Master Protocol

To be used with agent-specific appendices

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

Version 3.0
08 March 2022

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(Master protocol: NCT04843761)

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

Short Title: *Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO)*

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1 Protocol Summary

DESIGN

TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of investigational agents aimed at improving outcomes for patients with acute respiratory failure related to COVID-19. The focus in this master protocol, a sister protocol to the TICO master protocol, is on patients with critical respiratory failure (i.e., those receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO to treat acute hypoxemic respiratory failure caused by SARS-CoV-2 pneumonia).

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. If an investigational agent shows superiority over placebo, SOC for the study of future investigational agents may be modified accordingly.

The international trials within this protocol will be conducted in up to 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 within the same trial infrastructure. When more than one agent is being tested concurrently, participants may be randomly allocated across agents (as well as between the agent and its placebo) so the same control group can be shared, when feasible. In some situations, a factorial design may be used to study multiple agents.

The primary endpoint is a 6-category ordinal outcome that assesses the recovery status of the patient at Day 90. The categories of the ordinal outcome, from best to worst, start with 3 categories of "recovery" defined by the number of days alive at home and not on new supplemental oxygen, followed by 3 categories for "not recovered" defined as a) discharged but not to home or at home but still requiring continued new supplemental oxygen, b) hospitalized or receiving hospice care, and c) death at 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.

DURATION

Participants will be followed for 90 days following randomization for the primary endpoint and most secondary endpoints. Selected secondary endpoints will be measured at 180 days.

SAMPLE SIZE

This Phase III trial is planned to provide 80% power to detect an odds ratio of 1.5 for improvement in recovery status at Day 90 for an investigational agent versus placebo with use of the ordinal outcome. The planned sample size is 640 participants (320 per group) for each investigational agent / placebo. Sample size may be re-estimated before enrollment is complete based on an assessment of

whether the pooled proportions of the outcome are still consistent with adequate power for the hypothesized difference measured by the odds ratio.

POPULATION — All participants enrolled will include inpatient adults (≥18 years) who have documented SARS-CoV-2 infection within 14 days of enrollment and are receiving high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO at enrollment, in whom the current respiratory failure is thought to be due to SARS-CoV-2 infection and in whom respiratory support was initiated within 4 days prior to randomization.

STRATIFICATION — Randomization will be stratified by study site pharmacy and by receipt of invasive mechanical ventilation or ECMO at enrollment. Other agent-specific stratification factors may be considered.

REGIMEN — Investigational agents suitable for testing in the inpatient setting will be prioritized based on in vitro data, preclinical data, phase I pharmacokinetic and safety data, and clinical data from completed and ongoing trials. In some cases, a vanguard cohort/initial pilot phase may be incorporated into the trial.

MONITORING — An independent DSMB will review interim safety and efficacy data at least monthly. Pre-specified guidelines will be established to recommend early stopping of the trial for evidence of harm or substantial efficacy. The DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits.

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] Patients with respiratory failure, which in COVID-19 is likely best termed Acute Respiratory Distress Syndrome (ARDS), have extremely high morbidity and mortality. Novel treatments for these patients are an urgent clinical and public health need. (We use the term ARDS interchangeably with acute respiratory failure in this master protocol.)

Several clinical trials utilizing novel drugs and repurposing older agents have been implemented to investigate the treatment of adults hospitalized with severe or critical COVID-19 (see section 2.2.6). Standard-of-care is hence rapidly evolving (see Appendix I for current recommendations).

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.[4] While SARS-CoV-2 mostly causes a mild respiratory illness, some individuals, particularly those who are elderly[5,6] and have comorbidities,[7] 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)[8] 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.[9] COVID-19 illness is predominantly a respiratory disease typified by upper respiratory symptoms in mild cases and pneumonia and 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.[10]

Complications of COVID-19 illness include cytopenias (lymphopenia, thrombocytopenia and anemia), and acute cardiac events (elevated troponin, changes on electrocardiogram), vasopressor-dependent shock, acute kidney injury and dialysis-dependent renal failure, liver

impairment, and neurological events including acute cerebrovascular events, impaired consciousness, 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 virus.[11]

A proportion of those who progress then further deteriorate, including with the development of ARDS around 1-5 days after onset of respiratory symptoms.[6,12-14] 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% had severe disease at presentation; 67 persons (6%) reached a composite primary endpoint of intensive care admission, mechanical ventilation or death.[9,15] As described below, outcomes for those requiring mechanical ventilation and with other manifestations of end-organ failure are poor, and treatments for such patients are critically needed.

In this protocol, we aim to enroll patients hospitalized for medical management of COVID-19, with acute respiratory failure, defined as the use of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO (extracorporeal membrane oxygenation).

2.2.3 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.

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.[14] 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.[16] 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.[15] More recent mortality

estimates among patients with COVID-19-associated ARDS range from 30–45%. These mortality estimates underline the importance of testing and implementing new effective treatments for these critically ill patients.

2.2.4 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.[17] Viral ribonucleic acid (RNA) shedding from the pharynx gradually wanes as symptoms resolve, but viral RNA is still detectable weeks after symptom resolution.[18-20] 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 especially in more severe disease but is relatively rare among outpatients.[21-23] Viral detection in sputum is higher and outlasts pharyngeal swabs in those with pneumonia.[24] Persons with asymptomatic disease clear their virus faster than symptomatic individuals.[25]

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 one study reported that SARS-CoV2 viral loads were higher on admission and throughout the hospital course in patients who died,[26] a finding that matches well with evidence for impaired type-1 interferon responses with more severe COVID-19 illness.[27] SARS-CoV-2 viral RNA is also present in blood in large numbers of critically ill patients, with higher viral loads in blood among non-survivors than among survivors.[23] Distribution of virus in the body of severely ill patients is heterogeneous in both space and time, and even patients who die of COVID-19 ARDS may have high viral load in lung, especially in the first two weeks.[28]

2.2.5 COVID-19 ARDS, attributes and treatments

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 impaired.[29]

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.[30,31] 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 question.[32,33]

In addition, cohorts of patients with ARDS before COVID-19 (a physiology that is likely highly relevant to patients with COVID-19-associated ARDS) identify risks of ventilator-associated injury, immune depletion and associated risk of secondary infection, encephalopathy and delirium, dysfunctional repair mechanisms, oxidative stress, NETosis, surfactant dysfunction, impairment in GM-CSF and macrophage function, mitochondropathy, dysregulated

microvascular thrombosis and shunting, myocardial suppression, and multiple other insults, which together contribute to the high morbidity and mortality in ARDS. One recent study provided detailed information on COVID-19 ARDS[34] and a recent review considers features of classical ARDS and selected issues related to COVID-19 ARDS.[35]

Phenotypic variability of ARDS is also well described in multiple cohorts, especially with sorting into inflammatory and pauci-inflammatory phenotypes.[36] While COVID-19 has a single underlying cause (SARS-CoV-2 infection), phenotypic variability has also been observed in COVID-19.[34,35,37] The relevance of such subtypes to possibly heterogenous treatment effects is as yet unknown.

Standard supportive care for ARDS from COVID-19 including lung protective ventilation, prone positioning and fluid conservative care is still the most important approach to reducing mortality and morbidity when COVID-19 patients develop ARDS.[35,38] The addition of dexamethasone for treatment of patients who are mechanically ventilated was effective in reducing mortality in the large pragmatic UK RECOVERY trial,[39] although several outstanding issues relate to glucocorticoids for severe COVID-19.[40]

2.2.6 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 comparative effectiveness trials.

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 (the TICO master protocol and this paired TESICO master protocol). The TOC (and the agent selection committee) will select agents for study in the three protocols. Members of the protocol team (non-voting) and NIH are members of this committee. This committee reviews data for investigational agents and considers a number of factors relevant to the likely efficacy and safety of candidates for inclusion in the relevant protocols.

It is possible that several agents from different sources will be combined at some point in the conduct of this master protocol – but not initially. It is also possible that one agent will be identified as effective and then incorporated as SOC (providing there is good safety data and adequate supply of the agent).

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 aspects of study procedures outlined in this master protocol will need to be deviated from. The informed consent will describe any risks associated with the investigational agents.

In some cases, especially where additional data about safety and feasibility are desired, a vanguard cohort/pilot phase may be incorporated into a trial of a given investigational agent. Details of such vanguard cohorts—including design features, additional safety monitoring, and sample size—will be specified in the agent-specific appendix.

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 agent-specific appendix and in the sample informed consent. Other risks include having blood drawn, intravenous (IV) catheterization, and breach of confidentiality. Given the significant disease-related risks faced by this target population, there is felt to be a favorable risk/benefit profile, and significant risk acceptability.

3.1.1 Risks of Drawing Blood and IV Catheterization

Drawing blood may cause transient discomfort and, rarely, fainting. Fainting is usually transient and managed by having the participant lie down and elevate his/her legs. Bruising at the blood collection 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 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, each agent may have associated risks, which will be specified in the relevant agent-specific appendix.

