A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19

Short Title: Therapeutics for Inpatients with COVID-19 (TICO)

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1 Protocol Summary

DESIGN

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 directly enhancing viral control in order to limit disease progression.

Trials within this protocol will be adaptive, randomized, blinded and initially placebo-controlled. Participants will receive standard of care (SOC) treatment as part of this protocol.

The international trials within this protocol will be conducted in several hundred clinical sites. Participating sites are affiliated with networks funded by the United States National Institutes of Health (NIH) and the US Department of Veterans Affairs.

The protocol is for a phase III 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 will be randomly allocated across agents (as well as between the agent and its placebo) so the same control group will be used, when feasible. Randomization will be stratified by study site pharmacy and disease severity. There are 2 disease severity strata, defined as below:

Disease severity stratum 1: Absence of all of the following: stroke, meningitis encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, symptomatic congestive heart failure (NYHA class III or IV), arterial or deep venous thrombosis or pulmonary embolism, requirement for invasive mechanical ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new renal replacement therapy.

Disease severity stratum 2: Presence of at least one of the excluded conditions or treatments in disease severity stratum 1.

The primary endpoint is the time from randomization to sustained recovery, defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days prior to Day 90. The definition of home will be operationalized as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

An independent Data and Safety Monitoring Board (DSMB) will regularly review interim analyses that summarize safety and efficacy outcomes. For agents with minimal pre-existing safety knowledge, the pace of enrollment will be initially restricted and there will be an early review of safety data by the DSMB. For the study of all agents, at the outset of the trial, only participants in disease severity stratum 1 will be enrolled. This more restricted enrollment will continue until approximately 300 participants are enrolled and followed for 5 days. The exact number will vary according to the speed of enrollment and the timing of DSMB meetings. Prior to expanding enrollment to also include

patients in disease severity stratum 2 safety will be evaluated and a pre-specified futility assessment by the DSMB will be carried out using 2 ordinal outcomes (see below) assessed at Day 5. The first ordinal outcome is a 7-category outcome largely based on oxygen requirements. The highest (worst) category that applies on Day 5 will be assigned. This outcome is referred to as the "pulmonary" ordinal outcome, with categories described below:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
5. Non-invasive ventilation or high-flow oxygen
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
7. Death

The second ordinal outcome, also assessed at Day 5, captures the range of organ dysfunction that may be associated with progression of Coronavirus-Induced Disease 2019 (COVID-19), such as stroke and other coagulation-related complications. Again, the highest category that applies on day 5 will be assigned. Use of this outcome allows further characterization of the extra-pulmonary manifestations of COVID-19 and the capacity to identify agents that improve those extra-pulmonary manifestations. This outcome is referred to as the "pulmonary+" ordinal outcome.

The 7 categories of the pulmonary+ ordinal outcome assessed at Day 5 are:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset congestive heart failure (CHF) NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events.
5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14)

6. Invasive ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new receipt of renal replacement therapy
7. Death

Both ordinal outcomes are used to assess futility because it is currently unclear whether the investigational agents under study will primarily influence non-pulmonary outcomes, for which risk is increased with SARS-CoV-2 infection, in part, through mechanisms that may be different from those that influence pulmonary outcomes.

For investigational agents passing this futility assessment, enrollment of participants will be expanded, seamlessly and without any data unblinding, to include participants in disease severity stratum 2 as well as those in disease severity stratum 1. Future interim analyses will be based on the primary endpoint of sustained recovery and will use pre-specified guidelines to determine early evidence of benefit, harm or futility for the investigational agent.

DURATION

Participants will be followed for 18 months following randomization. Primary and most secondary outcomes will be collected during the first 90 days of follow-up only. Follow-up beyond 90 days is planned because the half-lives of some agents indicate that potentially meaningful amounts may remain in the body after 90 days of follow-up. During the follow-up between 90 days and 18 months hospitalizations and deaths will be ascertained.

SAMPLE SIZE

This phase III trial is planned to provide 90% power to detect a 25% increase in the rate of sustained recovery for an investigational agent compared to placebo at the 0.025, 1-sided level of significance. This requires 843 primary events (i.e., participants who achieve sustained recovery). Randomization of 1,000 participants, equally allocated to each investigational agent and placebo, followed for 90 days is estimated to result in the required number of primary events. The event target may be achieved earlier if more than 1,000 participants are enrolled. Sample size will be evaluated periodically by study team members who are blinded to interim results and may be increased to maintain power for the hypothesized difference in sustained recovery between the investigational agent and placebo.

POPULATION

The study population consists of inpatient adults (≥18 years) who have had COVID-19 symptoms ≤ 12 days. Initially, approximately 300 participants in disease severity stratum 1 will be enrolled. Afterwards, based on the review by the DSMB of safety and futility, eligibility for randomization will be expanded to also include patients in disease severity stratum 2.

STRATIFICATION

Randomization will be stratified by study site pharmacy and also by disease severity stratum.

REGIMEN

Investigational agents suitable for testing in the inpatient setting will be prioritized based on in vitro data demonstrating activity against SARS CoV-2 entry or replication, preclinical data, phase I pharmacokinetic and safety data, and clinical data from other ongoing trials. The protocol will initially focus on agents for which there is a hypothesized benefit from passive immunization including use of neutralizing monoclonal antibodies.

MONITORING

An independent DSMB will review interim data on a regular basis and use pre-specified guidelines to identify agents with clear evidence of efficacy for the primary outcome, and if so recommend unblinding of the trial results for that agent. Conversely, the DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits or if futility assessments indicate that there is low probability that an investigational agent will achieve statistical significance for the primary endpoint of sustained recovery.

For an investigational agent, if the trial is stopped early or if the trial continues until the pre-specified number of primary endpoints is reached, further enrollment of the investigational agent will be terminated if applicable, and the trial data for the investigational agent will be unblinded and reported with data through 90 days of follow-up. Follow-up of all participants will continue through 18 months using the data collection plan described in this master protocol.

A risk-based protocol monitoring plan will be developed to ensure participant safety, data integrity, and regulatory compliance during the conduct of the trial.

2 Introduction

2.1 Study rationale

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2). While most cases are mild or asymptomatic, progressive disease can result in hospitalization, requirement for mechanical ventilation, and substantial morbidity and mortality.[1] While the most common mode of disease progression is progressive respiratory failure following the development of pneumonia, other severe complications including thrombosis and ischemia are increasingly recognized.[2,3]

Several clinical trials utilizing novel drugs and repurposing older agents have been implemented to investigate the treatment of adults hospitalized with severe COVID-19 (see section 2.2.7). Standard-of-care is hence rapidly evolving (see Appendix I for current recommendations).

Our understanding of the humoral immune response is evolving, with some evidence that responses are variable between individuals and delayed in some cases.[4] It may therefore be that viral replication leads to extensive tissue damage and inflammatory responses in the lungs and other organs before the development of neutralizing antibodies. Augmentation of the humoral immune response to SARS-CoV-2 infection using passive immunotherapy to SARS-CoV-2 in hospitalized patients with moderate to severe COVID-19 may thus improve the disease course and reduce the time to recovery.

2.2 Background

2.2.1 SARS-CoV-2 Infection and Coronavirus Disease 19 (COVID-19)

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. A novel coronavirus was rapidly identified by sequencing and named SARS-CoV-2, and the illness caused by infection with SARS-CoV-2 has been named COVID-19.[5] While SARS-CoV-2 mostly causes a mild respiratory illness, some individuals, particularly those who are elderly[6,7] and have comorbidities,[8] may progress to severe disease requiring hospitalization, mechanical ventilation in intensive care units, and death. As of 5 October 2020, less than seven months following the declaration of a pandemic on 11 March 2020 by the World Health Organization (WHO), there have been more than 35 million cases diagnosed and more than 1 million deaths worldwide.[1] Over 300,000 cases continue to be reported daily.[5]

2.2.2 Natural history of COVID-19

SARS-CoV-2 has a median incubation period of 4 days (interquartile range [IQR] 2-7 days)[9] and the mean serial interval defined as the time duration between a primary case-patient (infector) having symptom onset and a secondary case-patient (infectee) having symptom onset for COVID-19 was calculated as 3.96 (95% confidence interval [CI] 3.53–4.39) days.[10] COVID-19 illness is predominantly a respiratory disease typified by upper respiratory symptoms in mild cases and pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS) in advanced disease. Initial symptoms typically involve the upper respiratory tract with cough, sore throat and malaise. Fever is present in approximately 44-98% of cases. Notably, persons with COVID-19 often experience loss of smell and taste.[11]

Complications of COVID-19 illness include cytopenias (lymphopenia, thrombocytopenia and anemia), and acute cardiac events (elevated troponin, changes on electrocardiogram), acute renal injury and renal failure, liver impairment, and neurological events including acute cerebrovascular events, impaired consciousness and muscle injury and thrombotic events.

In most patients (approximately 80%) symptoms resolve without the need for intervention within five to seven days of symptom onset up to a maximum of 14 days. However, approximately 20% of patients show signs of clinical disease progression, most notably pneumonia, around day 3 to 8 following symptom onset. Other manifestations of disease progression include thrombotic episodes including stroke and myocardial infarction (MI). This resembles the documented 6-8 fold excess risk of thrombosis when patients are infected with influenza.[12]

A proportion of those who progress then further deteriorate, including with the development of ARDS around 1-5 days after pneumonic symptom onset.[6,13,14,15] Acute kidney injury necessitating dialysis and failure of other organs may also occur at this severe stage of disease.

Of the nearly 1,099 persons described in the Wuhan cohort, 16.0% had severe disease at presentation; 67 persons (6.1%) reached a composite primary endpoint of intensive care admission, mechanical ventilation or death.[9,16] As described below, outcomes for those requiring mechanical ventilation and with other manifestations of end-organ failure are poor, and approaches to prevent this late stage of the disease among those with early evidence of progression are critically needed.

Initially in this protocol, we aim to enroll patients hospitalized for medical management of COVID-19, close to the onset of clinical symptoms but without end-organ failure having developed (disease severity stratum 1). For agents passing the initial futility assessment eligibility for enrollment will be expanded so that patients with or without overt organ failure will be enrolled (patients in disease severity stratum 1 or 2). The majority of patients will have emerging evidence of pneumonia, but recognizing the expanding range of other organs involved in clinical progression of COVID-19, neither the inclusion criteria nor the outcomes used in in this trial are limited only to assessment of pneumonia.

2.2.3 Risk factors for clinical progression

Studies investigating risk factors for progression of COVID-19 and related hospital admission are currently few. Reports to date have predominately been based on individuals already hospitalized. These include a mix of descriptive information on the patients as well as estimates of associations between patient characteristics and disease severity. Older age has been found to be strongly related to greater severity[16,17,18] and poorer outcome as has the presence of conditions such as hypertension, diabetes and coronary heart disease.[14,16,18,19] Other risk factors identified include ethnicity[18] , cigarette smoking[16,17,20] and high body mass index (BMI).[21,22,23,24] Gender has not shown a consistent relationship with disease severity.[16,18,25] However, reports of larger case series and cohorts suggest male gender is associated with an increased risk of hospitalization and mortality.[26,27,28] Specific symptoms at presentation that have notably been associated with greater likelihood of progression to more severe disease include shortness of breath and elevated body temperature.[16,29]

Patients with inborn errors of their interferon immunity or who have developed auto-antibodies that reduces this host-protective immunity appear to be at excess risk of disease progression.[30,31]

The COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) report on 1,482 persons who were hospitalized in 14 states in the US in March 2020 show nearly 75% were aged over 50 years, and nearly 90% had at least one underlying comorbid illness.[32]

Based on 2.6 million users of the COVID Symptom Tracker App, predominantly in the United Kingdom, being older, obese, diabetic or suffering from pre-existing lung, heart or renal disease placed participants at increased risk of visiting the hospital with COVID-19.[33] Pre-existing lung disease and diabetes were consistently associated with a higher risk of requiring respiratory support.[33] A meta-analysis showed that cardiac injury as measured by a high sensitivity troponin was associated with higher mortality, higher need for intensive care unit (ICU) care, and severe COVID-19 disease.[34]

2.2.4 Hospitalization of people with COVID-19

Countries and jurisdictions differ in the clinical management of COVID-19 patients. Early in the epidemic, faced with small numbers of infected persons, some resource-rich countries such as Singapore elected to admit all persons with COVID-19 regardless of symptom severity to facilitate strict isolation. Admission for reasons of public health or quarantine, rather than medical management, continues to be a requirement in some countries, notably in Asia. Elsewhere, it is more common for those with mild illness to be advised to self-isolate at home, while only those severely unwell are admitted for medical management.

Thresholds for ICU management also differ globally and are likely to vary significantly even within individual countries at different stages of the epidemic. For example, during peaks of high incidence, procedures commonly performed only in ICU may be extended to other care areas, while patients who might otherwise have been considered for ICU admission may be palliated if clinical services are overwhelmed.

Mortality rates for those who develop end-organ failure requiring intensive support, including those admitted to ICU, differ widely. Among 1,591 ICU patients from Lombardy, the region in Italy hardest hit by COVID-19, 88% required mechanical ventilation and 11% noninvasive ventilation.[35] The ICU mortality rate was 26%. Of 1,043 patients with available data, 709 (68%) had at least 1 comorbidity, 509 (49%) had hypertension, and 21% had cardiovascular disease. Younger patients (≤63 years) compared to older patients, had lower ICU mortality and higher rates of discharge from ICU. The median length of stay in the ICU was 9 days, though 58% remained in ICU at time of report.[35] In the United Kingdom, of the 4,078 COVID-19 patients admitted into critical care with reported outcomes, 50.7% died in ICU; those requiring advanced respiratory support and renal support had worse outcomes.[36] These data underline the importance of attenuating the disease in its early phase prior to the development of end-organ failure.

For recovering hospitalized patients who still require supplementary oxygen, an emerging clinical practice is to discharge such patients and administer oxygen at their home until it is no longer required.

2.2.5 Viral kinetics of SARS-CoV-2 infection

Viral kinetic studies have demonstrated extensive SARS-CoV-2 viral replication in the pharynx just before and early after symptom onset.[37] Viral ribonucleic acid (RNA) shedding from the pharynx gradually wanes as symptoms resolve, but viral RNA is still detectable weeks after symptom resolution.[37,38,39] Median duration of viral shedding was 20 days in survivors (longest 37 days), but SARS-CoV-2 was detectable until death in non-survivors.[7] Whether this is viable virus with the potential for continued transmission remains uncertain. RNAemia has been reported but is relatively rare.[38,40] Viral detection in sputum is higher and outlasts pharyngeal swabs in those with pneumonia.[41] Persons with asymptomatic disease clear their virus faster than symptomatic individuals.[42]

The contribution of ongoing viral replication to disease progression in the most severe stage of COVID-19 (i.e., on ventilator or ECMO) is unclear, but may be minor as we hypothesize that any organ damage from the infection may have occurred already and the predominant drivers of progression to severe disease/ARDS are those of the uncontrolled local and systemic immune response.

Case reports are emerging to suggest possible reinfection in patients who have recovered from SARS-CoV-2 infection.[43,44,45,46,47]

2.2.6 Immune responses to SARS-CoV-2 infection

Notwithstanding the observed high viral loads, and progression of viral shedding from the upper to lower respiratory tract in those with progressive disease, the humoral immune response to SARS-CoV-2 appears variable and may be slow. While data are still emerging, it appears that in a significant proportion of cases antibody responses are not yet evident at the time (day 5-7) when disease progression and hospitalization most commonly occur, supporting a role for supplementation of the antibody response at that time point.

