An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19

Short Title: Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)

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In collaboration with four International Coordinating Centers (ICCs) of the INSIGHT Network:

-Copenhagen HIV Programme (CHIP) - Copenhagen, Denmark

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1.1 Synopsis

1.1.1 Rationale for Proposed Clinical Study

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these patients. This novel coronavirus has been designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by this virus has been designated coronavirus disease 2019 (COVID-19). There were 59 confirmed cases on January 5, 2020, 2118 cases on January 26, 2020, rising to more than 20 million confirmed cases and 750,000 deaths as of August 16, 2020 according to various international health reporting agencies.

Hyperimmune intravenous immunoglobulin (hIVIG) to SARS-CoV-2, derived from the plasma of individuals who recover and develop neutralizing antibodies, is a potentially useful therapeutic approach to COVID-19. Augmentation of the humoral immune (antibody) response using passive immunotherapy with hIVIG to SARS-CoV-2 at the onset of clinical progression before end-organ failure has developed may reduce the subsequent risk of further disease progression and death.

1.1.2 Study Design

This protocol will serve as a platform for assessing treatments for adult patients hospitalized for medical management of COVID-19 without related serious end-organ failure. Trials will involve sites around the world strategically chosen to ensure rapid enrollment. Initially, this trial will compare hIVIG with matched placebo, when added to standard of care (SOC), for preventing further disease progression and mortality related to COVID-19. SOC will include remdesivir unless it is contraindicated for an individual patient.

In future versions of the protocol, one or more drugs from a different class and with different mechanisms of action may be studied. Such treatments could be studied along with hIVIG if it is found effective and safe in this initial version of the protocol.

The primary endpoint of this trial in hospitalized patients is an ordinal outcome based on the patient's clinical status on Day 7. It includes 7 mutually exclusive categories capturing the range of organ dysfunction that may be associated with progression of COVID-19, such as respiratory dysfunction and coagulation-related complications (see Appendix F for full definition):

7. Death

6. End-organ failure

5. Life-threatening end-organ dysfunction

4. Serious end-organ dysfunction

3. Moderate end-organ dysfunction

2. Limiting symptoms due to COVID-19

1. No limiting symptoms due to COVID-19

Secondary endpoints include time to the 3 least favorable categories, time to the 2 most favorable categories, and the pulmonary only and thrombotic only components of the primary ordinal outcome. Mortality, adverse events (AEs), including infusion reactions, and biological correlates of therapeutic activity are also assessed. Because there is no established endpoint for evaluating the clinical efficacy of treatments for COVID-19, other clinically relevant outcomes, including outcomes used in other COVID-19 treatment trials, will be recorded. Thus, the randomized groups (initially hIVIG + SOC versus placebo + SOC) can be compared for multiple outcomes, and results can be compared or combined with other trials.

Participants will be randomized (1:1) to a single infusion of hIVIG + SOC or placebo + SOC on the day of randomization (Day 0). Participants taking remdesivir prior to randomization may be enrolled if eligibility criteria are met. Randomized participants who were not taking remdesivir before randomization will start taking remdesivir immediately following the infusion of hIVIG or placebo unless remdesivir is contraindicated. Participants will be followed for 28 days and, if the trial goes to completion, the primary analysis will be completed after all participants are followed for 28 days.

The planned sample size is 500 participants (250 per group). After 150 participants are enrolled, sample size will be re-estimated, by investigators who are blinded to interim treatment results using pooled outcome data.

The study population will include consenting hospitalized patients with COVID-19 who have had COVID-19 symptoms ≤ 12 days, and who do not have life-threatening organ dysfunction or organ failure.

Many other clinical trials evaluating treatments for COVID-19 are either ongoing or being planned. If findings from another trial have implications for the design and conduct of this trial, the protocol may be modified depending on the strength of the trial results and the target population studied.

An independent Data and Safety Monitoring Board (DSMB) will review interim data and use pre-specified guidelines for early termination of the trial or protocol modification. The DSMB will also be consulted concerning protocol modifications for reasons described above (e.g., sample size re-estimation or other aspects of the design resulting from emerging data). All protocol modifications will be discussed with the independent DSMB. Protocol amendments will be submitted to ethics committees (ECs) and a central institutional review board (IRB) in the United States of America (US).

