines are required to elicit an effective immune response to SARS-CoV-2, with the first dose acting to 'prime' the immune system and the second dose providing effective long-term immunity. However, there are also emerging data from persons who have recovered from COVID-19 that the natural SARS-CoV-2 infection is able to prime the immune system and a single dose of an mRNA vaccine following recovery elicits a strong immune response. To address this objective we have formulated a 2-sided hypothesis to compare a one- versus two-dose vaccination strategy with the Moderna mRNA-1273 vaccine or the Pfizer BNT162b2 vaccine and have powered the trial to detect a 50% difference between the two dose groups (see section 6.2). This difference between vaccine dose groups that can be detected with 80% power may be reconsidered if data become available on antibody levels that provide protection from SARS-CoV-2 infection. Any treatment difference(s) observed in this study, together with immune correlates of protection, will further inform future dosing practices.

5.2. Secondary Objectives

1. To estimate the difference in NAb response to the Moderna mRNA-1273 vaccine or the Pfizer BNT162b2 vaccine among participants **with** prior investigational agent exposure in TICO compared to participants **without** prior investigational agent exposure (i.e., assigned placebo in TICO).

   The secondary objectives below will be addressed for those assigned placebo in TICO, for those assigned an investigational agent in TICO, and for both groups combined.

2. To explore the safety of the Moderna mRNA-1273 vaccine or the Pfizer BNT162b2 vaccine in persons with prior COVID-19 who did or did not receive prior TICO-defined investigational agents for COVID-19. In particular, a comparison will be made of the profile of reactogenic adverse effects between those vaccinated once versus twice; and whether this profile differs depending on whether the vaccination is given immediately following randomization or deferred.

3. To explore whether the timing of vaccination (immediate versus deferred) and/or use of one or two doses as studied in this protocol, affect the safety and tolerability of Moderna mRNA-1273 vaccine or the Pfizer BNT162b2 vaccine.

4. To estimate the percentage of participants in each of the four vaccination groups with >16, 8-16, 4-8, 2-4, and < 2-fold differences from baseline to Week 48.

5. To compare the one and two-dose vaccination strategies for the percentage of participants who experience a composite outcome of death, SAE, grade 3, grade 4 AEs from vaccination through Week 12 for the immediate group and from Week 12 (vaccination) through Week 24 for the deferred group. This comparison will be carried out separately for the immediate and deferred groups and after pooling the immediate and deferred groups.

6. To compare the percentage of participants who experience death or an SAE through 24 weeks for those in the immediate and deferred vaccination groups.

7. To explore whether host characteristics (i.e., age, race, geographical location of care, ethnicity, history of immunosuppression, body mass index (BMI), co-morbidities, co-medication), the course of prior COVID-19 (i.e. severity and duration of infection until recovery, use of immunosuppressive agents, etc.), type of vaccine (Moderna or Pfizer), interval between enrolment in TICO and this protocol, and baseline immune status affect humoral responses to SARS-CoV-2 vaccination and kinetics in NAb titers from 12 weeks after vaccination. These subgroup analyses will be carried out for both the immediate versus deferred randomized comparison and for the randomization of one versus two doses of vaccine.

8. To evaluate the reasons for non-adherence to the assigned vaccination schedule.

6. Study Design

In this Phase 4 trial, participants in the TICO master protocol who received certain pre-specified blinded investigational agents or matched placebos will be offered enrollment, with the understanding that this will require 2X2 randomized assignment of the timing and of the number of mRNA SARS-CoV-2 vaccinations to be received, via publicly-available m-RNA SARS-CoV-2 vaccination sites or via other routes, in keeping with the 4 specified study arm assignments.

This will address the objective of evaluating if the vaccine is best administered early or deferred after recovery, and whether one injection provides comparable immune response to a two injection course of vaccination. Participants (as well as the protocol team) will remain blinded to the interventions studied in TICO. Allocation to timing of vaccination and to one or two vaccinations is not blinded. Participants will be offered enrolment in this protocol at the Day 28 or Day 90 visits in TICO, or anytime between these visits.

Participants will have blood collected for research purposes at the time of enrolment and at Weeks 12, 24, and 48 (see section 9.1).

The study vaccine and regimen will not be blinded; there will be be no 'dummy/placebo' vaccine administered. Vaccines are expected to be made available either through the study directly, or through a reliable public vaccination program using vaccine available per the local regulatory mechanism (e.g., currently under EUA for the United States) or via other routes in case such local mechanisms are not available.

6.1. Randomization and Stratification

Participants will be equally allocated to 4 groups to inform each of two vaccine strategies:

- One injection versus two (for the immediate and deferred groups)
- Immediate versus deferred (for one and two vaccinations)

Hence, the outcome of the randomization will lead to one of the four following vaccination strategies for each study participant (**Figure 1**):

I1 – Immediate, one dose: vaccination at study entry only

I2 – Immediate, two doses: vaccination at study entry and Week 4

D1 – Deferred, one dose: vaccination at Week 12 only

D2 – Deferred, two doses: vaccination at Week 12 and Week 16

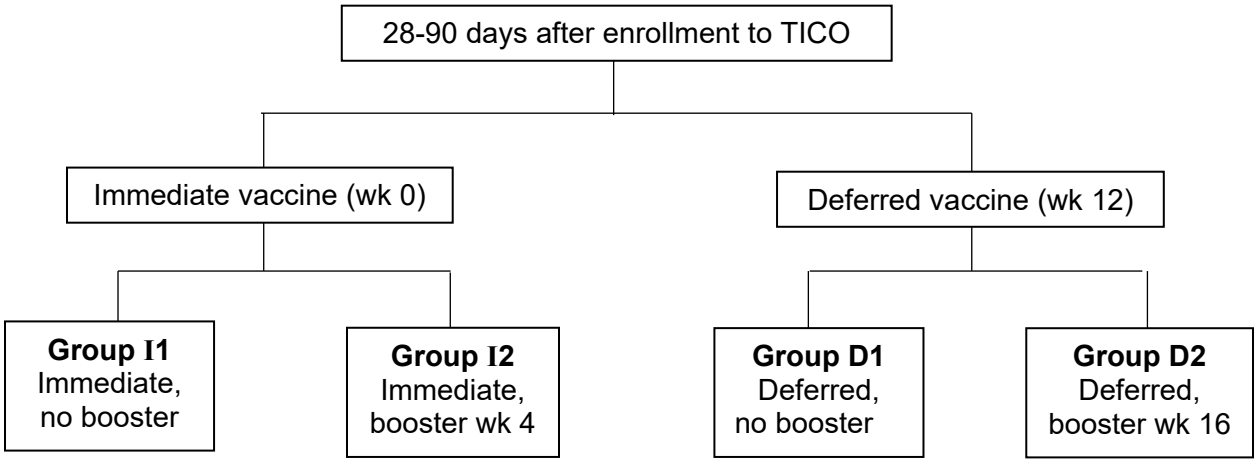

Figure 1. Overview of the randomization outcome.