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 improve participant status on an ordinal recovery outcome assessed at 90 days, the agents studied may or may not achieve 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. The complete approach to measurement and evaluation of trial endpoints will be specified in the statistical analysis plan before unblinding.

4.1 Primary and Secondary Outcomes to Evaluate Efficacy and Safety

The primary endpoint is an ordinal outcome that assesses participant recovery status at Day 90. The primary ordinal endpoint is referred to as ***recovery***. The outcome includes 6 categories, consisting of 3 ranked categories of the number of days alive, at home, and not receiving new supplemental oxygen ***at Day 90*** (77 or more consecutive days, 49–76 days, or 1–48 days) as well as an additional 3 categories for patients who are not recovered at Day 90: (1) discharged from the hospital but either not yet home, or home but receiving new supplemental oxygen, (2) still hospitalized or receiving hospice care, or (3) dead.

Consistent with the TICO protocol (NCT04501978), *home* is defined as the level of residence or facility where the participant was residing prior to onset of COVID-19 leading to the hospital admission that led 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 residing in a "long-term acute care" hospital recover when they return to the same or lower level of care.

Since some patients will be receiving supplemental oxygen before their COVID-19 illness, we define new supplemental oxygen as any supplemental oxygen in participants who were not receiving supplemental oxygen before their COVID-19 illness or an increase in supplemental oxygen above pre-COVID-19 baseline among patients who were receiving supplemental oxygen before their COVID-19.

The "last-off" method for assessing recovery will be used, as has been customary in the use of similar ordinal endpoints in ARDS trials for decades. According to the "last-off" method, periods of recovery that are followed by hospital re-admission, change from home to a higher level of care, or receipt of new supplemental oxygen will *not be counted* toward the number of days of recovery. In other words, only days between the last time the patient entered a recovered state (returned home, free of new supplemental oxygen), and Day 90 are counted as days of recovery. The categories of the primary endpoint are displayed in Table 1.

Table 1 Categories of the primary endpoint

Category	Status at 90 days
1 (Best)	At home and off oxygen. No. of consecutive days at Day 90 ≥ 77
2	49-76
3	1-48
4	Not hospitalized AND either at home on oxygen OR not at home
5	Hospitalized for medical care OR in hospice care
6 (Worst)	Dead

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. If such patients are receiving new supplemental oxygen, they will not be classified as recovered.

4.1.1 Rationale for primary outcome

The primary ordinal endpoint, recovery, was selected given the high mortality in COVID-19 ARDS and the expectation that agents may have effects on both mortality and time to recovery among survivors. The common use of new supplemental oxygen after discharge (as high as

40% of discharged patients among ARDS patients in prior cohorts) and frequent rehospitalizations also motivated the structure of this endpoint.

The primary outcome is intended to identify relevant efficacy among investigational agents using an endpoint that is patient-centered, clinically relevant, and appropriately efficient.

Whereas mortality may be the most important ultimate outcome, the sample size to detect a plausible treatment effect for such an outcome would be much larger than outlined in this protocol. It was determined that use of a mortality-only endpoint would unduly increase the amount of time and resources necessary to make a determination of efficacy and was thus not feasible in current pandemic circumstances. Importantly, mortality was not considered to be the only relevant measure of efficacy in COVID-19—among survivors, the duration of recovery at Day 90, which also reflects length of hospitalization, is also an important benchmark. This position is consistent with decades of work in ARDS trials. Notably, while data specific to COVID-19 have not yet been generated, in general ARDS populations, a longer time to recovery has been associated with worse long-term outcomes, making recovery evaluated at Day 90 an important patient-centered endpoint.[41-44]

The primary outcome is assessed at 90 days of follow-up, which is longer than for other trials of investigational agents for COVID-19, which have typically been 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 the TESICO target population, who are critically ill. Based on data from COVID-19 observational cohorts and ARDS trials before the pandemic, it is also projected that excess mortality will be observed between Day 28 and Day 90. A single category of death at Day 90 is used for the worst category of the primary endpoint instead of time to death given the 90 day follow-up period. Time to death is a secondary endpoint.

4.1.2 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 Day 90, dichotomous as well as time to death

2. (a) Composite endpoint that considers the number of days at home off new supplemental oxygen and the time to death as well as the other categories of the primary ordinal outcome;
   (b) a dichotomous composite endpoint of alive, at home, and off new supplemental oxygen at Day 90;
   (c) a three-category ordinal endpoint, measured at Day 90, with the following categories: recovered (alive, at home, and off new supplemental oxygen), alive and not recovered, and dead.

3. Time from randomization to recovery defined as alive, at home, and off oxygen (treating death as a competing risk).

4. Days alive outside of a short-term acute care hospital up to Day 90 (among survivors), using the "last off" method

5. 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; such conditions that existed at baseline are not counted):

    a. Worsening respiratory dysfunction
        1. Increase in the level of respiratory support from high-flow nasal cannula or non-invasive mechanical ventilation at baseline to mechanical ventilation or ECMO, or from invasive mechanical ventilation at baseline to ECMO.

    b. Cardiac and vascular dysfunction:
        1. Myocardial infarction
        2. Myocarditis or pericarditis
        3. Congestive heart failure: new onset NYHA class III or IV, or worsening to class III or IV
        4. Hypotension treated with vasopressor therapy
        5. Atrial or ventricular tachyarrhythmias

    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.

6. A composite of death, clinical organ failure or serious infections (see above) through Day 90.

7. Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate meta analyses and facilitate generation of norms, including an ordinal scale measuring the degree of oxygen support through Day 14, time to discharge from the initial hospitalization, and binary outcomes defined by worsening based on the worst 3 categories of the primary ordinal recovery outcome at day 90.

8. A composite of cardiovascular events (outcomes listed above in items 5b1, 5e2 and 5e3) and thromboembolic events (item 5f2) through Day 28 and Day 90.

9. Safety and tolerability as measured by
    a. A composite safety outcome of grade 3 and 4 clinical adverse events, SAEs, PSESEs (see 10.2.3), or death through Day 5 (*primary safety endpoint*) and through Day 28 (secondary safety endpoint)
    b. Infusion-related reactions of any severity
    c. Percentage of participants for whom the infusion was interrupted or stopped prior to completion for any reason and separately for an adverse event
    d. A composite of hospital readmissions or death through 90 days.

4.1.3 Rationale for secondary outcomes

The main secondary outcomes for the TESICO trial are constituents of the primary outcome (mortality, time to death, number of days home off oxygen) or closely related to them (days alive outside of the hospital). In addition, given the evolving information about the effects of COVID-19 outside of the lungs, measuring organ failure is important to understand the full range of COVID-19. Given that secondary infections are common among ARDS patients, including those with ARDS from COVID-19, measuring and monitoring secondary infections is also important to understanding the full scope of the effect of a COVID-19 therapeutic agent. In addition, the importance of understanding COVID-19 epidemiology (and supporting potential meta-analyses) across the range of therapeutic trials mandates collection of outcomes relevant to the calculation of endpoints from other trials. The rationale for the safety outcomes collected is presented in Section 10. If a specific secondary outcome is to be added for a given investigational agent, that additional outcome will be specified in the corresponding Appendix H.

5 Objectives

5.1 Primary Objective

The primary objective of this protocol is to determine whether investigational agents are safe and superior to control (initially and primarily placebo) when given with SOC for the primary endpoint of recovery (based on a 6-category ordinal outcome) evaluated at 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. SOC may also be studied in this master protocol along with investigational agents if data from trials indicate that efficacy is uncertain for this target population of patients with COVID-19 ARDS.

5.2 Secondary Objectives

Four key secondary objectives are to compare each investigational agent with control for:

1. Time to death through Day 90
2. A composite endpoint that considers the number of days at home off new supplemental oxygen and the time to death as well as the other categories of the primary ordinal outcome,
3. Time to recovery defined as alive, at home, and off new supplemental oxygen,
4. A three-category ordinal outcome, measured at Day 90, with the following categories: recovered (alive, at home, and off new supplemental oxygen), alive and not recovered, and dead.

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

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

- Receipt of invasive mechanical ventilation or ECMO
- Age
- Biological sex
- Race/ethnicity
- Type of residence/facility (home)
- Body mass index (BMI)
- History of chronic conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, hepatic impairment, or cancer)
- Geographic location
- Duration of symptoms prior to enrollment
- Concomitant treatments (including other randomized treatments) at enrollment
- SARS-CoV-2 vaccination status at baseline
- Disease progression risk score (defined using pooled treatment groups with the following baseline predictors of the primary outcome (recovery evaluated at 90 days): age, biological sex, duration of symptoms, receipt of invasive mechanical ventilation or ECMO vs. neither, and presence of chronic health conditions.