After consent and eligibility has been determined, a single infusion of hIVIG or placebo will be administered on the day of randomization (Day 0). Remdesivir infusions will follow the hIVIG/placebo infusion. Any infusion reactions and interruptions of the planned hIVIG/placebo infusion will be recorded. The ordinal outcome will be assessed throughout follow-up, including on Day 7 for the primary endpoint. On Day 0 (pre-hIVIG/placebo infusion), and on Days 1, 2, 3, 7, and 28, a blood sample will be obtained to centrally measure neutralizing antibody levels along with total immunoglobulin G (IgG) concentrations and its subclasses, immunoglobulin A (IgA), and immunoglobulin M (IgM); for participants at selected sites an additional blood sample for these measurements will be obtained at Day 90. Serious Adverse Events (SAEs), including deaths from any cause, will be collected through Day 28. hIVIG infusion related events of any grade will be collected. Grade 3 and 4 AEs will be collected through Day 7. AEs of any grade experienced on Days 1, 3, 7, and 28 will be recorded.

2 INTRODUCTION

2.1 Study Rationale

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

There is currently no vaccine to prevent infection with SARS-CoV-2 and no licensed therapeutic agent to treat COVID-19; emergency use authorizations and expanded access schemes have been instituted for certain interventions (including convalescent plasma and remdesivir, described below) prior to licensure. Several clinical trials utilizing novel drugs and repurposing older agents have been implemented to investigate the treatment of adults hospitalized with severe COVID-19 (see Section 2.2.7).

Our understanding of the humoral immune response is evolving, with some evidence that responses are variable between individuals and delayed in some cases. It may therefore be that viral replication may lead to extensive tissue damage and inflammatory responses in the lungs and other organs before the development of neutralizing antibodies. Augmentation of the humoral immune response to SARS-CoV-2 using passive immunotherapy with hIVIG to SARS-CoV-2 in hospitalized patients at the onset of clinical progression but before end-organ failure has developed may thus reduce the subsequent risk of further disease progression and death.

2.2 Background

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

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. A novel coronavirus was rapidly identified by sequencing and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the illness caused by infection with SARS-CoV-2 has been named coronavirus disease 2019 (COVID-19).[4] While SARS-CoV-2 mostly causes a mild respiratory illness, some individuals, particularly those who are elderly [5,6] and have comorbidities[7] may progress to severe disease requiring hospitalization, mechanical ventilation in intensive care units, and death. As of 28 June 2020, just 14 weeks following the declaration of a pandemic on 11 March 2020 by the World Health Organization (WHO),[4] there have been more than 20 million cases diagnosed and more than 750,000 deaths across 185 countries.[1] Over 100,000 cases continue to be reported daily.[4]

2.2.2 Natural History of COVID-19

SARS-CoV-2 has a median incubation period of 4 days (interquartile range 2-7 days)[8] and the mean serial interval defined as the time between a primary case-patient (infector) having symptom onset and a secondary case-patient (infectee) having symptom onset for COVID-19 was calculated as 3.96 (95% confidence interval [CI] 3.53–4.39) days.[9] COVID-19 illness is predominantly a respiratory disease typified by upper respiratory symptoms in mild cases and pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS) in advanced disease. Initial symptoms typically involve the upper respiratory tract with cough, sore throat and malaise. Fever is present in approximately 44-98% of cases. Notably, persons with COVID-19 often complain of loss of smell or taste.