Randomization will be stratified by study site and by randomization assignment in TICO for certain pre-specified investigational agents or their matching placebo.

When addressing the two co-primary objectives, the following groups are combined:

- Immediate vs deferred vaccine: groups I1 and I2 versus D1 and D2
- One versus two vaccinations: groups I1 and D1 versus I2 and D2

Similar comparisons will be made separately for each of the two principal TICO arms, i.e., for those assigned to one of the investigational agents and for those assigned to the matching placebo. Both of these comparisons are protected by the randomization in the present study. Given the factorial design, whether there is an interaction of one factor (timing of vaccination) with the other factor (number of doses) will need to be assessed although the study is not fully powered for this evaluation.

A key secondary objective is to address whether the investigational agent studied in TICO (versus matching placebo) is affecting the primary outcome in this protocol. Of note, this comparison may not always be protected by randomization, as there may be differential inclusion in this protocol between those receiving the investigational agent in TICO and those receiving its matching placebo. This is more likely to be the case if the investigational agent is demonstrated to affect the chance of achieving sustained recovery.

6.2. Sample Size Assumptions

The primary outcome at 48 weeks will be evaluated using geometric mean ratios (GMRs). Antibody levels will be $\log_{10}$ transformed and summarized with stratified analysis of covariance.

The comparison of each TICO investigational agent and placebo, overall, and for each of the randomized assignments in the 2x2 factorial design for this vaccine study will be descriptive. Among participants assigned to each investigational agent, GMRs (TICO investigational agent

versus placebo) will be estimated and compared to those for participants contemporaneously randomized to placebo.

The following assumptions were made to estimate sample size for the two primary objectives based on the 2x2 factorial design for the TICO placebo group:

- The primary analysis will be intention to treat.
- Participants will be randomized equally to the 4 groups in the 2x2 factorial design (**Figure 1**).
- The analysis for each factor will be pooled over those assigned to the other factor in the 2x2 factorial.
- Data from an outpatient study [4] were used to estimate the mean, standard deviation (SD), and coefficient of variation for $\log_{10}$ transformed NAb levels measured on 62 participants 60-119 days after symptom onset to SARS-CoV-2 infection. These estimates were 2.02, 0.51, and 0.25, respectively.
- Sample size was estimated assuming a type 1 error rate of 0.05 (2-sided) and power=0.80 for a range of geometric means. A constant coefficient of variation was assumed, and Welch's t-test was used assuming unequal variances (see **Table 1** below).

Table 1. *Sample size required to detect various geometric mean ratios with 80%-90% power.*

	Geometric Mean Ratio									
Power	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
90%	6514	1814	892	552	386	292	232	192	164	142
85%	5566	1550	762	472	330	250	198	164	140	122
80%	4866	1356	668	412	290	218	174	144	122	106
Total sample sizes required for various power levels with 5% type I error rate using Welch's t-test (i.e. unequal variances t-test). These calculations assume SD = 0.51 of $\log_{10}$(nAb) in the arm with lower $\log_{10}$(nAb) levels, and a constant coefficient of variation (SD/Mean) of 0.25 leading to greater variability in the arm with higher $\log_{10}$(nAb) levels.										

Based on this table, we are planning to enroll 320 participants from the TICO placebo group; 80 participants will be randomized to each of the 4 groups in the factorial. Sample size was inflated by 10% to account for a small number of participants who do not comply with the outcome of the randomization and for missing primary outcome data at Week 48. This will provide 80% power to detect a 50% difference between the randomized groups described in objectives 1 and 2. Assuming the true GMR is 1.0 and the SD is 0.51, the 95% CI will be 0.77 to 1.29.

We assume an equal number of participants will have been randomly assigned to the TICO

investigational agent and matching placebo. Thus, the total sample size planned is 640 participants.

6.3. Schedule of Assessments

Participants will be enrolled in this protocol at or between the Day 28 and Day 90 visits of the parent TICO protocol; this will be considered Week 0 of this protocol. All participants randomized will be followed through 48 weeks in this protocol for collection of study data (Appendix B and section 9.1 for details).

6.4. Approach to Intercurrent Therapies and Clinical Trial Co-enrollment

There are no restrictions on concurrent medications or other clinical trial participation, except that COVID-19 vaccination is strictly limited to that assigned via this study.

7. Study Population

7.1. Inclusion Criteria

1. Participating in the TICO trial and received a **selected** blinded investigational agent or placebo **for that agent** at selected sites.

NOTE: A list of selected investigational agents will be posted on the INSIGHT website.

2. Willingness to strictly adhere to the randomly allocated dosage number and schedule for vaccine administration.

3. Participant is between Day 28 and Day 90 TICO visits inclusive at the time of randomization.

4. At the time of screening for this protocol, experienced sustained recovery (i.e. the primary endpoint in TICO) for *at least* two consecutive weeks, i.e. having returned uninterrupted to the person's premorbid living facility (or equivalent) for at least 2 consecutive weeks.

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

7.2. Exclusion Criteria

1. Receipt of a SARS-CoV-2 (also known as COVID-19) vaccine after enrollment into TICO. Participants who received a SARS-CoV-2 vaccine prior to enrollment in TICO may be enrolled in this substudy.

2. Known allergy to any component of the study eligible vaccine(s).

7.3. Costs to Participants

There is no cost to participants for the research tests, procedures, and evaluations required by the study. There is currently no cost associated with the vaccine or its administration for locations participating in this trial. Procedures and treatment for clinical care may be billed to the participant, participant's insurance or third party.

8. Study Product

8.1. Regimens, Administration, and Duration

The study regimen is a 100 µg intramuscular injection of the Moderna mRNA-1273 or a 30 µg intramuscular injection of the Pfizer BNT162b2 COVID-19 vaccine given either once or twice (if twice, approximately 4 weeks apart) and either immediately or deferred (for 12 weeks to initial vaccination), according to randomization allocation. The vaccines will be offered either directly through the study or through a reliable mechanism.

8.2. Study Product Formulation and Preparation

The Moderna mRNA-1273 COVID-19 vaccine contains the following ingredients: mRNA, lipids (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

The Pfizer BNT162b2 vaccine contains mRNA, lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-Distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

Storage conditions and preparation for injection of the study-supplied Moderna vaccine is detailed in the pharmacy section of the protocol instruction manual (PIM).

9. Study Assessments and Procedures

9.1. Screening/Baseline and Follow-up Assessments

Data collection at each visit is outlined below (**Figure 2**) and summarized in Appendix B. Time "0" refers to the day randomization to this study occurred. Screening and randomization can be done in the same session. The term "baseline" refers to data that are collected before randomization.