6 Study Design

TESICO (Therapeutics for Severely Ill Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of multiple investigational agents for COVID-19 ARDS. Master protocols can be 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 general approach 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.

In some cases, more than one dose of an investigational agent will be studied. For such agents, specific details of the dose selection will be outlined in the relevant Appendix H.

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 to 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 or route of administration 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) but not whether the patient is receiving active agent versus placebo. 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 receipt of invasive mechanical ventilation or ECMO (vs. neither) at entry. Within each randomization stratum, mass-weighted urn randomization[45] 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" for 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 and at participating sites 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. In addition, some agents may undergo factorial randomization with other agents. Such details will be specified in the relevant agent-specific appendix.

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 may 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 remain blinded to whether the random assignment was to the active investigational agent or matching placebo.

If the blind is broken, whether by accident, or for safety reasons, this will be recorded, and the protocol chair will be notified of the event. 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.
b. A proportional odds model will be used to compare recovery at Day 90 for the investigational agent and placebo.
c. Patients will be assigned the worst category that applies at Day 90.
d. The "last-off" method (for return to home and liberation from new supplemental oxygen) is used to calculate days of recovery among those who are recovered on Day 90.
e. Approximately 80% of patients will enter the trial on high-flow nasal oxygen, while approximately 20% will enter with non-invasive or invasive mechanical ventilation or ECMO. Control-group event rates for these patients are based on findings from ACTT-1, the Intermountain Prospective COVID Registry (IPOC), ISARIC, and other data sources. This includes estimates of the percentage of patients in each category of respiratory support (i.e., high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO) at baseline.[46]
f. Most patients will be discharged in the first month after randomization; based on ACTT-1 and PETAL Network data, we estimate 25% will be discharged to their home and stay home for 14 days by day 28 following randomization; half of these patients will be discharged to their home on oxygen; and most will receive oxygen for 3-4 weeks. Thus, the category 1 percentage is approximately 12% considering re-initiation of home oxygen and re-hospitalization.
g. Categories 2 and 3 are wider and also consider home oxygen re-initiation and re-hospitalization.
h. Three categories of time at home off oxygen were considered because an intervention that shortened time on new supplemental oxygen and also decreased mortality was considered clinically relevant.
i. Based on data from PETAL Network and Intermountain Healthcare, 33% of participants will die by Day 90. A single category is used for death at Day 90 instead of time of death given the target population and planned follow-up.
j. At Day 90 < 10% of patients will be in the hospital; and about 10% will be on oxygen or not at home.
k. With type 1 error of 0.05 (2-sided) and 80% power to detect the OR of 1.5, sample size is 602. This is increased to 640 (320 in each group) to allow for a small percentage of patients who withdraw consent or are lost to follow-up before Day 90.

The estimated control and treatment arm distribution of endpoint categories used to calculate sample size and power is displayed in Table 2.

Table 2 Estimated Distribution of Endpoint Categories Used for Power Calculation

Category	Status at 90 days	Investigational Agent (%)	Control (%)
1	At home and off oxygen. No. consecutive days at Day 90 ≥ 77	17.0	12.0
2	49-76	27.7	23.0
3	1-48	17.2	17.0
4	Not hospitalized AND either at home on oxygen OR not at home	9.1	10.0
5	Hospitalized for medical care OR in hospice care	4.3	5.0
6	Dead	24.7	33.0
	Total	100.0	100.0

Sample size may be re-estimated before enrollment is complete to determine whether the pooled proportions are still consistent with 80% power to detect an OR 1.5.

6.4 Schedule of Assessments

Participants will be randomized and start therapy on Day 0. The primary endpoint and most secondary endpoints will be measured through Day 90. After Day 90 results are completed, data will be unblinded to allow expeditious reporting of primary results. In addition, all participants randomized will be followed through 180 days 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. 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/disallow use of any specific concomitant therapy found to be reasonably contraindicated for a well-defined portion of the study population (see 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.

Coenrollment in other trials will only be allowed where a coenrolling trial has been approved by trial leadership for coenrollment.

The planned analyses are by intention to treat (or modified intention to treat as noted). All participants will be compared throughout follow-up, irrespective of use of concomitant treatments or co-enrollment in other trials. Concomitant treatments will be recorded at baseline, daily through Day 7, and on Days 14 (which will reference Days 8–14), and 28.

7 Study Population

Pragmatic classifications of COVID-19 severity, largely based on an early WHO scale or variants, have been widely adopted in clinical trials. These scales generally specify the degree of respiratory impairment as determined by the location of care and the degree of organ support.[47] The target population of TESICO are patients with SARS-CoV-2 pulmonary involvement severe enough to cause acute hypoxemic respiratory failure that is treated with high flow nasal oxygen or mechanical ventilation (whether invasive or noninvasive). The TESICO target population is thus a subset of "critical COVID-19," as it is focused on hypoxemic respiratory failure due to COVID-19 pneumonia as the critical organ failure. The TESICO target population is also a subset of COVID-19 respiratory failure, since it is restricted to those with hypoxemia who are receiving advanced respiratory support. Based on unpublished data from a national and a regional cohort of hospitalized patients with COVID-19 pneumonia suggesting that >90–95% of patients in this target population would meet the Berlin consensus statement[48] oxygenation and radiographic criteria for ARDS, we at times use the term ARDS interchangeably with COVID-19-associated critical respiratory failure to describe our target population in this protocol. We anticipate that the members of the target population so defined will benefit from the investigational agents, as the vast majority will have bilateral pulmonary infiltrates from lung inflammation and injury due to life-threatening SARS-CoV-2 infection. (To facilitate inferences about generalizability and subsequent meta-analyses, we will record and report chest radiograph results and SF ratios to allow alignment with the Berlin definition and newly proposed modifications[49] at the conclusion of the trial.)

In the context of this understanding of COVID-19-associated critical respiratory failure, COVID-19 participants with ARDS will be enrolled at clinical trial sites globally. The estimated time from screening (Day -1 or Day 0) to end of study for an individual participant is 90 days for the primary endpoint and 6 months for some secondary endpoints.

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

Protocol inclusion and exclusion criteria are intentionally straightforward and are NOT subject to exception for even minor deviations, e.g., 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. 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.

4. Current respiratory failure (i.e., receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO used to treat acute hypoxemic respiratory failure).

5. SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing with most recent test within 14 days prior to randomization. (For non-NAT tests, only those deemed to have equivalent specificity to NAT by the protocol team will be allowed. A central list of allowed non-NAT tests will be maintained.)

6. Respiratory failure is believed to be due to SARS-CoV-2 pneumonia.

***Continuing consent**
Participants for whom 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.

7.2 Exclusion Criteria

1. Known allergy to investigational agent or vehicle
2. More than 4 days since initiation of support for respiratory failure (i.e., receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation or ECMO used to treat acute hypoxemic respiratory failure).
3. Chronic/home mechanical ventilation (invasive or non-invasive) for chronic lung or neuromuscular disease (non-invasive ventilation used solely for sleep-disordered breathing is not an exclusion).
4. Moribund patient (i.e., not expected to survive 24 hours)
5. Active use of “comfort care” or other hospice-equivalent standard of care
6. Expected inability to participate in study procedures;
7. 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;
8. Previous enrollment in TESICO

Exclusions that may be specifically 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 first administered. 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 laboratory diagnosis of SARS-CoV-2 infection in the appropriate timeframe

- 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
    - History of chronic and current medical conditions, including targeted conditions for outcome analysis
    - Targeted concomitant medications and SARS-CoV-2 vaccine receipt or trial participation

- A focused physical examination including vital signs (at least heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, and oxygen saturation), height and weight, baseline degree of oxygen supplementation/respiratory support

- Blood draw for local laboratory evaluations:
    - White blood cell count
    - Hemoglobin
    - Platelets
    - Lymphocyte and neutrophil counts
    - Ferritin
    - C-reactive protein
    - Basic metabolic panel
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)
    - Total bilirubin
    - INR
    - D-DIMER

- Plasma and serum specimens 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 8 aliquots. This includes antibody status and viral antigen, among other assays.
- A mid-turbinate nasal swab for SARS-CoV-2
- Among those who provide consent for host genetics, whole blood will be collected and stored for RNA (one 2.5mL PAXgene tube) and DNA (one 9mL EDTA tube to produce six 1-mL aliquots) extraction
- 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 be possible to draw blood for local laboratory assessments and storage prior to the time of randomization. In these cases, the blood draw can be performed 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, receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO by the participant should be verified.

On days of study drug administration, before and during study drug administration, the following data will be collected, and reported on appropriate case report forms as applicable:

- Adverse events of any grade severity present prior to the infusion (Day 0 only)
- Start and stop times of the infusion of the investigational agent/placebo
- Doses of study drug
- Infusion-related reactions to the investigational agent/placebo
- New adverse events of any grade severity during and up to 2 hours after the infusion
- On Days 0, 1, and 2, a blood draw for local laboratory evaluations

The details of monitoring during and immediately after the infusion will be specified in the agent-specific appendices. Participants who experience AEs during or immediately after the infusion should be followed closely until the resolution of the AE.

