A Multicenter, Adaptive, Randomized, Controlled Trial Platform To Evaluate Safety and Efficacy of Strategies and Treatments for Hospitalized Patients with Respiratory Infections

Short Title: Strategies and Treatments for Respiratory Infections & Viral Emergencies (STRIVE)

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- Nashville ICC - Vanderbilt University Medical Center, Nashville, Tennessee, US
- US Department of Veterans Affairs ICC

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1 Protocol Summary

DESIGN

Strategies and Treatments for Respiratory Infections & Viral Emergencies (STRIVE) is a master protocol designed to evaluate the safety and efficacy of unlicensed and licensed treatments and their sequential and combined use to optimize health of patients admitted to hospital for acute care of a respiratory infection.

The protocol aims to improve standard of care, by ensuring an agile research infrastructure, with an ability to rapidly assess interventions during epidemic transmission of one or more respiratory pathogens adversely affecting public health.

Trials within this protocol can be adaptive, will be randomized, and will have superiority as the primary objective. Comparisons in the trials may be between an unlicensed agent to a blinded placebo plus standard of care (SOC), between an approved off-label agent to a blinded placebo plus SOC, among several active interventions (blinded or non-blinded; i.e., a comparative effectiveness study), or among different treatment strategies.

Because this protocol includes a spectrum of potential respiratory pathogens, at different stages of disease, broad scope of potential interventions, and several trial comparisons, the STRIVE platform offers several choices for the selection of primary outcomes, eligibility criteria, data collection and monitoring from which trials can choose (i.e., a la carte menu). Each trial will specify its choices in its trial-specific appendix. Decisions on the conduct of each trial described in the trial-specific appendices will supersede the guidance in this master protocol.

The STRIVE platform may have a number of trials ongoing at any given time. To improve efficiency and scientific rigor, these trials may share participants either through sequential co-enrollment and/or through a shared control/placebo group across multiple trials (simultaneous co-enrollment). For example, the STRIVE platform may assess multiple agents within a single therapeutic class typically sharing a single control. The platform emphasizes conducting trials across the spectrum of disease severity for hospitalized patients. Thus, a common scenario will be enrollment in a STRIVE trial early in the hospital admission, with subsequent eligibility for another trial if the patient does not recover or worsens.

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

For agents with minimal prior experience in humans, a sentinel cohort of 20-30 participants, enrolled at selected sites, may be enrolled and followed for at least 5 days. The data and safety monitoring board (DSMB) will be requested to assess safety. If no safety concerns are identified, enrolment will be expanded to all eligible sites.

DURATION Participants will be assessed for the primary outcome at 60 days following randomization unless otherwise stated in the trial-specific appendix; additional follow-up may be added for some trials.

SAMPLE SIZE The principles used to determine the sample size for individual trials are described in the master protocol; the specific sample size for each trial is detailed in the trial-specific appendix. Unless otherwise stated in a trial-specific appendix, each trial will aim to include approximately equal numbers of participants in each arm. To ensure appropriate power for the trials, sample size re-estimations will be performed by a small group of blinded investigators.

POPULATION Trials conducted in STRIVE will include adults hospitalized with acute respiratory infections. Trial-specific appendices will further define the population for each trial, including the respiratory pathogen or syndrome and signs or symptoms a patient must exhibit to be eligible for enrollment.

Severity of illness is determined by the respiratory infection or syndrome being studied.

STRATIFICATION Randomization will usually be stratified by study site pharmacy, and severity of disease at entry unless stated otherwise in the trial-specific appendix.

REGIMEN The STRIVE platform is initially designed to study interventions within four therapeutic classes:1) anti-viral agents (small molecules); 2) microbial-directed passive immunotherapies; 3) agents affecting host pathways involved in organ injury, and 4) agents specific for treatment of patients with critical illness. Treatments will be prioritized based on data derived from *in vitro* and pre-clinical animal studies, and from earlier clinical trials of the treatment, and licensure status. Both pre- and post-licensure treatments will be evaluated.

MONITORING An independent data and safety monitoring board (DSMB) will review interim data and reports prepared by unblinded statisticians according to treatment allocation during the conduct of a trial at least twice a year and possibly more frequently as needed.

During the conduct of each of the trials, a number of pre-defined unblinded interim assessments for efficacy and safety outcomes will be performed and evaluated by the DSMB. These will be described in a Statistical Analysis Plan (SAP). Investigators will remain blinded during the trial. No pause in enrolment is planned while these interim assessments are undertaken.

The DSMB may recommend discontinuation of a trial at interim analyses for evidence of harm, efficacy, or futility.

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

Unless specified otherwise, guidance on halting a trial early for futility will be based on conditional power evaluations for the primary outcome. In some cases, an early futility assessment may be specified using an intermediate outcome.

2 Introduction

2.1 Study Rationale

Respiratory infections remain a threat to public health, as highlighted by the coronavirus disease 2019 (COVID-19) pandemic. They may circulate endemically, but may also lead to smaller outbreaks, epidemics, and pandemics. Current threats for epidemic and pandemic spread include the viral pathogens SARS-CoV-2 and influenza. Additionally, it is likely that novel respiratory pathogens will emerge.

Currently, while most cases of SARS-CoV-2 and influenza infection are mild, progressive disease can result in hospitalization, requirement for organ supportive care including mechanical ventilation, and substantial morbidity and mortality. The most common mode of disease progression is respiratory failure following the development of pneumonia. However, other severe complications may be caused from thromboembolic disease involving lung, heart and other organs, as well as failure of kidney, liver and central nervous function, and emerging complicating infections (“superinfections”).

Several clinical trials investigating novel drugs and repurposed older agents for the treatment of adults hospitalized with COVID-19 and influenza have been completed in the past and are ongoing (see section 2.2.1 and 2.2.2). The standard of care is hence evolving rapidly.

In contrast, for novel pathogens the potential treatment landscape will need to be defined.

STRIVE aims to provide an agile research platform able to investigate strategies and treatments that may improve the health of patients hospitalized with a respiratory infection. Types of agents that may be studied are outlined in section 2.3. The master protocol defines the scientific and operational framework of trials implemented as part of the platform. The specific design and conduct of each trial are described in the trial-specific appendices. This approach is intended to pre-position infrastructure and to facilitate rapid and flexible response with high standards of scientific rigor to support the development of consensus for standard of care. In general, scientific and operational decisions specified in the trial-specific appendices will supersede any decisions which are discrepant with the master protocol.

2.2 Background

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

A pandemic emerged in late 2019 due to a novel coronavirus, SARS-CoV-2. The virus has further evolved into several strains associated with distinct differences in terms of transmissibility, disease severity, and immune escape from infection with or vaccines designed against earlier variants.

It is expected that SARS-CoV-2 will continue to evolve. It is unknown how this evolution will affect the epidemiology of transmission, the clinical features of the infection including tropism for replication in pulmonary tissue, and responses to existing therapies including viral evasion of both immunotherapies and small molecule inhibitors.

Clinical disease caused by SARS-CoV-2 is termed COVID-19.

2.2.1.1 Natural History and Risk Factors for Clinical Progression

Some persons remain asymptomatic after infection with SARS-CoV-2. However, about 70-80% of infected persons develop COVID-19. After an incubation period of 3-6 days, early symptoms from COVID-19 are typically confined to the upper respiratory tract. A fraction of these patients (5-20% depending on the population affected) experience disease progression, which typically signifies dissemination of infection to the lower respiratory tract, and which typically manifests clinically as shortness of breath, respiratory failure and, less commonly, failure of other organs. This transition typically takes 5-8 days from time of symptom onset. Established risk factors for disease progression include older age, co-morbidities, and a dysfunctional immune system (in particular conditions affecting B-lymphocyte function, i.e., the cells producing antibodies) [1].

2.2.1.2 Hospitalization of People with COVID-19

Patients hospitalized for COVID-19 typically suffer from pneumonia, which in some rapidly advances to Acute Respiratory Distress Syndrome (ARDS). Therefore, criteria for grading severity of COVID-19 among hospitalized patients has used levels of supplementary oxygen and respiratory support. During 2020 and 2021, the typical distribution of recently admitted patients with COVID-19 was: 20-30% not receiving supplemental oxygen; 50-70% receiving low flow supplementary oxygen (ranging from 1-15 liters/min); and 10-30% receiving high-flow nasal oxygen therapy, non-invasive ventilation or mechanical ventilation. During the course of hospital admission, of those not immediately treated with mechanical ventilation,10-30% progressed to mechanical ventilation. Mortality through 90 days from time of admission also differed substantially depending on oxygen requirement and ranged from 3-5% in those not treated with supplemental oxygen, to 20-40% in those requiring high-flow oxygen cannula, non-invasive ventilation or mechanical ventilation [2-5].

All SARS-CoV-2 variants known today may cause serious extrapulmonary disease including thromboembolic events in both the venous and arterial vasculature, and acute kidney injury necessitating renal replacement therapy.

2.2.1.3 Current Treatment Strategies for COVID-19

Various interventions able to reduce viral replication of SARS-CoV-2, when instituted early or before symptom onset, have consistently demonstrated an ability to reduce the risk of disease progression to hospitalization or death. However, among hospitalized patients, drugs that reduce viral replication have less consistently demonstrated clinical benefit. A few drugs (remdesivir [2] and some anti-SARS-CoV-2 neutralizing monoclonal antibodies [6]) have demonstrated benefit for reducing the risk of progression to more severe disease, accelerating recovery, or improving survival in subsets of the admitted population. However, there is no global consensus on the optimal use of antiviral agents for patients hospitalized with COVID-19. Many clinicians use remdesivir as part of routine initial management, and a neutralizing monoclonal antibody for admitted patients with severely impaired B-lymphocyte function.

Among hospitalized patients, various types of immunomodulatory agents, when initiated in patients requiring supplementary oxygen, have consistently demonstrated clinical benefit, in terms of reducing the risk of disease progression, accelerating recovery, and in a few cases, improving survival. Common approaches to the use of immunomodulatory agents are the

prescription of glucocorticoids [7] to hospitalized patients treated with oxygen, and additional immunomodulation for patients more severely ill, such as with an IL-6 antagonist or JAK-inhibitor [8, 9].

Guidelines committees are regularly updating their COVID-19 treatment guidelines [10].

2.2.2 Influenza

Influenza virus is typed as A, B, C and D. Type A is subtyped and numbered based on permutations of features of the two main surface proteins, hemagglutinin (H) and neuraminidase (N). Via genetic reassortment, type A influenza virus has caused several pandemics in the last century including the Hong Kong influenza (H3N2) pandemic that emerged in 1968 and the 2009 H1N1 pandemic. Both strains continue to circulate and cause annual outbreaks and epidemics, partly because of antigen drift of N and H, resulting in reduced immune protection from previous infections, and partly because of waning immunity over time. Influenza B also causes epidemics, typically with two- to three-year intervals.

There are several avian influenza A strains causing outbreaks and smaller localized epidemics (e.g., H5, H6, H7, H9, H10; most frequent: H7N9). However, transmission efficacy in humans thus far has been low and hence easily controlled. It is likely that viral genome reassortment will lead to selection of a novel influenza strain with pandemic potential. Influenza B only circulates among humans and has 2 lineages that do not differ significantly in viral shedding or clinical severity [11].

The clinical disease caused by influenza virus infection is also called influenza.

2.2.2.1 Natural History and Risk Factors for Clinical Progression

Some persons remain asymptomatic after infection with influenza. However, about 60-70% of infected persons develop clinical symptoms. After an incubation period of 1-3 days, symptoms typically develop rapidly and include pharyngitis, rhinitis, bronchitis, malaise, and fever. Symptoms are self-resolving over 3 to 7 days for 60-80% of patients with symptomatic influenza. Complications typically develop between Day 3 and 5 after symptom onset, which can lead to hospitalization and death. Risk factors are overlapping with those associated with disease progression from COVID-19 (see Section 2.2.1.1 above).

2.2.2.2 Hospitalization of People with Influenza

The reasons for hospital admission for influenza are diverse. The leading causes include: pneumonia, sometimes caused by super-infections with a bacterial pathogen; dehydration in frail persons; and acute coronary syndrome [12]. The course of the pneumonia maybe complicated by ARDS, requiring intensive care. The mortality rate among hospitalized patients is 7-12%.

A few avian influenza strains (e.g., H5N1 and H7N9) are able to replicate in pulmonary tissue and cause a viral pneumonia as part of their initial clinical presentation. The case-fatality-rate is high (>20%).

2.2.2.3 Current Treatment Strategies for Influenza

Agents inhibiting one of two viral targets (neuraminidase (e.g., oseltamivir or zanamivir [13]) and cap-dependent endonuclease (baloxavir) [14]) can shorten the disease course by 12-16 hours, if initiated within the first 24-48 hours after symptom onset [15, 16]. No adequately powered randomized trial has been conducted to demonstrate whether the risk of complicated influenza is also reduced, although a meta-analysis of smaller trials assessing oseltamivir is suggestive [17]. Patients with influenza are rarely admitted within 24-48 hours of symptom onset, and it remains logistically challenging to ensure broad provision of the medication to at risk outpatients within this limited time window.

Some guidelines suggest use of oseltamivir at time of admission to hospital due to influenza, irrespective of time since symptom onset. Evidence for this practice comes exclusively from observational studies, in which oseltamivir use appears to be associated with reduced mortality [18-20]. The benefit of combining two antiviral agents remains uncertain [21].

A prevailing view is that the inflammatory response to influenza is not as detrimental as that seen in COVID-19. Unlike for COVID-19, in which corticosteroids are recommended and routinely prescribed for severe disease, corticosteroid therapy is generally not recommended for influenza and has been associated with increased risk of nosocomial infections and death in meta-analyses [22, 23].

2.2.3 Other Respiratory Pathogens

STRIVE primarily focuses on viral causes of respiratory infections. However, a number of bacterial and fungal pathogens may also lead to outbreaks and epidemics, and hence may be of interest to investigate in addition to other viral infections besides COVID-19 and influenza.

2.2.3.1 Known Pathogens

Upper respiratory tract infection with respiratory syncytial virus (RSV) may lead to admission among infants usually in their first year of life. Additionally, this virus can also cause severe respiratory tract infections in adults, particularly among immunocompromised and older frail patients [24, 25].

Other coronaviruses besides SARS-CoV-2 may lead to outbreaks of respiratory tract infections, including Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [26] and Severe Acute Respiratory Syndrome (SARS-CoV-1) [27]. It is possible that additional novel coronaviruses may emerge.

Bacterial pathogens most often causing respiratory tract infections include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Legionella spp*, *Mycoplasma pneumoniae*, and *Staphylococcus spp* [28, 29].

2.2.3.2 Unknown Pathogens

Animals may develop respiratory infection due to multiple viruses, bacteria, fungi and parasites. It is hence possible that those pathogens may cause zoonotic infections in humans.

2.2.4 Syndromes Associated with Respiratory Pathogens

Most trials in STRIVE will likely focus on patients infected with one respiratory pathogen. In the initial course of the symptomatic phase of the infection, typical clinical features may differ by pathogen. However, as the disease progresses and in particular among those with complicated courses, the clinical features overlap, especially in critical illness. Such syndromes may represent actionable target populations for trials within STRIVE.

2.3 Investigational Agents and Other Interventions

"Accelerating COVID-19 Therapeutic Interventions and Vaccines" (ACTIV) has formed both an overarching Agent Prioritization Committee (APC) and a Trial Oversight Committee (TOC) for STRIVE. The APC will conduct a first review of agents for the trial and determine if an agent is aligned with the mission of the trial and has sufficient evidence to warrant testing in a large Phase 3 or 4 trial. This will be evaluated by criteria created by the ACTIV Clinical-Therapeutics Working Group (WG), which includes review of data for investigational agents and considers a number of factors including safety, *in vitro* potency against the virus, resistance, scale-up potential in general and for completing a trial within the platform, and dose and route of administration. The APC will select agents for study in the STRIVE master protocol and then send them to the TOC to validate those recommendations by review of the APC's evaluation summary and then promote agents they deem to be of high priority to the STRIVE team by TOC majority vote. Members of the STRIVE protocol team are non-voting members of the TOC and have a chance to provide feedback on the acceptability of the agent during the TOC review.

It is possible that multiple agents will be combined in the conduct of this master protocol. It is also possible that an agent will be identified as effective in one trial within STRIVE and then incorporated as SOC (providing there is acceptable safety and adequate supply).