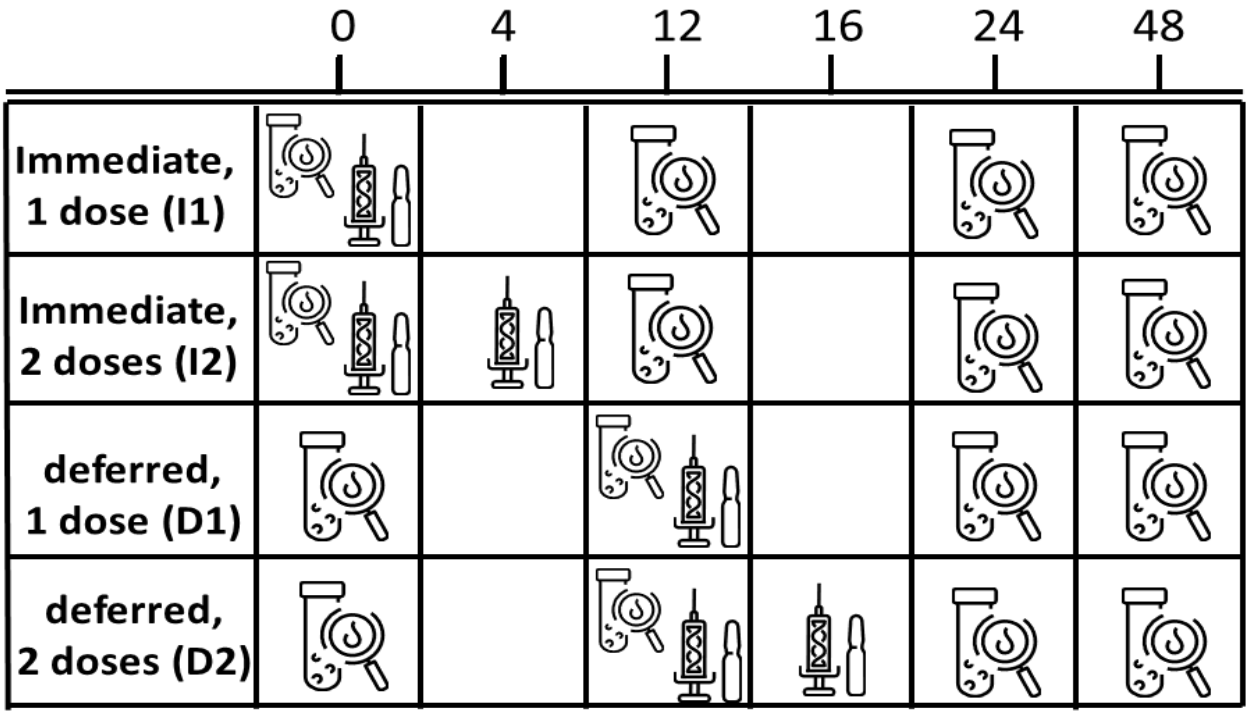

Figure 2. Vaccination and research sample schedule (in Weeks). The four groups (abbreviated as: I1, I2, D1, D2) are further explained in **Figure 1** and in section 6.1. Every 4 weeks from baseline through Week 24, all participants will be contacted either for a face-to-face visit (indicated in figure) or by phone. See Appendix B for schedule.

9.1.1. Screening/Baseline Assessments

After obtaining informed consent (Appendix A), the following assessments are performed within 7 days prior to randomization to confirm eligibility and to collect baseline data. Much of this information is collected in TICO:

- A focused medical history, including the following information:
    - PID for participant in TICO; data collected in TICO pertaining to demographics will be used for this study.
    - Targeted medical conditions.
    - Targeted concomitant medications and any prior SARS-CoV-2 vaccination and/or participation in trials.

- A symptom-directed assessment of current COVID-19 symptoms via interview

- Plasma and serum specimens for central testing for SARS-CoV-2 antibody determination and storage for future related research (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma). Two 9 mL tubes, one SST and one EDTA, of blood (18 mL total) will be drawn in order to obtain the 8 x 1 mL aliquots.

- Contact details (phone, e-mail or other types of contact) for the participant, and with the participant's consent, preferably at least two close relatives/friends, to ensure reliable data collection during follow-up in the trial.

The overall eligibility of the patient for the study will be assessed once all screening information is available. The screening process can be suspended prior to completion of the assessment at any time if exclusions are identified by the study team.

The interval between consent and randomization (up to 7 days), and the interval between randomization and administration of the first vaccine if the randomization indicates this (up to 7 days) intends to create maximal flexibility in scheduling time for research sampling and administration of the vaccine.

In some cases (e.g. if consent has been obtained and eligibility confirmed virtually), it may not be possible to draw blood prior to randomization. In these cases, the blood draw can be done after randomization but before the administration of the vaccination if allocated to receive it immediately. If not allocated to receive vaccination immediately, the blood draw should be done within 7 days of randomization.

Participants will be scheduled to be vaccinated if allocated to group I1 or I2 (**Figure 1**). Vaccination should be administered within 7 days after randomization and always after having drawn blood for research purposes.

Participants will be monitored for at least 15 minutes after vaccination for signs of adverse effects including possible anaphylactic reactions. Participants who experience AEs after the vaccination will be followed closely, and will be treated clinically as indicated, until the resolution or acceptable level of stabilization of the AE. Such events are considered a medically important SAE if any treatment is administered, or if otherwise considered medically important by the investigator.

9.1.2. Follow-up Assessments

Participants will be followed through 48 weeks following randomization for collection of study data (Appendix B). Clinical data will be collected on visits at 12, 24 and 48 weeks of follow-up. These data will include targeted concomitant medications (at the Week 48 visit) and targeted interim changes in medical history, including any SARS-CoV-2 vaccines administered and diagnosis and further characterization of any possible SARS-CoV-2 reinfection (at all three visits).

Timing of the administration of SARS-CoV-2 vaccines during the 48 weeks follow-up period is dictated by the outcome of the randomization. Some flexibility in the timing of the vaccine administration is incorporated into the study scheduling (the week in question plus or minus 1

week). For participants allocated to receive two doses, the same manufacturer's vaccine should be used for both vaccinations. The duration between the two doses of vaccination is 4 weeks plus or minus 1 week. The minimum duration between the two doses of an mRNA vaccine is 21 days.

At each follow-up visit (i.e. after 12, 24 and 48 weeks) plasma and serum specimens will be obtained for central testing for SARS-CoV-2 antibody determination and storage for future related research (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma). Two 9 mL tubes of blood, one each SST and EDTA (18 mL total), will be drawn in order obtain the 8 x 1 mL aliquots. Research visits for participants at their residence or home health and mobile phlebotomy services may be utilized to complete protocol-required data/specimen collection during follow-up. Of note, always draw blood for research purposes *prior to* the administration of any vaccine to be administered at the same visit.

See section 10.2 for details on reporting adverse events.