9.1.2 Follow-up Assessments

Participants will be followed through 180 days following randomization for collection of study data (Appendix B). Relevant clinical data will be collected on Days 0–7, 14, 28, 42, 60, 75, 90, and 180. These data will include discharge status, and interim changes in medical history (targeted to components of primary and secondary endpoints). Concomitant medications will be collected on Days 0-7, Day 14 (retrospectively for Days 8-14), and on Day 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 180 days.

Components necessary to determine the ordinal WHO/NIH ordinal outcome and the TICO Pulmonary endpoint will be collected to allow the computation of the ordinal outcome for every day through Day 14 and on Day 28. On Days 14 and 28 AEs of any grade severity will also be collected.

At Day 3 and Day 5 for all participants still hospitalized, plasma and serum specimens for central testing for SARS-CoV-2 antibody determination, viral antigen, 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.

At Day 3, among those participants who provided consent for host genetics, a whole blood specimen for RNA extraction will be collected (sufficient for one 2.5 mL PAXgene tube).

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 determine the time of return “home” and time of liberation from new supplemental oxygen (as well as readmissions or resumption of new supplemental oxygen). Entry into hospice care will also be collected.

For visits on Days 7, 14, 42, 60, 75, 90, and 180, contact with the participant for study data collection may be performed by telephone. However, other information will be gathered, as outlined in Appendix B. At Day 90 and Day 180, the EQ-5D-5L will be administered by telephone, with additional patient-reported outcomes (MRC Dyspnea, PROMIS fatigue, CONNECTS Recovery) also collected by telephone at Day 90 and Day 180. Safety data collection and reporting are described further in Section 10.

9.1.3 Stored Samples and Future Research

The plasma, mid-turbinate, and serum specimens collected as outlined above will be stored at a central specimen repository in the US. In addition to the specified testing to be done per protocol (collected at baseline and Day 3 for all hospitalized participants and collected at Day 5 among participants still in the ICU on Day 5), the specimens will be available for later use in research concerning COVID-19, SARS-CoV-2, and the impact of the study treatment. The whole blood specimens for RNA and DNA extraction from those participants who provided consent for host genetics will also be stored at the same central specimen repository in the US. Proposed research utilizing these specimens will be reviewed and approved by the study scientific steering committee and overseen by an ethics committee as appropriate. Results of research tests on individual specimens will not be provided to participants or their clinicians. Aggregate research results will be made available.

10 Safety Assessment

The safety monitoring and assessment within this trial reflects attributes of the anticipated investigational agents and the target population.

First, investigational agents studied in this protocol are commonly expected to have short half-lives and low probability of triggering a pathologic process or demonstrating a toxicity that would not manifest during, or shortly after treatment. As a consequence, the mainstay of safety monitoring will be broad safety monitoring through Day 90 plus collection and reporting of serious and/or high-grade events thought to be at least possibly related to the investigational agent for the duration of participation. If agents with longer half-lives or a likelihood of demonstrating effects that may potentially manifest with substantial delay are included, a longer duration of broad safety monitoring will be employed for those agents. Details of such additional safety monitoring will be specified in the corresponding agent-specific Appendix H .

Second, patients with ARDS may each be reasonably anticipated to experience multiple serious adverse events regardless of any study procedures. Therefore, certain reasonably anticipated serious adverse events will be collected as study outcomes (these are termed protocol-specified exempt serious events (PSESEs); see Section 10.2.3), and will be monitored by the DSMB rather than reporting these as adverse events per se.

Safety events and PSESEs will be monitored to ensure real-time participant protection through frequent unblinded DSMB review. The DSMB will review unblinded safety reports on an at least monthly basis.

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 any study provided SOC treatment(s).

Infusion-related reactions 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 any study provided SOC treatment).

Events will be reported to regulators and IRBs/ethics committees as appropriate/required.

Adverse events, infusion reactions and unanticipated problems will be regularly reviewed by the DSMB.

The following information will be collected on electronic case report forms, and will be regularly reviewed by the DSMB, to evaluate and help ensure safety:

- Infusion-related reactions during and within 2 hours post-infusion of the investigational agent/placebo.
- Clinical adverse events of grade 3 and 4 through study day 28 (isolated laboratory abnormalities that are not associated with signs or symptoms are not collected).
- Protocol-specified exempt serious events (see section 10.2.3) through Day 90.

- Serious adverse events, including laboratory-only serious events, through Day 90, if they are not being collected as clinical organ failure or serious infections (Item 5 of 4.1.2) or protocol-specified exempt serious events.
- Serious adverse events through Day 180 if they are related to study intervention
- Unanticipated Problems through Day 180
- Deaths through Day 180.
- Hospital readmissions through Day 180.

An overview of safety data collected during the study is given in Table 3.

Table 3 Overview of Safety Data Collection

	During and at least 2 hrs after infusion (all days on which infusion occurs)	Day 0–7	Day 14	Day 28	Day 90
Infusion-related reactions and symptoms of any grade[a]	X				
All grade 3 and 4 clinical AEs (new or increased in severity to Grade 3/4)	X	X	X[b]	X[b]	
Protocol-specified exempt serious events (PSESEs)[c]	Collected through Day 90				
SAEs that are not PSESEs	Collected through Day 90				
Unanticipated problems	Collected through End of Subject Participation (Day 180)				
Hospital admissions and deaths	Collected through End of Subject Participation (Day 180)				
Any SAE related[d] to study intervention	Collected through End of Subject Participation (Day 180)				

[a]This includes reporting of AEs of any grade present on day 0, before the first infusion. This allows assessment of whether a given AE is new after infusion.
[b]Participants will be asked about all new relevant adverse events of Grade 3 or 4 which have occurred since the last data collection, up to that time point. On these visits, AEs of any grade that are present on the day of the visit will also be collected.
[c]These are explained and defined in section 10.2.3.
[d]Relatedness determined as per protocol rules in section 10.

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

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 as 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 in Table 4 is to be used. Given the unique nature of the target population for this trial, hypotension will be graded according to the scale in Table 5 rather than the default DAIDS AE Grading Table.

Table 4 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

Table 5. Hypotension AE Grading

AE GRADING	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATENING
SERIOUSNESS GUIDANCE*	No	No	No (usually)	Yes
Hypotension criteia that apply to all assessments	No intervention or complication meeting criteria for higher grade.	IVF ≥500 mL **OR** low-dose vasopressor (e.g. <0.1 NE [or equivalent])	Moderate-dose vasopressor (e.g. ≥0.1 NE [or equivalent]) **OR** ≥2 vasopressors **OR** multiple interventions	Life-threatening or clinically significant complications **OR** *persistent* clinically significant deterioration.
Additional hypotension criteria for aviptadil/placebo infusion days	No infusion change for hypotension	Decrease infusion rate *for hypotension* **OR** pause infusion with resumption *for hypotension*	Study drug discontinued for day *for hypotension* **OR** study drug not given for day *for hypotension* **OR** study drug discontinued permanently *for hypotension*	No additional criteria

* Guidance provides suggested seriousness alignment with AE grade but does not overrule investigator judgment. In particular, the presence of critical illness influences the threshold for considering a given hypotension AE 'life-threatening' or an 'important medical event.' Evaluation of other factors, including the intensity of intervention required and the event's impact on the patient, are required to determine event seriousness.

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.
  NOTE: 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 a more reasonable/likely 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 IB(s) for the investigational agent(s) and any study-provided background therapy. Additional details of expectedness for a given agent will be specified in the relevant agent-specific appendix.

The expectedness assessment is based on available information at the time of the assessment of the event. The investigators and the sponsor 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

Certain infusion-related signs/symptoms will be collected as protocol-specified exempt serious events (see section 10.2.3) and will not be separately reported as adverse events.

Adverse events that are
(a) not protocol-specified exempt serious events, AND
(b) are of grade 3 or 4 (whether new or as an increase in grade), AND
(c) occur during or within 2 hours post infusion
will be reported as adverse events on an eCRF.

10.2.2 Grade 3 and 4 clinical adverse events on days of study drug administration, and Days 0–7, 14, and 28

From Day 0 through Day 28, adverse clinical events reaching Grade 3 or 4 severity level will be reported on an eCRF. For a clinical adverse event that was present at baseline, only those which newly reach Grade 3 or 4 will be reported.

Beginning 2 hours post-infusion of the investigational agent or matched placebo, on Days 0–7, clinical AEs of Grade 3 or 4 that are new or that have increased in grade compared to their pre-infusion level will be reported on eCRFs.

Adverse clinical events reaching Grade 3 or 4 severity level that occur between Days 7 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 reporting on the SAE eCRF or for protocol-specified exempt serious events reporting on the eCRF documenting the hospital course.