Information on dosing, administration, supply and distribution, matching placebo, and any special considerations as far as inclusion/exclusion criteria and safety monitoring for trials assessing each investigational agent studied as part of this protocol are outlined in a trial-specific appendix (see Appendix E), including reasonably anticipated benefits and risk, justification for dosing, etc. The appendix will also include any aspects of study procedures outlined in this master protocol that will need to be deviated from for a particular trial. The informed consent document for each trial will describe any potential risks or benefits associated with the interventions under study.

The investigational agents and other interventions that will be studied in STRIVE are grouped into therapeutic classes, based on either their mode of action, or according to groups of patients with shared clinical features. At the onset of the STRIVE platform, the following classes will be considered: antiviral agents, microbial-directed immunotherapies, host-response therapies, and therapies for critical illness. Additional therapeutic classes may be considered in the future. Prior experience of agents entering STRIVE for evaluation may span from limited (i.e., only Phase 1), to modest (completed Phase 2), moderate (completed Phase 3 but not yet licensed), or expansive (e.g., licensed agents for this or other indications). The platform will not conduct Phase 1 studies. The trial-specific appendices will accommodate the difference in approaches taken for agents in these categories; however, increased vigilance

will be incorporated into assessments of agents in Categories 1 and 2. This may include more detailed monitoring for adverse outcomes and the incorporation of sentinel recruitment and DSMB review for safety before recruitment is broadened.

2.3.1 Antiviral Agents

Antiviral agents investigated in the platform will have, at a minimum, data to support their ability to inhibit viral replication *in vitro* and reduce disease progression in at least one animal model suitable for such an assessment. Additionally, pharmacokinetic data should be used to consider the likelihood that the agent concentrates within tissues where replication occurs at a level that exceeds 90% inhibitory activity of viral replication. Both human studies of efficacy and safety and *in vitro* or animal studies will be considered.

Antiviral agents are typically pathogen-specific, as they are designed to inhibit an essential process (typically an enzyme or viral entry mechanisms) in the life-cycle of the virus. However, some agents may have cross-pathogen activity, and hence may be studied within the platform for more than one pathogen.

Viruses can develop drug resistance to all effective antiviral agents. The rate of selection for resistant viruses is a function of the type of virus, the viral genome position where such mutations may emerge (some being more conserved and hence essential for viral replication than others), effectiveness and rate of viral suppression, duration of treatment, and the host ability to control replication. As such, it should be possible to make a determination of the likelihood of resistance developing to an agent when studying it within the platform, and hence whether it is reasonable to invest additional resources in sampling of biological material to study the emergence of resistance. This will be considered prior to the launch of each trial.

Trials evaluating antiviral agents may evaluate the superiority of an investigational agent compared with placebo or against other antiviral agents. Strategic questions related to timing (when in the course of infection to initiate), exploration of combination therapy (use of one or several agents together), duration of antiviral use, or route of administration may also be evaluated. The specific questions being studied for a given agent will be in the trial-specific appendix.

2.3.2 Microbial-directed Passive Immunotherapies

For infections with a clear natural immune correlate of antibody-dependent protection and/or eradication, it is possible to quickly develop medical products containing high titers of such antibodies, or products with similar properties. These are “passive” immunotherapies as their intrinsic activity does not rely on the patient’s immune system.

There are two principal approaches for such medical products.

The first approach is to develop a product entirely in the laboratory such as monoclonal antibodies, or other molecules serving a function similar to antibodies. The clones are retrieved from convalescent persons, and among these clones, those expressing high titers of antibodies with effective neutralizing abilities are identified and propagated. The Fc section of the antibody may be genetically modified in order to reduce the natural Fc function or to extend

the half-life of the monoclonal antibody [30]. There are examples of other technologies able to induce neutralization similar to that of antibodies, for example the DARPin technology [31].

The alternative approach to developing microbial-directed immunotherapies is to retrieve antibodies from convalescent plasma using plasmapheresis. By using vaccinated donors, titers of the harvested neutralizing antibodies may increase relative to those retrieved from convalescent persons. The product from plasmapheresis may undergo subsequent refinement and purification. Such products are collectively called “hyperimmune intravenous immunoglobulin” (hIVIG) [32-35].

Trials investigating microbial-directed immunotherapies may evaluate the efficacy and safety of a specific immunotherapy, or address strategic questions related to dosing and timing for initiation of use.

2.3.3 Agents Affecting Host-pathways Involved in Organ Injury

Host-response therapies aim to improve clinical outcomes by modulating the body’s response to infection. These therapies may modulate the host immune response (immunomodulatory therapies) or other host pathways, such as the coagulation pathway and renin-angiotensin aldosterone pathway. Depending on the respiratory pathogen under study, the inflammatory response may be exclusively helpful to the host or may adversely contribute to the progression of the disease. As such, the study of immunomodulatory agents will be central to STRIVE. Most immunomodulatory agents are likely to be repurposed drugs already in use for the treatment of autoimmune diseases. Examples of immunomodulatory therapies that may be studied as treatments for severe respiratory infections include corticosteroids [7, 36, 37], JAK-inhibitors, and monoclonal antibodies [6] and other therapies that inhibit specific inflammatory pathways, cytokines, or chemokines, such as IL-6 [38-40], TNF-α, IL-1β, CXCL8, IL-1β, T2-mediated inflammation, IL-5 and/or its receptor, IL-4, IL-13, and IL-33.

Host-response therapies may also have specific tissue protective properties, either by protecting tissues from injury caused by the pathogen or the resulting immune response, or by accelerating the formation of healthy tissue (e.g., agents focused on stem cell function).

STRIVE trials evaluating host-response therapies may assess the efficacy and safety of a specific agent compared with placebo or compared with other host-response agents. Strategic questions related to timing (when in the course of infection to initiate), intensity (use of one or several agents together), or duration of use may also be evaluated.

2.3.4 Agents for Treatment of Patients with Critical Illness

Some patients hospitalized with a respiratory pathogen may experience extended critical illness, despite the use of best-practice treatment. Although the patient population is relatively small, the resources used for their care and the mortality risk are extensive. Despite this, the evidence guiding their care is limited.

In many such patients, the causative respiratory pathogen may no longer replicate, but tissue injury is extensive and requires prolonged organ support. For some, there is evidence of intense immunosuppression allowing for reactivation of latent infections with various herpes

viruses, including Cytomegalovirus. The clinical phenotype of such patients may overlap across infections with different respiratory pathogens.

Interventions to be evaluated may be derived from the host-response therapies described above, organ supportive care strategies, or therapies for superimposed infection complicating the initial disease.

3 Risk/Benefit Assessment

3.1 Known Potential Risks

Potential risks of participating in trials within this platform are those associated with the interventions under study, which are described in trial-specific appendices. Other risks include those from having blood drawn and intravenous (IV) catheterization (if needed in a particular trial) and breach of confidentiality.

3.1.1 Risks of Drawing Blood and IV Catheterization

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

3.1.2 Risks of Anaphylaxis and Fluid Overload due to Study Treatments

Administration of drugs may cause allergic reaction, which in its most severe form is anaphylaxis. The risks of allergic reaction will be minimized by studying treatments that have evidence of acceptable tolerability without demonstrating a significant risk of allergic reaction, and by administering the first dose of each study drug while the patient is hospitalized in a monitored setting.

For study drugs administered intravenously, the volume of fluid infused may exacerbate pre-existing chronic heart failure (CHF). The overall clinical picture of the targeted patient population will be evaluated in determining acceptability of the intervention with regards to this risk.

For antibody treatments studied on the platform, there is a theoretical risk that antibody infusion may worsen the disease course via antibody-dependent enhancement (ADE). ADE occurs if specific antibodies against a virus increase rather than decrease viral replication and hence worsen the disease course. ADE has been observed most clearly in the context of Dengue fever [41].

Host-response therapies may potentially dampen innate and adapted host immune responses, rendering the patient at excess risk of prolonged viral replication and complicating infections.

Clinical manifestations possibly caused by ADE or host-response therapies will be captured in trials evaluating such interventions as appropriate, and their occurrence reviewed by the trial DSMB while the trials unfold.

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 trials within STRIVE will not use information that identifies 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, and other authorized representatives of the institutional review board (IRB), NIH, and applicable regulatory agencies (e.g., Food and Drug Administration).

3.1.4 Early Phase Development

In the assessment of agents early in the development pathway for which there is only safety data derived from small sample size Phase 1 or 2 trials, there is the potential for participants to be at increased risk due to both foreseeable and unpredictable side effects or drug-drug interactions. Where this is the case, the limited data sets available will be acknowledged in the patient information material and as stated above the trial-specific appendix will have protocol-appropriate adverse event reporting, a plan for staged assessment of the agent by disease severity strata and more intensive safety monitoring. Where drug-drug interactions are known or foreseeable, the trial-specific appendix and Protocol Instructions Manual (PIM) will specify how these will be managed (e.g., co-administration of a drug with the study treatment is prohibited, or the dose of a drug is modified).

3.1.5 Sequential and Co-enrollment

We intend to co-enroll or sequentially enroll patients in clinical trials should the participant fail to improve, or if the clinical picture suggests additional interventions are justified, when such co-enrollment may be appropriate. Particularly with investigational agents in early development there is the potential for unforeseen drug interactions or additive toxicities. The trial-specific appendix will include appropriate adverse event reporting, a plan for staged assessment of the agent by disease severity strata, and more intensive safety monitoring by the DSMB.

3.2 Known Potential Benefits

While each trial conducted on this platform will be conducted to test a hypothesis that an intervention or strategy will benefit patients, the interventions or strategies studied may or may not benefit any individual who participates in one of the trials. There is an anticipated benefit to

society from a patient's participation in STRIVE trials from insights gained about the interventions under study as well as the natural history of severe respiratory infections.

4 Outcomes

This section describes three key outcomes (also referred to as endpoints) that will be used in most STRIVE trials. Where feasible, all 3 outcomes listed in this section will be ascertained for STRIVE trials. This will permit secondary analyses across trials to be carried out. We anticipate that most trials will select one of the 3 outcomes described as the primary outcome. Where that is not desirable because of the nature of the intervention and/or the target population, the primary outcome may be described in detail in the trial-specific appendix. Additional secondary and safety outcomes not listed in the master protocol may also be outlined in each trial-specific appendix.

4.1 Primary Outcome

Because this master protocol includes a spectrum of potential respiratory pathogens, at different stages of disease, and a broad scope of potential interventions, a flexible and pragmatic approach to the selection of the primary outcome for each trial is provided. The general principles are that the primary outcome should be patient-centered, acceptable to regulators for registration trials, interpretable to end users including guideline committees and front-line clinicians, easily and reliably ascertainable across hundreds of clinical sites across the globe, and appropriately efficient in terms of sample size required to complete a trial and data collection required.

Three examples of primary outcomes meeting these criteria are presented below:

1) All-cause mortality
2) Time to sustained recovery
3) Clinical Recovery Scale (CRS)

These outcomes are defined below. The follow-up duration during which these outcomes are ascertained will typically be ***60 days*** to optimize the potential to rapidly identify clinically important differences that are related to the acute presentation and potentially modifiable for the intervention being evaluated, while balancing timeliness and burden of data collection requirements. For circumstances in which later complications related to the intervention or patient population may be more likely, a longer follow-up duration (typically 90 days) for efficacy and/or safety outcomes may be considered by individual trials with compelling scientific justification. Similarly, for circumstances when more rapid ascertainment of the primary outcome is desired (e.g., emerging infections), a shorter follow-up duration (e.g., 28 days) may be considered.

4.1.1 Rationale for Primary Outcome

The primary outcome is intended to identify efficacy among the interventions in a STRIVE trial.

Generally, an individual trial will select one of these potential outcomes based on trial-specific considerations such as the pathogenesis of the infection, severity of illness, and mechanism of

the intervention. Trials in populations that have a high anticipated mortality during follow-up (e.g., >20% with usual care) should strongly consider all-cause mortality as the primary outcome (see Section 6.4.1). When all-cause mortality is selected as the primary outcome, time to sustained recovery and the CRS (see Section 4.1.4) will be secondary outcomes.

For trials in populations with relatively lower anticipated mortality, outcomes that incorporate the speed and quality of recovery among survivors (i.e., time to sustained recovery or the CRS), in combination with mortality being classified as the worst outcome in these composite outcomes, will typically be prioritized to optimize efficiency and patient-centeredness. In these cases, all-cause mortality will be an important secondary, and possibly in some trials a co-primary outcome.

4.1.2 All-cause Mortality

All-cause mortality will be assessed through the selected follow-up duration, typically Day 60. Near-complete ascertainment of all-cause mortality is critical, regardless of which primary outcome is selected. Therefore, substantial attempts will be made to determine vital status through the end of follow-up by a combined approach of follow-up visits with the participant or proxy, chart review, and review of other available information sources.

4.1.3 Time to Sustained Recovery

Time to sustained recovery is defined as being discharged from the index hospitalization, followed by being alive and *home* for 14 consecutive days prior to the end of follow-up [42-45]. The primary advantage of time to sustained recovery over the CRS is the ability to ascertain the primary outcome for most participants prior to the end of follow-up.

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

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

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

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

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

An alternative to the original definition of time to sustained recovery is to require a participant to be alive, home, and not receiving new supplemental oxygen (as defined in Section 4.1.4) for 14 consecutive days to achieve the primary outcome.

For this endpoint the focus is on comparing the cumulative incidence of sustained recovery for the 2 groups and death is considered a competing risk, effectively being counted as not recovered. Because death is not directly considered in this outcome, death and the CRS-60 outcomes will always be important secondary outcomes if this outcome is primary.

4.1.4 Clinical Recovery Scale

The ***Clinical Recovery Scale*** (CRS) is an ordinal ranked outcome that includes the concepts of mortality, duration of hospitalization, duration of being at home but not fully recovered, and duration fully recovered. It may include up to 63 categories, with a description of each level detailed in Table 4.1. At the end of the follow-up period, each patient is classified into one of the CRS levels. By default, trials in STRIVE will use a 60-day follow-up; the CRS evaluated at 60 days is termed *CRS-60*.

Ordinal outcomes, and corresponding summary measures to compare groups such as ratios of the odds of being in a better category if having received the active treatment (vs control) have been used extensively as a primary outcome in relation to acute infections. The CRS incorporates into one outcome both risk of progression to serious disease including death as well as the ability to recovery. To interpret the findings, summary statistics for median days fully recovered, the proportion not recovered (including those who died), by treatment arm, will be provided.

For the CRS, the definition of “home” is the same as used for time to sustained recovery.

The definition of what constitutes “recovery” after reaching home will be detailed in each trial; an example of “recovery” is being alive and at home without need of new supplementary oxygen.

The “last-off” method for assessing full recovery will be used, as has been customary in the use of similar ordinal outcomes [46]. According to the “last-off” method, periods of being at home that are followed by hospital re-admission, change from home to a higher level of care, or receipt of an intervention at home that defines the patient as not fully recovered (e.g., supplemental oxygen) will *not be counted* toward the number of days in recovery. In other words, only days between the last time the patient entered a fully recovered state (i.e., returned home, and fully (e.g., free of new supplemental oxygen) recovered), and the end of follow-up are counted as days of full recovery.

Table 4.1: Clinical Recovery Scale for a Trial with 60 Days of Follow-up (*CRS-60*) and Its Categories

CRS-60 category	Description
60-1 [1]	Days to recovery (i.e., at home and fully recovered)
0	Alive, at home but not fully recovered[1] by Day 60
-1	Still hospitalized by Day 60
-2	Dead

[1] Categories 1 to 60 depict the days fully recovered during the 60 days of follow-up (i.e., recovered for 60 days and down to 1 day). Individual trials may "bin" these categories, e.g., recovered for < 20, 21-30, 31-40, 41-45, 46-50, 51-55, and > 55 days (7 categories to classify the duration of recovery in addition to the first 3 categories representing death, still hospitalized at Day 60, and not recovered at Day 60).

[2] An example of a state where the patient is alive at home but not fully recovered is the need for continuous supplementary oxygen. The exact definition for not being fully recovered will be outlined in each trial-specific appendix.

If the CRS is ascertained at a different follow-up time than 60 days, the rationale for using a different timepoint will be explained in the trial-specific appendix. Options include ascertainment of the CRS at 28 days (*CRS-28*) and 90 days (*CRS-90*). For example, with *CRS-28*, the maximal number of days at home and fully recovered is 28 (and not 60 as in *CRS-60*). The CRS outcome requires full follow-up time to ascertain the final outcome status for individual participants, though earlier assessments may be used for interim analysis.

4.2 Secondary Outcomes

Primary outcomes outlined above not designated as the primary outcome for a specific trial will be assessed as important secondary outcomes. In addition, several secondary efficacy outcomes will be assessed for all participants.