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

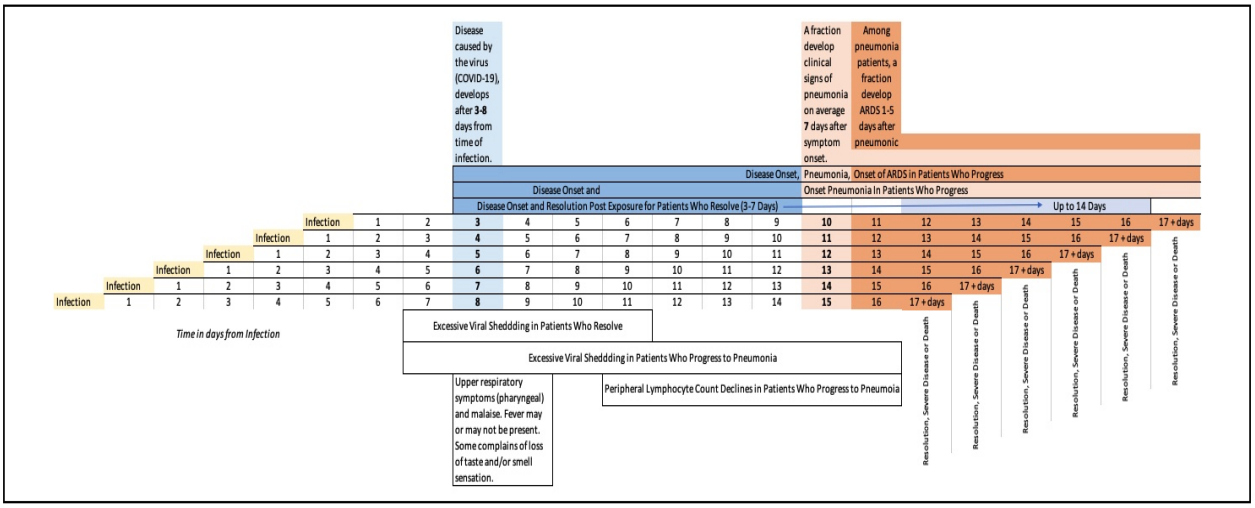
The natural history of COVID-19 as we understand it thus far is illustrated in Figure 1. In most patients (approximately 80%) symptoms resolve without the need for intervention within five to seven days of symptom onset up to a maximum of 14 days. However, approximately 20% of patients show signs of clinical disease progression, most notably pneumonia, around day 3 to 8 following symptom onset. Other manifestations of disease progression include thrombotic episodes including stroke and myocardial infarction (MI). This resembles the documented 6-8 fold excess risk of thrombosis when patients are infected with influenza.[10]

A proportion of those who progress then further deteriorate, including with the development of ARDS around 1-5 days after pneumonic symptom onset.[5,11,12,13] Acute kidney injury necessitating dialysis and failure of other organs may also occur at this severe stage of disease.

Of the nearly 1099 persons described in the Wuhan cohort, 16.0% had severe disease at presentation. 67 persons (6.1%) reached a composite primary endpoint of intensive care admission, mechanical ventilation and death; two-thirds had presented with severe disease.[8,14] As described below, outcomes for those requiring mechanical ventilation and with other manifestations of end-organ failure are poor, and approaches to prevent this late stage of the disease among those with early evidence of progression are critically needed.

In this trial, we aim to enroll patients hospitalized for medical management of COVID-19 at the onset of clinical progression but before end-organ failure has developed: the time period of their infection which is shaded light orange in Figure 1. The majority of these patients will have emerging evidence of pneumonia, but recognizing the expanding range of organs involved in clinical progression of COVID-19, neither the inclusion criteria nor primary endpoint are limited only to assessment of pneumonia and related clinical progression.

FIGURE 1. NATURAL HISTORY OF COVID-19



2.2.3 Risk Factors for Clinical Progression

Studies investigating risk factors for progression of COVID-19 and related hospital admission are currently few in the literature. Reports to date have predominately been conducted in individuals already hospitalized. These include a mix of descriptive information on the patients as well as estimates of associations between patient characteristics and disease severity. Older age has been found to be strongly related to greater severity[14,15] and poorer outcome as has the presence of conditions such as hypertension, diabetes and coronary heart disease.[12,14,16] Other risk factors identified include cigarette smoking[14,15,17] and raised body mass index (BMI).[18,19,20,21] Gender has not shown a consistent relationship with disease severity.[14,22] Specific symptoms at presentation that have notably been associated with greater likelihood of progression to more severe disease include shortness of breath and elevated body temperature.[14,23]

The COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) report on 1482 persons who were hospitalized in 14 states in the United States of America (US) in March 2020 show nearly 75% were aged over 50 years, and nearly 90% had at least one or more underlying comorbid illness.[24]

Based on 2.6 million users of the COVID Symptom Tracker App, predominantly in the United Kingdom, being older, obese, diabetic, or suffering from pre-existing lung, heart or renal disease placed participants at increased risk of visiting hospital with COVID-19.[25] Pre-existing lung disease and diabetes were consistently associated with a higher risk of requiring respiratory support.[25] A meta-analysis showed that cardiac injury as measured by a high sensitive troponin was associated with higher mortality, higher need for intensive care unit (ICU) care, and severe COVID-19 disease.[26]

2.2.4 Hospitalization of People with COVID-19

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

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

Reported mortality rates for those who develop end-organ failure requiring intensive support, including those admitted to ICU, differ widely. Amongst 1591 ICU patients from the Lombardy region in Italy, hardest hit by COVID-19, 88% required mechanical ventilation and 11% noninvasive ventilation.[27] The ICU mortality rate was 26%. Of 1043 patients with available data, 709 (68%) had at least 1 comorbidity and 509 (49%) had hypertension, 21% had cardiovascular disease. Younger patients (≤63 years) compared to older patients, had lower ICU mortality and higher rates of discharge from ICU. The median length of stay in the ICU was 9 days though 58% remained in ICU at time of report.[27] In one report of the Chinese experience in Wuhan, 31 of 32 persons who required mechanical ventilation died.[5] In the United Kingdom, of the 4078 COVID-19 patients admitted into critical care with reported outcomes, 50.7% died in ICU; those requiring advanced respiratory support and renal support had worse outcomes.[28] These data underline the importance of attenuating the disease in its early phase prior to the development of end-organ failure and the requirement of intensive care.

2.2.5 Viral Kinetics of SARS-CoV-2 Infection

Viral kinetic studies have demonstrated extensive SARS-CoV-2 viral replication in the pharynx just before and early after symptom onset.[29] Viral RNA shedding from pharynx gradually wanes as symptom resolve though viral RNA is still detectable weeks after symptom resolution.[29,30,31] Median duration of viral shedding was 20 days in survivors (longest 37 days), but SARS-CoV-2 was detectable until death in non-survivors.[6] Whether this is viable virus with the potential for continued transmission remains uncertain. RNAemia has been reported but is relatively rare.[30,32] Viral detection in sputum is higher and outlasts pharyngeal swabs in those with pneumonia.[33] Persons with asymptomatic disease clear their virus faster than symptomatic individuals.[34]

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

2.2.6 Immune Responses to SARS-CoV-2 Infection

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

Two large series have described antibody responses (IgG and IgM). In the first, samples from 82 confirmed and 58 probable cases of COVID-19 in a cross-sectional analysis demonstrated IgG detection 14 (interquartile range [IQR] 10-18) days after symptom onset, with IgM detected median of 5 days (IQR 3-6) after symptom onset. Antibodies were absent in around 22% of individuals at assessment (IgM), and IgM was most commonly absent in those assessed early (within 7 days of symptom onset)].[35] In the second study of 262 patients who provided 363 samples, antibody levels were examined by days from symptom onset. IgM antibodies were detectable in just under 40% of patients at day 5-7, rising to 50% at day 8-10, while interestingly IgG was detectable in a slightly higher proportion at those time points: just over 50% at day 5-7, rising to 60% at day 8-10.[36] This series was drawn from hospitalized patients, but the severity of illness and any relationship with disease outcomes were not described. Both studies show considerable individual variation in antibody kinetics. Further longitudinal studies are underway and will better characterize the kinetics of these responses in individuals.

SARS-CoV-2 infection may also induce significant changes in elements of the cellular immune response. As the disease process progresses, the peripheral lymphocyte count typically declines. The depletion of peripheral lymphocytes likely reflects translocation to the pulmonary tissue. The extent that this influx exclusively is helpful to the host, or possibly may contribute adversely to disease severity is currently unclear. In severe cases this decline in CD4+ and CD8+ lymphocytes is also associated with an increase in activated CD4+ and CD8+, increases in key proinflammatory cytokines including interleukin 6 (IL-6), and increases in natural killer (NK) cells.[37,38] Trials assessing the use of various immunomodulatory agents with the aim of dampening this migration and systemic inflammation are underway, and may help to clarify this.