On Days 14 and 28, AEs of any grade that are present on the day of the visit will also be collected.

10.2.3 Protocol-specified exempt serious events (PSESEs)

Consistent with FDA guidance on protocol-specified serious adverse events, the TESICO trial will systematically collect certain adverse events that are expected to occur commonly in the target population even in the absence of study interventions. These events, termed protocol-specified exempt serious events (PSESEs), are in general exempted from the usual expedited reporting requirements for SAEs. This approach is taken to avoid creating a 'noisy' safety oversight environment, obscuring genuine safety signals, and imposing potentially unmanageable burdens on clinical/study staff, particularly in a pandemic critical care setting. Even as they are exempted from expedited reporting requirements, PSESEs will be reviewed regularly (unblinded, by treatment arm) by the DSMB to maintain the integrity of safety monitoring for the trial.

PSESEs will NOT be reported as SAEs, even if they meet one or more of the criteria for seriousness, ***unless considered related to study intervention (blinded investigational agent/ placebo or study-supplied SOC treatment) (see section 10.2.4)***. 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.**

- 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
- Renal dysfunction treated with renal replacement therapy
- Hepatic decompensation
- Neurologic dysfunction, including acute delirium and transient ischemic events
- Disseminated intravascular coagulation
- Major bleeding events
- Serious infections
- Worsening respiratory failure
- Hypotension treated with vasopressor therapy
- Atrial or ventricular arrhythmias

Consistent with this approach, sites will evaluate a potential adverse event to determine whether it is a PSESE:

- If the event is not a PSESE, it will be reported as an adverse event as outlined in section 10 of the protocol.
- If the event is a PSESE, it will be evaluated for relatedness.
  - If the PSESE is related to study interventions (either investigational agent or study-supplied SOC therapy), then the event will also be reported as an SAE. Thus, the event will be reported on both eCRFs, the SAE eCRF and the PSESE eCRF.
  - If, however, the event is a PSESE and is not related to study interventions, then the event will be recorded on the PSESE eCRF as a study endpoint and not as an SAE.

As noted earlier in this section, PSESEs are included in the unblinded safety reports reviewed by the DSMB to allow early detection of important imbalances in the distribution of these events between arms in the trial.

10.2.4 Reportable SAEs

Reportable SAEs for this study are:

- Clinical SAEs which are not exempt from expedited reporting per the protocol-specified exempt serious event list and associated rules (10.2.3); and
- Any SAE related to the study intervention

Deaths, life-threatening events, and other SAEs considered potentially *related to the blinded investigational agent/placebo or study-supplied SOC treatment*, that occur from the time of infusion of the study intervention through the Day 180 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 PSESEs and that are not related to the study intervention must be reported on the SAE eCRF within 3 days of site awareness. Such SAEs will be recorded through day 90.

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."

10.2.5 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.

10.2.6 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.

10.2.7 Pregnancy

The investigator will collect pregnancy information on any female participants who are or become pregnant while participating in this study. (Where the agent-specific appendix excludes pregnant women, this applies to participants who become pregnant.)

The participant will be followed to determine the outcome of the pregnancy.

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. Information obtained on the status of the mother and child will be forwarded to the sponsor. Whether such monitoring will be required is outlined in the agent-specific appendix.

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 stated in section 4. A more detailed statistical analysis plan (SAP) will be 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.

All analyses will be intent to treat with comparisons to concurrent controls as described in section 6.3. 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 primary ordinal outcome—*recovery*—assessed at Day 90 includes 6 ordered categories, best to worst, that assess 4 clinical states. The categories correspond to (1) the number of consecutive days at home off oxygen (3 categories); (2) receiving oxygen at home or living in a location other than home; (3) hospitalized for medical care or in hospice care; and (4) death. The percentage of patients in each category (6 total) will be compared at Day 90. The primary analysis will use a proportional odds model to estimate a summary odds ratio (OR) for being in a better category in the investigational agent group compared with placebo; an OR > 1.0 will reflect a more favorable outcome for patients randomized to the investigational agent vs. placebo.

The proportional odds regression model will include a treatment indicator, and an indicator for receipt of mechanical ventilation or ECMO (vs. neither) at enrollment.

A test for the proportional odds assumption will be carried out. Even if the proportional odds assumption is violated, the overall summary OR will be the basis for inference in the primary analysis, given the robustness of proportional odds regression to violation of the proportionality assumption. In order to further characterize the summary OR and any deviations from proportional odds, separate ORs will be estimated for different dichotomized definitions of improvement formulated from the components of the ordinal outcome (e.g., alive versus dead, alive and out of the hospital versus hospitalized or dead, etc.)

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

Four key secondary objectives are to compare investigational agent with placebo for the following endpoints

1. Time to death through Day 90.

2. A composite endpoint that considers the number of days at home off new supplemental oxygen and the time to death as well as the other categories of the primary ordinal recovery outcome.

3. Time to recovery defined as alive, at home, and off new supplemental oxygen.

4. A three-category ordinal outcome, measured at Day 90, with the following categories: recovered (alive, at home, and off new supplemental oxygen), alive and not recovered, and dead.

Time to death will be summarized using a log-rank test, stratified by receipt of invasive mechanical ventilation or ECMO vs. neither at randomization. The hazard ratio (investigational agent vs control) 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.

The composite outcome will be summarized with a win ratio statistic that ranks patients by time to death (instead of just survival status at Day 90), hospitalization at Day 90, home on oxygen or not at home, and duration of time (in days instead of weekly intervals) at home off new supplemental oxygen. Matching on mechanical ventilation (or ECMO) and a disease progression risk score at entry will be used to estimate the win ratio statistic.

The cumulative incidence functions for recovery (at home and off new supplemental oxygen) taking into account death as a competing risk will be estimated using the Aalen-Johansen method and compared using Gray's test. The recovery rate ratio will be estimated using a Fine-Gray regression model. The comparisons between treatment groups will be stratified by receipt of invasive mechanical ventilation or ECMO vs. neither at randomization. Recovery is defined using the last-off method, as described in section 4.

If there is evidence of benefit for an investigational agent versus placebo for the primary ordinal outcome, the comparison of the investigational agent with placebo for these three outcomes will help to inform the interpretation of the treatment effect.

The primary safety outcome is a composite of grade 3 or 4 events, SAEs, PSESEs (see 10.2.3), or death through Day 5, and tests for differences between treatment arms will be conducted with a Cochran Mantel Haenszel test stratified by receipt of invasive mechanical ventilation or ECMO 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. Time to event analysis will also be used to summarize this composite safety outcome. Proportions of participants who experienced any of these events will be compared using stratified Mantel Haenszel tests and logistic regression. 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 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 receipt of invasive mechanical ventilation or ECMO 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 recovery. Readmissions will be summarized using methods for recurrent events (i.e. those who are readmitted will reenter the risk set).

Clinical organ failure is a composite of many different organ-specific events, listed in section 4.1.2, item 5. 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, thromboembolic events described in section 4.1.2, item 10, and worsening respiratory failure) will be analyzed using time-to-event analyses under competing risks, as described above for the primary analysis. Proportions of participants who experienced organ failure, serious infection or death will be summarized and compared between treatment arms at fixed time points using stratified Mantel Haenszel tests, overall and for specific organ dysfunctions.

The impact of study arm on the primary efficacy (recovery) and safety outcomes (primary composite safety endpoint, composite of grade 3 or 4 events, SAEs, PSESEs, and death through Day 5 and through Day 28, composite of SAEs, PSESEs, and death, and composite of hospital readmissions and death through Month 6) along with mortality will be assessed for subgroups defined by baseline characteristics, including demographics, baseline classification of "home", duration of symptoms at enrollment, clinical history and presentation, 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 is described in section 5.2. 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 on a regular basis and use pre-specified guidelines to identify agents with evidence of harm based on a difference in all-cause mortality. The DSMB will also monitor other adverse events and safety signals.

As a guideline, we do not recommend early termination for benefit based on the primary endpoint, which is most reliably estimated at Day 90. In addition, given the relatively short follow-up period of 90 days for this target population, full follow-up for the primary and all secondary endpoints is considered important to evaluate the investigational agents to be studied. An exception to this guideline is if the DSMB believe there is clear and substantial evidence of a mortality benefit for an investigational agent

11.3.1 Monitoring Guidelines for Interim Analyses

Multiple distinctive features of potential therapies for COVID-19-associated ARDS contribute to the monitoring guidelines for interim analyses within the master protocol. (If a specific investigational agent requires an alternative approach to interim monitoring, those details will be specified in the relevant agent-specific appendix.)

First, in many cases, potential agents may be relevant not only to COVID-19-associated ARDS but to other forms of ARDS. As such, even if an agent did not achieve its efficacy endpoint, enrollment to the planned sample size is expected to provide important insights relevant to future investigations in ARDS. These insights may especially pertain to potential effects among subgroups of patients or less common safety events of interest.