For example, two large studies have described antibody responses (immunoglobulin G [IgG] and immunoglobulin M [IgM]). In the first, samples from 82 confirmed and 58 probable cases of COVID-19 in a cross-sectional analysis demonstrated IgG detection at a median of 14 (IQR 10-18) days after symptom onset, with IgM detected at a median of 5 days (IQR 3-6) after symptom onset. Antibodies were absent in around 22% of individuals at assessment (IgM), and IgM was most commonly absent in those assessed early (within 7 days of symptom onset).[48] In the second study of 262 patients who provided 363 samples, antibody levels were examined by days from symptom onset. IgM antibodies were detectable in just under 40% of patients at day 5-7, rising to 50% at day 8-10, while interestingly IgG was detectable in a slightly higher proportion at those time points: just over 50% at day 5-7, rising to 60% at day 8-10.[49] This series was drawn from hospitalized patients, but the severity of illness and relationships with disease outcomes were not described. Both studies show considerable individual variation in antibody kinetics. Further longitudinal studies are underway and will better characterize the kinetics of these responses in individuals.[50,51]

SARS-CoV-2 infection may also induce significant changes in elements of the cellular immune response. As the disease process progresses, the peripheral lymphocyte count typically declines. The depletion of peripheral lymphocytes likely reflects translocation to the pulmonary tissue. The extent that this influx is exclusively helpful to the host, or possibly may contribute adversely to disease severity is currently unclear. In severe cases this decline in CD4+ and CD8+ lymphocytes is also associated with an increase in activated CD4+ and CD8+ subsets, increases in key proinflammatory cytokines including interleukin

6 (IL-6), and increases in natural killer (NK) cells.[52,53] Trials assessing the use of various immunomodulatory agents with the aim of dampening this migration and systemic inflammation are underway, and may help to clarify this.

2.2.7 Current treatment strategies for COVID-19

Hundreds of clinical trials have been completed or are underway to study the safety and efficacy of treatments for COVID-19. Treatments being studied include direct anti-viral treatments, including repurposed drugs found in vitro to have activity against SARS-CoV-2; immune modulators especially in patients with advanced disease; drugs to reduce inflammation, including corticosteroids, and modifiers of other pathophysiological pathways implicated in disease progression, including potentially anticoagulants and anti-platelet agents.

As results of randomized trials for these and other treatments become available and treatment guidelines are updated, standard of care (SOC) for hospitalized patients with COVID-19 will change. This may influence the background treatment recommended (or required) by this protocol and/or second line or supportive care treatments recommended by the protocol. To accommodate this fast-moving field Appendix I (which outlines the SOC to be recommended in addition to investigational agent or matched placebo) will be regularly updated.

Of note, whereas evidence supports use of the interventions outlined in Appendix I, the most optimal approach to applying these interventions remains uncertain, and is the subject of ongoing trials.

2.2.8 Neutralizing Monoclonal Antibodies (nMAbs)

The ability to rapidly and urgently develop novel therapeutic nMAbs is best illustrated in the setting of the 2014-2016 Ebola epidemic. A triple monoclonal antibody (MAb) cocktail, ZMapp, which first showed efficacy in guinea pigs,[54] was tested in PREVAIL II, a randomized controlled trial of 72 patients.[55] This trial did not meet pre-specified efficacy threshold. Two phase I studies that separately explored a single nMAb against receptor-binding domain (RBD) Mab114[56] and a triple nMAb cocktail of REGN3470-3471-3479[57] showed linear pharmacokinetics and a good safety profile, with mild headaches in the latter. A large 1:1:1:1 randomised study of 681 patients compared ZMapp as control; remdesivir: single nMAb, Mab114 (Ansuvimab) and a triple cocktail of REGN-EB3, with the latter two showing superior results for day 28 mortality.[58] Four events in three patients were thought to be directly related to trial drug – 2 in the ZMapp arm and 1 in the remdesivir arm. Mab114 was granted breakthrough therapy designation by the US Food and Drug Administration (FDA) and REGN-EB3 was approved for the treatment of Ebola virus disease by the FDA.

SARS-CoV-2 and other pathogenic human coronaviruses encode four major structural proteins. The homotrimeric spike (S) protein is essential to viral attachment, fusion, entry and transmission and has two functional subunits - S1 subunit for virus-receptor binding and S2 subunit for virus-cell membrane fusion. S1 has an N-terminal domain (NTD) and a RBD.[59,60,61] During infection, SARS-CoV-2 first binds the host cell through interaction between its S1-RBD and the cell membrane receptor (angiotensin-converting enzyme 2 or ACE2 receptor) triggering conformational changes in the S2 subunit that results in virus fusion and entry into the target cell.[62] Other structural proteins include the envelope (E) protein encompassing the viral envelope, the membrane (M) protein protruding from the cell membrane, and nucleocapsid (N) protein covering the viral RNA. There are approximately

16 non-structural proteins (nsp1–16), and five to eight accessory proteins.[59] As the S glycoprotein is surface-exposed and mediates entry into host cells, it is the main target of neutralizing antibodies upon infection and the focus of therapeutic and vaccine design[62].

Most currently developed anti-SARS-CoV-2 nMAbs target the viral S protein, most commonly the RBD.[6364] The structural homology and cross-reactivity across the *Coronaviridae* have enabled knowledge translation from SARS-CoV-1 and MERS to SARS-CoV-2. Cross-reactivity has been exploited for immune protection. Promising human-derived nMAbs have been identified from previous SARS-CoV-1 patients and convalescing SARS-CoV-2 patients. After the SARS epidemic in 2003, two promising nMAb therapeutics were identified - CR3014 and CR3022.[65] CR3022 rather than CR3014 showed promise against SARS-CoV-2[66] but recent structure modelling showed that CR3022 binds to a cryptic epitope distal to the RBD, only accessible when the RBD is in the up conformation and at a specific angle,[67] thus limiting its application.

A new promising S309 antibody targeting the RBD, identified from a previous SARS-CoV-1 survivor, showed cross-reactivity against SARS-CoV-2 and an Fc variant with a longer half-life is in accelerated development.[61] Similarly, 18F3 and 7B11 against RBD were identified from SARS-CoV-1 patients.[68] Many papers have detailed identification and development of nMAbs from currently convalescing patients with SARS-CoV-2, all targeting the RBD including: CB6 which also has shown promise as a prophylaxis and therapeutic model in monkey studies[69]; P2B -2F6,[70] 311mab-31B5 and 311mab-32D4.[71]

Viral escape mutants may render the virus resistant to the neutralising effects of nMAbs.[72]

2.3 Investigational Agents

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) has formed an overarching “trial oversight committee (TOC)” for both ACTIV-2 (a parallel study assessing COVID-19 therapeutics in outpatients) and ACTIV-3 (this master protocol). The TOC will select agents for study in the two protocols. Members of the protocol team (non-voting) and NIAID are members of this committee. This committee reviews data for investigational agents and considers a number of factors including safety, in vitro potency against the virus, resistance, epitope and adequacy of antibody titers if the agent is an antibody, scale-up potential in general, and for completing the phase 3 trial in particular, and dose and route of administration.

The same DSMB will review interim data from ACTIV-2 and ACTIV-3 and this should facilitate early identification of safety concerns. The protocol team will inform the DSMB about emerging data that impacts the study design (e.g., the safety of the investigational agent being studied or SOC).

It is possible that agents from different sources will be combined at some point in the conduct of this master protocol. It is also possible that one agent will be identified as effective and then incorporated as SOC (providing there is good safety and adequate supply).

Information on dosing, administration, supply and distribution, matching placebo, and any special considerations as far as inclusion/exclusion criteria and safety monitoring for each investigational agent studied as part of this protocol is outlined in an appendix (see Appendix H), including known benefits and risk, justification for dosing, and administration. The appendix will also include whether any deviations from aspects of study procedures

outlined in this master protocol will be needed. The informed consent will describe any risks associated with the investigational agents.

3 Risk/Benefit Assessment

3.1 Known Potential Risks

Potential risks of participating in this trial are those associated with the product, and these are described in an appendix and in the sample informed consent. Other risks include having blood drawn, intravenous (IV) catheterization, thrombosis, the volume of fluid infused, and breach of confidentiality.

3.1.1 Risks of Drawing Blood and IV Catheterization

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the participant lie down and elevate his/her legs. Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IV catheterization may cause insertion site pain, phlebitis, hematoma formation, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site of blood draw or at catheterization less likely.

3.1.2 Risks of Anaphylaxis, Thrombosis and Fluid Overload due to Study Treatments

Infusions of investigational agents likely to be used in this protocol are generally well-tolerated, except in rare cases of existing allergy to the products infused. However, the volume of fluid infused may exacerbate pre-existing CHF. There is slight elevation in the risk of thrombosis with standard antibody therapy, and in some cases COVID-19 is associated with thrombotic complications. There is a theoretical risk that antibody infusion may worsen the disease course via antibody-dependent enhancement (ADE). ADE occurs if specific antibodies against a virus increase rather than decrease viral replication and hence worsen the disease course. ADE has been observed most clearly in the context of Dengue fever.[73] It is unclear if this phenomenon is present and/or clinically significant in COVID-19, but close monitoring of disease outcomes will be maintained during interim safety analyses.

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), NIH, and applicable regulatory agencies (e.g. FDA).

3.2 Known Potential Benefits

While the trial is conducted to test the hypothesis that each investigational agent will reduce the risk of further disease progression or reduce the time to sustained recovery, the agents studied may or may not prevent these outcomes in any individual who participates in this trial. However, there is an anticipated benefit to society from a patient's participation in this trial, due to insights that will be gained about the investigational agent(s) under study as well as the natural history of the disease. While there may not be benefits for an individual, there will be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

4 Outcomes

This section describes the key outcome measures used in this phase III protocol. At the outset of the phase III trial for each investigational agent, only participants in disease severity stratum 1 will be enrolled. This more restricted enrollment will continue until approximately 300 participants are enrolled. Prior to expanding enrollment to include people in disease severity stratum 2, a pre-specified futility assessment by the DSMB will be carried out using two ordinal outcomes (see below) that are assessed at Day 5. This early futility assessment is designed to ensure some minimal level of activity for agents for which enrollment continues to the planned sample size of the phase III trial.

4.1 Ordinal Outcomes for Early Futility Assessments

Two ordinal outcomes will be used to assess futility after approximately 300 participants have been enrolled. Both outcomes are assessed 5 days after randomization (Day 5); the participant's highest (i.e. most severe) observed score on Day 5 is used.

The first ordinal outcome, referred to as the "pulmonary" ordinal outcome, is primarily defined based on oxygen requirements. The 7 categories of the pulmonary ordinal outcome are given below (see Protocol Instructions Manual [PIM] for criteria defining the categories and each of the conditions mentioned).

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
5. Non-invasive ventilation or high-flow oxygen
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
7. Death

The second ordinal outcome, referred to as "pulmonary+," also assessed at Day 5, captures extrapulmonary complications as well as respiratory dysfunction. The categories of the

pulmonary+ outcome are defined below (see PIM for criteria defining the categories and each of the conditions mentioned).

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset CHF NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events.
5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14)
6. Invasive ventilation, ECMO or mechanical circulatory support; vasopressor therapy; or new receipt of renal replacement therapy
7. Death

The term ”usual activities”, in categories 1 and 2 for both outcomes, refers to activities of daily living that the participant was able to undertake prior to the current illness.

4.1.1 Rationale for two ordinal outcomes

There is as yet no consensus on the optimal endpoint for determining clinical benefit from COVID-19 therapies, including the constituent elements of the endpoint and the timing of its assessment after randomization. Both may differ depending on the target population and the nature of the treatment studied.

While the pulmonary ordinal outcome focuses on the pulmonary components of COVID-19, the pulmonary+ ordinal outcome captures the range of complications experienced by hospitalized patients with COVID-19. The pulmonary+ outcome recognizes that end-organ manifestations in addition to pneumonia and ARDS are increasingly emerging as significant contributors to morbidity, including morbidity resulting from the thromboembolic pathology of the disease. Emerging extrapulmonary events are also likely to affect the primary endpoint of sustained recovery. This ordinal outcome includes 7 well-defined mutually exclusive categories, each of which assesses further progression of disease, as well as recovery from COVID-19.

While the two ordinal outcomes are correlated, it is yet to be determined which of these two outcomes will best identify the investigational agents that, when given with SOC, have activity that merits advancement.

Day 5 was chosen for the timing of these ordinal outcomes for several reasons based on the following assumptions. The impact of the investigational agent on disease progression may not be immediate; a few days may be needed to see the effects on clinical outcomes as measured by each ordinal outcome. Also, transient treatment effects that are no longer present at Day 5 may be clinically less relevant. Assessment of the ordinal outcome at a later time point may result in a diminished treatment difference because spontaneous recovery from COVID-19 may have begun in many participants. Use of Day 5 to characterize the clinical severity of participants in 7 categories as studied here, results in a distribution of participants in the placebo group for the ordinal outcome that is sufficiently

granular and not overly skewed to the most severe or least severe categories and, therefore, provides good power for comparing the two treatment groups (see section 6.3). Finally, an early time point of ascertaining the outcomes will facilitate more rapid interim analyses for these two ordinal outcomes.

4.2 Primary and Secondary Outcomes to Evaluate Efficacy and Safety

The primary endpoint is ***time from randomization to sustained recovery,*** defined as being discharged from the index hospitalization, followed by being alive and *home* for 14 consecutive days prior to Day 90.

Home is defined as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this protocol.

Residence or facility groupings to define home are: 1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel; 2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting); 3) **Other healthcare facility** (e.g., skilled nursing facility, acute rehab facility); and 4) **Long-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days).

Lower (less intensive) level of residence or facility will also be considered as home. By definition, “home” cannot be a “short-term acute care” facility. Participants previously affiliated with a “long-term acute care” hospital recover when they return to the same or lower level of care.

Readmission from “home” may occur and if this occurs within 14 days of the first discharge to “home”, then the primary endpoint will not be reached until such time as the participant has been at home for 14 consecutive days.

Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated.

Some recovering patients are discharged from the hospital while still requiring continuous low flow supplementary oxygen to maintain satisfactory blood oxygenation for some period of time. Sensitivity analyses will be carried out using outcomes which are variations of the definition of sustained recovery. These outcomes will use definitions of sustained recovery that consider continuous use of supplemental oxygen reported during the 14-day period at home following discharge. These outcomes are cited as secondary endpoints.

4.2.1 Rationale for primary outcome

The primary outcome is intended to identify efficacy among the investigational agents.

Whereas mortality may be the most important outcome, the sample size to detect a plausible treatment effect for such an outcome would be much larger than outlined in this protocol and was judged not to be feasible to be the primary outcome. Nor was mortality considered to be the only relevant measure of efficacy in COVID-19.

The primary outcome is assessed during 90 days of follow-up, which is longer than for other trials of investigational agents for COVID-19, which are typically 28 days. The longer follow-up will allow better ascertainment of recovery from the longer-term consequences of the

underlying disease, and hence the efficacy of the investigational agent. This is likely to be particularly true for patients who experience extra-pulmonary disease in conjunction with their COVID-19, and for patients enrolled while receiving care for life-threatening organ failure. It is also projected that excess mortality may still be observed beyond Day 28 until Day 90. All-cause mortality is an important secondary outcome (see below).

4.2.2 Secondary outcomes

In addition to the primary endpoint, several secondary efficacy endpoints will be assessed. These endpoints will be assessed for all participants enrolled.