All participants in this study will be under follow-up in the TICO protocol during the entire follow-up period of this protocol. Participant contacts for data collection will be coordinated between the TICO and VATICO protocols.

9.1.3. Stored Samples and Future Research

The plasma and serum specimens collected as outlined above will be stored at a central specimen repository in the US. In addition to the specified testing to be done per protocol, the specimens will be available for later use in research concerning COVID-19, SARS-CoV-2, and the impact of the study vaccine. Proposed research utilizing these specimens will be reviewed and approved by the study scientific steering committee. Results of research tests on individual specimens will not be given to participants or their clinicians. Aggregate research results will be made available to the public after completion of the study.

10. Safety Assessment

The safety evaluation of the study intervention includes several components, all of which will be regularly reviewed by the independent DSMB. For this protocol, the term "*study intervention*" refers to the vaccination.

Given the
- unprecedented breadth and depth and population diversity represented in the generally reassuring safety profiles of the eligible study vaccine(s),
- coupled with the fact that they will be administered to individuals with no known contraindications who are in all likelihood currently covid immune,
- coupled with the fact that the only significant difference between non-study and study administration is the number of vaccinations,
- coupled with the fact that all subjects will also be under concurrent safety reporting coverage per the gateway study (ACTIV-3/TICO),

this study will take a highly pragmatic 'real world' approach to safety data collection, focusing on events that are related to vaccination, of high grade, and/or serious.

10.1. Definitions

10.1.1. Adverse Event (AE)

An AE is any untoward or unfavorable medical occurrence in a study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with their participation in research, whether or not considered related to the research. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE.

10.1.2. Criteria for Seriousness

Events are serious if they lead to one of the following outcomes:
- Death
- Life-threatening (i.e., an immediate threat to life)
- Hospitalization or prolongation of hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormalities/birth defects
- Other important medical events that may jeopardize the participant and/or may require intervention to prevent one of the outcomes listed above

10.1.3. Unanticipated Problems

Unanticipated Problems (UP) will be reported to the US single IRB, and may additionally be reported to meet the requirements of other IRBs or ethics committees (ECs) with jurisdiction at a particular site.

An UP is generally defined as any incident, experience or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to:

a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure (IB) or other study documents; and

b. the characteristics of the population being studied; and

2. Possibly, probably, or definitely related to participation in the research; and
3. Places study participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

"Greater risk" is generally considered to be a risk that a reasonable research subject would consider to be significantly increased in seriousness, severity, potential outcome, and/or frequency/likelihood, over those known and disclosed in the informed consent document.

Events reported to the sponsor will be assessed as potential UPs. The sponsor will work with stakeholders and oversight bodies and sites to protect the rights and welfare of subjects, and to ensure appropriate reporting.

10.1.4. Severity

The investigator will evaluate all AEs as defined above with respect to both seriousness (results in outcomes as above) and severity (intensity or grade). AEs will be graded for severity according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* (also known at the DAIDS AE Grading Table; see Appendix D for the URL).

For specific events that are not included in the DAIDS AE Grading Table, the generic scale below is to be used:

Grade 1	Events causing no or minimal interference with usual social and functional activities, and NOT raising a concern, and NOT requiring a medical intervention/ therapy.
Grade 2	Events causing greater than minimal interference with usual social and functional activities; some assistance may be needed; no or minimal medical intervention/therapy required.
Grade 3	Events causing inability to perform usual social and functional activities; some assistance usually required; medical intervention/therapy required.
Grade 4	Events causing inability to perform basic self-care functions; medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.
Grade 5	Events resulting in death.

10.1.5. Causality

Causality refers to the likelihood that the event was caused by a study-specific procedure, including administration of a study-specified agent or intervention, whether considered investigational or standard of care. It will be assessed for SAEs and potential UPs. This assessment will be made using the following guidelines:

- Reasonable possibility: There is a clear temporal relationship between the study intervention and the event onset AND either
    - the event is known to occur with the study intervention, or
    - there is a reasonable possibility that the study intervention caused the event.

  Reasonable possibility means that there is **evidence to suggest a causal relationship** between the study intervention and the event.

- No reasonable possibility: There is no evidence suggesting that the study intervention caused the event AND/OR there is no temporal relationship between the study intervention and event onset, AND/OR a reasonable (defined above) alternate etiology has been identified.

The causality assessment is based on information available at the time of the assessment of the event. The investigator and/or the sponsor may revise their assessment as additional information becomes available.

10.1.6. Expectedness

For this strategy trial, expectedness will be assessed for vaccine-related SAEs using the most current "Observed Adverse Reactions/Overall Safety Summary" event list from the US Emergency Use Authorization (EUA) documents for both the Moderna and the Pfizer mRNA vaccines. A link to this list will be maintained on the INSIGHT website.

The expectedness assessment is based on information available at the time of the assessment of the event. The investigator and/or the sponsor may revise this assessment as additional information becomes available.

10.2. Schedule for Reporting of Specific Events

This section describes the schedule for reporting different types of safety outcomes via electronic case report forms (eCRFs) as part of the protocol data collection plan. It is recognized that in the care of study participants, more information may be collected and recorded in the participant's medical record. The information collected in the medical record serves as source documentation of events (e.g., signs, symptoms, diagnoses) considered for reporting on eCRFs as part of protocol data collection.

10.2.1. Reportable Grade 3 and 4 Clinical Adverse Events

Clinical adverse events of Grade 3 or 4 severity that occur between randomization and Week 12 visit (for groups I1 and I2) and between the visits at Weeks 12 to 24 (for groups D1 and D2), will be recorded and will be reported on an eCRF at the Weeks 12 or Week 24 visit, respectively.

The estimated date the event reached the indicated grade will be collected.

All AEs should be assessed for SAE/UP (sections 10.2.2 and 10.2.3) reporting, which will be via the SAE eCRF in addition to the AE eCRF.

10.2.2. Reportable SAEs

Reportable SAEs in this study are any adverse events that are considered serious, including isolated laboratory abnormalities considered serious, *irrespective of perceived relationship* to the SARS-CoV-2 vaccination. SAEs that occur from the time of randomization in the 2x2 factorial design (i.e., for any of the four treatment groups) through 24 weeks must be recorded by sites on the SAE eCRF and submitted to the database within 3 days of site awareness, **unless earlier reporting is required by applicable regulations**. SAEs considered related to the study vaccine must be reported **within 24 hours of site awareness**.

Suspected unexpected serious adverse reactions (SUSARs) are reportable SAEs that are assessed as having a reasonable possibility of being caused by a study intervention and are unexpected per the Reference Safety Information of the IB (or label) for that intervention. SUSARs are evaluated per applicable regulatory guidance, and will be reported from the INSIGHT Safety Office to regulatory and oversight bodies (e.g. DSMB, FDA, EMA, IRB, etc.) as required, within the shortest of all applicable timelines. If more than one regulatory platform applies (e.g. international studies with oversight by more than one regulatory authority), the more conservative reporting requirements will apply.