Second, the primary endpoint of this trial requires 90 days of follow-up since the final classification of a patient's recovery requires knowledge of their status on Day 90. While this duration of follow-up for the primary endpoint is essential for a patient-centered result at the conclusion of the trial, in the context of the anticipated rapid enrolment of the trial, this endpoint is infeasible to use for stopping boundaries for either efficacy or futility on the basis of conditional power.

Third, enrollment should stop early for any agent that shows clear evidence for increased mortality. A stopping boundary for harm is thus indicated.

Fourth, while it is important to avoid premature stopping for a potentially non-reproducible efficacy signal for the primary endpoint, clear and substantial improvement in mortality may appropriately lead to a DSMB recommendation to stop early for efficacy.

On the basis of these and related factors, the monitoring guidelines for this master protocol will focus on a stopping boundary for harm, a stopping boundary for efficacy based on mortality, and ongoing close monitoring of safety by the DSMB, based on the totality of evidence.

As a guideline to the DSMB for assessment of harm, a Haybittle-Peto boundary using a 2.5 standard deviation (SD) for the first 100 participants enrolled and 2.0 SD afterwards. Harm will be assessed using all-cause mortality, specifically using a hazard ratio from a proportional hazard model for the time to death associated with the investigational agent. As an additional guideline to the DSMB for assessment of efficacy, a Haybittle-Peto boundary using a 3.0 SD threshold will be used after 100 patients have been enrolled and followed for at least 5 days. Efficacy will be assessed using all-cause mortality, specifically using a hazard ratio from a proportional hazard model for the time to death associated with the investigational agent.

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, including especially NHLBI 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 workers 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 Regulation (EU 536/2014)/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. Many of the patients approached for participation in this research protocol will often have limitations of decision-making abilities due to their critical illness. Hence, some patients will not be able to provide informed consent. For patients who are incapacitated, informed consent may be obtained from a legally-authorized representative (LAR). Because the investigational agents are intended to treat critical illness and the impairment of decisional capacity is intrinsic to the critical illness, the use of LARs for consent is appropriate for this trial. The use of consent from LARs will follow applicable legislation (e.g., in the United States, 45 CFR 46.116 and 45 CFR 46 102 (i)). 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 reconsent should be obtained at the earliest feasible 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 responsible 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.

Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO) Master Protocol
Version 3.0, 08 March 2022

Appendix A Sample Informed Consent form

Short Title: Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO)

Sponsored by: The University of Minnesota (UMN)/National Institute of Allergy and Infectious Diseases (NIAID)

Funded by: The National Heart, Lung, and Blood Institute (NHLBI) and 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 Severely Ill 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.

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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 your choice. You can discuss this information with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting for COVID-19.

What is the research question we are trying to answer?

We are studying two treatments for COVID-19. We are asking you to join the study because you are in the hospital with COVID-19 and have significant trouble with your breathing.

First, we are studying an experimental medicine, aviptadil (also called VIP), supplied by NeuroRx. We are trying to find out if giving this experimental medicine can help sick people in the hospital with COVID-19 have fewer bad effects from the disease, and if it may possibly help them get better and go home faster. We are also trying to see if it is safe.

This experimental medicine is a man-made version of a naturally occurring hormone in the body. It may decrease COVID-19 virus levels, inflammation, and blood clotting, and help protect the lung against injury. We think this experimental medicine may possibly help patients with COVID-19, and we think it will be safe, but we are not sure and so we are doing this study.

Second, we are studying a drug called remdesivir (also called Veklury) supplied by Gilead. Remdesivir is approved in the United States and many other countries for the treatment for COVID-19 in people who are in the hospital. We are trying to find out if remdesivir helps patients with your level of COVID-19 illness get better and go home faster. Remdesivir may decrease COVID-19 virus levels and lung injury. Currently we do not know if remdesivir will help people with your level of COVID-19 illness which is why we are doing this study.

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. They will also check to see if you are able to get both of the drugs we are studying or just one of the drugs. For example, if you are pregnant you will not be able to receive the aviptadil or matching placebo (inactive salt solution) but you will be able to receive the remdesivir or matching placebo.

If you agree to be in the study, and you are able to get both treatments, we will assign you to one of four study groups. This will be done by random chance -- like flipping a

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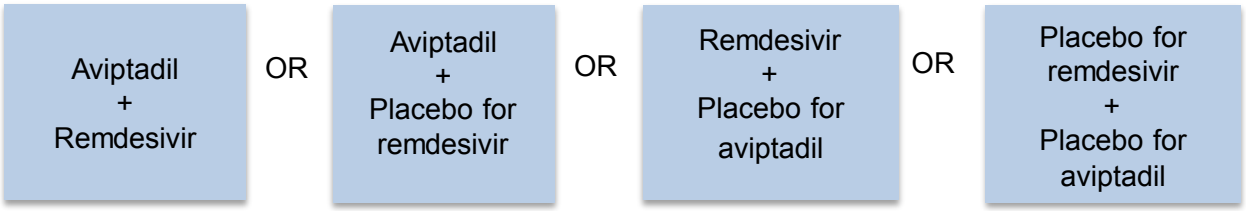
coin. You will have an equal chance of getting either the active drug or placebo (salt solution) for each drug.

You will be assigned to one of the following 4 groups:



Your doctor will NOT decide and will not know which of these four options you will get. The study staff will also not know which option you will get.

If you agree to be in the study, and you are ONLY able to get Aviptadil we will assign you to one of two study groups. This will be done by random chance -- like flipping a coin. You have an equal chance of being in each group.

If you agree to be in the study, and you are ONLY able to get remdesivir we will assign you to one of two study groups. This will be done by random chance -- like flipping a coin. You have an equal chance of being in each group.

Aviptadil: You will receive the Aviptadil study product (either the experimental medicine or the matching placebo) for three consecutive days starting on the day you join the study (study Day 0). You will get it by an intravenous (IV) drip through a tube in your vein. This is called an infusion. The infusion will take about 12 hours on each day that it is given.

Aviptadil is the only thing you may be given that is experimental. It is NOT approved for use in people with COVID-19 by the United States Food and Drug Administration (FDA) or any other regulatory body in the world. It is approved in some countries outside the US for another condition but is given in a different way. Its use in the United States is strictly limited to research.

Remdesivir: You will receive the remdesivir study product (either the active medicine or matching placebo) once per day for up to 10 days. You will also get this by an IV drip through a tube in your vein, which will generally take 1-2 hours. Remdesivir is approved

in the United States for the treatment of COVID-19 in people who are in the hospital. It's not known whether it works in people with more severe COVID-19.

Other treatments: As part of the study you may also get a drug called a steroid for up to 10 days while you are in the hospital, as care for your COVID-19, unless your doctor thinks the steroid would not be safe for you to take. Steroids have been shown in prior studies to help people survive COVID-19. Steroids are available for other diseases in the United States, so your doctor will be using it "off-label," which means that while there is not formal FDA approval for this use, your doctors think it is reasonable. It is likely that you would receive steroid medicine even if you were not in the study.

Any other medications or treatments you will be given will be what you would usually receive 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 180 days. We will check on your health every day while you are in the hospital, and regularly after you leave the hospital.

We will swab your nose to see how much of the virus that causes COVID-19 is present. We will take blood samples from you to better understand the body's response to the infection. Some of the blood may be used in future studies.

To be in the remdesivir/placebo part of the study, you will need to agree to not have sex that could make you or a partner pregnant for seven days after you finish the remdesivir or placebo infusion. This may involve not having sex at all (abstinence), or you may use effective contraception (hormonal contraception or barrier methods with spermicide) to avoid pregnancy. Methods like rhythm, sympto-thermal or withdrawal are not effective for the purpose of the study. You can ask the study team about this if you have questions or concerns.

If you are pregnant, you cannot be in the aviptadil/placebo part of the study. You can still be in the remdesivir/placebo part of the study.

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.

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We will need to do the following things with you, and gather detailed information at these times:

Study Timepoint	What will happen & what we will check
Up to 1 day before you get study product	• Informed consent (this document) • Check to see how you are feeling • Your medical history • Whether you are taking certain medicines • A swab of your nose for virus detection • Blood tests to check your health (9 mL, about ½ tablespoon) • Blood for future research (18 mL, about 1 tablespoon) • Collection of urine or blood for a pregnancy test • Contact information like telephone numbers and addresses for you and at least two close relatives or friends
Day 0, Day 1, Day 2	• Infusion of study product (the experimental medicine or else placebo) if able to get this drug • Infusion of remdesivir study product (active drug or placebo) if able to get this drug (you may get this treatment for up to 10 days) • Blood tests to check your health (9 mL, about ½ tablespoon), unless your treatment team has already performed those tests
Day 3, Day 5	• How you are feeling • Blood for future research (18 mL, about a tablespoon) • If you're not in the hospital, we will not draw your blood and the visit may take place by phone
Day 2, Day 4, Day 5, Day 7, Day 14, Day 42, Day 60, Day 75	• How you are feeling (Days 2, 4, 7, 14, 60) • Update on return to home (Days 14, 42, 60, 75) • On Days 0-7 and 14, also whether you have taken certain medicines These "visits" may take place by phone.
Day 28, Day 90, and Day 180	• How you are feeling • On Day 28, also whether you have taken certain medicines • On day 90 and 180 only: we will ask you additional questions about your health These "visits" will take place by phone.