4.2.1 Rationale for Secondary Outcomes

The main secondary outcomes for the STRIVE platform are constituents of or related to the potential primary outcomes. In addition, the ordinal outcome described in bullet point 5 below, extrapulmonary organ failure, and secondary infections are important to understand the full range of physiological recovery. The rationale for the safety outcomes collected is presented in Section 10. If additional secondary outcomes are to be added, refined, or not used for specific trials, these outcomes will be specified in the trial-specific appendix.

4.2.2 Secondary Efficacy Outcomes

1. Time to discharge from the initial hospitalization
2. Days alive and home through the end of follow-up, using the "last off" method as described in Section 4.1.4
3. Proportion of participants who are alive and at home, and proportion of participants who are alive, at home and free of new supplemental oxygen at days 14, 28, and at end of follow-up (typically Day 60) if home oxygen use is assessed in a given trial.

4. CRS-28
5. Ordinal outcome (categories defined below), on Days 1-7, 14, and 28:
    1. Can independently undertake usual activities with minimal or no symptoms
    2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
    3. Supplemental oxygen <4 liters/min (or <4 liters/min above premorbid requirements)
    4. Supplemental oxygen ≥4 liters/min (or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
    5. Non-invasive ventilation or high-flow oxygen
    6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
    7. Death
6. Health-related quality of life by EuroQol (EQ-5D-5L) at the end of follow-up [47]

4.2.3 Safety Outcomes

1. Death, clinical organ failure or serious infections defined by development of any one or more of the following clinical events after trial entry and through Day 60 (see PIM for criteria for what constitutes each of these conditions). These are also referred to as protocol-defined anticipated clinical events (PDACEs); see Section 10.2.7.
    a. Worsening respiratory dysfunction:
    1.Respiratory failure defined as receipt of high flow nasal oxygen or noninvasive ventilation, invasive mechanical ventilation, or ECMO, above the categorical level of respiratory support at enrollment
    b. Cardiac and vascular dysfunction:
        1. Myocardial infarction
        2. Myocarditis or pericarditis
        3. CHF: new onset NYHA class III or IV, or worsening to class III or IV
        4. Hypotension requiring institution of vasopressor therapy
    c. Renal dysfunction:
        1. New requirement for renal replacement therapy
    d. Hepatic dysfunction:
        1. Hepatic decompensation
    e. Neurological dysfunction
        1. Acute delirium
        2. Cerebrovascular event (stroke, cerebrovascular accident [CVA])
        3. Transient ischemic events (i.e., CVA symptomatology resolving within <24 hours)
        4. Encephalitis, meningitis or myelitis
    f. Hematological 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, intrathoracic, pericardial, intraabdominal, pelvic, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding).

g. Serious infection:
Intercurrent, at least probable, documented serious disease caused by an infection *other than* the qualifying respiratory pathogen, requiring antimicrobial administration and care within an acute-care hospital
h. Death

2. Clinical organ failure or serious infections (Items 1.a. through 1.g above)
3. A composite of cardiovascular events (outcomes listed above in safety items 1.b.1, 1.e.2 and 1.e.3) and thromboembolic events (1.f.2)
4. Safety and tolerability as measured by:
    a. A composite of SAEs, clinical organ failure or serious infections (PDACEs; see safety item 1 above) or death through Day 5 and 28. Grade 3 and 4 clinical adverse events will also be included in an additional composite for trials in which they are collected (see Section 10.3.2).
    b. Allergic reaction of any severity judged to be due to the investigational agent
    c. Infusion-related reactions of any severity and percentage of participants for whom the infusion was interrupted or stopped prior to completion – where applicable
    d. Premature stopping of planned course of a trial intervention, and reasons for stopping – where applicable.
    e. Adverse events of special interest (AESIs) identified in a given trial
    f. A composite of SAEs, clinical organ failure or serious infections (PDACEs; see safety outcome 1 above) or death through Day 60
    g. A composite of hospital readmissions or death through the end of follow-up

Note that the evaluation of safety outcome 4.g is not protected by randomization, as its occurrence is conditional on being discharged alive from the initial hospital admission during which randomization occurred.

5 Objectives

5.1 Primary Objectives

The primary objective of the STRIVE platform is to facilitate the efficient and rigorous execution of randomized clinical trials investigating the safety and efficacy of therapeutic interventions or strategies for acute respiratory infections among hospitalized adults. Each trial within STRIVE will have its own objectives outlined in its trial-specific appendix. The primary objective for each trial will be to compare efficacy of the intervention or strategy under investigation with control for the chosen primary outcome among participants randomized in that trial.

5.2 Secondary Objectives

Secondary objectives for each STRIVE trial will include the evaluation of secondary outcomes (section 4.2), evaluation for heterogeneity of treatment effect, and the enhancement of a pathophysiologic understanding of severe respiratory infections through the collection and analysis of biospecimens.

Characteristics considered for heterogeneity of treatment effect evaluations will include:

- participant age
- participant sex, race, and ethnicity
- participant comorbidities
- duration of illness prior to randomization
- severity of illness at randomization
- therapies and vaccines received before randomization
- geographic location
- baseline laboratory measurements, such as presence of neutralizing antibodies against the pathogen of interest and pathogen subtypes.

6 Study Design

6.1 Overview

STRIVE is a master protocol to evaluate the comparative efficacy and safety of antimicrobial, passive immunity, host-response, and supportive care treatments for hospitalized patients with respiratory infections or syndromes of global impact including but not limited to COVID-19 and influenza. This master protocol provides an efficient strategy for the evaluation of multiple interventions across classes and allows the evaluation of concomitant and sequential treatments to inform a strategy to improve recovery from the respiratory infection or syndrome.

In STRIVE, a trial is a study that is designed to answer a specific question about the efficacy and safety of one or more interventions or strategies. Individual trials are designed to investigate one primary question each and will not continue after that primary question has been answered, unless additional follow-up is required by regulators. ***STRIVE is designed to contain multiple trials actively enrolling patients at the same time and for trials to be dropped and added iteratively over time.*** The details of each trial will be described in a trial-specific appendix to the master protocol.

In general, the STRIVE platform will consider the following four trial types:

(1) trials of pre-licensure, investigational agents versus placebo

(2) trials of approved agents used off-label (i.e., repurposed agents) compared to placebo or other standard of care

(3) trials of comparative effectiveness of multiple agents

(4) sequential multiple assignment randomized trials (SMART).

The STRIVE platform may have a number of trials ongoing at any given time. To improve efficiency and scientific rigor, these trials may share participants either through co-enrollment (i.e., participant is enrolled in multiple STRIVE trials) or through a shared control/placebo group across multiple trials. Because the STRIVE protocol permits study of a variety of classes of agents across the spectrum of disease severity for different respiratory pathogens using a variety of trial types, the approach to co-enrollment and shared control/placebo is also flexible.

We describe the general approach to co-enrollment in Section 6.1.1 and how to randomize participants when they are eligible and consent to multiple trials in Section 6.2.

6.1.1 Co-enrollment

In general, we propose an inclusive approach to co-enrollment across trials, where appropriate. Appropriateness criteria include capacity to meet the requirements of (1) safety, (2) scientific rigor, and (3) regulatory reporting for adverse events. Each of these is addressed in turn, while emphasizing the important role of patient autonomy in assessment of co-enrollment.

The STRIVE platform emphasizes conducting trials across the spectrum of disease severity for hospitalized patients. Two common scenarios will lend themselves to co-enrollment: (1) a participant is eligible for two trials at the same time (e.g., on admission) and the trials permit simultaneous enrollment (e.g., two comparative effectiveness trials in which the possibility of drug-drug interactions have been previously studied); and (2) a participant is enrolled in a STRIVE trial early in the hospital admission, completes the initial trial therapy, with subsequent eligibility for another trial if the patient does not recover or worsens. For example, patients could be randomized into a STRIVE trial early during their hospital admission for COVID-19 while on low-flow oxygen. Patients who then deteriorate and receive more intensive oxygen support (e.g., HFNC, NIV, IMV, ECMO) may be eligible for different STRIVE trials using agents in the same or different intervention classes.

Patients should be allowed to enroll in subsequent trials as long as they meet the eligibility criteria for that trial. Clinicians may hesitate to offer a trial targeting less-sick patients if they think the patient is likely to worsen and become eligible for a different STRIVE trial with a promising intervention. Conversely, a trial only enrolling participants who are more severely ill may only enroll those who are *admitted* in a more severe state (rather than deteriorating after admission) if there is another STRIVE trial for less acutely ill patients and co-enrollment is not permitted.

In general, there is strong scientific rationale for encouraging co-enrollment of Phase 3 trials of pre-licensure, investigational agents with trials evaluating interventions already administered within usual care. Co-enrollment leads to random assignment and systematic recording of these co-interventions rather than haphazard assignment based on clinical judgment. Co-enrollment in two trials of pre-licensure investigational agents may pose more challenges. In general, co-enrollment will be avoided when there is reason to believe that there is an important interaction between interventions or study procedures in the two trials that unacceptably increases the risk of one or both of the interventions or if there is mechanistic incompatibility, e.g., the two drugs are expected to antagonize each other in an important way.

Two main statistical considerations are relevant to co-enrollment: safety monitoring and efficacy analyses. These are discussed in the master protocol statistical analysis plan and trial-specific appendices.

6.2 Randomization and Stratification

We describe below how randomization will be conducted when there is a single trial open for enrollment (Section 6.2.1) and when multiple trials are open for enrollment (Sections 6.2.2 and 6.2.3).

When multiple trials are open, participants may become eligible for more than one trial at either the same time or at different times throughout their hospitalization. Whether and how randomization/co-enrollment may proceed in each of these settings will be discussed in each trial-specific appendix. Considerations will include whether agents are pre- or post-licensure, the safety profile of the agents, and potential drug-drug interactions, among other concerns.

6.2.1 Single Trial Open for Enrollment

When only a single trial is enrolling (or a participant could only be eligible for a single trial regardless of disease progression), patients will be equally allocated to each intervention + SOC in that trial unless specified differently in a trial-specific appendix. For example, for a study of a single investigational (pre-licensure) agent, participants will be randomized in a 1:1 ratio to the investigational agent + SOC or placebo + SOC. Trials of post-licensure agents could study two or more active agents (with or without placebo) + SOC (i.e., comparative effectiveness trials). The randomization allocation ratio may differ from 1:1 for some trials and the rationale for this will be given in the trial-specific appendix.

6.2.2 Multiple Trials Open for Enrollment and Participants Eligible for Multiple Trials Simultaneously

The master protocol outlines three potential approaches for participants who may be eligible for multiple trials at one time. Although each of the following could apply to each trial type outlined in Section 6.1, certain trial designs lend themselves more naturally to each approach to handle eligibility for multiple trials simultaneously which we note below.

(a) Factorial randomization (co-enrollment across trials)

If a participant is eligible for multiple trials simultaneously, the participant may be randomized to each trial separately (i.e., factorial randomization). For example, if there are two investigational agents (A and B - studied in two trials and both are placebo-controlled) for which the participant is eligible, the participant would be randomized 1:1 to investigational agent A or placebo and then randomized again to investigational agent B or placebo. In this randomization, one quarter of participants would each receive both active agents simultaneously, active agent A and placebo for B, active agent B and placebo for A, and both placebos.

This is equivalent to permitting simultaneous co-enrollment across the multiple trials for which the participant is eligible. As noted in Section 6.2, co-enrollment is conceptually most straightforward for comparative effectiveness trials or trials of re-purposed agents in which the possibility of drug-drug interactions have been previously studied. For example, participants in the TESICO trial are randomized using a factorial design to aviptadil or placebo and remdesivir or placebo.

(b) Shared control/placebo

In some contexts, we would want to ensure that participants do not receive multiple active agents simultaneously. However, it might be possible for multiple trials to share a control group to improve efficiency. For example, if there are two investigational agents for which the participant is eligible, the randomization allocation could be 1:1:1 to investigational agent A + SOC, agent B + SOC, or placebo + SOC if the placebos for A and B were the same. If the two investigational agents (A and B) require different placebos (for example, when infusion volumes or drug delivery differ), equal allocation for treatment groups will be achieved through a two-step randomization procedure: in step 1, the participant is randomized 1:1 to trial A or trial B; in step 2, the participant is randomized 2:1 to the corresponding active agent or matching placebo (e.g., if the participant is randomized to trial A they would then be randomized 2:1 to investigational agent A + SOC or "agent-specific placebo for A" + SOC). With *k* trials, this can be viewed as an initial equal allocation to one of the *k* trials, followed by a second, *k*:1 allocation to the corresponding active agent or matching placebo.

Sites will be informed of the specific investigational agent/matching placebo (e.g., A or B) to which the participant was randomized (see Section 6.2).

Under this randomization framework, it is anticipated that the control groups will be pooled together for at least the efficacy analyses. A participant receiving the control condition would contribute to the analysis of both agents A and B only if the participant were eligible (and consented to) both agents A and B. Depending on the similarity of the matching placebo and approach to capture of safety data, the control groups may also be pooled together for safety analyses.

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.

This strategy is most appropriate for Phase 3 trials of pre-licensure, investigational agents and placebo-controlled trials of approved agents used off-label. For example, in the TICO platform, multiple monoclonal antibodies were studied simultaneously using a shared placebo group. Because sites will know which investigational agent/matching placebo the participant was allocated to, careful assessment of evolving possible differences in co-medication based on this knowledge, should also be evaluated when considering using a pooled control/placebo group. This allocation strategy only results in efficiency gains to the extent that there is overlap in the eligibility criterial among the trials. Thus, the eligibility criteria should be broadly similar among the trials for this allocation strategy. Finally, in order to pool data among the control conditions, the data collection schedule needs to be harmonized across the agents.

Comparative effectiveness trails of multiple evidence-based agents without a placebo-group would be more difficult to incorporate in this framework.

(c) Separate trials

Co-enrollment across the trials may not be permissible, and the mechanism of drug delivery and other considerations may preclude sharing a control group across multiple active agents. In this case, with *k* trials, participants will be initially equally allocated to one of the *k* trials,

followed by a second (equal) allocation to the corresponding agents/placebo being studied in that trial. Data will not be pooled between the different trials for any efficacy and safety analyses. For example, in the TICO platform, when the study agent required continuous infusion for 5 days, its placebo was sufficiently different from the placebo for the monoclonal antibodies (one or two infusions for an hour) that this was considered a separate trial.

6.2.3 Multiple Trials Open for Enrollment and Participants Eligible for Multiple Trials on Different Study Days

Participants may be eligible for multiple trials on different study days as their clinical condition changes. In this case, participants may co-enroll across multiple trials. For participants who co-enroll across multiple trials, the randomization will be independent in each trial as specified in the trials. Eligibility for certain agents may preclude co-enrollment into other trials due to safety or drug interactions. Unless specified in the trial-specific eligibility criteria, it is assumed that co-enrollment into multiple trials in the STRIVE platform is permitted.

6.2.4 SMART Design

This master protocol permits study of strategies of treatments given over time (i.e., dynamic treatment regimens or adaptive intervention strategies) through “strategy trials” or SMART. In these trials, at least some participants undergo a randomization across at least two different timepoints as their clinical condition changes. The multiple randomizations are explicitly specified in the trial-specific appendix (as opposed to two separate trials which allow for co-enrollment). In general, participants should not be randomized to a single strategy upfront but should be randomized each time their condition changes.

A SMART design would be considered a single trial in the platform even though it may involve multiple randomizations. Therefore, participants will consent to the trial and not specific randomizations within the trial. Details on informed consent are given in Section 12.3.

6.2.5 Stratification

Randomization will usually be stratified by study site pharmacy, and severity of disease at entry unless stated otherwise in the trial-specific appendix. Severity of disease is determined by the respiratory infection or syndrome being studied. For example, strata that define disease severity for COVID-19 are based on supplemental oxygen use at randomization such as 1) invasive mechanical ventilation (IMV) or extra corporal membrane oxygenation (ECMO), 2) high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV), 3) less than HFNC/NIV.

Within each stratum, mass-weighted urn randomization will be used to generate the active and placebo assignments. This will ensure the desired treatment allocation ratio is maintained throughout the trial.

6.3 Blinding

Investigational agents or placebo (as necessary) will be prepared by a pharmacist or equivalent, 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 (section 10.4).

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 administration, but they will be blinded to whether the random assignment was to the active investigational agent or matching placebo.

If the blind is broken for safety reasons, this will be documented. In that situation, every attempt will be made to minimize the number of people unblinded. See also section 10.4; specific unblinding procedures and instructions are found in the PIM.