1. All-cause mortality through 90 days of follow-up

2. Composite of time to sustained recovery and mortality through 90 days of follow-up

3. Time to discharge for the initial hospitalization

4. Days alive outside of a short-term acute care hospital up to day 90

5. Ordinal outcomes, pulmonary+ and pulmonary, on Days 1-7, and pulmonary ordinal outcome on Days 14 and 28

6. Clinical organ failure or serious infections defined by development of any one or more of the following clinical events through Day 28 (see PIM for criteria for what constitutes each of these conditions):

    a. Respiratory dysfunction:
        1. Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO

    b. Cardiac and vascular dysfunction:
        1. Myocardial infarction
        2. Myocarditis or pericarditis
        3. CHF: new onset NYHA class III or IV, or worsening to class III or IV
        4. Hypotension requiring institution of vasopressor therapy

    c. Renal dysfunction:
        1. New requirement for renal replacement therapy

    d. Hepatic dysfunction:
        1. Hepatic decompensation

    e. Neurological dysfunction
        1. Acute delirium
        2. Cerebrovascular event (stroke, cerebrovascular accident [CVA])
        3. Transient ischemic events (i.e., CVA symptomatology resolving <24 hrs)
        4. Encephalitis, meningitis or myelitis

    f. Haematological dysfunction:
        1. Disseminated intravascular coagulation

2. New arterial or venous thromboembolic events, including pulmonary embolism and deep vein thrombosis
3. Major bleeding events (>2 units of blood within 24 hours, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding).

g. Serious infection:
   1. Intercurrent, at least probable, documented serious disease caused by an infection *other than* SARS-CoV2, requiring antimicrobial administration and care within an acute-care hospital.

7. A composite of death, clinical organ failure or serious infections (see above)

8. Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate cross-trial comparisons and overviews (e.g. 6- , 7-, and 8-category ordinal scales assessed at Days 1-7, 14 and 28; time to improvement in 1 or 2 categories of ordinal scale; time to best 3 categories of ordinal scale, and binary outcomes defined by improvement or worsening based on other ordinal outcomes)

9. A composite of cardiovascular events (outcomes listed above in items 6b1, 6e2 and 6e3) and thromboembolic events (item 6f2)

10. Safety and tolerability as measured by:
    a. A composite of grade 3 and 4 clinical adverse events, SAEs, clinical organ failure or serious infections (see item 6 above) or death through Day 5 (primary safety endpoint) and through Day 28 (the components of this composite will also be summarized)
    b. Infusion-related reactions of any severity and percentage of participants for whom the infusion was interrupted or stopped prior to completion
    c. A composite of SAEs, clinical organ failure or serious infections (see item 6 above) or death through Day 90
    d. Adverse events of any grade through Day 7
    e. Prevalence of adverse events of any grade at day 14 and day 28
    f. A composite of hospitalization readmissions or death through 18 months.

11. Change in antibody profile, overall titers of antibodies and neutralizing antibody levels from baseline to Days 1, 3, 5 and 28 and 90

12. Outcomes that consider home use of supplemental oxygen above pre-morbid oxygen use for sensitivity analyses for the primary outcome:
    a. Alive at home and no use of continuous supplemental oxygen for an uninterrupted 14 day period
    b. Alive at home for an uninterrupted 14 day period and no use of continuous supplemental oxygen at the end of the 14 day time period.

4.2.3 Rationale for secondary outcomes

Mortality and the composite of time to death or sustained recovery (see section 11.2 for the analysis of this outcome using a win ratio statistic)[74] are the two key secondary outcomes.

An effective investigational agent should lead to a favorable trend for those these outcomes. Conclusive evidence for a treatment difference in mortality requires larger sample sizes than planned, and we expect that there is better power for detecting a treatment effect in the composite outcome than mortality.

Safety is assessed through a comprehensive review of data collected from baseline through follow-up. On day 0, during and immediately after the infusion, infusion-related reactions of any grade severity, and premature infusion termination are captured. From study entry through day 28, deaths, grade 3 and 4 clinical adverse events, and the components of the two ordinal outcomes assessed at Day 5 contribute to the safety assessment. A composite primary safety outcome is defined at Day 5. On Day 0 and Day 5, safety laboratory test results are reported, and grading determined (section 9.1). Finally, SAE's, SUSAR's, (re)admissions for acute care, organ disease, and organ dysfunction including supportive treatment hereof, are ascertained during the entire follow-up period.

The definitions of outcomes in different COVID-19 trials are evolving. It will be important to adequately capture data that enables the trial to "reconstruct" outcomes used in other trials.

Finally, continuous supplemental oxygen is increasingly prescribed for patients discharged from the hospital following treatment for COVID-19. Therefore, it will be important to carry out sensitivity analyses that consider home oxygen use in interpreting the results of the trial for the primary endpoint of sustained recovery.

5 Objectives

5.1 Primary Objective

The primary objective of this protocol is to determine whether investigational agents, initially focusing on those that are aimed at enhancing the host immune response to SARS-CoV-2 infection are safe and superior to control (e.g., placebo) when given with SOC for the primary endpoint of time to sustained recovery evaluated up to 90 days after randomization.

SOC may be modified (updated based on data from this or other trials) during the course of evaluating different investigational agents with this master protocol.

5.2 Secondary Objectives

Two key secondary objectives are to compare each investigational agent with control for all-cause mortality and a composite outcome which considers both time to sustained recovery and mortality.

Other secondary objectives are to compare each investigational agent with control for the secondary outcomes stated in section 4.

In addition, the primary endpoint of time to sustained recovery will be evaluated for subgroups defined by the following characteristics measured at enrollment:

- Disease severity as defined in the design for stratification
- Age
- Biological sex

- Race/ethnicity
- Type of residence/facility (home)
- BMI
- History of chronic conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, hepatic impairment, chronic kidney disease, cancer)
- Geographic location
- Upper respiratory SARS-CoV-2 viral load
- SARS-CoV-2 neutralizing antibody level
- Duration of symptoms prior to enrollment
- Respiratory function scale
- Organ/respiratory dysfunction category based on each ordinal outcome (pulmonary+ and pulmonary)
- NEW score
- Disease progression risk score (defined using pooled treatment groups with the following baseline predictors of the primary outcome (sustained recovery): age, biological sex, duration of symptoms, ordinal category at entry, NEW score, and presence of chronic health conditions).

6 Study Design

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 SARS-CoV-2 infection, or directly enhancing viral control in order to limit disease progression. Master protocols can provide a more efficient approach to the evaluation of multiple experimental interventions for a single disease such as COVID-19 in a continuous manner.

The trial described in this master protocol is a phase III randomized, blinded, controlled platform trial that allows investigational agents to be added and dropped during the study for efficient testing of new agents against placebo within the same trial infrastructure. When more than one agent is being tested concurrently, participants will be randomized across agents, as well as to agent/control. This will allow rapid testing of multiple agents as the pooling of controls across agents requires fewer patients to be randomized to the matched control arm of each agent. However, this will only occur when feasible and when multiple agents are available to be tested at the same time. If an investigational agent shows superiority over placebo + SOC as initially defined, SOC for future investigational treatment evaluations will be modified accordingly.

Figure 1. A Phase III Platform Trial for Efficiently Evaluating Multiple Investigational Agents Over Time

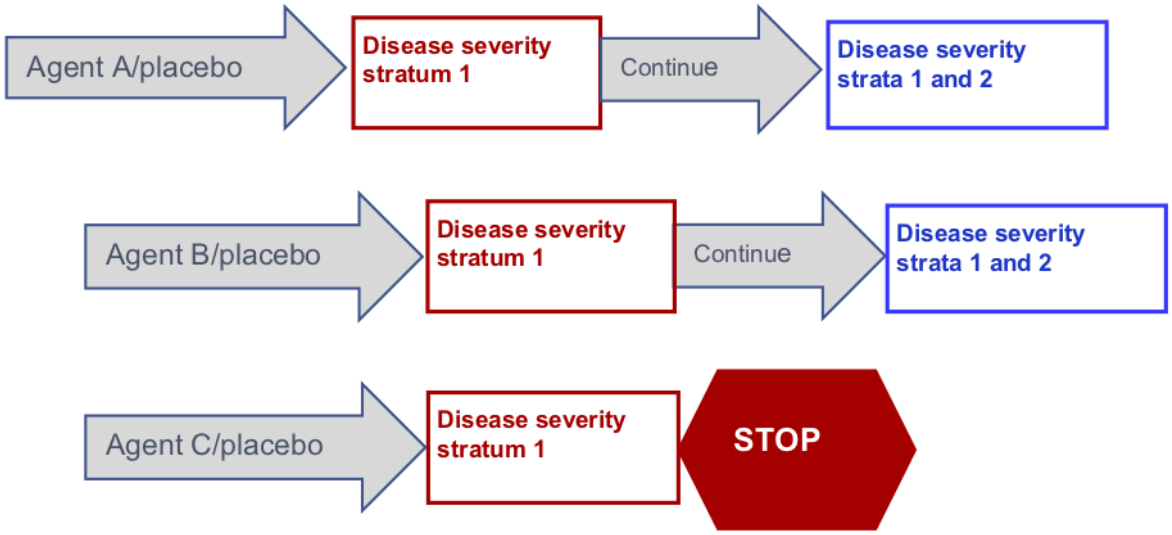

Figure 1 illustrates three aspects of the study design. Investigational agents may enter the trial simultaneously or sequentially. Agents B and C entered the trial simultaneously after agent A. During the time of overlapping randomization for the 3 agents, placebo is shared as described in section 6.1. All 3 agents share a placebo for part of the time in which patients in disease severity stratum 1 are enrolled. For a period of time participants in disease severity stratum 2 are only eligible for Agent A/placebo.

Agents which demonstrate an acceptable risk versus benefit profile in the initial cohort of participants in disease severity stratum 1 and pass the futility assessment based on the Day 5 ordinal outcomes continue enrollment with expanded eligibility criteria. This is illustrated by both agents A and B. Both agents advance to enroll participants in disease severity stratum 2 as well as 1. Agent A advances shortly before agent B.

Agent C illustrates an agent that did not pass the futility assessment in the initial cohort of patients in disease severity stratum 1. Enrollment stopped for agent C. Follow-up for the participants randomized (all in disease severity stratum 1) to agent C/placebo will continue through 18 months of follow-up in order to continue to assess safety and other outcomes.

In some cases, more than one dose of an investigational agent will be studied. For such agents, only one of the doses will be advanced to the expanded cohort that includes participants in disease severity strata 1 and 2.

6.1 Randomization and Stratification

Patients will be equally allocated to each investigational agent + SOC or to placebo + SOC. For example, for a study of a single investigational agent, participants will be randomized in a 1:1 ratio to the investigational agent + SOC or placebo + SOC. If a participant is eligible for two investigational agents, the allocation will be 1:1:1 to investigational agent A + SOC, agent B + SOC, or placebo + SOC. Because the two investigational agents (A and B) may require different placebos (for example, when infusion volumes differ), the 1:1:1 allocation ratio will be achieved through a two-step randomization procedure: in *step 1*, the participant

is randomized 2:1 to "active" versus "placebo"; in *step 2*, the participant is randomized 1:1 to A versus B. With k agents, this can be viewed as an initial k:1 allocation to "active" versus "placebo", followed by a second, even allocation to one of the available agents (for example, if a participant was allocated to "placebo" in step 1, then the step 2 allocation will be 1:1 to "agent-specific placebo for A" versus "agent-specific placebo for B"). Sites will be informed of the specific investigational agent/placebo (e.g., A or B) to which the participant was randomized (see section 6.2). For the analysis, the concurrent agent-specific placebo groups will be pooled, resulting in a 1:1 allocation ratio for comparing each investigational agent versus the (pooled) placebo group.

If investigational agents are added or dropped, the allocation ratio to active versus placebo will be appropriately modified, and overall sample size will be recalculated as appropriate.

Randomization will be stratified by study site pharmacy (several clinical sites may share one study site pharmacy) and severity of disease at entry. The two strata that define disease severity are:

Disease severity stratum 1: Absence of all of the following: stroke, meningitis encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, symptomatic congestive heart failure (NYHA class III or IV), arterial or deep venous thrombosis or pulmonary embolism, requirement for invasive mechanical ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new renal replacement therapy.

Disease severity stratum 2: Presence of at least one of the excluded conditions or treatments in disease severity stratum 1.

Within each stratum, mass-weighted urn randomization[75] will be used to generate the active and placebo assignments. This will ensure throughout the trial placebo allocation near the intended ratio while also ensuring near equal numbers of active and matched placebo assignments to each agent.

If more than one investigational agent is being compared with placebo and they have different contraindications, consideration will be given to allowing participants to enter with randomization to each agent versus placebo separately as well as randomization to both agents. If the number of participants expected to have a contraindication is small, they will be excluded from the trial rather than establishing a separate randomization mechanism. Comparisons will be of each investigational treatment against its control arm. The control arm consists of all participants who were "at risk" of being randomized to the investigational agent but were randomized to a control group instead. This concept is relevant when the randomization includes investigational agents with different eligibility criteria or introduction into the platform trial at different time points. Formal randomization includes a matched placebo group for each agent, and the placebo groups will be pooled across agents, but only participants who 1) were eligible for the investigational agent under consideration, and 2) were randomized contemporaneously in a stratum will be included in the control group for a given agent.

The default randomization allocation to agent (or its placebo) for which a participant is eligible is as outlined above. However, in some circumstances this allocation ratio may be changed by the (blinded) protocol leadership based on an overall assessment of how the master protocol framework is able to produce relevant and novel findings most effectively.

6.2 Blinding

Investigational agents or placebo (as necessary) will be prepared by a pharmacist who is not blinded to the treatment assignment. All other study staff, including those at sites, and those in roles spanning multiple sites or spanning the protocol as a whole, will be blinded unless otherwise specified herein.

For investigational agents infused, blinding of the participant and clinical staff will be achieved by placing a colored sleeve over the infusion bags used for investigational agents and placebos. Placebo will consist of an isotonic crystalloid, referred to as an isotonic saline solution.

When more than one investigational agent is available for randomization, the clinical staff will be informed to which investigational agent/placebo the participant was randomly assigned for infusion, but they will be blinded to whether the random assignment was to the active investigational agent or matching placebo.

If the blind is broken for safety reasons, this will be recorded, and the protocol chair will be notified. In that situation, every attempt will be made to minimize the number of people unblinded. Specific unblinding procedures and instructions are found in the PIM.

6.3 Sample size assumptions

All sample size calculations are aimed at pairwise comparisons between a given investigational agent and its control arm. The following assumptions were made in estimating the required sample size for this phase III trial.

a. The primary analysis will be intention to treat. Gray's test with rho=0 will be used,[76] with stratification by disease severity at entry for comparing each investigational agent to control for the primary endpoint of time to sustained recovery (see section 4.2.1). Gray's test with rho=0 is the analogue of the log-rank test in the presence of competing risks; it is used here to account for the competing risk of death when analysing time to sustained recovery.

b. Type 1 error will be set at 0.025 (1-sided). This type 1 error will not be adjusted for the number of investigational agents being compared with placebo as each of the agents is expected to impact the primary endpoint through different mechanisms. If this is not the case, a type 1 error adjustment may be considered.

c. Power is set at 90% to detect a 25% increase in the rate of sustained recovery for the investigational treatment compared to placebo. This moderate efficacy is assumed considering the findings from ACTT-1 and the percentage of patients in each baseline risk category of the pulmonary ordinal outcome.[77] For an investigational agent that passes the initial futility assessment based on participants in disease severity stratum 1 that are initially enrolled, we expect approximately 50% of participants enrolled in the cohort expansion that includes both disease severity strata 1 and 2 to be in categories 5 or 6 of the ordinal outcome. Since most participants enrolled in the initial cohort will be categories 2, 3 or 4 of the ordinal outcome, we assume that 35% of patients in the final analysis will be in the more severe categories of the ordinal outcome; mortality is expected to be higher for participants in the more severe categories at entry. Among surviving patients we assume most will have met the criteria for sustained recovery.

d. With these assumptions for type 1 and type 2 error and a sustained recovery rate ratio of 1.25 for the investigational agent versus control, 843 sustained recoveries are needed.[78,79]

e. Given the planned 90 day follow-up for each participant, we estimate that the sample size is slightly larger than the number of recoveries (i.e., we expect a low rate of loss-to-follow-up or deaths). For 2 groups, we assume that the sample size is approximately 20% higher than the number of recoveries, to account for deaths, a small number of withdrawals of consent, and a small number of patients remaining in the hospital at Day 90. Total sample size for 2 groups is approximately 1,000 (500 per group).

f. In order to observe 843 sustained recoveries among 1000 participants, and assuming 3% withdrawal of consent, at least 87% of participants (pooled across the two treatment arms) would have to achieve sustained recovery by Day 90. Assuming a recovery rate ratio of 1.25, this corresponds to 89.9% with sustained recovery among those randomized to the investigational agent, compared with 84.1% in the control group.