The INSIGHT Safety Office will generate a Safety Report for each SUSAR for distribution to investigators and other parties.

- The sponsor will report SUSARs to the US single IRB on behalf of US sites.
- Investigators are responsible for submitting Safety Reports to other overseeing IRB/EC per that bodies requirements.

SAEs are followed until the outcome of the SAE is known. If the outcome of an SAE is still unknown at the time of the final follow-up visit, the outcome will be entered in the database as “unknown.”

10.2.3. Unanticipated Problems (UPs)

Suspected UPs must be reported via the appropriate eCRF to the INSIGHT Safety Office no later than 7 calendar days after site awareness of the event. The sponsor will evaluate UP submissions for reportability per applicable regulations, agreements, and guidelines. The sponsor will report UPs to the US single IRB on behalf of US sites. Investigators are responsible for submitting UPs that are received from the sponsor to their overseeing IRB/EC per that entity’s requirements.

10.2.4. Deaths

All deaths are reported on the eCRF for deaths **through the parent TICO protocol**. Deaths considered **related to the study intervention** (vaccine) must **also** be reported on the VATICO SAE eCRF.

10.2.5. Pregnancy

Pregnant women may enroll in this study. Pregnancy outcomes will be reported through the parent TICO protocol.

10.3. Medical Monitor

A Medical Monitor appointed by the sponsor will be responsible for reviewing all SAEs and UPs, making an independent assessment of causality and expectedness, assessing reportability per the protocol and applicable regulations and guidance, preparing sponsor safety reports, and communicating as needed with the DSMB through the study safety office or other mechanism mutually agreed to and documented.

10.4. Halting Enrollment for Safety Reasons

The sponsor Medical Monitor or the DSMB may request that enrollment be halted for safety reasons (e.g., unacceptably high rate of unanticipated AEs). If the study is temporarily halted or stopped for safety reasons, IRBs/ethics committees (ECs) will be informed. The sponsor, in collaboration with the protocol chair and the DSMB, will determine if it is safe to resume the study. The sponsor will notify the site investigators of this decision. The conditions for resumption of the study will be defined in this notification. The site investigators will notify their local IRBs/ECs of the decision to resume the study.

11. Statistical Analyses and Monitoring Guidelines

11.1. Analysis of Baseline Characteristics

Baseline characteristics of the four randomized groups in the 2x2 factorial trial will be summarized with summary statistics, including means (standard deviations), medians (25^{th}, 75^{th} percentiles), and percentages. Descriptive summaries of baseline characteristics will be carried out separately for those assigned an investigational agent in TICO and those assigned placebo. Characteristics summarized will include baseline factors collected prior to randomization in TICO as well as follow-up data collected in TICO prior to randomization to the 2x2 factorial in VATICO.

11.2. Analysis of the Primary Efficacy Endpoint

We anticipate that a small number of participants enrolling into TICO have received vaccines against SARS-CoV-2 infection prior to their COVID-19 illness. These patients are still eligible for enrollment into VATICO but the primary analysis will exclude these participants. These participants will be separately analyzed, and subgroup analyses based on prior vaccination at the time of enrollment in TICO will be carried out.

Antibody levels at baseline and at Weeks 12, 24, and 48 will be summarized with box plots by treatment group.

For the comparison of antibody levels at Week 48 (the primary endpoint) for the TICO placebo group, levels will be $\log_{10}$ transformed and summarized with stratified analysis of covariance. The antibody level prior to randomization will be included as a covariate. Stratification will be according to the factor of the factorial which is not the focus of the analysis. The $\log_{10}$ transformation will be undertaken as is conventional for NAb measurements (as the distribution of log responses is generally closer to a normal distribution), and then the estimates and confidence intervals will be anti-logged to provide estimates and confidence intervals for the ratio of GMRs.

For example, the comparison of the early and deferred vaccination groups will be carried out with stratification by randomization to 1 or 2 doses, with baseline $\log_{10}$ antibody level as a covariate. The comparison of the 1 versus 2 doses will be carried out with stratification by randomization to immediate/deferred vaccination, with baseline $\log_{10}$ antibody level as a covariate. An interaction test will be carried out between the two factors being studied, immediate/deferral and 1 or 2 doses.

A GMR of one indicates that there is no difference between treatment groups in NAb response, for example, among participants who were randomized to immediate compared with those randomized to deferred vaccination. A GMR less than 1.0 provides indication of lower NAb response among those who received immediate compared to those who received vaccination deferred.

The percentage of participants with a 4-fold increase in antibody levels from baseline will be summarized for each of the randomized comparisons in the 2x2 factorial using Mantel-Haenszel chi-square statistics.

These analyses will be repeated for participants randomized to a particular agent in TICO, and the TICO active and placebo groups will be compared using the methods described above. These

analyses will be adjusted for duration of time since infection at the time of randomization to the 2x2 factorial.

11.3. Analyses of Other Endpoints and Subgroups

Mantel-Haenszel chi-square statistics will be used to compare the composite safety outcome of grade 3 or 4 AE, SAE, or death for the one versus two dose strategy separately for the immediate and deferred groups, as well as pooled over these groups. Similar methods will be used for the composite endpoint of SAE or death through Week 24, which will be compared for the one vs two dose strategies as well as for the immediate vs deferred strategies.

Mantel-Haenszel chi-square statistics will also be used to summarize non-adherence to the assigned vaccination schedule.

Subgroup analyses for each primary objective and the comparisons of TICO active and placebo groups will be performed using regression analysis.

A number of additional subgroup analyses are planned for each treatment comparison, taking advantage of the data collected at baseline and during follow-up on TICO. In addition to subgroups according to the other factor in the factorial design and the randomization assignment in TICO, prior vaccination at entry to TICO, subgroups according to age, gender, race/ethnicity, geographic region, duration of infection at time of randomization, severity of infection as measured by the highest ordinal category experienced and time to sustained recovery, baseline antigen and antibody level in TICO, manufacturer of vaccine (Moderna or Pfizer), and baseline antibody level at the time of randomization to VATICO will be carried out. These analyses will be performed by including an interaction term with treatment in the regression model.

11.4. Data Monitoring by the Protocol Team

The trial will be conducted under the direction of the VATICO (INSIGHT 016) protocol team. The protocol will be blinded to summaries of interim antibody levels and AE differences by treatment group. The protocol team will monitor adherence to the randomized assignments.

11.5. Data Monitoring Guidelines for an Independent DSMB

An independent DSMB will review interim analyses on safety outcomes at regular intervals during follow-up. The primary focus of the DSMB will be on differences in safety outcomes among the four randomized groups in VATICO and between the TICO investigational agent and placebo groups.