6.4 Sample size and Statistical Considerations

For the endpoints considered, for any single trial, sample size will have to consider the target population (this may include the variant) and the treatment being studied (e.g., adherence).

This section provides illustrative sample size estimate examples for each of the three primary outcomes defined in section 4.1, under a range of assumptions. All sample size estimates below are for superiority trials, comparing a given investigational agent versus its control arm. For each trial, the specific sample size estimate and the assumptions used will be described in detail in the trial-specific appendix.

The following assumptions are used for each of the three outcomes:

a. Treatment and control groups are of equal size (1:1 randomization).

b. The primary analysis will by intention to treat.

c. The type 1 error is set at 0.025 (one-sided). If several agents are investigated in parallel, each pairwise comparison of investigational agent versus placebo is considered a separate trial, and the type 1 error will not be adjusted for the number of comparisons. In specific cases, such as a trial with two or more co-primary comparisons, a type 1 error adjustment may be considered and would be described in the trial-specific appendix. Lower Type 1 error limits require higher sample sizes.

6.4.1 Primary Outcome: Mortality

The primary outcome of all-cause mortality, typically through Day 60; in this section, we provide sample size estimates for assumed cumulative mortality rates of 20%, 30%, and 40% by Day 60, and a range of hypothesized treatment effects corresponding to hazard ratios between 0.65 and 0.80.

The following assumptions were used, in addition to assumptions a-c above:

d. Treatment groups will be compared for time to death using a log-rank test.
Comment: Estimated sample sizes change only minimally if replacing the log-rank time-to-event analysis by a comparison between treatment groups of the cumulative proportions of participants who died by Day 60 using logistic regression; cumulative proportions in the two treatment groups corresponding to given hazard ratios are summarized in Table 6.1 below.

e. Power is set at 80% or 90% to detect a hazard ratio of 0.80, 0.75, 0.70, or 0.65 for time to death comparing the investigational treatment versus control. This corresponds to decreases in the relative hazard of mortality of 20%, 25%, 30% and 35%, respectively.

We chose these hypothesized treatment effects to cover a range of plausible values: decreases of less than 20% in relative hazard require prohibitively large sample sizes and may be less clinically relevant (e.g., hazard ratio of 0.80 corresponds to a decrease from 30% mortality in the control group to 24.8% in the treatment group, an absolute difference of 5.2%); conversely, it would be difficult to achieve more than 35% reduction in mortality with any single treatment.

f. With these assumptions for type 1 and type 2 error, and treatment effects corresponding to hazard ratios between 0.65 and 0.80, the needed total number of events is shown in the first row of Table 6.1 below. For example, 252 primary events are sufficient to detect an HR of 0.70 with 80% power.

g. The total sample size needed to accrue the required number of events depends on the underlying rate of mortality in the control group. Table 6.1 summarizes the total sample size needed for cumulative mortality rates of 20%, 30% and 40%, respectively, inflated by 5% to account for withdrawal of consent or loss to follow-up. For example, given a mortality rate of 30% in the control arm, a total sample size of 1016 participants is sufficient to detect an HR of 0.70 with 80% power.

Table 6. 1. Estimated Total number of Events Needed to Detect Differences in Mortality Between the Treatment and Control Groups. For hazard ratios (HR) of 0.65, 0.70, 0.75, and 0.80 with 90% power, and total sample size needed assuming cumulative mortality rates of 20%, 30% and 40%, respectively.

	Hazard Ratio (Agent versus Control)			
	HR=0.65	**HR=0.70**	**HR=0.75**	**HR=0.80**
Total number of events, 80% power	175	252	385	636
90% power	234	338	515	851
Event rate control (%)	20.0	20.0	20.0	20.0
Event rate agent (%)	13.5	14.5	15.4	16.3
Total sample size, 80% power	1094	1537	2283	3675
Total sample size, 90% power	1466	2058	3053	4918
Event rate control (%)	30.0	30.0	30.0	30.0
Event rate agent (%)	20.7	22.1	23.5	24.8
Total sample size, 80% power	690	1016	1512	2436
Total sample size, 90% power	968	1361	2022	3261
Event rate control (%)	40.0	40.0	40.0	40.0
Event rate agent (%)	28.3	30.1	31.8	33.5
Total sample size, 80% power	512	756	1126	1816
Total sample size, 90% power	720	1012	1506	2432

6.4.2 Primary Outcome: Time to Sustained Recovery

Sustained recovery is achieved when a participant has been discharged to home and stayed home for a continuous period of 14 days. In this section, we provide sample size estimates for assumed cumulative recovery rates at Day 60 between 65% and 85% by Day 60, and a range

of hypothesized treatment effects corresponding to recovery rate ratios (sub-hazard ratio for recovery) between 1.20 and 1.35 for comparing time to recovery in the investigational agent group versus placebo.

The following assumptions were used, in addition to assumptions a-c above:

d. Treatment groups will be compared for time to sustained recovery using Gray's test with rho=0. This test is the analogue of the log-rank test, taking into account that death is a competing risk for recovery; in the context of competing risks, the treatment effect is expressed as sub-hazard ratio for recovery.

e. Power is set at 80% or 90% to detect a recovery sub-hazard ratio of 1.20, 1.25, 1.30, or 1.35 for time to sustained recovery comparing the investigational treatment versus control. We chose these hypothesized treatment effects to cover a range of plausible values, although it may be difficult to achieve an improvement of 30% or more (recovery sub-hazard ratio of 1.30 or higher) in a moderately ill study population where a substantial proportion of participants in the control group is expected to be discharged from the hospital within a few days.

f. With these assumptions for type 1 and type 2 error, and treatment effects corresponding to recovery sub-hazard ratios between 1.20 and 1.35, the needed total number of events is shown in the first row of Table 6.2 below. For example, 951 primary events are sufficient to detect a sub-hazard ratio of 1.20 with 80% power.

g. The total sample size needed to accrue the required number of events depends on the proportion achieving sustained recovery during the follow-up period in the control group (deaths before recovery are patients who do not recover). Table 6.2 summarizes the total sample size needed for cumulative recovery rates of 70%, 80%, and 90%, respectively, inflated by 5% to account for withdrawals of consent, losses to follow-up, and other reasons for missing data. For example, given a recovery rate of 80% in the control arm, a total sample size of 1205 participants is sufficient order to detect a recovery sub-hazard ratio of 1.20 with 80% power.

Table 6. 2 Estimated Total Number of Recovery Events Needed to Detect Differences in Sustained Recovery Between the Treatment and Control Groups. For a range of sub-hazard ratios (sHR) between 1.20 and 1.35 with 80% or 90% power, and total sample size needed assuming cumulative recovery rates between 70% and 90%. Sample sizes were estimated using formulas for the log-rank test (identical to Gray's test with rho=0 under complete follow-up).

	Recovery Rate Ratio (Agent versus Control)			
	sHR=1.20	**sHR=1.25**	**sHR=1.30**	**sHR=1.35**
Total Number of events:				
80% power	951	637	462	355
90% power	1273	852	619	475
Recovery rate, control (%)	70%	70%	70%	70%
Recovery rate, agent (%)	76%	78%	79%	80%
Total sample size, 80% power	1363	905	651	496
Total sample size, 90% power	1825	1210	874	664
Recovery rate, control (%)	80%	80%	80%	80%
Recovery rate, agent (%)	86%	87%	88%	89%
Total sample size, 80% power	1205	802	580	441
Total sample size, 90% power	1615	1073	775	590
Recovery rate, control (%)	90%	90%	90%	90%
Recovery rate, agent (%)	94%	94%	95%	96%
Total sample size, 80% power	1088	724	525	401
Total sample size, 90% power	1455	970	701	538

6.4.3 Primary Outcome: Clinical Recovery Scale (CRS) at Day 60

The CRS at Day 60 (CRS-60) is an ordinal outcome that combines information about mortality and duration of recovery for those that do so (section 4.1.4). *CRS-60* is defined as follows: participants who died at any time through Day 60 are in the worst category (value -2); those who are alive at Day 60 but hospitalized or receiving hospice care at Day 60 are in the second-worst category (value -1); participants who are alive, at home but not fully recovered at Day 60 are in the third-worst category (value 0; these participants are not recovered at Day 60, and thus have been recovered for 0 days). For participants who recovered (i.e., at home and fully recovered), the ordinal category is the number of days that a participant had been recovered by Day 60. The treatment difference is expressed as a summary odds ratio, comparing the odds of being in a better category for participants randomized to the investigational agent versus the placebo group. The primary analysis for the treatment comparison uses proportional odds models, with an indicator variable for the treatment effect.

The sample size required to detect a treatment difference in *CRS-60* depends on the distribution of the ordinal outcome across the many categories as well as on the hypothesized size of the treatment effect. Assuming that the proportional odds model for the treatment effect is correct, power is highest for an approximately even distribution across categories. This is typically not fulfilled, since by design probabilities of recovery on any given study day tend to be higher in early study days than towards the end of follow-up, and death forms its own

category. Below we are using the distribution of the *CRS-60* ordinal outcome in the ACTIV-3 trial for tixagevimab/cilgavimab combination monoclonal antibody treatment for COVID-19, assessed at Day 60, to inform a plausible assumption for the distribution of participants across the categories of the ordinal outcome, pooled across treatment groups.

Sample size calculations used the following assumptions, in addition to assumptions a-c above:

d. Treatment groups will be compared for CRS-60 using a proportional odds model with an indicator variable for the treatment group; the treatment effect is estimated as summary odds ratio.

e. Power is set at 80% or 90% to detect an odds ratio of 1.20, 1.25, 1.30 and 1.35 comparing the investigational treatment versus control.

f. The total sample size needed to accrue the required number of events depends on the underlying distribution across the ordinal categories, pooled across treatment groups. Table 6.3 summarizes observed distributions in the ACTIV-3 trial for tixagevimab/cilgavimab. Table 6.4 summarizes the total sample size needed to detect odds ratios between 1.20 and 1.35, inflated by 5% to account for withdrawal of consent, loss to follow-up, and missing data. For example, for distributions similar to those in the trial, a total sample size of 2986 participants is sufficient order to detect rate ratio of 1.20 with 80% power.

Table 6. 3: Distribution Cross Categories of the *CRS-60* Outcome (values -2 to 60) Used to Calculate Sample Sizes in Table 6.4. For the 1397 participants with ascertained outcome out of 1417 participants in the ACTIV-3 tixagevimab/cilgavimab trial. The summary OR comparing Active versus Control for this outcome is OR=1.15 (95% CI: 0.95, 1.38), p=0.14.

Days recovered	**Death (-2)**	**Hosp. (-1)**	**0**	**1**	**…**	**57**	**58**	**59**	**60**
Active	0.086	0.033	0.033	0.000	…	0.093	0.064	0.071	0.057
Control	0.121	0.025	0.037	0.000	…	0.059	0.069	0.077	0.052
Pooled	**0.103**	**0.029**	**0.035**	**0.000**	…	**0.076**	**0.067**	**0.074**	**0.054**

Table 6. 4: Sample Size Needed to Detect Odds Ratios Between 1.20 and 1.35 with 80% and 90% Power. Given the distribution of days recovered through Day 60 described in Table 6.3.

	Odds Ratio (Agent versus Control)			
	OR=1.20	**OR=1.25**	**OR=1.30**	**OR=1.35**
Total sample size, 80% power	2986	1994	1442	1102
90% power	3998	2669	1931	1476

6.4.4 Sample Size Re-Estimation

Blinded sample size re-estimation will be carried out before enrollment is complete to determine whether the planned sample size will be sufficient to maintain the nominal, unconditional power the trial for the hypothesized treatment effect or to accrue the planned number of events for an event-driven trial. The blinded sample size re-estimation does not

involve unblinding of the treatment difference and will be carried out by statisticians who are blinded to the treatment comparisons. The re-estimation will be based on the pooled outcome data, baseline characteristics of the enrolled study population, the number of withdrawals, adherence to the blinded study treatment, and the amount of missing data. Details on the sample size re-estimation depend on the type of the primary endpoint and will be discussed in the trial-specific appendix.

6.5 Blood and Respiratory Tract Material for Research

Blood and respiratory tract material may be collected for central laboratory assessment and kept for future research purposes.

6.6 Whole Blood for Host Genetics

Whole blood for host genetic analysis will be collected from consenting participants at participating sites as part of this protocol. Sites may elect not to participate in collecting whole blood for genetic analysis. At participating sites, participants will be provided with the option to consent to whole blood collection for genetic analysis. If the participant consents, sufficient blood will be drawn to obtain six 1.0 mL aliquots of whole blood after processing. This will only be conducted once for each participant who consents to a trial under this protocol (i.e., participants will not be approached for consent to blood for genetic analysis in a trial if they have already consented to do so in a previous STRIVE trial).

6.7 Approach to Intercurrent Therapies and Clinical Trial Co-enrollment Outside of STRIVE Platform

In general, the trials within STRIVE will take a pragmatic approach to the use of intercurrent medications. For each trial within the platform, prior use of specific treatments may be exclusionary, as may certain treatments before a certain follow-up day, as detailed in the trial-specific appendix, but otherwise there are few restrictions.

The sponsor and/or protocol leadership may, based upon convincing new evidence, act in the interest of participant protection, and in avoidance of confounding, to make exclusionary the use of any specific concomitant therapy found to be reasonably contraindicated for a well-defined portion of the study population (see Appendix F). 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.

Trial-specific considerations for co-enrollment outside of the STRIVE platform will be detailed in trial-specific appendices. It is recognized that, in the case of progression during follow-up to life-threatening disease and end-organ failure there will considerable clinical concern, and participation in an additional clinical trial at that time will not be restricted as a general principle.

Prior participation in clinical trials is generally not an exclusion criterion for STRIVE trials.

7 Study Population

7.1 STRIVE Population Overview

Participants will be enrolled into trials within the STRIVE platform at clinical trial sites globally. Study personnel at the enrolling site will confirm eligibility and obtain consent prior to randomization. Randomization will signify trial entry. Eligibility criteria in the STRIVE protocol and trial documents are absolute and are not subject to exception by investigators, site monitors, or sponsors.

The study population for the STRIVE platform includes patients admitted to the hospital with acute respiratory infections. Overarching platform eligibility criteria are described in this section of the master protocol. Each trial conducted within the STRIVE platform may have additional trial-specific eligibility criteria, which will be described in the trial-specific appendix. For a patient to enroll in a trial, that patient must meet the platform eligibility criteria and the trial-specific eligibility criteria. Efforts will be made to harmonize eligibility for different trials as much as possible.

7.2 STRIVE Platform Eligibility Criteria

STRIVE Platform Inclusion Criteria:

1. Age ≥18 years.
2. Informed consent for trial participation.
3. Hospital admission (or boarding in an emergency department or other area awaiting hospital admission) with signs and/or symptoms of a respiratory infection.

STRIVE Platform Exclusion Criteria:

1. The patient is expected to be discharged from the hospital within the next 24 hours.
2. Medical condition other than the acute respiratory infection (and its manifestations) that is likely to result in death within 7 days of randomization.
3. Moribund condition, defined as prior cardiac arrest during this hospitalization and life expectancy less than 48 hours of randomization.
4. Patient undergoing comfort care measures only such that treatment focuses on end-of-life symptom management over prolongation of life.
5. Expected inability or unwillingness to participate in study procedures.
6. In the opinion of the investigator, participation in a trial is not in the best interest of the patient.

7.3 Eligibility Criteria Considerations for Trial-specific Appendices

Each trial in the STRIVE platform will define additional eligibility criteria in the trial-specific appendix. These trial-specific appendices will specify the following eligibility criteria:

1. Pathogen- or syndrome-specific inclusion criterion: the specific pathogen (e.g., influenza) or clinical syndrome (e.g., community acquired pneumonia) being studied in the trial. For pathogen-specific trials, the inclusion criterion should outline methods of pathogen detection that are acceptable for eligibility.
2. Signs and/or symptoms inclusion criterion: the specific clinical signs and/or symptoms a patient must exhibit to be eligible (if any).

3. Duration of signs and/or symptoms inclusion criterion: time window for duration of signs and/or symptoms from a respiratory infection in which a patient is eligible (if any) (e.g., acute respiratory infection symptoms for <14 days).
4. Illness severity inclusion criterion: stages of illness severity (e.g., receipt high flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation) which make the patient eligible for enrollment.
5. Other trial-specific inclusion criteria (if any).
6. Exclusion criteria related to contraindications of the therapy being studied (if any) (e.g., pregnancy, eGFR <30 mL/min/1.73m^2).
7. Exclusion criteria related to receipt of other therapies (if any) (e.g., receipt of COVID-19 convalescent plasma or an anti-SARS-CoV-2 neutralizing antibody therapy in the past 30 days).
8. Exclusion criteria related to participation in other clinical trials (if any).
9. Other trial-specific exclusion criteria (if any).