Sample size will be re-estimated before enrollment is complete to determine whether the planned sample size of 1,000 participants followed for 90 days will yield the planned number of primary events. Sample size may be increased to achieve the event target in the planned follow-up of 90 days. A sample size increase may also be considered in order to achieve the event target before all participants are followed for 90 days.

6.4 Schedule of Assessments

Participants will be randomized and given their initial infusion on Day 0. All participants randomized will be followed through 18 months following randomization for collection of study data (Appendix B and section 9.1 for details).

6.5 Approach to Intercurrent Therapies and Clinical Trial Co-enrollment

In general, the study will take a pragmatic approach to the use of intercurrent, concomitant medications. Except for use of convalescent plasma, hyperimmune SARS-CoV-2 immunoglobulin or nMAb which is not permitted prior to entry or before Day 5, there are few restrictions.

Sponsor and/or protocol leadership may, based upon convincing new evidence, act in the interest of participant protection, and in avoidance of confounding, to exclude/dis-allow use of any specific concomitant therapy found to be reasonably contraindicated for a well-defined portion of the study population (see a)i)(1)(a)(i)Appendix I). Such a determination may be made, communicated, and implemented by a Protocol Clarification Memo until it is reasonable to amend the protocol for other reasons.

Participants will be asked at screening to agree to refrain from participation in other clinical trials until at least the assessment at Day 5 except for trials comparing different approaches for implementing SOC interventions that are recommended in a)i)(1)(a)(i)Appendix I and approved by trial leadership. It is recognised that, in the case of progression during follow-up to life-threatening disease and end-organ failure (broadly categories 5 and 6 of the

intermediate outcome measure; section 4.1) there will be considerable clinical concern, and participation in an additional clinical trial at that time will not be restricted.

The protocol leadership will use the following principles to judge the appropriateness of a trial for which co-enrolment will be allowed.

1. Applicable trials should **not** address a research question of whether the intervention should be applied or not, but rather how to apply it (e.g., dose, intensity, duration).

2. The target population must be patients in whom the intervention is commonly applied as part of SOC.

3. The trial intervention should be outlined in a)i)(1)(a)(i)Appendix I , Standard of Care, and hence viewed already as part of appropriate SOC.

4. Interventions that are contraindicated in combination with the investigational agent are not permitted (see a)i)(1)(a)(i)Appendix H for details of possible contraindications for each investigational agent).

5. Study procedures of the co-enrolling trial must not impose an undue burden on research participants or research staff when viewed within the context of other study procedures. For example, volume of blood drawn for research purposes must not be excessive when added to the volume drawn for study procedures.

6. Participation in the TICO trial is the principal trial for the study participant, and study procedures for TICO should be prioritized.

7. The trial must be open-label (non-blinded) in order to facilitate interim and final analyses of data for this trial, including treatment interactions, and the attribution of causality of serious adverse events and unanticipated problems (see section 10.1.5)

Prior participation in clinical trials (except receipt of hIVIG, convalescent plasma or another nMAb) is not restricted, recognising for example that participants may have enrolled in a study for mild disease prior to progression and then may wish to participate in this study at the onset of progression.

All participants will be compared throughout follow-up, irrespective of use of concomitant treatments. Concomitant treatments will be recorded at baseline, Day 5 and Day 28. The study randomization and study site pharmacy stratification will balance the use of concomitant medications on average at baseline and these will be summarized with other baseline characteristics. Follow-up use of concomitant treatments may differ by treatment group reflecting different efficacy/safety of the study treatments and use of concomitant treatments will be summarized by treatment group.

7 Study Population

For each investigational agent, an estimated 1,000 COVID-19 participants will be enrolled at clinical trial sites globally. The time from screening (Day -1 or Day 0) to end of study for an individual participant is 18 months.

Patient eligibility must be confirmed by a study clinician named on the delegation log.

Initially, approximately 300 participants in the disease severity stratum 1 will be enrolled. For investigational agents passing an initial futility assessment for these participants, enrollment will be expanded, seamlessly and without any data unblinding, to include participants in disease severity stratum 2 as well as those in disease severity stratum 1.

Protocol inclusion and exclusion criteria are intentionally straightforward and are NOT subject to exception for even minor deviations by Study Medical Officers or by the Sponsor Medical Monitor.

7.1 Inclusion Criteria

1. Age ≥ 18 years;

2. Informed consent by the patient or the patient's legally-authorized representative (LAR)*;

3. SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing within 3 days prior to randomization OR documented by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator (For non-NAT tests, only those deemed with equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests will be maintained.);

4. Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator;

5. Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes.

***Continuing consent**
For participants whose consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in hospital will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR should reflect that such consent should be obtained.

7.2 Exclusion Criteria

1. Prior receipt of
   - Any SARS-CoV-2 hIVIG, convalescent plasma from a person who recovered from COVID-19 or
   - SARS-CoV-2 nMAb at any time prior to hospitalization;

2. Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5 (with the approval of study leadership, enrollment before or on Day 5 is permitted for trials comparing different approaches for implementing SOC interventions that are recommended in a)i)(1)(a)(i)Appendix I);

3. In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol specified assessments;

4. Expected inability to participate in study procedures;

5. Women of child-bearing potential who are not already pregnant at study entry and who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with men or practice appropriate contraception through 18 months of the study.

6. Men who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with women of child-bearing potential or to use barrier contraception through 18 months of the study.

Prior to the initial futility assessment for an investigational agent, the following two additional exclusions (7 and 8) which define disease severity stratum 2 apply:

7. Presence at enrollment of any of the following:
    a. stroke
    b. meningitis
    c. encephalitis
    d. myelitis
    e. myocardial infarction
    f. myocarditis
    g. pericarditis
    h. symptomatic CHF (NYHA class III-IV)
    i. arterial or deep venous thrombosis or pulmonary embolism

8. Current requirement for any of the following:
    a. invasive mechanical ventilation
    b. ECMO
    c. mechanical circulatory support
    d. vasopressor therapy
    e. commencement of renal replacement therapy at this admission (i.e. not patients on chronic renal replacement therapy).

Exclusions that may be appropriate for an investigational agent studied are referenced in the relevant appendix (H) for the investigational agent. The contraindications for use of components of SOC are outlined in Appendix I and in the PIM.

7.3 Costs to Participants

There is no cost to participants for the research tests, procedures/evaluations and study product while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay may be billed to the participant, participant's insurance or third party.

8 Study Product

Investigational agents and SOC treatment to be used are described in Appendices H and I, respectively.

9 Study Assessments and Procedures

9.1 Screening/Baseline and Follow-up Assessments

Data collection at each visit is outlined below and summarized in Appendix B. Day 0 refers to the day on which randomization occurs and on which the investigational agent/placebo is infused. Screening and randomization can be done in the same session. The term "baseline" refers to data that are collected prior to randomization.

9.1.1 Screening/Baseline Assessments

After obtaining informed consent, the following assessments are performed within 24 hours prior to randomization to confirm eligibility and to collect baseline data:

- Documentation of SARS-CoV-2 infection by NAT or equivalent testing that was performed within 3 days prior to randomization, OR documentation by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection)

- A focused medical history, including the following information:
    - Demographics including age, gender, and type residence or facility prior to current illness (i.e. "home")
    - Day of onset of COVID-19 signs and symptoms
    - Components of ordinal outcomes
    - History of chronic medical conditions, including targeted conditions for outcome analysis
    - Targeted concomitant medications and SARS-CoV-2 vaccine trial participation

- A focused physical examination including height and weight

- Respiratory function scale

- Blood draw for local laboratory evaluations:
    - White blood cell count
    - Hemoglobin
    - Platelets
    - Lymphocytes
    - CRP
    - Serum creatinine
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)

- Vital signs for NEW score

- 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 obtain the 8 aliquots.

- Midturbinate nasal swab procedure for central determination of SARS-CoV-2 viral load
- Contact details (phone, e-mail or other types of contact) for the participant and at least two close relatives/friends, to ensure reliable data collection during follow-up in the trial.
- Urine or serum pregnancy test in women of childbearing potential who do not already have evidence of pregnancy

In some cases, it may not possible to draw blood for local laboratory assessments and storage and/or to obtain a midturbinate nasal swab for storage prior to the time of randomization. In these cases, the blood draw and swab collection can be obtained after the time of randomization but before the infusion of the blinded investigational agent/placebo.

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.

Participants who qualify will be randomized within 24 hours of consent and given the infusion of the blinded investigational agent/placebo. Immediately prior to randomization, the disease severity stratum of the participant should be verified.

On Day 0 following randomization the following are assessed:

- Adverse events of any grade severity present prior to the infusion
- Start and stop times of the infusion of the investigational agent/placebo and remdesivir
- Infusion-related reactions to the investigational agent/placebo
- Medication used prophylactically or therapeutically to manage infusion-related reactions
- New adverse events of any grade severity during and after the infusion

Participants should be monitored for at least 2 hours post infusion and have a final check 2 hours later. Participants who experience AEs during or after the infusion should be followed closely until the resolution of the AE.

9.1.2 Follow-up Assessments

Participants will be followed through 18 months following randomization for collection of study data (Appendix B). Clinical data will be collected on Days 0-7, 14, 28, 60, 90, 6 months, 12 months, and 18 months. These data will include discharge status, and interim changes in medical history (targeted to components of the intermediate ordinal outcomes and secondary endpoints). Local laboratory measurements will also be obtained on Day 5. Concomitant medications will be collected on Days 5 and 28, clinical (i.e., not limited to a laboratory abnormality) incident AEs of grade 3 and 4 severity through Day 28, and hospitalization readmissions and deaths through 18 months.

Both intermediate ordinal outcomes will be assessed on Days 1-7. Adverse events of any grade severity will be collected on Days 0-7. The pulmonary ordinal outcome will also be assessed on Days 14 and 28. On Days 14 and 28 AEs of any grade severity will also be

collected. Components necessary to determine the pulmonary ordinal outcome will be collected to allow the computation of the ordinal outcome for every day through Day 14.

At the time of discharge, the residence/place of living to which the participant was discharged and whether it was the type of residence (i.e. "home") occupied at the time of onset of COVID-19 symptoms will be ascertained. All changes in this status (e.g., re-admission to another hospital or an intermediate care facility) will be collected at approximately 2 week intervals, starting with the day 14 visit, to assess when the participant meets the criterion for the primary endpoint of 14 consecutive days "home". With this plan we will also address the secondary outcome of total days alive outside of a short-term acute care hospital.

For participants who are no longer hospitalized, in-person visits will be done on study Days 1, 3, 5, 28 and 90, when blood is collected. At each of these visits, plasma and serum specimens for central testing for SARS-CoV-2 antibody determination and storage (four 1.0 mL aliquots of serum and four 1.0 mL aliquots of plasma) will be obtained for future related research. Two 9 mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots. If it is not possible to do an in-person visit on Day 3 or Day 5, the participant should be contacted to record the required clinical data on the study day and blood draws may be done one day earlier or one day later. In person research visits for participants at their residents or home health and mobile phlebotomy services may also be utilized to complete protocol-required data/specimen collection during follow-up.

For other visits on Days 7, 14, 42, 60, and 75, 6 months, 12 months, and 18 months, contact with the participant for study data collection may be performed by telephone or other electronic communication. Other information will be gathered, as outlined in Appendix B. This will include information on hospital readmissions (e.g., date of readmission, date of discharge, and reason for readmission) and deaths through 18 months. Safety data collection and reporting are described further in section 10.

9.1.3 Stored Samples and Future Research

The plasma and serum specimens collected as outlined above and the inoculum from the baseline mid-turbinate nasal swab 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 treatment. 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.

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 investigational agent or placebo, and to study provided SOC treatment(s).

Infusion-related reactions of any grade are only collected for the blinded investigational agent/placebo. All other AEs are collected for the study intervention (either the blinded investigational agent/placebo or study provided SOC treatment).

The following information will be collected on eCRFs to evaluate safety:

- Infusion-related reactions of any grade severity during, or within 2 hours post-infusion of the investigational agent/placebo.
- Targeted laboratory results centrally graded for severity at Day 5.
- Clinical adverse events of any grade severity on Days 0-7, on Day 14 and on Day 28 (isolated laboratory abnormalities that are not associated with signs, symptoms, or a specific clinical diagnosis/syndrome are not collected).
- Clinical adverse events of grade 3 and 4 through Day 28 (isolated laboratory abnormalities that are not associated with signs, symptoms, or a specific clinical diagnosis/syndrome are not collected).
- Clinical events, including death, that are reported on eCRFs as part of the pulmonary+ ordinal outcome or as secondary outcomes through Day 90. These are considered as protocol specified exempt serious events (see 10.2.5) and are not reported on SAE eCRFs unless they are considered related to the study intervention (either the blinded investigational agent/placebo or a study-provided SOC treatment). Protocol exempt serious events are listed in section 10.2.5 and the PIM.
- Serious adverse events, including laboratory-only serious events, through Day 90 that are:
  - Related to the study intervention; or.
  - Not exempt from reporting on the SAE eCRF (events listed in section 10.2.5 are exempt).
- Unanticipated problems through Day 90.
- Deaths through 18 months.
- Hospital readmissions through 18 months.

An overview of safety data collected during the study is given in Table 1.

Table 1 Overview of Safety Data Collection

	Infusion +2 hrs	Days 0-7	Day 14	Day 28	Day 90	Months 6, 12 and 18
Infusion-related reactions and symptoms	X					
Clinical AEs of any grade severity		X	X	X		
Grade 3 and 4 clinical AEs from Day 7 through Day 28*			X	X		
Targeted laboratory abnormalities of any grade		X (Day 5)				
Hospital admissions and deaths		Collected through Month 18				
Targeted clinical events collected as study endpoints**	Collected through Day 90					
SAEs not exempt from reporting (i.e., not considered a protocol specified exempt event)	Collected through Day 90					
Any SAE related to study intervention	Collected through Day 90					
Unanticipated problems	Collected through Day 90					
* Grade 3 and 4 clinical AEs on Days 1-7 are reported each day; those occurring between Days 8 and 14 are reported at the Day 14 visit, and those occurring between Days 15 and 28 are reported at the Day 28 visit. ** see section 10.2.5 for protocol specified exempt serious events and the PIM						

Definitions and methods of reporting each type of event are given below.

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE is any untoward or unfavourable 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.

In Appendix H details are outlined for each investigational agent under study of the following: specific AEs observed to be possibly associated with the agent in question, and how to monitor for, clinically handle and report such AEs, should they arise.

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

An Unanticipated Problem (UP) is 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 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 per the Investigator's Brochure(s) (IBs).

Furthermore, a UP could be an expected event that occurs at a greater frequency than would be expected based on current knowledge of the disease and treatment under study. The DSMB providing oversight to the study may make such an assessment based on an aggregate analysis of events.

10.1.4 Severity

The investigator will evaluate all AEs 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:

Table 2 GENERIC AE GRADING SCALE

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 is related to the study intervention. It will be assessed for SAEs and UPs. This assessment will be made for both the blinded investigational agent/placebo and any study-supplied SOC treatment using the following guidelines:

- Reasonable possibility: There is a clear temporal relationship between the study intervention and the event onset, and 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, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

The causality assessment is based on available information at the time of the assessment of the event. The investigator may revise these assessments as additional information becomes available.