2.2.7 Current Treatment Strategies for COVID-19

There has been no proven therapy for COVID-19, and no international standard of care has been established, though many clinical trials are underway. Approaches include direct anti-virals, including repurposed drugs found in vitro to have activity against SARS-CoV-2; immune modulators especially in patients with advanced disease, and modifiers of other pathophysiological pathways implicated in disease progression, including potentially anticoagulants and anti-platelet agents. In certain regions, local standards of care have been established, generally with agents hypothesized to have clinical activity but where robust comparative data are not yet available. For example, lopinavir, hydroxychloroquine, and favipiravir have all seen widespread use in hospitalized patients in different regions.

The most promising current antiviral agent is remdesivir, a nucleotide analogue previously studied for Ebola.[39] A preliminary report of the National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial (ACTT) showed that participants receiving remdesivir had a shorter median time to recovery compared with those receiving placebo (11 vs 15 days; p<0.001). There was a trend toward a survival benefit after 14 days; estimates of mortality were 7.1% and 11.9% (hazard ratio [HR]=0.70; 95% CI: 0.47-1.04).[40] In contrast, a smaller randomized study from China did not show a significant benefit for remdesivir in a similar hospitalized population (HR for time to clinical improvement 1.23 [95% CI 0.87–1.75]); however that trial was stopped early due to slow enrollment and power was substantially less than planned (58% instead of 80%).[41] A number of other remdesivir trials are ongoing and may clarify the extent of its therapeutic effect and other issues including optimal dosing and optimal timing of therapy.

Based on the findings of ACTT, remdesivir will be provided to all study participants as SOC unless contraindicated for an individual patient. As in ACTT, remdesivir will be administered as a 200 milligram (mg) IV loading dose following the hIVIG/placebo infusion, followed by a 100 mg once-daily IV maintenance dose while hospitalized up to a 10 day total course. Participants taking remdesivir prior to randomization will continue their daily remdesivir infusions while hospitalized up to a 10 day course.

Other chemotherapeutic agents with hypothesized direct antiviral activity undergoing clinical study include antimalarial agents, hydroxychloroquine and chloroquine, lopinavir-ritonavir (protease inhibitors) and favipiravir (an RNA-dependent RNA polymerase inhibitor). Despite some early trials that did not establish the efficacy of high-dose chloroquine[42] and lopinavir-ritonavir,[43] and uncontrolled studies showing minimal benefit and possible harm with hydroxychloroquine and azithromycin,[44] these agents along with favipiravir have been incorporated into some local institutional protocols as SOC, especially in patients hospitalized with advanced and progressive disease.

Other agents under exploration modulate pathophysiological pathways implicated in disease progression. Given the apparent role of excessive IL-6 production in patients with advanced disease, tocilizumab and other inhibitors of IL-6 and associated cytokine pathways (such as Janus kinase, JAK, inhibitors) are all under evaluation, and off-label use of tocilizumab in critical illness is common in some settings. Similarly given the apparent role of platelet dysfunction and pro-coagulant effects of SARS-CoV-2 infection, there is interest in the use of antiplatelet agents and anticoagulants especially at the onset of progressive disease.

A further promising line of approach is the use of passive immunotherapies to enhance the host immune response to SARS-CoV-2 infection, potentially enhancing viral control and limiting disease progression. Convalescent plasma, generic intravenous immunoglobulin (IVIG) and hIVIG to COVID-19 are all gaining interest. While their characteristics differ, convalescent plasma and hIVIG are examples of passive antibody therapy involving administration of antibodies against SARS-CoV-2 as prevention or therapy. High doses of standard IVIG have also been hypothesized to be useful for their immunomodulatory effects (as for example in their use in immune thrombocytopenia) and are under evaluation as described below. The concept of passive immunotherapy is based on the historical concept of serotherapy developed in the 1890s where serum from immunized animals containing an antitoxin factor that could neutralize the toxin and be transferred onward to non-immune animals offered protection.[45,46]