Antibody levels will likely be measured at the end of the trial and hence not available for evaluation as the trial progresses.

12. Protection of Human Subjects and Other Ethical Considerations

12.1. Participating Clinical Sites and Local Review of Protocol and Informed Consent

This study will be conducted by major medical centers participating in INSIGHT and partnering networks. It is anticipated that potential participants will be recruited by the site investigators (and/or their delegates, as appropriate). Information about this study will be disseminated to health care providers at enrolling sites.

Prior to the initiation of the study at each clinical research site (CRS), the protocol, informed consent form and any participant information materials will be submitted to and approved by a central/national IRB/EC and/or the site's local IRB/EC as required. Likewise, any future amendments to the study protocol will be submitted and approved by the same IRB(s) or EC(s). After IRB/EC approval, sites must register for this study before screening potential participants, and must register for any protocol amendments. Protocol registration procedures are described in the PIM.

12.2. Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, European Union (EU) Clinical Trials Directive (2001/20/EC), and EU GCP Directive (2005/28/EC); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines; Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greater protection of human subjects.

12.3. Informed Consent of Study Participants

Informed consent (see sample in Appendix A) must be obtained prior to conducting any study-related procedures. Given the population of the parent TICO study, some individuals maylack capacity to provide legally effective consent. While such individuals will NOT be targeted, informed consent may be obtained from a legally authorized representative (LAR).

Capacity will be assessed according to local standards and policies. Local standards and policies will also determine who is legally authorized to consent for an individual who lacks capacity. Should the individual regain capacity during the study, their direct consent should be obtained at the earliest opportunity.

Electronic consent may be used when a validated and secure electronic system is in place to do so, if in compliance with national legislation and approved by the local IRB/EC. No matter how the participant's consent is obtained and documented, it is expected that consent will be preceded by research staff providing an explanation of the research and an opportunity for the participant (or their LAR) to have questions answered. Sites should follow all available local or national guidance on suitable methods for obtaining documentation of participant (or their LAR) consent.

12.4. Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP guidelines and national regulations.

12.5. Regulatory Oversight

The protocol will follow the monitoring plan of the TICO protocol.

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Appendix A Sample Informed Consent form

Short Title: Vaccination for Recovered Inpatients with COVID-19 (VATICO)

Sponsored by: The University of Minnesota (UMN)

Funded by: The National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH)

Full Title of the Study: SARS-CoV-2 Vaccination Strategies in Previously Hospitalized and Recovered COVID-19 Patients

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ PHONE: _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR PARTICIPANTS

US Office for Human Research Protections (OHRP) Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER OR COLLABORATING NETWORK. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

Key information:

You are being asked to take part in this research study because you were treated with investigational therapy or placebo in the ACTIV-3/TICO research study and have not yet had a COVID-19 vaccination. We are trying to find out the best time to give COVID-19

vaccine to people who have already had COVID-19. We are also trying to find out the best number of shots to give after you recover from COVID-19. It is your choice whether or not you want to join. This form gives you information about the study that will help you make your choice. You can discuss this information with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting.

WHY IS THIS STUDY BEING DONE?

New vaccines are being developed for the virus that causes COVID-19. Some of the vaccines have received Emergency Use Authorization from the US Food and Drug Administration (FDA). This means the FDA has given permission for them to be used even though they have not completed the full FDA approval process. Studies of these vaccines are still going on, and there are some scientific and medical questions that have not yet been answered. For example:

- we do not know how well a person's immune system responds to a COVID-19 vaccine if they have had SARS-CoV-2 infection, and
- we do not know how a person's immune system responds to vaccination after being treated for COVID-19.

This study is for people who had COVID-19 and received the study treatment or placebo as part of the ACTIV-3/TICO study. This study is looking at how the immune system responds to one type of COVID-19 vaccine called an mRNA vaccine. The vaccines made by Moderna and Pfizer, for example, are mRNA vaccines. You might respond more or less strongly to the vaccine because you've had COVID-19. There may be no change.

We will be trying different vaccine schedules to find out if a person's response to the vaccine changes due to when the vaccine is given or the number of doses given. We think that the immunity you get from having COVID-19 might be like getting one dose of

vaccine. If that is so, then getting just one more shot would be like getting a "booster" shot. You might have the same response as someone who never had COVID-19 and gets 2 doses of vaccine.

At least one study has shown that it might be better to wait longer between vaccine doses than the usual 3 to 6 weeks. If your COVID-19 infection is like a first vaccine dose, we want to see if your immune response to the shot is stronger if you wait longer to get vaccinated. We do not know if this is what will happen.

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

The study staff following you in TICO will check to see if there is any reason you should not be in the study. They will check your medical history, including whether you have already been vaccinated. If you have already been vaccinated, you cannot be in this study.

Everyone in this study will be scheduled to get an available mRNA vaccine to help prevent another SARS-CoV-2 (COVID-19) infection. We are studying whether you should get the vaccine right away or about 12 weeks from now. We are also studying whether you should get one or two doses of the vaccine. If you join the study, you will be assigned by random chance – like rolling dice – to one of 4 groups:

1. You will be scheduled to get ONLY one dose, given as soon as you can and no later than 14 days from now.
2. You will be scheduled to get a dose right away AND to get a 2nd dose about 4 weeks from your first dose.
3. You will be scheduled to get ONLY one dose. This will be given to you about 12 weeks from now.
4. You will be scheduled to get a first dose in about 12 weeks from now AND a 2nd dose about 4 weeks after that.

You will have an equal chance of being in each of the above 4 groups.

You will get the vaccine as a shot in your upper arm. You will have to stay at the site where you get the vaccine for at least 15 minutes after you get the vaccine. This is to make sure you are not having any side effects right away from the vaccine that need medical care . You may need to stay longer if you have any side effects that need attention.

In addition to getting the vaccine you will have 4 in-person study visits. These will happen just after you are randomized in the study, and 12, 24 and 48 weeks after that. The study staff will also contact you every 4 weeks for the first 24 weeks to see how you are feeling. A member of the study staff will give you your exact schedule.

At the in-person visits, you will have some blood taken from a vein in your arm, using a needle. We will use the blood to test how your immune system responded to your previous COVID-19 infection and treatment. We will test your immune system's response to the study vaccine. We will also store some of this blood for future studies to learn more about COVID-19, the virus that causes it, and the vaccine.

We will also use your information and samples from ACTIV-3/TICO for this study

At the 4-week contacts, we will ask you about your health and any medications you are taking or have taken since the last time we contacted you. After your vaccination, we will also ask about any symptoms or side effects you may be having.

We will not use identifiers like your name or birthdate on your samples or on any private information that we collect about you. This means that no one looking at the labels on your samples or at other information will be able to know that the samples or information came from you. We will keep a locked-up secure list of the code numbers used on your study samples and forms, so that we can notify you if there are any issues or concerns.