10.1.6 Expectedness

Expectedness will be assessed for SAEs using the Reference Safety Information section of the IBs for the investigational agent and any study-provided background therapy.

The expectedness assessment is based on available information at the time of the assessment of the event. The investigator may revise these assessments 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 on 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 Infusion-related reactions

Infusion-related signs/symptoms of any grade that are new or have increased in grade compared to their pre-infusion level are reported on the infusion eCRF checklist for the investigational agent/or matched placebo if they occur during or within 2 hours post infusion. Any infusion related reaction assessed as meeting SAE criteria will also be reported on an SAE eCRF.

10.2.2 Targeted Laboratory Abnormalities

Selected laboratory tests are reported from assessments made on Day 0 and Day 5. These values will be associated with a severity grade centrally using the laboratory test results reported on the eCRFs (using normal ranges when applicable), and with the DAIDS AE Grading Table.

Other laboratory abnormalities identified in the course of the participant's routine clinical care (e.g., an isolated elevated glucose level) are not reportable as AEs unless they are associated with signs or symptoms, or associated with a specific clinical diagnosis/syndrome (e.g., diabetic ketoacidosis), in which case the syndrome/diagnosis is reported on the appropriate adverse event eCRF. In addition, if an isolated laboratory test result meets SAE reporting criteria (e.g., the laboratory abnormality meets the criteria for a serious event as outlined in section 10.1.2), it should be reported as an SAE on the SAE eCRF.

10.2.3 Clinical adverse events of any grade severity on Days 0-7, 14 and 28

Beginning 2 hours post-infusion of the investigational agent or matched placebo, on Days 0-7, clinical AEs that are new or that have increased in grade compared to their pre-infusion level will be reported on eCRFs.

On Day 14 and on Day 28 AEs of any grade severity that the participant reports that day will also be collected on an eCRF.

These reportable AEs should be assessed for SAE/UP (sections 10.2.6 and 10.2.7) reporting on the SAE eCRF or for protocol specified exempt serious events (section 10.2.5) reporting on the eCRF documenting the hospital course.

This information supplements the data collected on Grade 3 and 4 events since the last study visit described in section 10.2.4.

10.2.4 Grade 3 and 4 clinical adverse events through Day 28

Adverse clinical events reaching Grade 3 or 4 severity level that occur between days 8 and 28 will be reported on an eCRF at the Day 14 and Day 28 visits. The date the event reached the indicated grade will be collected to permit time-to-event analyses.

These reportable AEs should be assessed for SAE/UP (sections 10.2.6 and 10.2.7) reporting on the SAE eCRF or for protocol specified exempt serious events (section 10.2.5) reporting on the eCRF documenting the hospital course.

10.2.5 Protocol specified exempt serious events

Protocol specified exempt serious events are listed below. These events are reported systematically on eCRFs as study endpoints during follow-up and are further defined in the PIM. They will NOT be reported on the SAE eCRF ***unless the investigator considered that there was a reasonable possibility that the study intervention (blinded investigational agent/ placebo or study-supplied SOC treatment) caused the event (see section 10.2.6)***. These events may occur during the initial hospitalization, lead to a re-admission, or occur in a later hospitalization during follow-up.

The following are **protocol specified exempt serious events.** As noted above, these events are not reported on the SAE eCRF unless they are considered related to the study intervention (blinded investigational agent/placebo or study provided SOC).

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep vein thromboembolic events
- Respiratory failure defined as receipt of high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO
- Hypotension requiring vasopressor therapy
- Renal dysfunction requiring renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections

10.2.6 Reportable SAEs

Reportable SAEs for this study are serious events that are:

- Related to the study intervention; or.

- Not exempt from reporting on the SAE eCRF (events listed in section 10.2.5 are exempt).

Deaths, life-threatening events, and other SAEs considered potentially *related to the blinded investigational agent/placebo or study-supplied SOC treatment*, irrespective of whether the event is mentioned above as a protocol specified exempt serious event, that occur from the time of infusion of the study intervention through the Day 90 visit must be recorded by sites on the SAE eCRF **within 24 hours of site awareness**.

Suspected unexpected serious adverse reactions (SUSARs) are reportable SAEs that are assessed as related to a study intervention and are unexpected per the Reference Safety Information of the IB for that intervention. SUSARs are reported from the INSIGHT Safety Office to applicable regulators in an expedited fashion. SUSARs that result in death or are immediately life-threatening are reported to regulators within 7 calendar days of receipt. All other SUSARs are reported to regulators within 15 calendar days. The INSIGHT Safety Office will generate a Safety Report for each SUSAR for distribution to investigators and other parties. Investigators are responsible for submitting Safety Reports to their overseeing IRB/EC per requirements.

SAEs that are not protocol specified exempt serious events and that are not related to the study intervention (blinded investigational agent/placebo or study-supplied SOC treatment) must be reported on the SAE eCRF within 3 days of site awareness.

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.”

10.2.7 Unanticipated Problems (UPs)

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. Investigators are responsible for submitting UPs that are received from the sponsor to their overseeing IRB/EC. Investigators must also comply with all reporting requirements of their overseeing IRB/EC.

10.2.8 Deaths

All deaths are reported on the eCRF for deaths. Deaths considered **related to the study intervention** (blinded investigational agent/placebo or study-supplied SOC) must **also** be reported as an SAE.

10.2.9 Pregnancy

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who is or becomes pregnant while participating in this study.

The participant will be followed to determine the outcome of the pregnancy and reported on the Pregnancy Outcome eCRF.

Male participants with partners who become pregnant

If an investigator learns that a male participant’s partner becomes pregnant while the male participant is in this study, the investigator is asked to attempt to obtain information on the

pregnancy, including its outcome, after obtaining consent from the pregnant partner. The outcome of the pregnancy will be reported on the Pregnancy Outcome eCRF.

10.3 Medical Monitor

A Medical Monitor appointed by the sponsor will be responsible for reviewing all SAEs, making an independent assessment of causality and expectedness, preparing sponsor safety reports, and communicating as needed with the DSMB and the Investigational New Drug (IND) holder 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 infusion-related reactions or other unanticipated AEs). If the study is temporarily halted or stopped for safety reasons, IRBs/ethics committees will be informed. The IND holder and 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/ethics committees of the decision to resume the study.

11 Statistical Analyses and Monitoring Guidelines

This section describes the analysis for primary and secondary outcomes of the trial. A more detailed statistical analysis plan (SAP) has been developed as a separate document. The SAP for each investigational agent may be updated by the blinded statisticians prior to unblinding for a specific treatment comparison.

Comparisons between each investigational agent and concurrent controls will be by intention to treat unless otherwise stated. Safety comparisons will be carried out on participants who received a complete or partial infusion of the investigational agent unless otherwise specified. It is anticipated that all study site pharmacies serving active sites will be randomizing all agents under study at any given time, but if this is not the case, comparisons will be restricted to the set of controls enrolled at study site pharmacies where the drug was available for randomization. Specifically, the control group for an investigational agent will consist of those participants who could have been randomized to the agent, but were randomized to a control group instead (i.e., randomized to the matched control group of one of the agents included in the randomization). Agents will be compared to controls, but not to each other, unless explicitly specified in the analysis plan.

All analyses will utilize 2-sided tests with a 5% significance level unless otherwise noted.

11.1 Analysis of the Primary Efficacy Endpoint

The evaluation for the primary efficacy outcome of the phase III trial, time to sustained recovery through Day 90, will be based on Gray's test with rho=0.[80] The test will compare the investigational agent versus the control group by intention to treat, and will be stratified by disease severity at entry and study site pharmacy. Gray's test compares the cumulative incidence functions for *sustained recovery* between the treatment groups, taking into account the "competing risk" of death in analysing *sustained recovery*. Gray's test with rho=0 is the analogue of the log-rank test in the presence of competing risks. Cumulative incidence functions for *sustained recovery* will be estimated by treatment group using the

Aalen-Johansen estimator,[81] and the recovery rate ratio (RRR) (investigational agent versus control) for *sustained recovery* will be estimated using the Fine-Gray method,[82,83] stratified by disease severity at entry and study site pharmacy; the RRR will be estimated as a point estimate with a 95% CI. The Aalen-Johansen estimator for cumulative incidence functions is the analogue of the Kaplan-Meier estimator in the presence of competing risks. The Fine-Gray method is the competing risks equivalent of Cox proportional hazards models; the RRR compares the cumulative incidence rates of *sustained recovery* between the study arms, and is a sub-distribution hazards ratio. Analyses for the *sustained recovery* endpoint require methods that take into account the competing risk of death, as participants may die before ever achieving *sustained recovery*. The "sustained recovery" outcome requires knowledge of a participant's residence status for at least 14 days after arriving "home" (as defined in section 4.2); since all participants are hospitalized at study entry, it takes at least 15 days to attain this outcome.

Sensitivity analyses for the primary endpoint comparisons will include consideration of home oxygen used as described in section 4.2.2.

11.2 Analyses of Secondary Efficacy Endpoints, Safety Outcomes, and Subgroups

Mortality is a key secondary outcome; time to death will be compared between the investigational agent versus control using a log-rank test, stratified by disease severity and study site pharmacy; the hazard ratio will be estimated using a stratified Cox proportional hazards model, and the proportion of participants who died by fixed time points (for example, Day 28 or Day 90) will be estimated using Kaplan-Meier estimates. To supplement the separate analyses of *time to sustained recovery* and *time to death*, the two endpoints will be analyzed jointly using the "win ratio" method[74] for the composite outcome of time to recovery or death. At a given time point (Day 90), the win ratio statistic ranks participants' outcomes into three ordered categories, death, alive but not achieved sustained recovery, alive and achieved sustained recovery, and ties are broken by time since randomization. So, time to death is first used to determine the winning group (i.e., longer time to death), then time to sustained recovery is used to determine the winning group (i.e., shorter time to recovery): in this manner these conflicting outcomes can be combined into a composite while recognizing the importance of mortality. Matching on baseline disease severity will be used to estimate the win ratio statistic. This combination of time to sustained recovery and time to death is also a key secondary analysis.

The primary safety outcome is a composite of grade 3 or 4 events, SAEs, clinical organ failure or serious infections, or death through Day 5, and tests for differences between treatment arms will be conducted with a Cochran Mantel Haenszel test stratified by study site pharmacy and disease severity at study entry, comparing the proportion of participants who had experienced any of these events by Day 5. Treatment differences for each of the components of this composite outcome will also be summarized. This composite safety outcome will also be assessed at Day 28 and Day 90. Proportions of participants who experienced any of these events will be compared using stratified Cochran Mantel Haenszel tests and logistic regression. Time to event analyses will also be used to summarize this composite safety outcome. SAEs and grade 3/4 events will be classified by system organ class according to MedDRA®.

Safety analyses also include infusion reactions collected during or within 2 hours after the infusion of the investigational agent or placebo. Proportions of participants who

experienced infusion reactions or prematurely terminated infusions will be summarized by study arm, and Cochran Mantel Haenszel tests will be used to test for differences across arms.

Several other secondary efficacy outcomes will also be investigated. The models will include an indicator for treatment group, and stratify by study site pharmacy and disease severity at study entry as appropriate. Time from study entry to discharge from the hospital admission during which randomization took place will be analyzed using the same methods as described above for time to sustained recovery. Readmissions will be summarized using methods for recurrent events (i.e. those who are readmitted will reenter the risk set).

Both the pulmonary and pulmonary+ ordinal outcome will be assessed on Days 1 through 7; the pulmonary ordinal outcome will also be assessed at Days 14 and 28. Proportional odds models will be used to compare treatment groups for each ordinal outcome. These models will control for study site pharmacy and categories of the pulmonary+ ordinal outcome at baseline. A test for the proportional odds assumption across cumulative categories and stratification covariates will be performed by testing for separate slopes (a partial proportional odds model). In addition, cumulative probabilities of the ordinal outcome categories will be compared between treatment groups using logistic regression models.

Clinical organ failure is a composite of many different organ-specific events, listed in section 4.2.2, item 7. This outcome will be summarized as part of both safety and efficacy analyses. The incidence of organ failure, serious infection or death through Day 28 will be compared between arms using the log-rank test and Cox proportional hazards models. In addition, specific components (e.g., cardiac and vascular dysfunction, or the composite of cardiovascular outcomes and thromboembolic events described in section 4.2.2, item 10) will be analyzed using time-to-event analyses under competing risks, as described above for the primary analysis of sustained recovery. Proportions of participants who experienced organ failure, serious infection or death will be summarized and compared between treatment arms using stratified Mantel Haenszel tests, overall and for specific organ dysfunctions.

Longitudinal models for the logarithm of antibody titers will be fit using generalized estimating equation-based approaches to titers measured at baseline and Days 1, 3, 5, 28 and 90 and interactions between time and treatment group will be investigated to assess if the treatment effect changes over time. The same approach will be used to examine neutralizing titers should such data be available.

The impact of study arm on the primary efficacy (time to sustained recovery) and safety outcomes (composite of grade 3 or 4 events, SAEs, clinical organ failure or serious infections, or death through Day 5 and through Day 28, composite of SAE and death through Day 90) along with mortality will be assessed for subgroups defined by baseline characteristics, including demographics, social determinants, baseline classification of “home”, duration of symptoms at enrollment, clinical history and presentation (including disease severity stratum and pulmonary+ ordinal outcome at baseline), and tests for homogeneity of the treatment effect across subgroups will be carried out. Additionally, subgroup analyses will be conducted for subgroups formed by a disease progression risk score at baseline. The construction of this risk score will be revisited as new investigational agents move through the trial. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error.

11.3 Data Monitoring Guidelines for an Independent DSMB

An independent DSMB will review interim data and use pre-specified guidelines for early evidence of sufficient activity of an investigational agent that justifies continuing enrollment for the agent and expanding eligibility criteria to include participants in disease severity stratum 2 as well as stratum 1. This assessment will be made by the DSMB when Day 5 data for approximately 300 participants in disease severity stratum 1 are available.

For agents which advance to enroll participants in both disease severity strata 1 and 2, the DSMB will continue to review interim data on a regular basis and use pre-specified guidelines to identify agents with clear evidence of efficacy for the primary outcome, and if so recommend unblinding of the trial results for that agent. Conversely, the DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits or if futility assessments indicate that there is low probability that an investigational agent will achieve statistical significance for the primary endpoint of sustained recovery.

11.4 Rationale for Early Futility Analysis

The early futility analysis based on the intermediate outcome of efficacy using the pulmonary and pulmonary+ ordinal outcomes assessed at Day 5 will be carried out for approximately 300 participants entering the trial when only enrolling in disease severity stratum 1. The exact number may vary depending on the rate of enrollment and the timing of the DSMB meeting. The potential benefit of the investigational agents studied is expected to be greatest in this cohort and the Day 5 data provide an early assessment of activity to assess the potential for benefit in the expanded cohort of participants evaluated for the primary endpoint. This early futility analysis is based on Day 5 outcomes because too few primary endpoints of sustained recovery are expected when 300 participants with 5 days of follow-up are available. It allows resources for the platform trial to be more efficiently used by identifying agents early that have a low probability of being efficacious and stopping enrollment for those agents, while at the same expanding enrollment for promising investigational agents that have potential for showing efficacy with a larger sample size based on the primary endpoint.

The sample size of 300 participants in stratum 1 provides 95% power to detect an odds ratio (active/placebo) of 1.60 at the 0.30 (1-sided) level of significance. Data from the ACTT-1 trial (remdesivir group) were used to estimate the category percentages for the placebo group shown in Table 3 below. The percentages shown correspond to an odds ratio of 1.60 and are the basis for the sample size used for the early futility assessment.