For trials that shared control, the data above for each trial will be collected across all participants in such trials, in order to understand which patients can be considered for sharing the control/placebo.

8 Study Products

Investigational agents and any study-supplied SOC treatment to be used are described in Appendices E and F, respectively.

9 Study Assessments and Procedures

9.1 Approach to Enrollment into Multiple Trials under This Master Protocol

While there is not a limit to the number of trials under this master protocol into which a participant may enroll, any pair of randomizations for distinct trials not taking place on the same day may have a minimum interval between randomizations stipulated in the trial-specific appendices. The same participant identifier will be used across all trials into which a participant is co-enrolled.

To minimize participant burden, a single study visit can be used for more than one trial. Visit windows abut to facilitate data collection from participants enrolled in more than one trial. Data collection for participants enrolled in one trial should take place as close as possible to the intended study visit day. For participants in two or more trials the common visit day should be selected so that it corresponds to a visit day for the most recent randomization. This will make the visit later than expected for earlier randomizations.

While a single visit can be used for more than one trial, research specimens should be collected for each of the trials into which the participant has enrolled (other than whole blood specimens for genomic analysis). This may entail, for example, doubling the amount of blood drawn on some days. While there is no limit on the number of trials into which a participant may enroll, no more than 120 mL of blood should be drawn within a 24-hour period for

someone over 68 kg (for lower weights and further detail about this limit see Baron et al., 2020 [48]).

9.2 Schedule of Assessments

Participants are randomized and the intervention starts on Day 0. All participants are followed through the Day 60 study visit. The choice of a schedule of assessments for clinical data collection and specimen collection must be specified for each trial. The schedule of assessment chosen must consider the potential for sharing placebos in other trials. In general, in-person visits are only required for visits that require specimen collection (see Section 9.3.2 for further details).

Templates for clinical data schedules and specimen collection schedules will be posted to the INSIGHT website for use in trial-specific appendices. The time and events table for the maximal schedule is in Appendix A.

SAEs, UPs, PDACEs (Sections 10.2.5-7) and death will be reported for all trials. Grade 3 and 4 clinical adverse events (Section 10.2.3) will be reported only for trials where prior safety information of the intervention is limited to Phase 2. Whether grade 3 and 4 adverse events will be reported will be stated in the trial-specific appendix. Assessment and reporting of AESIs and other safety data will be described in the trial-specific appendices.

Efforts should be made to minimize changes to the template schedules posted to the INSIGHT website. If a new schedule is introduced for a trial, that schedule will be a potential schedule for future trials and posted to the INSIGHT website.

The selection of schedules for data collection should be informed by considerations such as

1. Controlling the extent of contact between study staff and infectious patients
2. Novelty of the infection
3. Novelty of the intervention
4. Safety profile of the agent
5. Speed of progression of the disease
6. Regulatory requirements
7. Demands on hospital staff, e.g., data collection or in-person visits in the setting of epidemic-associated local resource limitations.

9.3 Study Assessments and Procedures

A general summary of possible study assessments and procedures is below. Each trial-specific appendix will contain details on the required study assessments and procedures.

Data will be collected consistently across trials for a specific virus or intervention when possible.

9.3.1 Baseline/screening Assessments

Day 0 refers to the day the participant is randomized and the study treatment is initiated. Baseline refers to assessments conducted on Day -1 or Day 0 prior to randomization.

All trial-required screening and baseline assessments must be completed within 24 hours before randomization to ensure eligibility of the patient for the trial. Trial consent must be obtained before any procedures are conducted solely for trial purposes.

- Confirmation of infection by documentation of a positive diagnostic test (as defined in the trial)
- Demographics
- Type of residence immediately prior to the current illness (i.e., “home”)
- Vital signs, including respiratory rate and oxygen saturation
- A focused physical exam
- A focused medical history
- Blood for local laboratory evaluations
- Plasma and serum specimens for central testing for antibody, antigen, and biomarker level determination and storage for future related research
- A mid-turbinate nasal swab for central determination of viral genome levels
- Urine or serum pregnancy test in women of childbearing potential who are not already documented to be pregnant
- Contact details of the participant and contact details for 2 close friends or relatives (kept at the site).

It may not be possible to obtain a nasal swab or blood at the time of the baseline assessment. In this event, these specimens can be obtained after randomization but before the initiation of the study treatment.

Once all screening information is available, overall eligibility will be assessed. If exclusions are identified during screening, the screening process can stop.

Patients found to be eligible must be randomized and the treatment started within 24 hours after consent. If randomization is delayed and will occur more than 24 hours after consent, consent must be documented to be re-affirmed, and all tests (confirmation of infection, laboratory measurement) must be re-done so as to be within 24 hours before randomization.

On Day 0, after randomization and before the initiation of the study treatment, any new or worsening signs and symptoms should be recorded.

Additional data collection for a specific viral infection or intervention may be specified in the trial-specific appendix. These items should be collected consistently across trials for a specific virus or intervention when possible.

9.3.2 Follow-up Assessments

For all trials, participants will have data collected for Days 0-7, Day 28, and Day 60. Each trial-specific appendix will describe the required data collection using the template schedules.

All changes in location status (e.g., re-admission to another hospital or an intermediate care facility) will be collected to assess when the participant meets the criteria for the endpoint of 14 consecutive days “home”. Use of supplementary oxygen at home will also be captured. This

will also allow for determination of the outcome of total days alive outside of a short-term acute care hospital.

Data on concomitant medication will be collected in a targeted fashion. Current use at Days 0, 5 and 28 will be captured for any type of medication. Additionally, medicines used for the disease under study will be more comprehensively collected from prior to enrolment and through Day 5 in particular.

Blood and respiratory tract material for research is collected at certain visits (see section 6.5). At each of these visits, plasma, and serum specimens are obtained for central testing for immune response biomarkers, microbiological characterization, host response biomarkers, as well as drug levels, biomarker level determination and storage. The visits requiring stored specimens and the required aliquots for the maximal schedule are described in Appendix A. Each trial-specific appendix will specify the visits requiring stored specimens and the required aliquots. In-person research visits for participants at their residence or mobile phlebotomy services may also be utilized to complete protocol-required data/specimen collection during follow-up. Individual trials may incorporate one or more substudy(ies) at selected sites, that focus on collection of additional data and specimens.

Study visits that do not require in-person contact can be done over the phone or by any other means (e.g., electronic health records) that facilitates data collection. The trial-specific appendices will indicate which, if any, visits do not require in-person contact, and any additional data collection requirements for visits.

Information collected at follow-up visits may vary depending on the virus or treatment. Every effort will be made to standardize data collection across all trials of that virus and treatment.

9.3.3 Stored Samples and Future Use of Specimens

Specimens obtained under this protocol will be shipped to and stored at a central facility in the U.S. In addition to the use of these specimens as described in this protocol, these specimens will be available for future research on viral respiratory pathogens, or the treatment used in a specific trial. Proposals to use these specimens will be reviewed by the STRIVE scientific steering committee. Results of research tests will not be shared with participants or investigators, but aggregate summaries of results will be made available.

10 Safety Assessment

This section defines the types of safety data that will be collected in this platform protocol and outlines the procedures for appropriately assessing, collecting, grading, recording, and reporting those data. Investigators, IRBs/ECs, and health authorities will be notified of safety events as required.

Safety reporting and monitoring in STRIVE complies with International Conference on Harmonisation (ICH) Guideline E2A: “Clinical Safety Data Management: Definitions and

Standards for Expedited Reporting," ICH Guideline E-6: "Guideline for Good Clinical Practice (GCP)," and US 21CFR Parts 312 and 320.

10.1 Trial Safety Oversight

The primary responsibility for monitoring safety data in STRIVE trials rests with an independent Data and Safety Monitoring Board (DSMB). The DSMB will review safety data in an unblinded fashion at frequent intervals defined in each trial to assure participant protection. Unblinded monitoring by an independent group of experts is critical to identify true safety signals while maintaining the integrity of blinded comparisons. The DSMB will review unblinded safety data weekly in most cases. The frequency of DSMB safety review may vary depending on considerations such as the nature of agents and conditions being studied and the pace of enrollment and will be addressed in each trial-specific appendix.

The Medical Monitor at the sponsor safety office provides immediate real-time review when sites report certain events defined below (SAEs, AESIs, UPs). The sponsor Medical Monitor makes an independent assessment of the relatedness of the event to study intervention and the expectedness of the event. The sponsor Medical Monitor may convene a committee of medical officers identified by each ICC as well as trial leadership to discuss individual cases or potential safety issues arising from review of accumulating events and advises the protocol team regarding appropriate responses to safety issues.

The outline of the roles and responsibilities of the DSMB and the sponsors Medical Monitor for STRIVE can be found in the DSMB charter, and the INSIGHT Safety Monitoring Plan.

10.2 Definitions

10.2.1 Study Intervention

For trials in the STRIVE platform, the term "*study intervention*" refers to

- the investigational agent or placebo, if applicable;
- the treatment strategies being tested, if applicable; and
- any study-provided SOC treatment(s).

10.2.2 Baseline Signs and Symptoms

Baseline signs and symptoms are graded and recorded immediately before the first administration of a study intervention. This permits creation of a baseline from which to determine if an AE is treatment-emergent (first occurring after the study intervention begins), or if the AE is a preexisting event and if so, whether the event is worsening over time.

10.2.3 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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 "Guidelines for Good Clinical Practice").

In STRIVE, *reportable* AEs are those that:

- Are clinical, i.e., are not restricted to an isolated laboratory abnormality without associated signs or symptoms, and not worrisome for an organ toxicity, and
- Are new grade 3 or 4 events or events of lower grade that have increased in grade to grade 3 or 4

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 or, if applicable, as a PDACE (see section 10.2.7).

10.2.4 Adverse Event of Special Interest (AESI)

An Adverse Event of Special Interest (AESI) is an AE that is of scientific and medical concern specific to a study intervention, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. AESIs may be serious or non-serious. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

AESIs will be defined in each trial, if applicable.

AESIs will be collected, reported, and assessed per the same mechanism as SAEs (see section 10.3.3). An AESI may also be an SAE, and if so, will be reported on a single form.

10.2.5 Serious Adverse Event (SAE)

Whether an adverse event is **serious** is determined by the **outcome** resulting from the event. A serious adverse event is:

- an AE that results in death;
- an AE that is life threatening (places the subject at immediate risk of death from the event as it occurred);
- an AE that requires inpatient hospitalization or prolongs an existing hospitalization; Hospitalization is considered required if outpatient treatment would generally be considered inappropriate.

  Same-day surgical procedures that are required to address an AE are considered hospitalizations, even if they do not involve an overnight admission.

  Hospitalization due to a condition that has not worsened and that pre-dates study participation (eg, elective correction of an unchanged baseline skin lesion), or due to social circumstance (eg, prolonged stay to arrange aftercare), or that is planned/required “per protocol” AND that proceeds without prolongation or complication, is NOT considered an event that requires or prolongs a hospitalization by this criterion.
- an AE that results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital abnormality/birth defect in a fetus or neonate where parental exposure to a study intervention may have reasonably impacted the pregnancy;

- any other important medical event that may jeopardize the participant or may require intervention to prevent one of the outcomes listed above, based on appropriate medical judgment.

10.2.6 Unanticipated Problems

Unanticipated problems involving risks to trial participants or others are defined by US Health & Human Services (HHS) Office of Human Research Protections (OHRP) guidance, "Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" (2007) [49].

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 procedures and risks that are described in the IRB-approved research protocol, 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 relevant trial or agent documentation.

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 of a trial may make such an assessment based on an aggregate analysis of events.

10.2.7 Protocol-defined Anticipated Clinical Event (PDACE)

Protocol-defined anticipated clinical events are important events that are reflective of characteristics of the study population, natural progression of disease, background regimens, and comorbid conditions with similar populations, and are secondary outcomes for all STRIVE trials. These are collected on eCRFs throughout the trial. All PDACEs must be assessed promptly by a site investigator for relationship to study intervention.

- Those PDACEs which are assessed by the investigator as definitely, probably, or possibly related (see Section 10.2.9) to study intervention are *additionally* reported as SAEs.
- If defined as an AESI in the trial-specific appendix, a PDACE must also be reported as an AESI.
- They are not otherwise reported as AEs (i.e., are not reported as Grade 3/4 AEs).

See Section 4.2.3 for the list of PDACEs.

10.2.8 Severity Grading

The investigator will evaluate all AEs with respect to both seriousness (results in outcomes as described in Section 10.2.5) and **severity** (intensity or grade). AEs will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) [50] table.

10.2.9 Causality/relatedness

Causality is the likelihood that the event is caused by the study intervention. Causality will be assessed by a site investigator by considering the following factors:

- Definitely Related
  - reasonable temporal relationship
  - follows a known response pattern
  - clear evidence to suggest a causal relationship
  - there is no alternative etiology
- Probably Related
  - reasonable temporal relationship
  - follows a suspected response pattern (based on similar agents)
  - no evidence of a more likely alternative etiology
- Possibly Related
  - reasonable temporal relationship
  - little evidence for a more likely alternative etiology
- Unlikely Related
  - does not have a reasonable temporal relationship
    - AND/OR
  - there is good evidence for a more likely alternative etiology
- Not Related
  - does not have a temporal relationship
    - AND/OR
  - definitely due to an alternative etiology

Note: Other applicable factors (e.g., de-challenge, re-challenge) should also be considered for each causality category when appropriate. Causality assessment is based on information available at the time of the assessment of the AE. The investigator assessing the event may revise the causality assessment as additional information becomes available.

For SAEs, the sponsor will make an independent determination on causality. In this multinational protocol, if either the investigator or the sponsor assesses the event as “related” (definitely, probably, or possibly related), it will be considered related for the purpose of determining whether an event is reportable to health authorities.

10.2.10 Expectedness

The sponsor will assess SAEs and AESIs for expectedness. The specific reference document to be used for this assessment will be specified in each trial document. For investigational agents, this assessment will be made against the Reference Safety Information section of the Investigator’s Brochure(s) (IB) for the investigational agent(s). For approved products, the appropriate approved labeling will be used.

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

10.2.11 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A suspected unexpected serious adverse reaction (SUSAR) is an SAE which is both related to the trial intervention (either definitely, probably, or possibly related; see Section 10.2.9) and unexpected per the definition above. SUSARs will be evaluated by the sponsor to ensure that all applicable regulatory reporting requirements to health authorities are met, as described below.

10.3 Collection and Reporting of Safety-related Events

This section describes the schedule for reporting different types of safety outcomes on eCRFs as part of the STRIVE protocol data collection plan. It is recognized that in the care of trial participants, more information may be documented 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.

In this multinational protocol, the most conservative applicable regulations will be used to determine whether an event is reportable to health authorities. Events determined in this way to be reportable will be submitted to all health authorities engaged in the protocol.

10.3.1 Safety-related Events Reported for All Trials

Participants will be monitored for safety as clinically appropriate. Events will be recorded in the source document. The investigator will promptly review events and assess them for seriousness, severity grade, relatedness to the trial intervention, and whether they are reportable. These assessments are recorded in the source document.

STRIVE trials will focus on reporting events that are serious or severe (at least grade 3 or 4 if applicable and certainly SAE's), or are judged related to trial intervention. In a population hospitalized with acute illness, lower-grade events (grade 1 or 2) are anticipated to be extremely common and are likely to be very challenging to attribute accurately.

Table 10.1 below shows the schedule for reporting safety outcomes on eCRFs in all STRIVE trials, regardless of study intervention type or participant population. The time period for reporting refers to the time from the participant's most recent randomization into a STRIVE trial.

Table 10. 1: Schedule of Reporting for Safety-related Events

Event type	Report*	Reporting timelines
Baseline signs and symptoms	All grades	After randomization, before study intervention
SAE	Throughout follow-up	Immediately** upon site knowledge of event.
AESI (where applicable)	Throughout follow-up	Immediately** upon site knowledge of event.
Unrelated PDACE	Throughout follow-up	Reported at each study visit. *Do not report as G3/4 AE*.
Related PDACE	Throughout follow-up	Reported as an SAE immediately upon site knowledge of event
Death	Throughout follow-up	Immediately upon site knowledge of event.
UP	Throughout follow-up	Immediately upon site knowledge of event

* Unless otherwise specified in the trial-specific appendix. See Section 10.3.2 below.