The tests and blood storage 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.

HOW MANY PEOPLE WILL BE IN THIS STUDY?

About 640 people from the ACTIV-3/TICO study will be in this vaccine study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for 48 weeks.

WHAT ARE THE RISKS OF THE STUDY?

As with any vaccine, the vaccine used in this study may have side effects. Some of these are listed below.

We do not know if getting a COVID-19 vaccine is more or less effective in people who have already had COVID-19. We do not know if it is more or less effective in people who were treated with study medicines like those in TICO. You should keep following the most current public heath advice where you live, on things like physical distancing and wearing a mask to keep yourself and others safe until your doctor or health authorities advise that you no longer need to do this.

Risks of mRNA vaccines

These side effects are common after a vaccine against any disease. They have been seen with the mRNA vaccines made by Moderna and Pfizer:

- Reactions where you get the shot: pain, swelling (hardness), and redness in the arm where you got the shot, tenderness and swelling of the lymph nodes in the same arm.
- General side effects: tiredness, headache, muscle aches, joint pain, chills, nausea and vomiting, and fever.

These side effects usually happen 12-24 hours after the vaccination. They usually go away on their own in a few days.

Any vaccine can cause an allergic reaction. This chance is very small. However, **severe allergic reactions can cause death if not treated.** A severe allergic reaction would usually occur within a few minutes after getting the vaccine. This is why we ask you to stay at the place where you get your vaccine for at least 15 minutes after your shot.

You should not get an mRNA COVID-19 vaccine if you:

- had a severe allergic reaction after a previous dose of this type of vaccine
- had a severe allergic reaction to any ingredient of the vaccine

You might have other serious or unexpected side effects. The place where you get your vaccine will be ready to treat you for side effects if needed.

Risks of having blood taken

You might have some slight pain, bleeding, bruising, and/or swelling where the needle goes into your body. In rare cases you might faint. There is a small risk you could get an infection.

[The following risks may differ substantially from one locality to another, and may change over time as policies shift with the pandemic. Please modify or remove as appropriate for your local situation.]

Risk of not being considered “fully vaccinated”

If you are assigned to get only one dose of the vaccine, you might not be considered “fully vaccinated” by your public health authorities. This may cause problems for you if your work requires you to be vaccinated. You may not be able to travel to places that require all visitors to be “fully” vaccinated. You might have to wear a mask in places that you would not have to if you had gotten two doses of vaccine. These restrictions are likely to become less over time.

Risks to privacy

As part of this study, we will collect health information about you. We will keep this information secure, but there is a slight risk that someone who should not see this information will see it.

ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING?

Pregnancy

We do not have any information about using mRNA vaccines in people who are pregnant or breastfeeding. However, the American College of Obstetrics and Gynecology (ACOG) recommends that pregnant and breastfeeding people should have the chance to be vaccinated. This is because ACOG considers pregnant women at higher risk of getting very sick or dying from COVID-19. Therefore, you can still be in the study if you are pregnant or breastfeeding.

The vaccine may have risks to you (or to the embryo or fetus), if you or your partner (if you are male) become pregnant, which we do not know about at this time.

If at any point during the study you think you may be pregnant, you should let the staff at your site know so they can do a pregnancy test. If you get pregnant during the study, you can stay in the study and still get the vaccine

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

We cannot promise you will have any direct benefit from being in this study. Getting vaccinated might help you. However, since COVID-19 vaccines are available in the community, you can still get a vaccine even if you do not join this study.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- getting a COVID-19 vaccine from your healthcare provider
- getting an experimental COVID-19 vaccine, if you qualify for a study testing such a vaccine
- not getting vaccinated

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

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the research tests, procedures, evaluations, and vaccinations done as part of this trial.

[The next paragraph is for US sites only. Sites in other countries should delete the next paragraph and replace it with the language appropriate for your location.]

You, your insurance company, or some other third-party payer must pay for all other medicines and health care costs.

WHAT IF YOU ARE HURT AS PART OF THIS STUDY?

If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment.

The study cannot pay you or pay for any care for study-related injuries or for your illness.

[If the above is not true for your site, i.e., if trial insurance covers such cost, please replace the above with appropriate language.]

[The following section, up to "How do we protect your privacy?", is for US sites only.]

A Declaration under the Public Readiness and Emergency Preparedness (PREP) Act was issued by the Secretary of the United States Department of Health and Human Services on March 10, 2020. This Declaration limits the legal rights of a subject participating in clinical studies utilizing COVID-19 countermeasures. Because this study is covered by the Prep Act Declaration, covered persons, such as the manufacturers, study sponsor, researchers, healthcare providers and others have liability immunity (that is, they cannot be sued by you or your family under the laws of the United States).

If you believe that you may have been harmed as a result of this research study, certain claims for serious injury or death caused by the countermeasure may be eligible for compensation through the Countermeasures Injury Compensation Program. This is a program set up by the United States Government.

Information about this program can be found at https://www.hrsa.gov/cicp/about/index.html or by calling 1-855-266-2427. If you are eligible for this program, you must file a claim within one year of the administration or use of the covered countermeasure.

HOW DO WE PROTECT YOUR PRIVACY?

We will take every reasonable step to keep your health information private and to keep anyone from misusing it.

Your information (data) and samples will not be identified by name, or in any other way, in anything published about this study.

We will do everything we can to keep your personal information private, but we cannot guarantee that nobody will get it. We may have to release your personal information if required by law.

These people may see your medical and research information:

- the *[insert the name of the hospital/clinic]* ethics committee (institutional review board [IRB]);
- the sponsor, the group paying for the research (US NIH), other study research staff and study monitors
- US and other participating countries' health regulatory agencies

They are committed to protecting your privacy.

As the research staff at *[inset the name of the hospital/clinic]*, we must make sure that people not involved with this study cannot see your research and medical information. We will keep your research files in a safe place and will handle your personal information very carefully.

[Note for US sites: The following brief HIPAA authorization is provided. Your site-specific consent should be modified to reflect the HIPAA authorization language requirements at your site.]

To do this research, we will collect and use your personal data, as described above and in any HIPAA Authorization Form we have given you. It is your choice whether you allow us to collect and use your data. However, you will not be able to be in this study if we cannot collect and use your data. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

____**Yes**, I agree to the collection and processing of my personal data.

____**No**, I do not agree to the collection and processing of my personal data.

[The following section ("What are my rights regarding my data?") is for countries subject to the GDPR or similar legislation requiring this information. It should only be included in consents for sites subject to such legislation.]

WHAT ARE MY RIGHTS REGARDING MY DATA?

The UMN is a public research university, and this study is paid for mostly by the US Federal government. The sponsor (UMN) must follow regulations and policies that are meant to protect your privacy. UMN must comply with the General Data Protection Regulation (GDPR), because it handles data from people in Europe.