Table 3. Hypothesized percentage of participants in each category on Day 5 in the Investigational agent and placebo groups based on aforementioned assumptions

Pulmonary+ Category	Investigational Agent + SOC	Placebo + SOC
1. No limiting symptoms due to COVID-19	3.2	2.0
2. Limiting symptoms due to COVID-19	53.5	43.0

3. Moderate end-organ dysfunction	20.6	23.0
4. Serious end-organ dysfunction	12.8	17.0
5. Life-threatening end-organ dysfunction	5.0	7.3
6. End-organ failure	4.5	7.0
7. Death	0.4	0.7
Total	100.0	100.0

The rationale for a 1-sided alpha level of 0.30 and power 0.95 is based on previous work for 2-stage cancer trials, where like this platform trial an intermediate outcome was used to assess early activity, and a definitive outcome was used to assess efficacy at the end of the trial. A re-analysis of 4 trials suggested a 1-sided significance level between 0.2 and 0.3 was optimal for making a good decision in the early futility assessment. A subsequent paper focused on the potential for estimation bias in selected and stopped treatments and concluded that its degree was generally small.[84,85]

As part of the development of this platform trial, additional work was carried out to support the design. That work is briefly summarized below (personal communication).[86]

Follmann and Proschan considered a 2-stage trial (where a drug would enter the 2nd stage once it had passed the futility assessment) and assumed a sample size of 300 for the initial stage, the decision whether the investigational agent would proceed to the 2nd stage taking place when all 300 participants had completed Day 5, a total sample size of 1000 for the trial, a significance level of 0.30 (1-sided) and power of 0.95 for the initial stage, and a significance level of 0.025 (1-sided) and power of 0.90 for the 2nd stage primary endpoint comparison. For simplicity, one ordinal outcome was assumed. With these assumptions, they showed that power with use of a stage 1 assessment was reduced only slightly from the power without the stage 1 review (0.87 versus 0.90). They cite two advantages to the approach used here compared to the standard phase III trial without an early evaluation: 1) more treatments can be evaluated; and 2) if one-half of the treatments are efficacious and one-half are not efficacious, 40% more efficacious treatments are identified.

11.5 Interim Analyses Guidelines

Stopping guidelines for use by the DSMB are described below. More specific guidance may be specified in the SAP. When several investigational agents are investigated in parallel, each agent will be compared to its corresponding, contemporaneously randomized pooled placebo group. Each investigational agent versus placebo comparison will be treated as a separate clinical trial; stopping boundaries will be derived to allow for multiple interim looks, but will not be additionally inflated to adjust for simultaneous analysis of multiple investigational agents, except when explicitly stated in the agent-specific protocol appendix and statistical analysis plan.

The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference.

11.5.1 Early Assessment of Safety and Futility

For investigational agents with minimal pre-existing data, the pace of enrollment will be initially restricted and the DSMB will be asked to review safety data for the first 20 to 30 participants before increasing the pace of enrollment.

Subsequently the DSMB will carry out regular reviews of safety data reports. These reports will include summaries of lower grade AEs and infusion–related events as well SAEs and deaths, including the primary safety outcome. At the discretion of the DSMB, these reports will be prepared at a frequency they specify.

When approximately 300 participants have been enrolled and followed for 5 days, a futility assessment will be carried out. The criteria that will be used for the early futility assessment of each investigational agent are summarized below:

a. If the investigational agent is superior (i.e. 1-sided $p \leq 0.3$) to placebo for both ordinal intermediate outcomes, then enrollment for the agent will expand to complete the phase III trial.

b. If there is insufficient evidence for superiority versus control (i.e., 1-sided $p>0.3$) in each of the two outcomes, then stop randomization.

c. If there is evidence (1-sided $p \leq 0.3$) for an association for one endpoint and not the other, then the agent may or may not advance depending on the risk/benefit profile emerging from the data at this early stage. If the effect estimate for both outcomes is on the side of benefit, the preference would be towards advancing the agent and expanding enrollment to include disease severity stratum 2.

The DSMB will be asked to review whether the discordance is attributable to a positive or negative effect on extra-pulmonary organ dysfunction (the difference in the two ordinal scale categories, the conditions included in pulmonary+ but not in the pulmonary endpoint), and whether the same ordinal outcomes assessed on other days yield similar results, and weigh the risk/benefit profile. For example, if there is a significant positive effect on the pulmonary score and the lack of significant effect on the pulmonary+ score is driven by a lack of difference in the milder thrombotic symptoms in category 4 of the pulmonary+ scale (e.g. deep venous thrombosis) and there is no evidence of any raised risk of thrombosis overall, the agent will advance. Conversely, if the agent is superior to the control group with respect to the pulmonary outcome, but clearly inferior to the control group with respect to the pulmonary+ outcome or has a concerning safety profile, it will not advance. Analyses of the primary endpoint, “time to sustained recovery”, will also be provided to the DSMB, as supporting information.

After considering the aforementioned guidelines, the DSMB will be asked to consult with the Food Drug Administration before making their recommendation in order to consider any relevant external information.

The power and type 1 error of the complete decision rule considering both outcomes depends on the correlation between the two outcomes and on the DSMB’s assessment of discordant outcomes. Table 4 shows the power to identify an agent with an hypothesized OR=1.60 using the two-outcome decision rule, along with the simultaneous type 1 error, assuming correlations of r=0.8 and r=0.9 between the test statistics for the two outcomes.

For example, if an agent is advanced when one or both of the outcomes show superiority, and assuming a correlation of 0.8, then an agent with OR=1.60 will be ”detected” and advanced with probability of 98% (power), while an ineffective agent would be advanced with probability of 39% (type 1 error). This balance between power and type 1 error is selected for the intended approach to making the early futility assessment.

Table 4. Power and type 1 error for the two-outcome decision rule to expand enrollment to strata 1 and 2 for an investigational agent for correlations of r=0.8 and 0.9 between the marginal test statistics for the two outcomes. OR=1.60, total sample size 300.

	r = 0.8		r =0.9	
Treatment of discordant intermediate outcomes	**Power**	**Type 1 error**	**Power**	**Type 1 error**
Expand enrollment if one or both outcomes show superiority	0.98	0.39	0.97	0.36
Expand enrollment if both outcomes show superiority	0.93	0.21	0.93	0.24

During the enrollment of approximately 300 participants in disease severity stratum 1, the safety reviews by the DSMB will include treatment comparisons of the safety outcomes described in section 4.2.2 that are measured in the first 28 days of follow-up. In addition, for each ordinal outcome at Day 5, a Haybittle-Peto boundary using a 2.5 standard deviation (SD) for the first 50 participants enrolled and 2.0 SD afterwards will used as a guideline for harm.

11.5.2 Monitoring Guidelines for the Primary Endpoint

As a guideline, asymmetric boundaries will be provided to the DSMB to monitor the primary endpoint (time to sustained recovery) for each pairwise comparison of investigational agent versus control. For monitoring overwhelming benefit of an investigational agent, the Lan-DeMets spending function analogue of the O’Brien-Fleming boundaries will be used; for monitoring harm for the primary endpoint, a Haybittle-Peto boundary using a 2.5 standard deviation (SD) for the first 50 participants enrolled and 2.0 SD afterwards will used as a guideline. The Lan-DeMets boundary used will be chosen to preserve a 1-sided 0.025 level of significance. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the number of sustained recoveries at the interim analysis (divided by the number of sustained recoveries planned) (843). With this approach, less evidence will be required for crossing a boundary for harm than for benefit. To account for a possible delay in the ascertainment of the primary endpoint status, sensitivity analyses will be provided to the DSMB.

Futility analyses will be carried out. The aim of these analyses will be to consider whether an investigational agent should be discontinued due to a low probability of achieving statistical significance for the primary endpoint of sustained recovery at the completion of the 90 day follow-up. Conditional power calculations for time to sustained recovery will be presented under a range of scenarios. In the primary futility analysis, the treatment effect for the future, as yet unobserved follow-up will be assumed as hypothesized in the study design (RRR=1.25); in alternative scenarios, the treatment effect for future follow-up will be assumed to be similar to the observed effect, or more favourable for the investigational agent. Typical futility guidelines recommend stopping a trial when conditional power is

below 10%-15%, with the higher value later in follow-up as measured by information time.[87] These analyses will be presented to the DSMB by the unblinded statisticians for each pairwise comparison.

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) and/or that positive SARS-CoV-2 laboratory testing will be used to enquire about potential enrollment. 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, 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, 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 must be obtained (see sample in Appendix A) prior to conducting any study-related procedures. For patients who are incapacitated, 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 is incapacitated. 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. Other methods of obtaining documentation of consent may be used when site staff are unable to be in direct contact with a potential participant or a legally-authorized representative due to infection-control restrictions. 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

Sites in the US will conduct this trial under the terms of the IND and will adhere to FDA regulations found in 21 CFR 312, Subpart D. Sites in countries other than the US will not conduct the trial under the IND. As stated in Section 12.2 above, all sites will conduct the trial in accordance with the requirements of GCP as codified in their local law and regulation, under the oversight of their institution and competent regulatory authority.

As part of fulfilling GCP and FDA requirements for adequate trial monitoring, multiple modalities will be employed. The objectives of trial monitoring are to ensure that participant rights and safety are protected, to assure the integrity and accuracy of key trial data, and to verify that the study has been conducted in accord with GCP standards and applicable regulations.

A specific risk-based protocol monitoring plan will be developed. The plan will include strategies for central monitoring of accumulating data and will take into account site-level quality control procedures. On-site monitoring visits for targeted source document verification and review of regulatory and study pharmacy files will be conducted when possible, but these tasks will most likely need to be handled remotely during the pandemic. The monitoring plan will outline the frequency of this aspect of monitoring based on such factors as study enrollment, data collection status and regulatory obligations.

Appendix A Sample Informed Consent form (not agent-specific)

Sample Informed Consent form

Short Title: Therapeutics for Inpatients with COVID-19 (TICO)

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: **A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19**

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:

We are asking you to join a research study about 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

PID: _____

your choice. You can talk about this 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 for COVID-19.

Why are we doing this study?

We are studying experimental medicines called neutralizing monoclonal antibodies (nMAbs). This general type of medicine has been approved to treat many other diseases, but we do not know if it will help in treating COVID-19. We are trying to find out if giving these nMAbs can help people in the hospital with COVID-19 get better and go home faster. We are also trying to see if it is safe. The nMAbs in this study are not yet approved by the FDA or any other government agency.

We are asking you to join the study because you are in the hospital with COVID-19.

What do you have to do if you decide to be in the study?

The study staff at your hospital will check to see if there is any reason you should not be in the study. They will check your medical history. They will look at tests commonly done for your condition.

We are testing more than one type of nMAbs. If you join the study, you will be assigned by random chance – like flipping a coin or rolling dice – to get one of these nMAbs or a placebo. For example, if nMAbs were under study, you could be in any of the groups below:

Investigational nMAb A

Investigational nMAb B

Placebo (a salt water solution that has no medicine in it)

Not all of the nMABs listed abovemay be available to you right now

If this is the case, then you will be told which ones are available.

You will have an equal chance of getting any of the available nMAbs or the inactive placebo. If all of them are available, then you have a 1 in chance of being in each of the groups listed above. *[Insert number of possibilities from the list above, including placebo, e.g. "3"]*

This means your chances of getting an nMAbs drug instead of placebo are ___ out of ___, or __%. *[insert the number of active possibilities from the list above, then the total number of possibilities, e.g., "2 out of 3." Then record the % to which that corresponds, e.g., "67%." Repeat the above for each possibility as an active treatment is eliminated.]*

Your doctor will not decide which group you are in and, just like you, will not know whether you are getting an experimental nMAb or inactive placebo. None of the study staff will know whether you are getting an nMAb or the placebo.

PID: _____

We will tell you more about each nMAb you could get in a separate information sheet. You will be given an information sheet for each of the available nMAbs.

You will get the study product (either the experimental nMAb or the inactiveplacebo) only once, on the day you join the study (study Day 0). You will get the study product through a plastic intravenous (IV) tube attached to a needle in your arm. This is called an infusion. The information sheets will tell you how much liquid the infusion will be and how long it should take. It may sometimes take longer depending on how your body reacts to the infusion.

The nMAb is the only thing you will be given that is completely experimental.

None of the nMAbs we are studying have been approved by the United States Food and Drug Administration (US FDA) or any other regulatory body in the world, and they can only be used in research. There are many treatments being studied for COVID-19, and some have received US FDA emergency approval or other types of approval to be used in some people with COVID-19. Your doctor and the study team will tell you about any treatment options you may have.

As part of the study, you will also get a drug called remdesivir (also called Veklury) for your COVID-19, unless your doctor thinks remdesivir would not be safe for you to take. Remdesivir is given once a day by infusion for up to 10 days while you are in the hospital, Remdesivir was shown in an earlier study to help people get better more quickly from COVID-19. Remdesivir was recently approved by the US FDA and also has approval in other countries.

Any other medicines or treatments you get will be what you would usually get in this hospital for your condition. There may be some additional procedures or testing done for study purposes. We will describe these below.

You will be in the study for 18 months. Most of the information we need for the study will be recorded in the first 3 months.

We do not know what effects nMAbs may have on a pregnancy or unborn baby. There may be bad effects or no effects. If you decide to join the study, we strongly advise you to not have sex that could make you or a partner pregnant during the year you are in the study. This may involve not having sex at all (abstinence), or you may use effective birth control (hormonal contraceptives like birth control pills or barrier methods with spermicide) to avoid pregnancy. Methods like rhythm, sympto-thermal or withdrawal are not considered effective for preventing pregnancy. You can ask the study team about this if you have questions or concerns.

If you become pregnant during the study, please let your study team know as soon as possible. We will ask to follow you until your pregnancy is over, to see if there were any problems that may have been caused by any of the study treatments.

PID: _____

If your partner becomes pregnant, please let your study team know as soon as possible. We will ask your partner for consent to allow us to get basic information about her pregnancy.

You will also need to agree to not be in any other COVID-19 study for the first 5 days you are in this study. There may be exceptions to this requirement. We will tell you about any other studies you can be in during the first 5 days of this study so you can make a choice.

This is what you will be doing for the study:

Up to 1 day before you get study product	**Day 0 (the day you get study product)**	**Day 1, Day 3, Day 5**	**Day 2, Day 4 Day 6, Day 7, Day 14, Day 42, Day 60, Day 75**	**Day 28 and Day 90**
Informed consent (this document) Check to see how you are feeling Your medical history Contact information like telephone numbers and addresses for you and at least two close relatives or friends	Infusion of study product (the experimental nMAb or else placebo) Whether you are taking certain medicines Blood tests to check your health (9 mL, about ½ tablespoon) Blood for future research (18 mL, about 1 tablespoon) A swab of your nose for virus	How you are feeling Blood for future research (18 mL, about a tablespoon) On Day 5, also whether you have taken certain medicines, and blood tests to check your health (9 mL, about ½ tablespoon)	How you are feeling (Days 2, 4, 6, 7, 14, 60) Update on return to home (Days 14, 42, 60, 75) These “visits” may take place by phone.	How you are feeling Blood for future research (18 mL, about a tablespoon) On Day 28, also whether you have taken certain medicines Update on return to home

If you leave the hospital after just a few days, we will ask you to come back to give a blood sample on Day 3 and Day 5 of the study. You might instead be visited in your home by a professional working for the study to get this blood sample. We will also need to take a blood sample from you on Day 28 and Day 90.

After Day 90, we will contact you three more times by phone, at 6 months, 12 months, and 18 months, to see how you are doing and whether you have been in the hospital for any reason.

We may need to get some information from your medical record:

- By signing this consent, you agree to let us get information for this study from your medical record.
- By signing this consent, you are giving us permission to contact other hospitals or medical facilities if you are admitted there during the time you are in the study. We will contact them to be sure we know how you are doing.