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.

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- 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.
- 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.

We will send the information we collect 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 are responsible for keeping your identifying information safe from anyone who should not see it.

We will send the blood 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 study drug, it is possible it may help you get better, or that you may get home faster, but we do not know that.

It is important to remember that some people in this study will get inactive placebo and will not get study drug.

By being in this study, you will help doctors learn more about how to treat COVID-19 in people in the hospital. Because so 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 is shown to be effective.

Why would you NOT want to be in the study?

Since only some people in this study will get study drug, you may not receive it. Even if you do get study drug, it may not be useful, or it may have harmful side effects, so being in the study would not be of any direct help to you.

What are the risks or side effects of the study treatments?

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

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

You will be monitored very closely while you are being given the infusion of the study product (aviptadil or placebo) and for at least 2 hours after the infusion is finished. We will give you prompt medical care if needed to treat any side effects from the infusion.

There are discomforts and risks associated with blood draws. You will have these things done while you are in the hospital even if you are not in the study. These discomforts and risks are no different from what you would experience if they were performed as part of your regular hospital care for COVID-19.

What are the risks or side effects of Aviptadil?

One effect of aviptadil is that it relaxes smooth muscle such as in your lungs, blood vessels, and intestines. Relaxing this type of muscle opens up your airways so it is easier to breathe and get oxygen into your body.

The most common side effect of aviptadil infusion is decreased blood pressure. In early studies of very ill patients with lung injury, about 1 in 5 people (20%) had lower blood pressure during the infusion of aviptadil. The decrease was usually small and went away within 10 minutes of stopping the infusion.

Facial flushing is common with aviptadil and is not dangerous. It is caused by relaxation of the blood vessels in the skin and goes away when the infusion is stopped.

Increases in heart rate are common and usually not dangerous. The increase in heart rate is mostly due to blood vessel relaxation.

Some people getting aviptadil have had mild to moderate diarrhea. The diarrhea goes away when the infusion is stopped.

What are the risks or side effects of Remdesivir?

The most common side effects of remdesivir included abnormal liver function test results, abnormal blood clotting test results, constipation, diarrhea, 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 document was written, one person in another 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 some side effects after the infusion of remdesivir. Other people may have no side effects.

What are the risks and benefits of taking steroids?

Steroids may cause your sodium (salt) and glucose (sugar) levels to rise in your blood. You may feel anxious while taking steroids. You may be given steroids to treat your COVID-19 even if you do not join this study.

What if you are pregnant or breastfeeding?

If you are pregnant or breastfeeding, you can still join this study, although you cannot participate in the aviptadil portion of the study. However, we do not have any information about how either aviptadil or remdesivir may affect your baby. The risks to a pregnant woman or an unborn baby might be serious. Please take this into account as you make your decision about whether to 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 comply with all rules and regulations for human research as well as the laws of each country where the study is taking place.

This study is taking place in several countries. We expect to enroll about 800 people around the world.

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 now 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.

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 Aviptadil because it is experimental.

What are the costs to you?

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 UNITED STATES SITES ONLY. SITES IN OTHER COUNTRIES SHOULD DELETE THE NEXT PARAGRAPH.

PID: _____

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

SITES OUTSIDE THE UNITED STATES: Please replace the paragraph above with language appropriate for your location

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 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 samples?

We will send the blood 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 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 blood samples will also measure the amount of virus in your blood and other results related to your COVID infection.

Any blood 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.

You can withdraw your consent for us to keep these specimens at any time. Let your study team know if you do not want the study to keep your specimens anymore, and every effort will be made to destroy all of your specimens 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 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 specimens 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 specimens 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 will be available at http://www.ClinicalTrials.gov, and on the EudraCT website (https://eudract.ema.europa.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. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

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

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

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.

*[The following section (up to "What are your rights regarding your data?") is for **US sites only.**]*

There are a lot of studies trying to find out more about COVID-19 and how people do after they have had COVID-19. Sometimes other researchers studying COVID-19 may ask if we know of people who might be interested in being in a study. If you think you might be interested in future studies, you can let us know now. We are asking you for permission to share your contact information (name, email, phone number, mailing address) with other researchers outside the study team who ask us to help them. We would only share your contact information with researchers who have appropriate ethics approval for their study. We will never share your contact information with researchers doing studies aimed at making money ("commercial research"). Even if you let us give other researchers your contact information, you do not have to be in any future studies. You always have the choice to say "no" if someone contacts you for a future study. If you tell us now that we can share your contact information but later you change your mind, let us know. If you change your mind, we will no longer share your contact information with other COVID-19 researchers.

Please put your initials by your choice:

____**Yes**, you **can** share my contact information with other qualified researchers.

____**No**, **do not** share my contact information with other qualified researchers.

It is your choice whether to let us share your contact information with other researchers studying COVID-19. You can still be in this study even if you do not want us to share your contact information.

*[The following section (up to "What if you have problems or questions?") is for **only 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 independent supervisory 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 would like to inform 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: 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:

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: _____

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SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE TESICO STUDY

I have read the consent or have had it explained to me. I believe that I understand the information. By signing and dating this consent, I am stating that I want 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 the 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 subject, and the subject 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.

Additional Consent for Genetic Testing on Stored Specimens

WHY IS GENETIC TESTING BEING DONE? The study team would like your permission to collect a small amount of your blood and store them for researchers who will do genetic testing (testing on your genes) and other related tests in the future. These tests will help us understand how the genetic makeup of people affects the COVID-19 virus and how it makes people sick.

Any future research done on the blood collected for this study will be related to the COVID-19 virus for which you are being studied in ***this trial.***

WHAT WILL HAPPEN DURING GENETIC TESTING?

If you agree to take part in this study, three blood specimens will be collected along with other blood being drawn for the study, approximately 15 mL (about 1 tablespoon) in total. The blood will be taken with other laboratory test samples so you will not get an extra needle stick.

HOW WILL YOUR BLOOD BE USED? Your blood will be used to learn more about the health problems that may be caused by COVID-19. This may include tests to better understand why some people have more severe complications (get sicker) than others and why medicines to prevent or treat these infections might work better in some people than in others.

Researchers involved with this blood collection project do not know yet exactly which tests will be done.

You and your study doctor or nurse will not get any results from the tests done on your blood collected for this genomics study. These tests will only be used for research and may not apply to your medical care.

Your blood sample collected for this study will:

- Become the property of INSIGHT.
- Not be sold or used to make commercial products.
- Not be tested for any specific research study unless the plan for using your blood is approved - based on scientific and ethical considerations - by the INSIGHT Scientific Steering Committee, the U.S. National Institutes of Health (NIH), and a special committee (an Institutional Review Board or Ethics Committee) at the researcher's institution.

HOW WILL YOUR PRIVACY AND THE CONFIDENTIALITY OF YOUR INFORMATION BE PROTECTED?

Every reasonable step will be taken to protect your privacy and the confidentiality of your health information and to prevent misuse of this information, and to make sure your blood sample is handled with care at the storage facility. For example, your research records will be identified only by a code. Your blood sample and results of any genetic testing will be identified by a second code. Only a few statisticians (persons who analyze the study results) associated with the INSIGHT studies will have access to both codes in order to analyze the test results. These statisticians will not have access to any information that can identify you.

Researchers will write reports, including information they learn from future tests on your blood. These reports will be shared with participating research sites. These findings will also be submitted for publication in scientific or medical journals. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

However your records may be seen by:

- Institutional Review Boards (IRBs) or Ethic Committees (ECs) who review the study to make sure it is ethically acceptable
- Agencies of the U.S. government that fund or oversee this research, for example, the U.S. National Institutes of Health (NIH) or the U.S. Office for Human Research Protections (OHRP)
- Research staff and study monitors, and their designees.

Staff at ***[insert the name of the site]*** will handle your personal information very carefully. They are required to make sure that people not involved with this study do not have access to your research and medical records.

[For U.S. Sites Only]

In addition to these efforts to keep your information confidential, the INSIGHT Genomics study is covered by a *Certificate of Confidentiality* from the U.S. Department of Health and Human Services. This certificate means that researchers cannot be forced to give information collected as part of this study to people who are not involved with the study, for example, the court system. However, this certificate has limited protection rights. You should know that it does not stop the doctor in charge of this study from taking appropriate steps to prevent serious harm to yourself or others. Federal and state laws also help protect research participants and others who have genetic testing done.