The most widely used of these agents at present is convalescent plasma containing COVID-19 antibodies (CCP). CCP is collected by apheresis from individuals who have recovered from COVID-19 and tested for the presence of SARS-CoV-2 antibodies, preferably with a target neutralizing antibody titer. Despite relatively widespread use, data for its efficacy in SARS-CoV-2/COVID-19 is very limited. Convalescent sera were previously evaluated in an uncontrolled study for SARS-CoV-1 illness in Hong Kong. This was shown to be more effective when given early, and in those who were polymerase chain reaction (PCR) positive and seronegative.[47] In a pilot uncontrolled study of CCP in China, one dose of 200 milliliters (mL) of CCP with neutralizing antibody titers ≥ 1:640 dilution was used in 10 patients with severe COVID-19.[48] This was shown to be safe and showed a possible improvement in clinical outcomes. Another study in New York reported that 39 patients given convalescent plasma had improvements in supplemental oxygen requirements and survival compared to retrospectively matched controls.[49] An initial report of the first 5,000 hospitalized patients with COVID-19 given convalescent plasma through an expanded access program in the US reported that SAEs within 4 hours of infusion occurred in less than 1% of patients.[50] This study was not controlled.

2.2.8 Hyperimmune Intravenous Immunoglobulin (hIVIG)

Anti-Coronavirus Hyperimmune IVIG contains polyvalent antibodies with neutralizing specificity for SARS-CoV-2. It has the potential to provide a standardized therapy to augment host immunity to SARS-CoV-2 and prevent disease progression in symptomatic patients. Hyperimmune IVIG differs from standard IVIG in its derivation from donors who have mounted an immune response to the infection of interest (natural infection as undertaken in this protocol, or following vaccination for other disease states), and its standardization as a product based on neutralizing antibody titers or similar assays demonstrating its activity against the infection of interest. Hyperimmune globulin requires plasma from otherwise healthy individuals in the convalescent phase of the infection, and it is clear that there will be many individuals fitting this criterion with most patients recovering from COVID-19 and therefore able to safely provide a plasma donation during convalescence. Therefore, this resource will be rapidly available and will serve as an accessible therapeutic modality across multiple jurisdictions globally.

In other respects, hyperimmune and standard IVIG have similarities in their production, constituents, and safety profiles. Production of IVIG requires care when selecting donors, optimum screening of collected products for known infective agents, use of virus inactivation methods like fractionation, and physical and chemical treatment including solvent detergent treatment and caprylation (a short-chain saturated fatty acid which results in a product enriched for IgG) and nanofiltration.[45] Stabilizers currently used in IVIG are nonessential amino acids like glycine and L-proline unlike previous sucrose-containing preparations which could predispose to acute renal failure.

Standard IVIG is by far the more widely used product compared with the various hyperimmune globulins, and contributes considerably to our understanding of the safety and administration of hyperimmune IVIG. Standard IVIG became a commercially available product in the early 1980s and remains an important therapeutic agent in those with primary immunodeficiencies, where it replaces absent or deficient immunoglobulins, and in immune thrombocytopenia and other autoimmune conditions, where it acts as an immunomodulator.[45] Collected from large pools of human plasma, polyvalent and highly diverse monomeric IgG is the key product constituent. Very low levels of other plasma constituents such as other immunoglobulins including IgA and IgM and possibly IgE, solubilized membrane components, complement proteins, coagulation factors, and possibly other solubilized receptors, as well as specific antibodies to human leukocyte antigen (HLA) determinants and lymphocyte surface molecules are also present, and in some circumstances may contribute to its mechanism of action.[51]

Standard IVIG is currently being studied as a therapy for COVID-19 illness in small trials, primarily as an immunomodulatory agent. For this purpose, it is given at

relatively high doses (in the range of 2 grams (g) per kilogram (kg) divided over 4 to 5 days). Ongoing trials include NCT04261426, NCT04350580, and NCT04264858. Some efficacy for standard IVIG has also been reported in a retrospective comparison[52] and a small case series.[53]