** See Section 10.3.3 below for details.

Trials being conducted under the STRIVE platform may specify additional safety data collection if warranted based on the intervention or population being studied:

- For trials where there is limited prior information on the intervention related to safety (i.e., the intervention is only studied maximally in Phase 2 trials), grade 3 and 4 AEs will be collected through Day 28. Consideration may even be made to also collect AEs of lower grade while study medication is prescribed during follow-up.
- Detailed reporting of a specific anticipated effect that is not identified as an AESI. An example might be reporting of all hypotension events of any grade during treatment with a vasoactive agent.
- Pregnancy identified in a trial participant during trial follow-up, including pregnancy outcome with permission of the mother.

10.3.2 Reporting of SAEs and AESIs From the Investigator to the Sponsor

Timely reporting of events from the investigator to the sponsor is required by national and international guidelines. Investigators report events by submitting the appropriate eCRF. The eCRFs on which SAEs and AESIs are reported are forwarded upon receipt to the sponsor safety offices for sponsor assessment and action. The same eCRF is used to report SAEs, AESIs, and UPs.

Investigators will report all SAEs and AESIs that are **deaths or life-threatening** events and **all related** SAEs within 24 hours of discovering the event.

Investigators will report all other SAEs and AESIs within 3 calendar days of site awareness. If a health authority requires a shorter reporting period, for example, for all SAEs to be reported

within 24 hours of site awareness, this shorter period must be followed by sites under that authority's jurisdiction.

The fact that some details of the event may be currently unavailable will not delay submission of the known information. Initial SAE/AESI eCRFs should include as much information as possible, but at a minimum must include the following:

- Event term
- Relationship to study intervention, including the rationale for this assessment
- Reason why the event is considered serious or AESI
- Narrative description of the event

As additional details become available, the investigator will update and re-submit the SAE/AESI eCRF.

The sponsors Medical Monitor will be responsible for reviewing all reported SAEs and AESIs, making an independent assessment of causality, and determining whether the event is expected. The Medical Monitor or qualified designee will prepare sponsor safety reports, and communicate as required with the DSMB, pharmaceutical partners, the Investigational New Drug (IND) holder if applicable, and other safety stakeholders as needed through the sponsor's safety offices or other mechanism mutually agreed to.

10.3.3 Reporting from the Sponsor to Health Authorities

The sponsor must report safety information to health authorities in two ways, expedited reporting and annual reporting.

10.3.3.1 Expedited Reporting

All SAEs reported on eCRFs are treated as potential SUSARs and are assessed for reportability by the sponsor Medical Monitor against applicable regulatory requirements and within the timelines needed to meet regulatory obligations. SUSARs which are fatal or life-threatening are reported as required to health authorities, generally within 7 days of sponsor awareness. Other SUSARs are reported as required to health authorities, generally within 15 days of sponsor awareness.

Events will generally remain blinded to treatment assignment to all parties except the DSMB and the unblinded statistician, unless other unblinding rules are triggered; see Section 10.4 below. This includes the sponsor Medical Monitor. Thus, SUSARs are reported to health authorities in a fashion that maintains the blind for investigators and sponsor. Specific individual or grouped events of concern will be promptly referred to the DSMB for their unblinded review and guidance, which will be included in any required regulatory reporting.

In addition to SUSARs, if the sponsor identifies any findings from other studies that suggests a significant human risk such that it requires a safety-related change in the protocol or informed consent, or other changes to the overall conduct of the study, the sponsor will take any action that may be indicated and will report these findings to health authorities as appropriate.

10.3.3.2 Annual Reporting

For trials conducted under an IND or Investigational Medical Product (IMP) designation, the sponsor will report safety outcomes in the IND Annual Report or in the Development Safety Update Report (DSUR) submitted to health authorities overseeing that trial. This report will contain blinded data only, unless a trial has been completed and unblinded. Data will be summarized for each ongoing trial as a whole, not by treatment group.

10.4 Unblinding

As stated above, STRIVE trials are conducted in such a way as to preserve the integrity of a blinded trial. Unblinding is kept to a minimum. INSIGHT's policy and procedures for unblinding is outlined in the INSIGHT Safety Monitoring Plan, and detailed in the PIM.

In the event of a medical emergency, investigators should treat the participant under the assumption that they received an active study intervention. If knowledge of the participant's study intervention assignment would impact the choice of treatment, e.g., if a particular treatment would be contraindicated if the participant received an active intervention, an investigator may request local and limited unblinding. The investigator makes this request directly to the site's study pharmacy team, as these are the only study staff with access to the actual treatment assignment. The number of study staff and clinical staff unblinded to a participant's study treatment assignment should be kept to a minimum, and these staff will be reminded that the study assignment is still considered blinded for study purposes and must not be casually documented or shared. Any staff who are unblinded should not then be responsible for assessing the relationship of events to study intervention for that participant.

The process for notifications and documentation of any unblinding event to study personnel is specified in the PIM. The occurrence of an unblinding event will also be reported to the DSMB and other oversight bodies as required, without disclosing the actual treatment assignment.

It is possible that regulators may request unblinding of an individual event or a series of events. In this case, the INSIGHT policy for unblinding as outlined in the INSIGHT Safety Monitoring Plan will be followed. This assures that any unblinding is for cause, stepwise, limited to those with a need to know, and is documented in trial records.

10.5 Halting Enrollment for Safety Reasons

The sponsor Medical Monitor or the DSMB may request that enrollment be halted for safety reasons. If a trial is temporarily halted or stopped for safety reasons, IRBs/ethics committees will be informed. The sponsor, in collaboration with the protocol chair, the DSMB, and relevant health authorities, will determine if it is safe to resume the trial. The sponsor will notify site investigators of this decision. The conditions for resumption of the trial will be defined in this notification. Site investigators will notify their local IRBs/ethics committees of the decision by the sponsor to resume the trial.

11 Evaluation

This section describes the analysis approach for the primary and key secondary outcomes described in Section 4. This section also outlines interim monitoring guidelines for the Data and Safety Monitoring Board (DSMB). A more detailed statistical analysis plan (SAP) will be developed as a separate document. The general principles described here will be adapted to the individual trials, with details described in trial-specific SAPs. The SAP for each trial may be updated by the blinded statisticians prior to unblinding for a specific comparison.

Unless specified otherwise, for blinded trials, efficacy and safety comparisons will follow a modified intention to treat (mITT) principle that includes all participants who received some of the investigational agent or the control. For open label trials, safety analyses will also follow this mITT principle, whereas efficacy analyses will follow an intention to treat (ITT) principle that includes all participants who were randomized. When specific trials employ a shared control group, comparisons will be restricted to the set of controls from participants that were randomized contemporaneously. 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). Investigational agents will be compared to controls, but not to each other, unless explicitly specified in the analysis plan, e.g., comparative effectiveness trials.

All analyses will report 2-sided tests with a 5% significance level and point estimates alongside 95% confidence intervals unless otherwise noted.

11.1 Analyses of Primary Outcomes

All-cause mortality comparisons will be based on a log-rank test stratified by disease severity and study site. The summary hazard ratio will be estimated using a Cox proportional hazards model stratified by disease severity and study site pharmacy, and the proportion of participants who died by fixed time points (e.g., Day 14 or 60) will be estimated using Kaplan-Meier estimates.

Time to sustained recovery comparisons will be based on Gray's test (rho=0) stratified by disease severity and study site [51]. Cumulative incidence functions for sustained recovery will be estimated by treatment group using the Aalen-Johansen estimator [52], and the recovery rate ratio (RRR) for sustained recovery will be estimated using the Fine-Gray method [53, 54], stratified by disease severity and study site pharmacy. Analyses for the sustained recovery outcome require methods that take into account the competing risk of death, as participants may die before ever achieving sustained recovery. The "sustained recovery" outcome requires knowledge of a participant's residence status for at least 14 days after arriving "home" (as defined in section 4.1.3); since all participants are hospitalized at study entry, it takes at least 15 days to attain this outcome. Gray's test compares the cumulative incidence functions for sustained recovery between the comparison groups, taking into account the competing risk of death. Gray's test with rho=0 is the analogue of the log-rank test in the presence of competing risks. The Aalen-Johansen estimator for cumulative incidence functions is the analogue of the

Kaplan-Meier estimator in the presence of competing risks. The Fine-Gray method is the competing risks equivalent of Cox proportional hazards models; the RRR compares the cumulative incidence rates of sustained recovery between the study arms and is a sub-distribution hazards ratio. Importantly, these analyses do not censor deaths before recovery as is done in Kaplan-Meier and Cox proportional hazards; in contrast, the information that a participant died will be carried forward through the remainder of the trial, thus avoiding over-estimation of the recovery rate. We will report all sub-hazard ratios (e.g., death and withdrawals/losses/missing data).

Clinical recovery scale comparisons will be based on a proportional odds models stratified by disease severity and study site. Summary adjusted odds ratios will be reported. A test for the proportional odds assumption across cumulative categories and stratification covariates will be performed by testing for separate slopes (a partial proportional odds model). In addition, cumulative probabilities of the ordinal outcome categories will be compared between treatment groups using logistic regression models.

To avoid loss of power when stratifying analyses by study site, unless specified otherwise, sites that contributed fewer than 20 participants to the analysis cohort will be pooled with other sites within the same geographic region, defined first by country and second by wider geographic organizational units, e.g., continent.

11.2 Analyses of Secondary and Safety Outcomes, and Subgroups

Secondary efficacy outcomes will be analyzed similarly to the primary outcome with an analogous structure. Time to discharge from initial hospitalization will be analyzed using a competing risks approach, similar to time to sustained recovery. Death in hospital is a competing risk to discharge. Days alive and home through the end of follow-up, EuroQol (EQ-5D-5L) and the 7 category ordinal outcome on Days 1-7, 14 and 28 will each be analyzed using proportional odds models, similar to the clinical recovery scale. These analyses will be stratified by disease severity and study site.

Effects on the primary efficacy and safety outcomes will be assessed for subgroups defined by baseline characteristics, including demographics, social determinants, duration of symptoms at enrollment, clinical history and presentation (including disease severity). Tests evaluating effect heterogeneity across subgroups will be carried out. Subgroup analyses will be interpreted with caution due to limited power and uncontrolled type I error. Unless specified otherwise, corrections for multiple testing will not be applied.

The clinical organ failure or serious infection (PDACE) safety outcome will be summarized and compared at various study days (e.g., Day 5, 14, 28 and 60) using Cochran Mantel Haenszel test stratified by study site and disease severity. Summaries and comparisons will be provided for each component of this composite as well, with comparisons being conducted when 5 or more events in that component have occurred. Time to event analyses will also be used to summarize the PDACE safety outcome. The other safety outcomes defined in Section 4.2.3 (composite of death, clinical organ failure or serious infection; the composite of cardiovascular events and thromboembolic events; and safety and tolerability outcomes) will be analyzed similarly.

11.3 Data Monitoring Guidelines for an Independent DSMB

An independent data and safety monitoring board (DSMB) will review all trials conducted in the STRIVE platform. Each individual trial will be reviewed at least twice a year and may be reviewed more frequently as needed. These full DSMB reviews include the general trial conduct as well as extensive data summaries of the primary outcome and other major clinical outcomes.

In addition to the full reviews, interim safety reviews by the DSMB may be scheduled more frequently. In particular, for investigational agents with limited safety data, an early safety review with 20-30 participants will be included, followed by frequent interim safety reviews. The monitoring plan for safety, efficacy and futility is described below. If a modification of the monitoring plan is needed for an individual trial, it will be pre-specified in the trial-specific protocol appendix and statistical analysis plan.

The monitoring guidelines for the DSMB described in this section are guidelines, not binding rules. The DSMB is expected to use their independent judgment in determining whether a trial should be terminated or modified, based on comprehensive reviews of data from the current trial and available external data since there are many considerations in determining whether a trial should be stopped early.

The DSMB will be asked to recommend early termination of a trial for efficacy only when there is clear and substantial evidence of a treatment difference. Conversely, the DSMB may recommend discontinuation of an investigational agent if the risks are judged to outweigh the benefits, or if pre-specified futility assessments indicate that there is low probability that the investigational agent will achieve statistical significance for the primary outcome. In addition to the unblinded data summaries, the DSMB will also review other relevant data that might impact the trial design, e.g., emerging data from other trials.

When several agents are investigated in parallel with a shared control group, each agent will be compared to its corresponding contemporaneously randomized pooled placebo group. Each investigational agent versus control comparison will be treated as a separate trial; the DSMB may recommend stopping one arm of the trial but continuing others. Stopping boundaries will be adjusted for multiple looks, but will not be additionally inflated to adjust for simultaneous analyses of multiple agents, except when explicitly stated in the trial-specific appendix and statistical analysis plan.

11.3.1 Monitoring Guidelines for Efficacy and Harm

11.3.1.1 Trial of Investigational Agent versus Control

As a guideline, asymmetric boundaries will be provided to the DSMB to monitor the estimated treatment difference for benefit or harm. For monitoring overwhelming benefit of an investigational agent, the treatment difference in the primary outcome will be assessed using the Lan-DeMets spending function analogue of the O'Brien-Fleming boundaries [55]. The Lan-DeMets boundary will be chosen to preserve a 1-sided 0.025 level of significance. For computing the Lan-DeMets boundary, the information fraction accrued at each interim review will be used; for example, if the primary outcome analysis is by time-to-event, then the

information fraction at an interim analysis will be the number of accrued events divided by the total number of events planned in the sample size estimation.

Monitoring boundaries for efficacy will be presented at each full DSMB review, starting when 25% information time has accrued, or as requested by the DSMB. The O'Brien-Fleming Lan-DeMets boundary allows for frequent looks and has a high barrier for stopping the trial based on full DSMB reviews with low information time. The boundary will be capped so that it never exceeds Z=3.5, with values above 0 indicating benefit of the investigational agent compared with control, corresponding to a one-sided p-value of 0.0002 very early in the trial.

If an individual trial is designed with co-primary hypotheses, the monitoring boundaries will be presented separately for each of the planned co-primary hypothesis tests, with multiplicity adjustments similar to those planned for the co-primary hypotheses, such as the Holm-Bonferroni method [56]. Details will be specified in the trial-specific appendices and statistical analysis plans.

Trials should be stopped for efficacy only when there is overwhelming evidence of benefit, with consistent results across important clinical outcomes and subgroups. For example, if the primary efficacy outcome is time to recovery, and the recovery outcome is crossing the monitoring boundary for efficacy, then the trial should not be stopped unless there is a convincing signal in important, life-altering clinical outcomes, such as mortality. These decisions rely on the independent expertise and judgment of the DSMB; further guidance may be included in the trial-specific appendices.

Monitoring boundaries for harm will be based on safety outcomes of high clinical importance. For example, for trials conducted in critically ill participants, the monitoring boundaries for harm would typically be based on mortality, while trials conducted in study populations with low expected mortality would use composite endpoints such as SAEs, clinical organ failure, serious infections or death through Day 28, or a composite of grade 3 or 4 events, SAEs, clinical organ failure, serious infections, or death (safety outcome 4a defined in Section 4.2.3). Unless specified otherwise, the monitoring boundary for harm will be a one-sided 2.0 SD Haybittle-Peto boundary for the Z-statistic comparing the treatment groups for the pre-defined safety endpoint. [57, 58]. For time-to-event outcomes, the Z-statistic will typically be based on a stratified log-rank test. For example, if the monitoring boundary is based on time to death, a 2.0 SD Haybittle-Peto boundary corresponds to stopping the trial for safety if mortality is higher in the active group than in the control group with a one-sided p-value of 0.023 or less. Unless specified otherwise, this boundary will be used after 100 or more participants are enrolled and at least 20 events have occurred; with fewer participants or events, a Haybittle-Peto boundary with 2.5 SD will be used. A 2.5 SD boundary corresponds to a one-sided p-value of 0.006 or less.

In addition, the DSMB will review data summaries for major safety outcomes, including allergic or infusion-related reactions, and the components of the composite safety outcome of grade 3 and 4 clinical adverse events (if captured; see section 10.3.2), SAEs, clinical organ failures, serious infections, and death through Days 5 and 28; and SAEs, clinical organ failures, serious infections, and deaths through Day 60. The frequency and content of safety reviews will be

determined by the DSMB. Safety reviews will be part of each full DSMB meeting but may be scheduled substantially more frequently for individual trials. The DSMB may request safety reviews, targeted analyses, or full DSMB reports at any time.

11.3.1.2 Comparative Effectiveness Trials

Comparative effectiveness trials will compare two active interventions for efficacy, and thus require two-sided hypothesis tests and upper and lower monitoring boundaries for efficacy. For these trials, the O'Brien-Fleming Lan-DeMets alpha-spending function will be used to calculate symmetric upper and lower boundaries for efficacy. These boundaries will be capped at 3.5 SD.