PID: _____

- We will ask you to give us information about other people we can contact if we are not able to reach you after you leave the hospital, so we can find out how you are doing.

PID: _____

We will send the information you give us to the University of Minnesota (UMN) in the US where it will be stored and analyzed. In this information, only a code number, your year of birth, and a 3-letter code that the study staff chooses identifies you.

The study staff here at this site is responsible for keeping your information safe from anyone who should not see it.

We will send the blood and nose swab samples to a laboratory in the US for storage. We will keep them for as long as we have the funding and space to do so, which we expect to be many years. There is more information below about how we will use these samples.

Why would you want to be in the study?

If you get the experimental medicine, it is possible it may help you get better, or that you may get home faster, but we do not know that.

Remember that some of the people in this study will get inactive placebo, and will not get any experimental nMAb.

By being in this study, you will help doctors learn more about how to treat COVID-19 in people in the hospital. Because many people are getting hospitalized with COVID-19, this could help others. There may be a large health impact if a treatment proves to be safe and to work.

Why would you NOT want to be in the study?

If you do get the nAb, it may not help, or it may have harmful side effects, so being in the study may not help you.

What are the risks or side effects of the experimental nMAbs?

All treatments have risks and may cause side effects. These may happen to you from the study treatment.

Any medicine can cause an allergic reaction. You may have an allergic reaction to the study treatment, including hives, trouble breathing, or other allergic responses. Allergic reactions like these are likely to be rare, but may be severe or life-threatening.

Getting nMAbs like the ones in this study may cause your body to release chemicals called cytokines. A cytokine reaction may have any of the symptoms listed above, as well as:

fever

muscle aches

PID: _____

nausea

vomiting, and/or

headache.

We will watch over you while you are being given the infusion of the study product and for at least 2 hours after the infusion is finished. We will give you medical care right away if you need it to treat any side effects from the infusion.

The fluid needed to give the experimental nMAb or the placebo may overload your body if you have problems managing fluids due to COVID-19 or other conditions. We expect this to be rare.

There are discomforts and risks with blood draws and getting a swab of your nose. You will have these things done while you are in the hospital even if you are not in the study. You may have some pain, bleeding, or bruising when a needle is put into your vein to draw blood or to give the study infusion. Getting your nose swabbed can be uncomfortable and you might gag. These discomforts and risks are not very different from what you would experience if they were done as part of your regular hospital care for COVID-19.

What if you are pregnant or breastfeeding?

If you are pregnant or breastfeeding, you cannot join this study.

Additional information:

Here is some additional information about the study that may help you make your choice about whether you want to be in the study.

The NIH, an agency of the US Federal government, is paying for this study.

We are required to follow all rules and regulations for human research as well as the laws of each country where the study is being done.

This study is taking place in several countries. We expect to enroll about 1,000 people around the world for each nMAb we are studying.

You do not have to join this research study if you do not want to. If you choose to join the study, you can stop at any time. If you choose not to join or to stop, the medical care you are getting outside of the study will not change.

If we get any new information that might change whether you want to join or stay in the study, we will tell you right away.

PID: _____

If you do not want to be in this study, you will still get the usual care to treat COVID-19. However, you cannot get the nMAb medicine, because it is experimental.

Vaccines against the virus that causes COVID-19 are starting to be available. The US Centers for Disease Control and Prevention (CDC) recommends that people wait for at least 90 days after they've been given nMAbs before they get the vaccine. Some nMAbs stay in the body for about 90 days. We do not know if these antibodies change how you respond to the vaccine during that time. The nMAbs being used in this study are specially made to stay in your body for more than 90 days. We do not know if these longer-lasting nMAbs will change how you respond to the vaccine if you get the vaccine after more than 90 days.

What are the risks and benefits of taking remdesivir?

Remdesivir has been shown to help people who are in the hospital and moderately to severely sick with COVID-19 get better about 4 days faster than people who got a placebo. You may be given remdesivir to treat your COVID-19 even if you do not join this study.

The most common side effects of remdesivir included abnormal liver function test results, abnormal blood clotting test results, constipation, nausea, vomiting, decreased appetite, and headache. The abnormal liver function tests lasted longer than a few days in some people, but went back to normal within a few weeks or less.

Remdesivir might affect the way that other medications are processed by your body. They might stay in your body longer, or shorter, at higher or lower levels. At the time this consent was written, one person in this study had an increase in the level of a medication in their blood that was considered by study doctors to be at least possibly related to having taken remdesivir. There did not appear to be any harm from this temporary change. You can ask the study team more about this if you are concerned.

Some people may have side effects after the infusion of remdesivir. Other people may have no side effects. People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. Allergic reactions may be severe or life-threatening. This is very rare but is also a possible effect of any drug. You will be monitored closely while you are getting remdesivir, and short-term medical care will be provided to treat any side effects.

What are the costs to you?

PID: _____

We will give you the study treatment at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

[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 hospital costs.

Will you be paid to be in the study?

We will compensate you for your time and inconvenience participating in the study. *[Specific details to be completed by site.]*

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 "What happens to the blood and swab samples?", 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.

What happens to the blood and swab samples?

PID: _____

We will send the blood and swab samples to a central laboratory in the United States. You and your doctor will **not** get the results of any tests done on these samples. We will **not** test your DNA (your genes). We will not sell your samples and they will not be used for research aimed at making money (commercial research). The laboratory where the samples are stored will not have any information that could identify you.

The blood samples will measure how many COVID-19 antibodies are in your blood. This will tell us how your immune system responded to your COVID-19. The swab sample will be used to see how much virus is in your body.

Any blood or swab samples that are left over after these tests will be stored at the central laboratory for as long as we are able to keep them. We hope to use these in the future to answer other questions about COVID-19, the virus that causes it, and how people respond to treatment. You and your doctor will **not** get any results from these tests. Some of the blood will also be given to the company that made the study medicine to help them learn more about its effects.

You can withdraw your consent for us to keep these samples at any time. Let your study team know if you do not want the study to keep your samples anymore, and every effort will be made to destroy all of your samples that are still at the central laboratory.

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, including the US FDA.

They are committed to protecting your privacy.

As the research staff at *[inset the name of the hospital/clinic]*, we are required to make sure that people not involved with this study cannot see your research and medical

PID: _____

information. We will keep your research files in a safe place and will handle your personal information very carefully.

Your study data are sent electronically to the UMN in the US through a secure system. By signing this consent, you agree to having your data sent to UMN. No information that could directly identify you is sent to UMN. This is called "pseudonymized data". Access to the data at UMN is limited through security measures, and no data breach or unauthorized access has ever occurred in this system. After the study is over, the data will be stored securely for the period required by law.

Your study data will be shared with the US National Institutes of Health (which is paying for this study), and with regulators that oversee the study, including the US FDA, as required by law. Your study data will also be shared with the drug company that provides the study medicine to help them develop the drug.

UMN may share your data and samples with other people who study COVID-19. UMN will remove any information that could possibly be used to identify you before sharing. This is called "anonymizing the data." We will not ask you for additional consent for this sharing. UMN will only share data and samples for research projects that are approved by the group that is conducting this study.

This study has a Certificate of Confidentiality from the US Federal Government. This means that UMN cannot share any data it has about you with national, state, or local civil, criminal, administrative, legislative, or other authorities unless you specifically allow us to share it.

A description of this clinical trial is available at http://www.ClinicalTrials.gov, as required by law, and on the EU Clinical Trials Register (http://www.clinicaltrialsregister.eu/). These websites will not include your name or any other direct identifiers such as your contact information. These websites will include a summary of the results of this research once the study has been completed. You can search either website at any time.

[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.

PID: _____

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

[The following section (up to "What if you have problems or questions?") 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. It will vary from place to place whether it must be in this consent document, a separate consent document, or an information sheet that does not require signature. The amount of information provided may be reduced to meet the requirements of a particular country (e.g., not all countries/ECs require an enumeration of all of a data subject's rights).]

What are your rights regarding your data?

The UMN is a public research university, and this study is funded primarily by a grant from the US Federal government. UMN and the study funding source require the sponsor (UMN) to follow regulations and policies that are meant to protect your privacy. UMN is also required to comply with the General Data Protection Regulation (GDPR), because it processes data obtained from people in Europe.

There is no specific authority overseeing the processing 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.

The GDPR gives you additional rights which we tell you about below.

Right to Information

You have the right to know what data about you is being processed. You can also get a free copy of this data provided.

Right to Correction

You have the right to correct any information about you which is incorrect or had become incorrect.

Right to Erasure/Anonymization

PID: _____

The sponsor is required under both EU and US law to retain data from research studies like this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your study center that links your identity to the pseudonymized data held by the sponsor. This means that no one would ever be able to link the data held by the sponsor to you personally.

Right to Restriction of processing

Under certain conditions, you have the right to demand processing restrictions, i.e. the data may then only be stored, not processed. You must apply for this. Please contact your study physician or the data protection officer of the study center if you want to do so. This right may be limited if the restriction would affect the reliability of the study results.

Right to Data portability

You have the right to receive the personal data that you have provided to the study center. This will allow you to request that this information be transmitted either to you or, where technically possible, to another agency designated by you.

Right to Contradiction

You have the right to object at any time to any specific decision or action taken to process your personal data. This right is limited for data that have already been processed and may be limited if your objection would affect the reliability of the study results.

Right to Withdrawal of this consent

You may withdraw your consent at any time with effect for future data collection. This withdrawal may be in an informal or verbal communication to your investigator. If you withdraw your consent this will not affect the lawfulness of the data processing that has been or will be done with data collected until you withdraw consent. Data already collected will be anonymized.

If you would like to use one of these rights, please first contact the person responsible for the data collection at your study center:

PID: _____

Person responsible for data collection at the study center:	
Name:	
Address:	
Phone:	
Email	

For concerns about data processing and compliance with data protection requirements you can also contact the data protection officer responsible for the study center:

Data protection officer responsible for the study center:	
Name:	
Address:	
Phone:	
Email	

In addition, you have the right to lodge a complaint with the competent authority if you believe that the processing of personal data concerning you is contrary to the GDPR:

Data protection authority responsible for the study center:	
Name:	
Address:	
Phone:	
Email	

What if you have problems or questions?

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]

PID: _____

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE TICO STUDY

I have read this consent or have had it explained to me. I have had a chance to learn about each of the nMAbs that I could be assigned to get. I have been given a copy of that information to keep. I believe that I understand the information. By signing this consent, I am stating that I volunteer to join this study. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of this signed and dated consent.

If you agree to be in this study, please sign 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

_____

PID: _____

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

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 Schedule of assessments

	Screen or Day 0	Day 0	Follow-up Study Day; shaded columns denote in-person visits															
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**6M**	**12M**	**18M**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+10**	**±14**	**±14**	**±14**
ELIGIBILITY & BASELINE DATA																		
Informed consent	X																	
Baseline medical (incl. duration of COVID-19) and social history	X																	
Baseline medications	X																	
Symptom-directed physical exam by the clinical team	X																	
Review SARS-CoV-2 test results	X																	
Local laboratory testing	X						X											
Urine pregnancy test or other documentation of pregnancy status	X																	
STUDY INTERVENTION																		
Randomization		X																
Study Drug/Placebo Administration		X																
Assess infusion completion and adverse reactions		X																
STUDY PROCEDURES																		
Clinical assessment for pulmonary ordinal outcome	X	X	X	X	X	X	X	X	X	X	X							
Clinical assessment for pulmonary+ ordinal outcome	X	X	X	X	X	X	X	X	X									
Vital signs for NEW score assessment	X																	
Respiratory function scale assessment	X																	
Hospitalization status					X		X		X	X	X		X		X	X	X	X
Changes in residence/facility										X	X	X	X	X	X			
Interim medical history									X	X	X		X		X			
Interim medications							X				X							

Clinical AEs of any grade on days indicated		X	X	X	X	X	X	X	X	X	X						
Clinical AEs reaching grade 3 or 4 severity through Day 28										X	X						
Research sample storage (plasma and serum)[2]		X	X		X		X				X				X		
Midturbinate swab for central SARS-CoV-2 viral load testing[2]		X															
SAEs and unanticipated problems			Report as they occur														
Deaths			Report as they occur														
Hospitalization Summary			Report upon hospital discharge														
Hospital Readmissions			Report upon hospital discharge														

[1] Screening must be performed within 24 hours of randomization.

[2] Blood draw and swab collection in some cases can be obtained after randomization but before the infusion. If it is not possible to do an in-person on Day 3 or Day 5, the blood draws may be done one day earlier or one day later (but the participant should be telephoned to record the clinical data on the indicated study day).

Appendix C INSIGHT 014 / ACTIV-3 protocol team

To oversee the implementation of this master 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 representatives
- Representatives from collaborating trials networks
- Representative from ACTIV-2 protocol team
- Representatives from collaborating laboratory representatives
- Representatives from collaborating manufacturers of investigational agents
- 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 014 protocol and to other information pertinent to the study:

- DAIDS toxicity table: (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables)

- INSIGHT Publications and Presentations Policy (http://insight.ccbr.umn.edu/resources/P&P_policy.pdf)

- Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control (ECDC) guidance on how to handle infection control measures (https://www.cdc.gov/sars/guidance/i-infection/healthcare.html and https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings).

- Treatment guidelines, incl from NIH and WHO (https://www.covid19treatmentguidelines.nih.gov/, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation and https://www.ersnet.org/covid-19-guidelines-and-recommendations-directory)

Appendix E LIST OF ACRONYMS

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
ADE	antibody-dependent enhancement
AE	adverse event
ARDS	acute respiratory distress syndrome
CCP	convalescent plasma containing COVID-19 antibodies
CDC	Centers for Disease Control and Prevention (US)
CHF	Congestive heart failure
CI	confidence interval
COVID-19	Coronavirus-Induced Disease 2019
CTSN	Cardiothoracic Surgical Trials Network
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
hIVIG	hyperimmune intravenous immunoglobulin from COVID-19 survivors
HR	hazard ratio
ICC	International Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Institutional Ethics Committee

IgG	immunoglobulin G
IL-6	interleukin 6
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	interquartile range
IRB	Institutional Review Board
IV	intravenous
IVIG	intravenous immunoglobulin
LAR	Legal Authorized Representative
mAb	monoclonal antibody
MI	Myocardial infarction
mL	milliliter
NAT	Nucleic acid test (to identify genomic material; some uses amplification)
NEW	National Early Warning
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
NIHSS	National Institutes of Health Stroke Scale/Score
nMAb	Neutralizing Monoclonal Antibodies
OHRP	Office for Human Research Protections (US)
OR	odds ratio
PCR	polymerase chain reaction
PETAL	Prevention and Early Treatment of Acute Lung Injury
PHI	personal health information
PIM	Protocol Instruction Manual
RBD	receptor-binding domain
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TOC	trial oversight committee
UMN	University of Minnesota
UP	Unanticipated problem
US	United States of America
VA	Veterans Administration
WHO	World Health Organization

Appendix F National Early Warning (NEW) Score

Criteria	Point Value
Respiratory Rate (breaths per minute)	
≤8	+3
9-11	+1
12-20	0
21-24	+2
≥25	+3
Oxygen Saturation (%)	
≤91	+3
92-93	+2
94-95	+1
≥96	0
Any Supplemental Oxygen	
Yes	+2
No	0
Temperature in °C (°F)	
≤35.0 (95)	+3
35.1-36.0 (95.1-96.8)	+1
36.1-38.0 (96.9-100.4)	0
38.1-39.0 (100.5-102.2)	+1
≥39.1 (≥102.3)	+2
Systolic BP	
≤90	+3
91-100	+2
101-110	+1
111-219	0
≥220	+3
Heart Rate (beats per minute)	
≤40	+3
41-50	+1

51-90	0
91-110	+1
111-130	+2
≥131	+3
AVPU	
A	0
V, P, or U	+3

AVPU – Alert, Voice, Pain, Unresponsive.