[For International Sites Only]

Efforts will be made to keep your personal information confidential, but we cannot guarantee complete confidentiality. Your personal information may be released if

required by law. Any publication of this study will not use your name or identify you personally.

HOW LONG WILL YOUR BLOOD BE KEPT?

Your blood specimen will be stored as long as funding is available for storage and testing.

[Alternative to Previous Paragraph for non-US Sites Only]

Your blood specimen will be stored safely and securely at a special facility called a specimen repository. The repository may be located in the United States. This facility follows strict procedures so that only approved researchers can use the stored specimen for future testing. The employees at this facility who will store and track your blood specimen will not have information that identifies you by name.

Risks: There are few risks involved with your participation in this study. Having your blood drawn may result in a little pain and slight bruising where the needle goes into your skin. You may also feel lightheaded, bleed, develop a small blood clot where the needle goes into your skin, or faint. Very rarely, your skin may get infected. Another small but unlikely risk is the possibility of others finding out about your participation in this study.

Benefits: You will not receive any direct benefit from your samples. Information obtained from the tests may provide useful information, to help other patients, about the causes, risks, and prevention of the COVID-19 virus.

WHAT IF YOU DON'T WANT YOUR BLOOD FOR GENETIC TESTING STORED ANY LONGER? If you sign the consent that your blood can be stored for research to be done at a later date you can change your mind at any time. If you change your mind, you must write a letter to ***[insert the name of the principal investigator*]** at the ***[insert the name and address of the site]*** to let them know that you do not want your blood specimen collected for this study used for future research. A sample letter will be given to you as a guide to help you express your request in writing.

When ***[insert the name of the principal investigator]*** receives your letter, the research staff will contact you to come to the clinic to verify your decision by signing and dating this original informed consent form. A second copy of this consent will be given to you as proof that we received your request. If we do not hear from you within 30 days after getting your letter to withdraw from this study, we will send your request to the storage facility.

If you decide to withdraw consent for this study, your blood sample, including any parts separated from the sample, will not be used. Every effort will be made to destroy your

blood sample and any parts separated from it. If some testing has already been done on your blood sample, the results from this testing will remain as part of this research. The research staff at the ***[insert the name of the site]*** will notify you of the date your blood specimen and any of its parts were destroyed.

Costs or compensation of study: There will be no costs to you or compensation.

Consent: Please ***mark the box for*** yes or no and ***sign your name***, indicating you have freely given your answers and consent:

- My blood samples may be stored and used for future genetic research in COVID-19 or other serious illness: **Yes** ☐ **No** ☐

_____ _____

Signature (subject or surrogate) Date

_____

Subject or Surrogate Printed Name

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name and Title of Person

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Appendix B Schedule of Assessments

	Screen or Day 0	Day 0	Study Day													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
ELIGIBILITY & BASELINE DATA																
Informed consent	X															
Baseline medical and social history	X															
Baseline concomitant medications	X															
Symptom-directed physical exam by the clinical team (includes vital signs)	X															
Nasal swab for virus detection and review SARS-CoV-2 test results	X															
Baseline study labs (CBC with differential, ferritin, CRP, BMP, INR, D-DIMER, AST, ALT, bilirubin)[2]	X															
Research sample storage (includes DNA and RNA at baseline among patients who consent to genetics)	X															
Urine pregnancy test or other documentation of pregnancy status	X															
STUDY INTERVENTION																
Randomization		X														

	Screen or Day 0	Day 0	Study Day													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
Study Drug/Placebo Administration[3]		X	X	X												
Assess infusion completion and adverse reactions[3]		X	X	X												
STUDY PROCEDURES																
Post-randomization concomitant medications		X	X	X	X	X	X	X	X	X[4]	X					
On-study labs (BMP, CBC with differential, INR, D-DIMER, AST, ALT, bilirubin)[2,5]		X	X	X												
Clinical labs (BMP, CBC with differential, INR, D-DIMER, AST, ALT, bilirubin)[5,6]					X[7]		X[8]									
Research sample storage (includes RNA at day 3 among patients who consent to genetics)[4,5]					X[7]		X[8]									
Vital signs[5]	X	X	X	X			X			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	X	X[9, 10]	X[9, 10]
Oxygen support (for WHO/NIH/TICO ordinal outcome)	X	X	X	X	X	X	X	X	X	X[4]						

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	Screen or Day 0	Day 0	Study Day													
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**	**75**	**90**	**180**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+2**	**+3**	**+3**	**+5**	**+5**	**+ 10**	**± 14**
Clinical AEs of grade 3 and 4 severity		X	X	X	X	X	X	X	X	X	X					
Clinical AEs of any grade on day indicated										X	X					
SAEs and PSESEs		Report through 90 days														
SAEs related to study interventions		Report as they occur														
Unanticipated problems		Report as they occur														
Deaths and readmissions		Report as they occur														
Hospitalization Summary		Report upon hospital discharge														

[1] Screening must be performed within 24 hours of randomization.
[2] These laboratory evaluations will only be performed as study procedures if they are unavailable clinically on that study day
[3] Duration of study drug administration may vary by investigational agent; the sample provided here is for 3 successive days. Where the duration of study drug administration varies from this schedule, the duration will be specified in the relevant agent-specific Appendix H .
[4] The Day 14 visit will record values for Days 8–14.
[5] These will be not be collected after hospital discharge.
[6] These laboratory assessments will only include clinically available results
[7] It is acceptable to perform the Day 3 draw on Day 4.
[8] It is acceptable to perform the Day 5 draw on Day 5±1, but the Day 3 and Day 5 draws cannot both be performed on Day 4.
[9] Includes telephone administration of the Euro-QOL-5D-5L instrument.
[10] Includes telephone administration of Patient-Reported Outcomes (MRC Dyspnea, PROMIS fatigue, CONNECTS Recovery)

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Appendix C TESICO / ACTIV-3b 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
- NHLBI Program Officers
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center representatives
- Representatives from collaborating trials networks, including PETAL, CTSN, and VA
- 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, NIH 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)

Therapeutics for Severely Ill Inpatients with COVID-19 (TESICO) Master Protocol
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Appendix E LIST OF ACRONYMS

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
AE	adverse event
ARDS	acute respiratory distress syndrome
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
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
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	interquartile range
IRB	Institutional Review Board

IV	intravenous
LAR	Legal Authorized Representative
MI	Myocardial infarction
mL	milliliter
NAT	Nucleic acid test (to identify genomic material; some uses amplification)
NHLBI	National Heart, Lung, and Blood Institute, NIH (US)
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 Network
PHI	personal health information
PIM	Protocol Instruction Manual
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

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Appendix H Investigational Agent.

This appendix will include the following information for each investigational agent studied. The rationale for studying the agent 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 agent in question relative to what is stated in the master protocol. Finally, the text will also clarify whether the manufacturer of the 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 agents
- 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, the only licensed treatment for COVID-19 is remdesivir, but the *registration trials for remdesivir were too small to demonstrate efficacy in patients with critical illness from COVID-19.* 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 treating patients with critical illness from 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 + 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

Although remdesivir is licensed for use in the United States and is SOC for most hospitalized patients with COVID-19, the key registration trials[50] included insufficient patients in this subgroup to provide strong evidence in favor of remdesivir for critically ill patients. It is anticipated that this master protocol may include a placebo-controlled investigation of remdesivir, possibly in a factorial design, in this patient population. Thus remdesivir is not considered SOC presently for this protocol: the protocol does not recommend routine initiation of remdesivir in this patient population (except potentially as an investigational agent). For patients who have already initiated remdesivir by the time of enrollment, this protocol makes no recommendation regarding whether to continue or discontinue remdesivir as part of background therapy. (For patients enrolling in a remdesivir randomization, see the remdesivir appendix for further guidance on receipt of remdesivir prior to randomization.)

I3.2 Dexamethasone and Other Corticosteroids

Based on the findings of the RECOVERY trial,[39] a meta-analysis of glucocorticoid trials,[51] and in line with NIH treatment guideline (Appendix D), it is recommended to consider initiation of corticosteroid therapy in participants with COVID-19 who have respiratory failure—the target population of this master protocol. 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, but the balance of evidence favors glucocorticoid therapy. 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[52] (high quality evidence) and prone positioning for mechanically ventilated patients with more than moderate ARDS (high quality evidence[53,54]), 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).[55] 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 0.5 m/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

It is not recommended to use chloroquine as SOC due to excess harm and no demonstrable benefit. Neither hydroxychloroquine nor chloroquine have documented clinical benefit, and hence are not recommended for use as SOC. Similarly, it is not recommended to use lopinavir/ritonavir as SOC, since there are studies suggesting no clinical benefit.[56,57] These recommendations are consistent with current guidelines by the Infectious Disease Society of America, as included in Appendix D.

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.

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