In addition, the DSMB will review safety data summaries for major safety outcomes. Safety reviews will be part of each full DSMB meeting, but may be scheduled substantially more frequently for individual trials. The DSMB may request safety reviews, targeted analyses, or full DSMB reports at any time.

11.3.2 Monitoring Guidelines for Futility

The DSMB will review interim data on a regular basis and use pre-specified guidelines to inform a recommendation for discontinuation of an investigational agent if futility assessments indicate that there is low probability that an investigational agent will achieve statistical significance for the primary outcome. These interim analyses will be presented to the DSMB by the unblinded statisticians. The guideline to recommend stopping early for futility is a conditional power below a threshold percent (typically in the range of 10%-40%), where conditional power is calculated assuming as yet unobserved primary outcome data will arise as assumed under the hypothesized effect size used in estimating the sample size of the trial [59]. Additionally, we will also present conditional power calculation under a range of values for the as yet unobserved primary outcome data (including the estimated effect size observed in the trial). The boundary which is used will depend on a variety of factors (pace of enrollment, resources, type of trial) and will be communicated in the trial-specific appendices. In a comparative effectiveness trial, conditional power will be reported for the superiority of each intervention relative to the other. Conditional power assuming that future, yet unobserved data correspond to the effect size that was observed so far will be presented as supplemental information. Should conditional power fall below 10%-20%, consideration should be given to continuing the trial due to incongruent signals on important secondary outcomes, evidence of benefit in important subgroups, or the need for greater certainty of an overall null result to affect practice.

As an illustrative example, Table 11.1 shows the probability of observing conditional power below 10% under the null effect and hypothesized effect for a trial with 90% power assuming interim futility assessments are carried out with 50%, 67% and 83% information. Under this analysis plan, the probability of stopping early for futility under the null is 84%, whereas under the hypothesized effect it is 2.5%. Under the null, early stopping is relatively likely at each of the three interim analysis, with a 21% probability at the first interim futility analysis, 36% at the second, and 27% at the third.

Table 11.1: Probability of observing a conditional power below 10% assuming no effect or the hypothesized effect. In a trial with 90% power and three evenly-spaced interim analyses during the latter half of the trial.

Information Time	0.50	0.67	0.83	**Overall**
No Effect	0.211	0.359	0.269	**0.840**
Hypothesized Effect	0.001	0.006	0.018	**0.025**

11.3.2.1 Early Futility Assessment

In some cases, an early futility assessment may be specified using an intermediary futility outcome. For example, in a trial where the primary outcome is an ordinal scale assessed at Day 60 (e.g., *CRS-60*), an early futility assessment could be based on time to hospital discharge, or on the 7-category ordinal outcome assessed at Day 14. This might be warranted when there is an acceptable intermediate outcome and many competing agents in the platform combined with the need to quickly identify and concentrate resources on the most promising agent(s), or when preliminary data supporting activity of the investigational agent in the trial population is lacking and thus establishing such activity is warranted to justify further resource intensive evaluation based on the primary outcome. Rationale and details regarding such an approach will be prespecified in the trial-specific appendix.

12 Protection of Human Subjects and Other Ethical Considerations

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

This protocol will be conducted by hospitals participating in INSIGHT. It is anticipated that potential participants will be recruited by the site investigators (and/or their delegates, as appropriate) and/or that hospital screening test information for the infectious organism being studied in a given trial will be used to enquire about potential enrollment. Information about this protocol will be disseminated to health care workers at enrolling sites.

Prior to the initiation of the STRIVE platform protocol and any trial within the protocol 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 these documents will be submitted and approved by the same IRB(s) or EC(s). After IRB/EC approval, sites must register with the sponsor for the platform protocol and each trial before screening potential participants, and must register for any amendments. Protocol registration procedures are described in the PIM.

12.2 Ethical Conduct of the Study

All trials within the STRIVE platform 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), 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 including the EU General Data Protection Regulation (EU 2016/679); 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 will be obtained for each trial for which a patient is believed to be eligible at the time they are approached for consent. The informed consent form for each trial will state that the trial is part of a larger undertaking, and inform patients that may be approached for additional trials, if their disease progresses to meet eligibility criteria for subsequent trials.

Patients may be presented with and choose to consent to multiple trials for which they are currently eligible. If trials share a control group, patients would be given the opportunity to consent to both trials at the same time if they are eligible for both (see section 6.2.2). At the time of recruitment, if a patient meets eligibility criteria for more than one available trial and consents to simultaneous enrollment in two or more trials, the procedures and schedule of the trial with the longest follow-up period will be used.

Trials in the STRIVE platform may be SMART (section 6.2.4), involving multiple randomizations in sequence. Patients must agree to all components of the SMART trial at the time of consent in order to participate in that trial.

Informed consent must be obtained prior to conducting any study-specific procedures. Many of the patients approached for participation in this research protocol may 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 with regard to legally effective consent, informed consent may be obtained from a legally-authorized representative (LAR). Because the investigational agents are intended to treat acute illness and the impairment of decisional capacity is intrinsic to the acute illness of the severity that may be studied in trials under this protocol, 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, and the investigator's assessment of the participant's capacity and the reason that capacity is diminished will be documented. Local standards and policies will also determine who is legally authorized to consent for an individual who is incapacitated; this will also be documented for each participant for whom an LAR is giving consent. Should the individual regain capacity during the study, their direct consent must 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, including the General Data Protection Regulation (EU) 2016/679 (GDPR).

12.5 Regulatory Oversight

Trials being conducted under the STRIVE platform protocol may study investigational agents, repurposed approved agents, or strategies of use for approved agents. Regulators will determine which trials are to be conducted under a US IND or equivalent. For IND trials, sites in the US will conduct the trials 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, but will conduct the trial under the appropriate regulatory scheme in their country. As stated in Section 12.2 above, all sites will conduct all STRIVE trials 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 risk-based protocol monitoring plan will be developed for the platform, with appendices defining additional monitoring requirements, if any, for individual trials. 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 may be conducted when possible; such tasks may need to be handled remotely during epidemic or pandemic situations. The monitoring plan will outline the frequency of this aspect of monitoring based on factors such as the specific trial being monitored, study enrollment, data collection status and regulatory obligations.

Appendix A Maximal Schedule of Assessments

Baseline Data Collection

- Confirmation of infection by documentation of a positive diagnostic test (as defined in the trial)
- Demographics, including age, gender, sex at birth, race, and ethnicity
- Type of residence immediately prior to the current illness (i.e., “home”)
- Vital signs, including respiratory rate and oxygen saturation
- A focused physical exam, including height and weight
- A focused medical history which includes:
    - Date of onset of signs and symptoms of the current infection
    - Targeted history of chronic medical conditions
    - Targeted concomitant medications
    - Relevant vaccinations
- Blood draw for local laboratory evaluations:
    - White blood cell count
    - Hemoglobin
    - Platelets
    - Lymphocytes
    - CRP
    - Serum creatinine
    - INR
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)
- Urine or serum pregnancy test in women of childbearing potential who are not already documented to be pregnant
- Contact details of the participant and contact details for 2 close friends or relatives (kept at the site).

Follow-up Assessments

Clinical data, including use of supplemental oxygen, will be collected at visits for Days 0-7, Day 14, Day 28, and Day 60. Hospital discharge status and changes in residence will also be collected at these visits. Local laboratory measurements will be obtained on Day 5 (the same set as obtained on Day 0). Concomitant medications will be collected on Day 5 and on Day 28. At the visit for Day 42, only changes in residence and use of supplemental oxygen will be collected.

All changes in location (e.g., re-admission to another hospital or an intermediate care facility) will be collected to assess when the participant meets the criteria for the endpoint of 14 consecutive days “home”. Use of supplementary oxygen at home will also be captured. This will also allow for determination of the outcome of total days alive outside of a short-term acute care hospital.

Clinical Time and Events Table

	Screen or Day 0	Day 0	Follow-up Study Day: shaded columns denote in-person visits										
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+6**	**+13**	**+13**	**+17**	**+20**
ELIGIBILITY & BASELINE DATA													
Informed consent	X												
Baseline medical (incl. duration of illness) and social history	X												
Targeted baseline and prior medications and vaccines	X												
Symptom-directed physical exam by the clinical team	X												
Review test results for specific viral infection	X												
Local laboratory testing	X						X						
Urine or serum pregnancy test or other documentation of pregnancy status for women of childbearing potential	X												
STUDY INTERVENTION													
Randomization		X											
Baseline signs/symptoms		X											
Initiation of study drug/placebo administration[2]		X											
Initiation of monitoring for adverse reactions[2]		X											
Initiation of monitoring for completion of drug administration[2]		X											
STUDY PROCEDURES													
Clinical assessment for ordinal outcome		X[3]	X	X	X	X	X	X	X	X	X		X
Hospitalization status					X		X		X	X	X		X
Changes in residence/facility			X	X	X	X	X	X	X	X	X	X	X
Interim medical history									X	X	X	X	X

	Screen or Day 0	Day 0	Follow-up Study Day: shaded columns denote in-person visits										
Day	**−1/0**[1]	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**	**42**	**60**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+1**	**+6**	**+13**	**+13**	**+17**	**+20**
Current medications							X				X		
Clinical AEs reaching grade 3 or 4 severity through Day 28[4]			X	X	X	X	X	X	X	X	X		
EuroQol (EQ-5D-5L)													**X**
SAEs and unanticipated problems			Report as they occur										
AESI[5]			Report as they occur										
Vaccinations for source of infection			Report when received										
PDACEs (section 4.2.3)			Report as they occur										
Deaths			Report as they occur										
Hospitalization summary			Report upon hospital discharge										
Hospital readmissions[6]			Reported as a change in residence/facility										

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

[2] These activities continue for length of time required to fully administer the study agent.

[3] Recorded prior to randomization.

[4] Defined for each trial – see section 10.3.1.

[5] Defined for each trial – see section 10.2.4.

[6] May also be reportable as an SAE

Specimen Time and Events Table

This section will be completed in the trial-specific appendix based on the chosen Specimen Schedule.

	Screen or Day 0	***Day 0***	***Follow-up Study Day: shaded columns denote in-person visits***										
Day	***−1/0[1]***	***0***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***14***	***28***	***42***	***60***
Acceptable deviation from day	***0***	***0***	***0***	***0***	***+/-1***	***0***	***+/-1***	***+1***	***+6***	***+13***	***+13***	***+17***	***+20***
Research sample storage (plasma and serum													
Airway swab for central determination of viral genome levels													
Whole blood for genomics		*Collected only once for participants who consent to optional collection of whole blood for host genetic analysis. This is not required for any trial. Consent for whole blood collection for genetic analysis may be offered at the time of consent to a trial.*											

Appendix B STRIVE / INSIGHT 018 / ACTIV Protocol Team

To oversee the implementation of this master protocol, a protocol team has been formed and includes:

- STRIVE Scientific Steering Committee chair and co-chairs
- Chair and co-chair of each trial currently active within the platform
- NIAID, Division of Clinical Research representatives
- NCATS representative
- STRIVE Statistical and Data-Management Center representatives
- STRIVE International Coordinating Center representatives
- Central laboratory representatives
- Representatives of collaborating manufacturers of investigational agents
- Study biostatisticians
- Community representative(s)

The STRIVE scientific steering committee will convene regularly to review study progress and address study conduct and administrative issues that arise. This committee is accountable and makes recommendations to the STRIVE leadership group, approving the platform design, onboarding of trials within the platform, scientific projects, and budget. The leadership decides on the composition of the scientific steering committee.

Appendix C References on the INSIGHT Website

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the INSIGHT 018 protocol and to other information pertinent to the study:

- CTCAE toxicity table: (https://safetyprofiler-ctep.nci.nih.gov/safety-profiler/static/#/home/(body:ctcDictionary)?version=5.0)

- 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 infection control measures.

- Treatment guidelines, including those from NIH and WHO

Appendix D List of Acronyms

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ACTT	Adaptive COVID-19 Treatment Trial
ADE	antibody-dependent enhancement
AE	adverse event
ARDS	acute respiratory distress syndrome
CCP	convalescent plasma containing COVID-19 antibodies
CDC	Centers for Disease Control and Prevention (US)
CHF	congestive heart failure
CI	confidence interval
COVID-19	Coronavirus-Induced Disease 2019
CRS	Clinical Recovery Scale (see section 4.1.4 for details)
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
EU	European Union
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
hIVIG	hyperimmune intravenous immunoglobulin from COVID-19 survivors
HR	hazard ratio
ICC	International Coordinating Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Institutional or Independent Ethics Committee
IgG	immunoglobulin G

IL-6	interleukin 6
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	interquartile range
IRB	Institutional Review Board
IV	intravenous
IVIG	intravenous immunoglobulin
LAR	Legal Authorized Representative
mAb	monoclonal antibody
MI	myocardial infarction
mL	milliliter
NAT	nucleic acid test (to identify genomic material; some uses amplification)
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
PDACE	protocol-defined anticipated clinical events; see Section 10.2.7.
PHI	personal health information
PIM	Protocol Instruction Manual
RBD	receptor-binding domain
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMART	dequential multiple assignment randomized trials
SOC	standard of care

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

Appendix E Trial-specific Appendix Template

Appendix E*n*: *company type of molecule/agent (agent name)*

Version: *number, date*

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1 Trial Synopsis

Design:	Treatments are needed to improve outcomes among patients hospitalized for *[disease]*. This trial will evaluate *[agent name/treatment strategy]*, *[1 line agent/treatment strategy description]*, developed by *[company name].* The study design is a randomized, xx-controlled, multi-center international clinical trial that will evaluate the clinical efficacy of *[agent/treatment strategy]* when given in addition to standard of care (SOC) for inpatients with *[disease]*-associated respiratory failure. The SOC will be determined by local established guidelines and may include *[x, x and x]* treatment strategies.
Primary Endpoint:	The primary endpoint is *x* through Day *x.*
Duration:	Participants will be followed for x days following randomization for the primary endpoint (and through x months in total).
Sample Size:	*[sample size considerations]*
Population:	*[short description of population]*
Intervention:	*[Randomization allocation and administration of agent/intervention]* Co-enrollment and/or use of shared placebo group with other active agents is specified in ancillary documentation.
Stratification:	Randomization will be stratified by study site pharmacy and by severity of respiratory failure (HFNO/NIV vs. IMV/ECMO).

Monitoring:	An independent data and safety monitoring board (DSMB) will regularly review interim safety and efficacy data of this trial along with the conduct of other trials within the STRIVE platform. Pre-specified guidelines will be established to recommend early stopping of the trial for evidence of harm, futility or substantial efficacy. The DSMB may recommend discontinuation of the investigational agent if the risks are judged to outweigh the benefits.

2 Introduction

2.1 Target Pathogen or Syndrome for this Trial

Add specifics for the trial.

2.2 Premise for Investigational Agent *(agent name)*

[high level information on agent and mechanism in the disease studied]

[some information on the company]

[high level summary of preclinical and clinical data e.g., IC_{50}, PK, dose etc.]

2.2.1 *if applicable*: Importance of Anti-viral Therapies Among Hospitalized Patients with xxx

2.3 Human Studies and Preclinial Information on Investigational Agent Treatment Effect and Safety

2.3.1 Preclinical Efficacy and Toxicology Data

Pre-clinical evaluation.

Efficacy across viral variants.

Etc.

2.3.2 Clinical Efficacy and Safety Data

Clinical trials experience with agent. *Summary of all available clinical data*

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of agent may be found in the Investigator's Brochure, Participant Information Leaflet, and/or Development Safety Update Report.

2.4 Rationale for the Trial Intervention Dose and Duration

[Outline of considerations, taking preclinical and available clinical data (both efficacy and safety) into account.]

Based on the above justifications and the extensive safety data available, the following dose of agent has been chosen for study in STRIVE: *x mg [mode of administration].*

3 Objectives and Endpoints

3.1 Primary Objective and Endpoint

Add specific considerations for the trial.

3.1.1 Primary Endpoint

The primary endpoint for this trial will be x through Day *x.* Details on the definition and ascertainment of this endpoint as well as other endpoints evaluated in STRIVE, are reviewed in Section 6.4 of the master protocol. *Add specifics for the trial if applicable.*

3.1.2 Rationale for the Trial Primary Endpoint

Add specifics for the trial.

3.2 Secondary Objectives and Endpoints

Secondary objectives and endpoints are as specified in the master protocol section 4.2.

Key secondary endpoints will be: the secondary endpoints specified in the master protocol in Sections 4.2.