There is no specific independent supervisory authority overseeing the use of data in the US. Any complaint you might have about the use of your data would be made to your national data protection authority.

Your rights under the GDPR regarding your data were described to you when you joined the TICO study. They also apply to this study. You can ask the study staff to go over these rights again if you would like.

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. We will not give you your individual results from tests done as

part of this research. If we do a pregnancy test for you during the study, we will give you the test result.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

If you ever have questions about this study, or about the storage or use of your data or samples, or if you are hurt by being in the study, contact:

- *[name of the investigator or other study staff]*
- *[telephone number of the above]*

If you have questions about your rights as a research participant, you can call:

- *[name or title of person on the ethics committee (IRB) or other organization appropriate for the site]*
- *[telephone number of the above]*

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE VATICO STUDY

I have read this consent or have had it explained to me. I have had a chance to learn about the vaccine I will get. I believe that I understand the information. By signing and dating this consent, I am stating that I volunteer to join this study. I agree to have my data sent to and used by the sponsor as described in this consent. I understand that I do not give up any of my legal rights as a study participant by signing this consent. I understand that I will get a copy of this signed and dated consent.

If you agree to be in this study, please sign **and date** below.

_____ Date: _____
Signature of participant

_____
Printed name of participant

_____ Date: _____
Signature of investigator/designee

_____
Printed name of investigator/designee

FOR ADULTS NOT CAPABLE of GIVING CONSENT

_____ Date: _____
Signature of Legally Authorized Representative (LAR)

_____
Printed name of LAR

_____
Relationship of LAR to Participant
(Indicate why the LAR is authorized to act as a surrogate health care decision-maker under state or applicable local law)

Witness to Consent Interview (if applicable)
On the date given next to my signature, I witnessed the consent interview for the research study named above in this document. I attest that the information in this consent form was explained to the participant, and the participant indicated that his/her questions and concerns were adequately addressed.

_____ Date: _____
Signature of witness

_____
Printed name of witness

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy of the signed and dated consent must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

If no-touch / electronic consent is used, the participant must be provided with a copy of the consent in a manner appropriate to the method used to obtain it. A record of the act of consent must also be appropriately retained in the participant's medical record.

Appendix B Overview of Study Procedures

	Screen or Day 0 [1]	Day 0 [1]	Visits in weeks after time of randomization (visits in grey are for vaccination of groups I2 and D2, respectively)				
Day or Week ± window	**-7/0**	**0 ± 7**	**4 ± 1 [2]**	**12 ± 2**	**16 ± 1 [2]**	**24 ± 2**	**48 ± 2**
ELIGIBILITY & BASELINE DATA							
Informed consent	X						
Targeted medical history (incl. status of COVID-19)		X					
Selected baseline medications		X					
Symptom-directed interview by the clinical team	X						
VACCINATION							
Randomization		X					
Vaccination administration (consult randomization for administration schedule) [2,3]		Gps I-1 & I-2	Gp I-2	Gps D-1 & D-2	Gp D-2		
STUDY PROCEDURES							
Interim targeted medical history [4]				X		X	
SARS-CoV-2 vaccination history [5]				X		X	
Clinical AEs reaching grade 3 or 4 severity through week 8 and from week 12 through week 20				Since day 0 visit for Gps I-1 & I-2		Since wk 12 visit for Gps D-1 & D-2	
SAEs and UPs through week 24		X	X				

	Screen or Day 0 [1]	Day 0 [1]	Visits in weeks after time of randomization (visits in grey are for vaccination of groups I2 and D2, respectively)				
Day or Week ± window	**-7/0**	**0 ± 7**	**4 ± 1 [2]**	**12 ± 2**	**16 ± 1 [2]**	**24 ± 2**	**48 ± 2**
Research sample storage (plasma and serum)		X [6]		X [6]		X	X
Death	Report as they occur into TICO parent protocol reporting system						

[1] Screening must be performed within 7 days prior to randomization. Vaccination must be performed within 7 days of randomization. Hence, maximal time is 14 days from time of obtaining informed consent to vaccination if allocated to groups I1 and I2.

[2] Week 4 and 16 visit is for administration of vaccination should the randomization allocation indicate that this is relevant; i.e. for groups I2 and D2, respectively.

[3] Randomization will determine the timing of the administration of vaccination. The possible random allocations are group: ***I-1*** at day 0 only; ***I-2*** at day 0 and week 4; ***D-1*** at week 12 only; ***D-2*** at week 12 and 16.

[4] Focused interview pertaining to history of diagnosis of SARS-CoV-2 infection (i.e. a positive diagnostic test), and if yes, COVID-19 symptoms and severity and viral genetic sequences if available thereof since last visit, death and hospital admissions through visit at Week 48, any SAE or UPs through visit at Week 24, and any grade 3 or 4 AE through visit at week 12 for group I1 and I2, and Week 24 for groups D1 and D2

[5] Report into the TICO parent protocol reporting system using the form “SARS-CoV-2 Vaccination During Follow-up”.

[6] Research samples should be collected *prior to* the administration of the vaccine scheduled to be administered at the same visit (based on outcome of randomization).

Appendix C INSIGHT 016 protocol team

To oversee the implementation of this protocol, a protocol team will be formed and include:

- Protocol co-chair(s)
- NIAID, Division of Clinical Research representatives
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center (ICC) representatives
- Representatives from collaborating trials networks
- Representative from ACTIV-2 protocol team
- Representatives from collaborating laboratory representatives
- Representatives from site investigators
- Study biostatisticians
- Community representative(s)

A core team consisting of the co-chair(s), ICC leaders, NIAID representatives, study statisticians, representatives from collaborating trials networks, and other representatives and the INSIGHT PI will also regularly convene to review study progress and address study conduct and administrative issues that arise.

Appendix D References on the INSIGHT Website

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the INSIGHT 016 protocol and to other information pertinent to the study:

- DAIDS toxicity table (https://rsc.niaid.nih.gov/clinical-research-sites/daidsadverse-event-grading-tables)
- INSIGHT Publications & Presentations Policy (http://insight.ccbr.umn.edu/resources/P&P_policy.pdf)
- WHO vaccination overview (https://www.who.int/news-room/q-a-detail/vaccines-and-immunization-what-is-vaccination?adgroupsurvey={adgroupsurvey}&gclid=Cj0KCQjwo-aCBhC-ARIsAAkNQivrsnToGg_NJFxW_gI10tzzuRb0jotDJOEgFd7aRTtZjyKfkLqY8NUaAl_AEALw_wcB)
- US CDC Advisory Committee on Immunization Practices (ACIP) recommendations (https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html)
- ESCMID COVID-19 resource centre (https://www.escmid.org/research_projects/covid_19_resource_centre/)
- US FDA regulatory evaluation of COVID-19 vaccines (https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines)
- EMA regulatory evaluation of COVID-19 vaccines (https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19)