Hyperimmune globulin preparations have been described to have therapeutic utility in varicella zoster, cytomegalovirus (CMV) pneumonitis,[54] parvovirus induced red cell aplasia,[55] and respiratory syncytial virus (RSV) infection[56] in patients with underlying impairments of immunity. In addition, hyperimmune globulins for hepatitis A,[57] hepatitis B,[58] and rabies[59] have proven prophylactic efficacy and their use is recommended in clinical guidelines. The potential utility of this approach has also been explored in severe respiratory infections caused by other pathogens including influenza[60] and severe acute respiratory syndrome (SARS).[61,62,63] However, the evidence for efficacy of hyperimmune globulin in SARS infection is limited because in that disease outbreak, its use was assessed only in small, poorly controlled clinical studies.[64]

While there are some mechanistic similarities between hIVIG and convalescent plasma,[65] individual doses of convalescent plasma are inherently variable from unit to unit. Unlike hIVIG, convalescent plasma cannot be standardized as a therapeutic product at the required scale. In contrast to convalescent plasma where generally, a single unit of plasma obtained from a single ABO compatible donor is used, hIVIG is a highly purified preparation containing high titers of neutralizing antibodies pooled from multiple donors, and would be safer and have higher activity than CCP. Regulatory compliance and availability of assays to detect SARS-CoV-2 in serum and virologic assays to measure viral neutralization are critical.

2.2.9 Study Treatments

Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin (hIVIG)

Anti-Coronavirus hIVIG is a human hyperimmune product of the purified gamma globulin (IgG) fraction of human plasma containing polyvalent neutralizing antibodies to SARS-CoV-2. hIVIG is prepared from pooled plasma collected from healthy, adult donors who have recovered from SARS-CoV-2 infection.

Multiple hIVIG products will be used in this trial. These hIVIG products are described below. Each hIVIG is labelled with the following name: “Anti-COVID-19 Hyperimmune Globulin (Human)”. An aliquot from each lot of hIVIG prepared for this trial will also be tested centrally at the NIAID Integrated Research Facility at Fort Detrick, Maryland. This batched central testing will not form part of the release criteria for hIVIG lots. The test results for each lot will be used in efficacy subgroup analyses by lot.

Emergent BioSolutions

Emergent BioSolutions' Anti-Coronavirus disease hIVIG, is a liquid product containing approximately 100 mg/mL (10g%) protein of which at least 96% is purified human IgG, stabilized with 250 millimoles (mmol) proline and 0.03% PS80 at pH 5.8. The vialed product will be clear to slightly opalescent, and colorless or pale-yellow liquid, essentially free of foreign particles.

The manufacturing process for SARS-CoV-2 hIVIG contains two steps implemented specifically for virus clearance. The solvent and detergent step (using TnBP and TX-100, respectively) is effective in the inactivation of enveloped viruses such as HBV, HCV, and HIV. Virus filtration, using a Planova™ 20N virus filter, is effective for the removal of viruses based on their size, including some non-enveloped viruses. These two viral clearance steps are designed to increase product safety by reducing the risk of transmission of enveloped and non-enveloped viruses. In addition to these two specific steps, the process of anion exchange chromatography was identified as contributing to the overall viral clearance capacity for small non-lipid enveloped viruses.

Grifols Therapeutics, Inc.

Grifols Therapeutics' Anti-Coronavirus hIVIG is a ready-to-use sterile, preservative-, pyrogen-, and latex-free solution of human immune globulin for IV administration. The drug product consists of approximately 100 mg/mL (9.0 to 11.0%) protein in 0.16 to 0.24 M glycine. The pH of the drug product is 4.0 to 4.5 and the osmolality is close to the physiologic range. The protein composition consists of not less than 98% purified IgG. The product is clear to opalescent and colorless to pale yellow liquid.