Key subgroup analyses in this trial will be: *a), b) and c)*. Additional subgroup analyses for assessment of heterogeneity of treatment effect are specified in the master protocol in Section 5.2.

Add specifics for the trial if applicable.

3.3 Safety Endpoints

Safety endpoints are as specified in the master protocol section 4.2.3.

4 Trial Design

4.1 Trial Design Overview

Add specifics for the trial.

Figure 1: Trial Design Schematic

4.2 Trial Design Rationale and Justification

The approach and rationale for elements of the overall study design can be found in section 6 of the STRIVE master protocol. *Add specifics for the trial if applicable.*

Placebo control is appropriate to answering the study question for this trial. Specifically, potentially effective treatments as part of usual care will not be withheld from participants in either treatment group. Standard of care (SOC) as defined by local guidelines and utilized at the clinical sites is permitted in the background for both treatment groups in the trial. This includes the antiviral treatment xx as well as immunomodulatory treatments recommended by local guidelines.

4.3 Randomization and Blinding

An overview of the approach to stratification can be found in the STRIVE master protocol (section 6.3.4). Stratification will occur by study site pharmacy and disease severity, defined as xxx.

For participants enrolled only into this trial, randomization will be x:x allocation to agent plus SOC or matched control/placebo plus SOC (*or alternate design*). For participants eligible for simultaneous co-enrollment into this trial, the approach for "shared controls" is detailed in section 6.2.1 of the master protocol. The pooled placebo group will then be used as comparison with agent active group for both efficacy and safety analyses (see section 9 within this appendix). In this case, as outlined in the master protocol, only participants who were randomized contemporaneously to agent and another STRIVE trial and were assigned to placebo will be included in the pooled placebo group for the agent trial. This approach is illustrated in Figure 1.

Blinding will be accomplished by use of matching 0.9% saline infusion, with an amber sleeve placed over the infusion bags of both active agent and placebo (see section 6.3 of the master protocol for additional details).

Add specifics for the trial if applicable.

4.4 Enrollment in Other Trials within STRIVE Master Protocol

The principles for co-enrollment in this trial will follow those specified within the master protocol, see Section 6.1.1. Co-enrollment in other trials will only be allowed where a trial has been approved by STRIVE leadership for co-enrollment. Details of such co-enrollment authorization will be managed, maintained, and communicated by the STRIVE Data Coordinating Center. Where appropriate, the Statistical Analysis Plan will specify any analytic modifications relevant to co-enrollment.

For participants in this trial (agent) who are enrolled simultaneously into another STRIVE trial, the approach described for a 'shared placebo' will be used (see section 6.2.2 of master protocol and Figure 1 in this appendix).

4.5 Sample Size Assumptions

We estimated control event rates on the basis of multiple recent trials, including TICO and TESICO, and other published trials. We estimated the proportion in different severity strata on the basis of distributions in TESICO and the anticipated enrolling sites for STRIVE.

Sample size calculations used the following assumptions.

a. xxx
b. xxx

xxx

5 Trial Population

5.1 Target Population

The target population for this trial is as outlined in the master protocol section 7. *Add specifics for the trial if applicable.*

5.2 Trial-specific Eligibility Criteria

For this trial, additional ***inclusions*** not outlined in the master protocol include:

1. xxx
2. xxx

For this trial, additional ***exclusions*** not outlined in the master protocol include:

1. Xxx
2. xxx

6 Investigational Agent(s) and Standard Care

6.1 Formulation, Dosing and Administration of Investigational Agent

Detailed descriptions for interventional agent distribution, accountability, storage, preparation and administration can be found within trial specific Pharmacy Procedures and PIM specific to this trial.

Table 1 shows a summary of study medication.

[Short description of how many vials/tablets make one dose. mode of administration, composition of matched Placebo etc.]

Table 1. Study Medication Overview

Intervention Name	**Placebo**	**agent**
Dose Formulation	xxx	xxx
Dosage Level(s) (mg)	xxx	xxx
Dose Volume (mL)	xxx	xxx
Route of administration	xxx	xxx
Use	Placebo	Experimental
IMP and NIMP	IMP	IMP
Sourcing	xxx	xxx
Packaging and Labeling	xxx	xxx

[*use for infused agents. Change as necessary:* The infusion rate may be reduced as deemed necessary, if an infusion reaction is observed. Participants will be closely monitored during the infusion and every 30 minutes for at least 2 hours after completion of the infusion. Additional monitoring may be necessary based on clinical judgement of the study investigator(s) and/or site staff, and in accordance with the master protocol. The site must have resuscitation equipment, emergency drugs and appropriately trained staff available during the infusion and for at least 2 hours after the completion of the infusion. Any interruptions or changes in the infusion will be recorded, as will the total amount infused.

The clinical site should have necessary equipment and medications for the management of any infusion reaction, which may include, but is not limited to, oxygen, IV fluid, epinephrine (adrenaline), acetaminophen (paracetamol) and antihistamine. All participants should be monitored closely for 2 hours after the infusion, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent. Potential anaphylaxis reactions will be graded by the Brighton Criteria (Ruggeberg et al. Vaccine 25 (2007) 5675-5684).

Premedication for infusions is not planned. The investigators and sponsor may elect to recommend premedication, if the frequency of infusion reactions among participants warrants. If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants. The decision to implement premedication for infusions in subsequent participants will be made by the investigators and sponsor and recorded in the study documentation. Any premedication given will be documented as a concomitant therapy.

Investigators will use their clinical judgement and standard of care to evaluate and manage all infusion reactions. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms. If a severe and potentially life- threatening infusion reaction occurs with agent/placebo, its use should be permanently discontinued.

If a participant is not infused with agent/placebo or the complete infusion is not given, all follow-up procedures and reporting's outlined in section 8.1, should be adhered to as indicated.]

6.2 Pharmacokinetics (PK)

xxx

6.3 Drug-Drug Interactions (DDI)

Add specifics for the agent if applicable.

Whenever a concomitant medication or the study agent is initiated or a dose changed, investigators must review the concomitant medication's prescribing information and the relevant protocol appendix/appendices, as well as the most recent package insert, Investigator's Brochure, or updated information from DCR, NIAID to obtain the most current information on drug interactions, contraindications, and precautions

6.4 Standard Care Treatments (Trial-specific Considerations)

Appendix F describes the standard of care for hospitalized patients with COVID-19. For this trial, there are no deviations from standard care as specified in the master protocol.

7 Risk/Benefit Assessment

Potential risks and benefits associated with participation in the STRIVE protocol are reviewed in section 3 of the master protocol.

Potential risks from this trial: *[specifics to the agent]*

Potential benefits from this trial: *[specifics to the agent]*

8 Assessment and Procedures

8.1 Summary of Trial-specific Assessments and Specimens

A detailed listing of clinical and specimen data collection, along with specific visit schedules are reviewed in the STRIVE master protocol Section 9.3 and Appendix A.

This trial will utilize *x follow-up and specimen schedule* as outlined in this section and Table 3 and 4, respectively.

8.1.1 Clinical Events Schedule

Baseline Data Collection

Add specifics for the trial if applicable.

Follow-up Assessments

Add specifics for the trial if applicable.

At the visits specified in the Clinical Time and Events Table, collected blood samples may be used to determine agent serum concentration for pharmacokinetic assessment. The PK/Immunogenicity assessment will require 2 mL of the serum collected. PK samples may be assessed by a validated assay at a bioanalytical lab. Analysis of samples from placebo-treated subjects is not planned. Remaining sample used for PK may be pooled and used for exploratory metabolism, pharmacodynamic, virologic, or bioanalytical method experiments as deemed appropriate.

Table 2. Clinical Time and Events Table- *choose applicable schedule from master protocol*

Table 3: Specimen Time and Event Table. ***choose applicable schedule from master protocol***

8.2 Trial-specific Monitoring and Reporting of Safety Data

A detailed overview of safety data collection and reporting for trials is included in STRIVE master protocol Section 10.3. *Add specifics for the trial if applicable.*

Adverse Events of Special Interest (AESI) collected in this trial will include- *if applicable:*

- xxx
- xxx

Collection of AESI information will be performed as the event occurs.

Pregnancy information on any female participant who becomes pregnant while participating in this study will be collected. The participant will then be followed to determine the outcome of the pregnancy, which will be reported on the Pregnancy Outcome eCRF.

If an investigator learns that a male participant's partner has become pregnant while the male participant is in this study, the investigator is asked to attempt to obtain information on the pregnancy, including its outcome, after obtaining consent from the pregnant partner. The outcome of the pregnancy will be reported on the Pregnancy Outcome eCRF.

Monitoring of this trial by the DSMB and guidelines for interim estimates of efficacy, futility, and safety are described in detail within section 11 of the STRIVE master protocol. This trial will be conducted to preserve the integrity of the blinded treatment where possible, and the process for unblinding is reviewed in section 10.4 of the STRIVE master protocol and within the trial PIM.

9 Data Analysis

Please refer to the master protocol for a detailed overview of analysis plan for study endpoints assessed for all trials conducted within the STRIVE master protocol, including safety endpoints and data monitoring (see Sections 10 and 11). A formal statistical analysis plan (SAP) will be written and utilized for analysis of trial results. *Add specifics for the trial if applicable.*

9.1 Analysis of Trial Primary Endpoint

Analysis of mortality through Day 60 is reviewed in detail within section 11.1 of the master protocol. In addition, as outlined in section 4.5 of this appendix, we will employ a co-primary analysis, as was used in TICO, whereby an effect in the HFNO/NIV stratum and in the overall population will be estimated. Type 1 error will be managed as outlined in section 4.5 of this appendix. *Add specifics for the trial if applicable.*

9.2 Trial-specific Secondary Objectives and Safety Endpoints

Analysis of secondary endpoints, safety outcomes, and subgroup comparisons are specified in the master protocol section 11.2. *Add specifics for the trial if applicable.*

10 References

Appendix F Standard of Care

F.1. Master protocol principles for Standard of Care

General principles regarding Standard of Care (SOC) in STRIVE trials are outlined below. Details of defining SOC for specific trials within STRIVE will be maintained on the trial website. An example of SOC for COVID-19 trials is shown below in section F.3.

SOC may include general supportive care appropriate for the participant's clinical status, specific therapeutic agents, and measures to reduce the risk of pathogen transmission. When designing a STRIVE trial, investigators will define SOC after examining the peer-reviewed literature and consulting relevant guidelines from NIH and professional societies and experts in the field. Specific therapeutic agents and approaches may be recommended for inclusion within SOC or recommended against being part of SOC. Data collection will include information on SOC interventions administered to trial participants. SOC interventions with a high level of evidence (e.g., Class A/Grade 1) may be ***required*** by the protocol and may be supplied by the study. Investigators may update SOC based on new information that emerges during the conduct of a trial.

The design of each trial in STRIVE will consider the current SOC for treating patients hospitalized with the infection and severity of illness under investigation. Depending on the scientific question, an experimental treatment will be added on top of or compared to SOC. When known effective treatments are incorporated into both the investigational and control arms of a trial, they are called "background therapy." In this scenario, the scientific question addressed is whether a new treatment added to SOC is superior to SOC alone.

Whether an individual SOC treatment is provided by the trial or not is based on multiple factors, including clinical and scientific considerations. There may be local variation in the clinical availability of one or more agents chosen to be part of 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 current SOC treatments) is a crucial, high-priority question. There is no possible way to answer the question of efficacy for a new therapy on top of the background of a proven (high level of evidence) effective agent without providing that agent – if not readily available - within the trial. Thus, SOC agents may be provided to sites by the trial in some circumstances.

The use of a given SOC therapy may apply to all or to a subgroup of the participants within a trial; the subgroup may be defined based on severity of disease, a clinical state, or a laboratory feature. An SOC agent may be mandated for participants (required for protocol entry); mandated when not contraindicated (participants may enter the trial if they receive the SOC agent or have a contraindication to the SOC agent); or recommended subject to clinical discretion (recommended but not mandated). Data collection will include use of SOC interventions in all of these circumstances.

F.2. General Supportive Care within SOC

All participants will be given supportive care consistent with current best practice for management of hospitalized adults with acute respiratory infection, including care for such conditions as: pneumonia, hypoxemic respiratory failure, exacerbation of obstructive lung disease, ARDS, sepsis, cardiomyopathy, arrhythmia, acute kidney injury, and complications

from prolonged hospitalization, including bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy.

Sites participating in STRIVE trials must have the ability to manage patients on invasive mechanical ventilation and those treated with continuous infusion of vasopressors. Supportive care SOC includes lung-protective ventilation for patients receiving invasive mechanical ventilation [60], prone positioning, when indicated, for mechanically ventilated patients with more than moderate ARDS [61, 62], treatment with anti-bacterial agents for patients believed to have bacterial infection, and guideline-consistent management of sepsis [63] when it is present. Use or non-use of extra-corporeal life support (ECLS) is not mandated as part of SOC. A specific approach to renal replacement therapy is not mandated as part of SOC.

Consideration should be given to the use of pharmacological thromboprophylaxis (thrombosis prevention) consistent with published literature and local clinical guidelines for hospitalized patients as appropriate for an individual participant, in addition to approaches to maintain mobility and minimize other thrombotic risks.

F.3. SOC for Specific Conditions Studied in STRIVE

Approach to SOC for a given condition under study in STRIVE is likely to evolve over time as new evidence accumulates. To ensure that investigators are kept up to date on evolving detailed aspects of SOC for conditions under study, statements that cover appropriate contemporary SOC will be displayed on the trial website. To ensure broad compliance, SOC will be a recurring topic for discussion and debate at investigator meetings.

As an example of how such statements will look, below is contemporary (May 2022) guidance for SOC treatment of adults hospitalized with COVID-19 in STRIVE trials.

F.3.1. COVID-19

Investigators will frequently examine SOC for COVID-19 trials, which will include careful consideration of COVID-19 treatment guidelines maintained by the US National Institutes of Health (NIH) [10], the Infectious Diseases Society of America (IDSA) [64], and other groups. The STRIVE master protocol does not mandate any specific therapeutic agent be used as SOC for the treatment of COVID-19.

F3.1.1 Glucocorticoids for COVID-19

In STRIVE trials, it is recommended that participants who are hospitalized with COVID-19 and on new oxygen therapy are treated with a glucocorticoid. This recommendation is based on clinical trial data [7], a meta-analysis [65], and NIH treatment guidelines [10]. 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 in hospitalized patients with COVID-19 treated with oxygen. Treatment with a corticosteroid is recommended for a total of 10 days, using doses outlined in the table below.

Glucocorticoids name	Daily dose
Dexamethasone	6 mg oral or IV
Prednisone	40 mg oral
Methylprednisolone	32 mg IV
Hydrocortisone	160 mg IV

F3.1.2 Remdesivir for COVID-19

The STRIVE master protocol does not make any recommendations or mandates regarding the use of remdesivir for the treatment of hospitalized patients with COVID-19 participating STRIVE trials. Thus, unless otherwise stated in a trial specific appendix, patients with COVID-19 may participate in STRIVE trials regardless of whether or not they are treated with remdesivir. Remdesivir is licensed by the US FDA for treatment of most hospitalized patients with COVID-19. Approval of remdesivir by the FDA was driven largely by results from the ACTT-1 trial, which demonstrated that remdesivir shortened the time to clinical recovery for patients hospitalized with COVID-19 [2]. ACTT-1 was conducted before most hospitalized COVID-19 patients were treated with glucocorticoids and generalizability of these findings to patients treated with corticosteroids has been questioned [66]. Subsequent global remdesivir trials conducted by the Solidarity [67] and DisCoVeRy [68] groups reported uncertainty regarding a mortality benefit for remdesivir among hospitalized patients with COVID-19. Hence, in STRIVE trials, remdesivir for patients hospitalized with COVID-19 will be allowed but not recommended or mandated.

F.3.1.3. Anticoagulation medication

Due to substantially elevated rate of thromboembolic events among hospitalized adults with COVID-19, there is consensus to administer anticoagulation medication to hospitalized patients with COVID-19 without a contraindication. Although several trials have been performed [69, 70], there remains uncertainty regarding the specific agent and dose that is optimal. Hence, in STRIVE trials, anticoagulation is recommended for hospitalized patients with COVID-19 without a contraindication to anticoagulation and local guidelines will be used to guide the type of medication and its dosing.

F3.1.3 Recommendations Against Therapies for COVID-19

Consistent with high-quality evidence suggesting no benefit, it is recommended to <u>not</u> administer the following therapies to patients with COVID-19 in STRIVE trials: hydroxychloroquine [71], chloroquine, lopinavir/ritonavir [72], and glucocorticoids for patients not requiring new supplementary oxygen.

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