Appendix G Phase I Studies as Part of this Master Protocol

It is anticipated that novel investigational agents entered into this master protocol will have enough safety and dosage data available by studies outside the master protocol, to enable them to move directly intoal this protocol. *In some instances, sufficient safety and dosage data will not be available, and the investigational agent will first require a safety evaluation in the form of a phase I dose escalation and dose determination before moving into the main master protocol.*

A separate protocol for the Phase I study will be developed for each individual investigational agent as a stand-alone document with its own consenting procedure, and included here as Appendix G1, G2, etc.

In this appendix, we describe the overarching framework as to how safety will be evaluated in a Phase I dose escalation study, with the understanding that additional details will be required as agents identified as being of interest for the master protocol but with insufficient prior safety data for entry into the master protocol.

The dose escalation study described below provides a framework for a Phase I dose escalation but a number of design parameters have been left intentionally unspecified because they will depend on the specific investigational agent under consideration and the current status of the master protocol. *Key scientific decisions regarding other design parameters including the number of dose levels to be investigated, the definition of dose-limiting toxicities (DLTs), and the appropriate target population will be determined by the protocol leadership together with the overarching ACTIV-2/3 TOC in collaboration with the drug developer and study statisticians.* Efforts will be made to harmonize these across study products, while allowing for learning from prior evaluations and also the incorporation of any issues predicted to be critical for a specific agent. This information will be included as new sub-appendices (H1, H2, etc.) in addition to other information regarding the new agent when it is entered into the master protocol for stage 1 evaluation.

a. Dose Escalation

The goal of the Phase I component is to identify the maximum tolerated dose (MTD) of the investigational agent, defined as the maximum dose with probability of dose limiting toxicity (DLT) less than a specific pre-specified threshold. The basic framework of the Phase I component will be a dose escalation study where initial study participants are treated at the lowest dose and subsequent participants are treated at progressively higher dose levels until the MTD is identified. Dose finding will be guided by the continuous reassessment method (CRM). Briefly, the CRM is a Bayesian adaptive Phase I trial design first proposed in O'Quigley, et al[88]) and later modified by Piantadosi, et al[89] and Goodman, et al.[90] The CRM is a model-based design that relies on a simple, one-parameter model for estimating the probability of DLT at each dose and uses the estimated probabilities of DLT at each dose to guide dose escalation. For this trial, we will model the probability of DLT using the power model:

$$P(\text{DLT} \mid \text{dose} = j) = d_j^{\exp(\alpha)}$$

Where *j* is the dose level and $(d_{-1}, \ldots, d_J)$ is the "skeleton" for the probability of DLT at each dose and the probability of DLT is estimated by estimating the α parameter.

For the purposes of this appendix, the number of doses or the specific skeleton are unspecified.

Dose finding in the CRM begins by treating the first cohort of three subjects at the initial dose level. After the toxicity outcomes for the first cohort are observed, the posterior distributions for the probabilities of DLT are updated. The next cohort is treated at the current estimate of the MTD, defined as the dose level with estimated probability of DLT (posterior mean) closest to the target probability of DLT, under the restriction that untried dose levels may not be skipped when escalating. This process continues until the maximum sample size is reached or until a pre-specified number of consecutive cohorts are treated at the same dose level, whichever comes first. The dose level with estimated probability of DLT (posterior mean) closest to the target probability at study completion is declared the MTD, and that dose may be carried forward to the master protocol. If at any point in the study, the posterior probability suggests that the lowest dose level is excessively toxic, the trial will terminate for excess toxicity. The specific threshold for determining excess toxicity will be determined when a new treatment is entered into the Phase I portion of the master protocol.

b. Other considerations in dose determination

It is possible that the MTD determined using the above may be higher than the optimal dose for evaluation in the next protocol stages. At present, correlative markers of clinical activity in COVID-19 are not well understood. As these markers (for example, but not limited to, SARS-CoV-2 viral load) are better understood, the above framework could also accommodate an approach allowing comparison of identified predictive biomarkers across two or more tolerable doses with the goal of identifying recommended doses for subsequent clinical evaluation that are below MTD. For example, MTD and one or more tolerable dose levels below MTD could be evaluated with respect to performance against the biomarkers, with a view to identifying a tolerable dose below MTD that is predicted to be effective, to carry forward to the next stage of evaluation in the master protocol (stage 1). This biomarker comparison would be secondary to the MTD determination.

c. Definition of DLTs and Sample Size

The dose escalation study described above provides a framework for a Phase I dose escalation but a number of design parameters, including the definition of DLTs and the sample size, have not been specified. These depend on the specific investigational agent under consideration and the current status of the main master protocol. Efforts will be made to harmonize DLT definitions across study products, while allowing for learning from prior evaluations and also any toxicities predicted to be critical for a specific agent. Other design parameters, including the sample size, will similarly be determined by the protocol team's study statisticians in collaboration with the drug developer to achieve desired operating characteristics.

d. Population

Given the early phase of evaluation, this population is likely to differ from the population in the master protocol, which includes hospitalized patients with varying stages of progression. Accurate determination of toxicity of an agent in early clinical phase is likely to be more challenging in patients with significant clinical progression. Consideration may therefore be given to restricting enrollment to patients with the lowest risk of clinical progression within a hospitalized population, or to populations that are not in need for

hospitalization except for the purpose of participating in the Phase I study.

e. Study Sites

While it is anticipated that the main master protocol will enroll participants at a large number of sites in multiple countries, it is anticipated that sites for Phase I studies will be much more restricted. Sites will be selected based on Phase I expertise, including ideally the availability of dedicated Phase I clinical evaluation units. While multiple sites may participate in Phase I studies during the life of the master protocol, for individual agents it is anticipated that in most cases evaluation will be performed at a single site. This will streamline integration of toxicity assessments into the CRM and the dose escalation process. In certain circumstances two or more sites may participate together in evaluation of a single Phase I agent, in which governance structures to facilitate rapid communication of toxicity data between sites and to the oversight team will be established.

f. **Relationship Between Phase I and the Master Protocol**

Agents evaluated in Phase 1 may or may not proceed to the master protocol, depending on results of the Phase 1 evaluation and review by the ACTIV steering committee. At a minimum, evaluation in Phase I will be used to determine the following key elements required for evaluation in the main master protocol should the agent proceed.

- Dose(s) for evaluation for later stages. In master protocol, up to three doses maybe evaluated.
- Any required specific exclusion and inclusion criteria, over and above the general criteria outlined in the main master protocol (this will be informed by toxicity and other agent characteristics in Phase I).

While the focus of Phase I evaluation will be safety and dose determination, markers of clinical efficacy including the ordinal endpoint at Day 5 may be assessed and information will be collected up to 90 days as in the main master protocol will also be collected to inform the clinical development of these agents.

While these data will be used to identify the correct dose or doses to investigate in the master protocol, the Phase 1 study will be distinct, and the data will not be incorporated into the master protocol.

Appendix H Neutralizing monoclonal antibody.

This appendix will include the following information for each nMAb studied. The rationale for studying the agent, justification for entry into the master protocol, and the description and administration of the agent. Also, as appropriate, specific AEs observed to be possibly associated with the agent in question, and how to monitor for, clinically handle and report such AEs, should they arise. Changes in endpoint, SOC, inclusion and/or exclusion criteria, sample size estimation and approach to interim analyses and data analyses will also be included if appropriate for the investigation of the nMAb in question relative to what is stated in the master protocol. Finally, the text will also clarify whether the manufacturer of investigational agent plans to pursue licensure in the countries where the trial will occur, should the investigational agent be demonstrated in the trial to have overall benefit.

Introduction/Rationale for studying the agent

  - Potential risks and benefits of agent
  - Motivation for agent selection with consideration of results from trials of other nMAbs
- Agent-specific eligibility criteria
- Description of investigational agent
  - Administration and duration
  - Formulation and preparation
  - Supply, distribution, and accountability
  - Contraindicated medications
  - Precautionary medications
- Clinical and laboratory evaluations in addition to master protocol
  - Timing
  - Special instructions
- Clinical management issues
  - Infusion-related reactions
  - Hypersensitivity
- Pregnancy and breast-feeding considerations
- Criteria for discontinuation of infusion
- References

Appendix I Standard of Care

I1. Overview

Currently, there are no licenced treatments for COVID-19. One investigational agent, remdesivir, is now accepted by several countries' regulatory bodies for use as part of routine care; in the US, FDA has been granted the drug an Emergency Use Authorization. Considering the number of randomized trials being conducted to study treatments for COVID-19, it is likely that other effective treatments will be identified during performance of this master protocol.

When treatments for COVID-19 are demonstrated to have safety and efficacy, those treatments should be considered in designing new studies. Depending on the scientific question, an experimental treatment will be coupled with or compared to a known effective treatment. When such known effective treatments are incorporated into both arms, they are called "background therapy" or standard of care (SOC). In this case, the scientific question addressed is whether a new treatment added to an already effective treatment is superior to the established effective treatment alone.

SOC may include general supportive care appropriate to the participant's clinical status, and specific therapeutic agents, and measures to reduce risk of SARS-CoV-2 transmission to the participant and health care givers.

As stated in section 5.1, the objective of this protocol is to evaluate investigational agents - aimed at enhancing the host immune response to or impair replication of SARS-CoV-2 infection - for safety and efficacy compared to placebo control, when all eligible participants receive background therapy that is considered effective. Consistent with precedent, we refer to background therapy as standard of care (SOC). All participants will receive an investigational agent (initially a nMAb) + SOC vs. placebo + SOC.

Below, principles for defining SOC are provided, and recommendations and guidance on SOC are given. Whether an individual SOC treatment is provided by the trial or not is based on multiple factors, including clinical and scientific considerations. In some cases, the decision to administer an SOC treatment is left entirely to the research participant's primary medical team.

I2. Guiding principles for inclusion of measures as part of SOC

The SOC will be regularly updated based on review of the scientific literature and updated authoritative treatment guidelines on this topic. The standard for including one or more measures as SOC, includes a careful review of the existing literature and current guidelines (see Appendix D). As for therapeutic agents, those having been shown to be clinically effective in properly powered phase III or phase IV trials (i.e., high quality/level 1 evidence) and with a reasonable safety profile will be considered by the protocol team for inclusion, if recommended by at least one major treatment guideline. This evaluation may also lead to a statement that one or more agents are either not recommended or should not be used as part of SOC. As knowledge will likely continue to accumulate rapidly, the protocol leadership team may occasionally decide to include or exclude an intervention as part of SOC before it is recommended in at least one major treatment guideline. In such cases, the

relevant literature that lead to the determination will be cited.

The use of a given SOC intervention may apply to all or to a subgroup of the participants in the master protocol based on available evidence – the subgroup may be defined based on severity of disease, a clinical or laboratory defined feature, or a clinically or laboratory defined contraindication for using the SOC treatment. An SOC agent may be mandated for participants (required for protocol entry); mandated where not contraindicated (participants may enter if that SOC is unsuitable, and not receive that SOC); or recommended subject to clinical discretion. SOC may be protocol-supplied where mandated.

The master protocol acknowledges that there may be local variation in the clinical availability of one or more agents chosen to be part of mandated protocol-supplied SOC from site to site. While acknowledging risks of inadvertent coercion, the importance of the scientific question (how candidate agents perform against the background of the current SOC treatments) is a crucial, high-priority question. There is no possible way to answer the question of efficacy against the background of an already proven effective agent without providing the agent – if not readily available - within the trial.

I3. Current SOC in the master protocol:

I3.1 Remdesivir Background Therapy

Based on the findings of the Adaptive COVID-19 Treatment Trial (ACTT),[91] remdesivir will be provided to all study participants as SOC unless contraindicated for an individual patient. As in the ACTT trial, remdesivir will be administered as a 200 mg IV loading dose, followed by a 100 mg once-daily IV maintenance dose while hospitalized up to a 10-day total course. Participants taking remdesivir prior to randomization will continue their daily remdesivir infusions while hospitalized up to a 10-day course and possibly longer should evidence emerge to support this. The primary medical team has discretion to plan for 5 days duration in patients that do not require mechanical ventilation or ECMO. If as part of clinical care a patient has received a loading dose of remdesivir before randomization, the loading dose will not be repeated. Details relating to contraindications, dosing, and monitoring of remdesivir are included in the Protocol Instructions Manual [PIM].

I3.2 Dexamethasone and Other Corticosteroids

Based on the preliminary findings of the RECOVERY trial (https://pubmed.ncbi.nlm.nih.gov/32678530/and in line with NIH treatment guideline (Appendix D), it is recommended to consider initiation of corticosteroid therapy in participants with COVID-19 who are mechanically ventilated and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated**.** In patients with minimal oxygen need, however, special consideration weighting benefits vs potential risk should be given whether to initiate a corticosteroid. Corticosteroids may increase the probability of reactivating latent infections including herpes viruses and tuberculosis, hyperglycemia, hypernatremia, secondary infections, and may delay clearance of SARS-CoV-2. In participants not requiring supplementary oxygen, it is recommended not to initiate a corticosteroid. As the RECOVERY trial was performed at or near sea level, for patients enrolled at altitude, investigators and clinicians may appropriately avoid corticosteroid administration in patients receiving modest flow rates of supplemental oxygen. Treatment with a corticosteroid is recommended for a total of 10 days, using doses outlined in this table.

Corticosteroid name	Daily dose
Dexamethasone	6 mg PO or IV
Prednisone	~40 mg PO
Methylprednisolone	~32 mg IV
Hydrocortisone	~160 mg IV

I3.3 Other Supportive Care

All participants will be given *supportive care* for most complications of severe COVID-19 including: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy. Links to details of such care can be found in Appendix D. Supportive care components of SOC include lung-protective ventilation for patients who require invasive mechanical ventilation[92] (high quality evidence) and prone positioning for mechanically ventilated patients with more than moderate ARDS (high quality evidence), treatment with anti-bacterial agents for patients believed to have bacterial infection (high quality evidence), guidelines-compliant management of sepsis when it is present (moderate quality evidence)[93]. Use or non-use of extra-corporeal life support (ECLS) is not mandated as part of SOC; nor is any specific approach to renal replacement therapy.

Consideration should be given to the use of pharmacological thromboprophylaxis (thrombosis prevention) in line with local clinical guidelines for hospitalized patients as appropriate for an individual participant, in addition to approaches to maintain mobility and minimize other thrombotic risks. Standard approaches to thromboprophylaxis supported by high quality evidence include the use of low molecular weight heparin (for example, enoxaparin 0.5m/kg daily), which is the preferred agent in some COVID-19 treatment guidelines. However other standard approaches in accordance with local and institutional guidelines and the medical circumstances of an individual participant may also be considered, including the use of low (prophylactic) dose unfractionated heparin (high quality evidence). Specialist advice should be sought for participants with pre-existing prothrombotic states, or who are pregnant.

I3.4 Cautions and Contraindications

Remdesivir is recommended not to be combined with (hydroxy)chloroquine. The effectiveness of remdesivir may be reduced if combined with (hydroxy)chloroquine, and hence it is not advisable to combine these two medications.[94]

It is not recommended to use high dose chloroquine (600 mg twice daily) as SOC due to excess harm and not demonstrable benefit. (Hydroxy)chloroquine has no documented clinical benefit, and hence not recommended for use as SOC.

I3.5 SARS-CoV-2 Infection Control

Minimum standards of protection to *reduce the risk of SARS-CoV-2 transmission* from trial participants to research personnel, participants in other trials, or patients treated in the

same facility can be found in links displayed in Appendix D.

Appendix J References

[1] Johns Hopkins University and Medicine - Coronavirus Resource Center. https://coronavirus.jhu.edu

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