The purification process used to manufacture hIVIG includes multiple segments with virus clearance capacity, such as caprylate-induced precipitation followed by filtration, caprylate incubation, ion-exchange chromatography, 35 nanometers (nm) nanofiltration, and low pH incubation. The capacity of these manufacturing segments to inactivate and/or remove virus was assessed via laboratory experiments in which a test virus was spiked into starting material that was then processed comparably to the commercial scale by means of a small-scale model, and the processed material was assayed for residual viral infectivity. The purification process demonstrated a large overall virus clearance capacity for enveloped and non-enveloped viruses of diverse physico-chemical properties, providing a very high margin of safety from the risk of transmission of infectious viruses.

Takeda Pharmaceuticals

Takeda's anti-COVID-19 Hyperimmune Globulin (Human) is a ready-for-use sterile, liquid preparation of highly purified and concentrated IgG antibodies. The product

contains 100 mg/mL protein of which at least 98% is IgG; average IgA concentration is 37 micrograms (µg)/mL and IgM is present in trace amounts. Glycine (0.25 M) serves as a stabilizing and buffering agent. There is no added sugar, sodium, or preservatives. The pH is 4.6 to 5.1; the osmolality is 240 to 300 mOsmol/kg. Only clear or slightly opalescent and pale yellow solutions may be administered. Vials found to contain particles or discoloration must not be used.

The manufacturing process for anti-COVID-19 Hyperimmune Globulin (Human) contains three dedicated virus clearance steps, i.e., S/D treatment,[66,67] nanofiltration (35 nm),[68,69] and low pH incubation at elevated temperature.[70,71] Viral safety studies used virus models and target viruses to evaluate the clearance of lipid enveloped and nonenveloped deoxyribonucleic acid (DNA) and RNA viruses by the manufacturing steps specific for viral reduction. These studies demonstrated that the 3 dedicated virus inactivation/removal steps provide effective and robust clearance of HIV, West Nile virus (WNV), hepatitis A virus (HAV), parvovirus B19 (B19V), as well as of model viruses for HCV, HBV, HAV, and B19V.

CSL Behring

Anti-COVID-19 hyperimmune globulin comes as a ready-for-use sterile, 10% protein liquid preparation in single-use vials. It contains 100 mg/mL protein stabilized with 250 mmol/L L-proline. Anti-COVID-19 hyperimmune globulin has an osmolality of 320 mOsmol/kg (range: 240 to 440 mOsmol/kg) and a pH of 4.8 (range: 4.6 to 5.0), with an IgG purity ≥ 98%. The vialed solution is clear or slightly opalescent and colorless to pale yellow.

Production of Anti-COVID-19 hyperimmune globulin requires sourcing plasma from convalescent donors collected at qualified plasma collection centers, optimum screening of collected products for known infective agents, and use of virus reduction methods like low pH incubation, clarifying depth filtration, and 20 nm nanofiltration, which demonstrated a large overall virus clearance capacity for enveloped and non-enveloped viruses of diverse physico-chemical properties. Stabilizers currently used in IVIG are nonessential amino acids like L-proline unlike sucrose-containing preparations which could predispose to acute renal failure.

Placebo

Participants assigned to the placebo group for hIVIG will be given infusions of a commercially available isotonic saline solution. There are color differences between the infusion preparations for hIVIG and placebo. Therefore, site pharmacists will be instructed to place a colored sleeve or other suitable covering over all infusion bags to mask the color of the contents and reduce the risk of unblinding. The volume used for hIVIG and for placebo will be comparable.

3 RISK/BENEFIT ASSESSMENT

3.1 Known Potential Risks

Potential risks of participating in this trial are those associated with having blood drawn, IV catheterization, possible reactions to hIVIG infusions, thrombosis, the volume of fluid infused, and breach of confidentiality. These risks are discussed below.

3.1.1 Blood Draw 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 Study Treatments

The hIVIG used in this study is manufactured in the same manner and to the same standards as commercially available IVIG. This includes screening for blood borne pathogens, and manufacturing steps including solvent/detergent to inactivate any viruses. The risks are anticipated to be the risks of standard IVIG preparations. Specific considerations related to the use of hIVIG in COVID-19, including thrombosis and the theoretical risk of antibody-dependent enhancement, are summarized at the conclusion of this section.

As IVIG is made from human plasma, transmittable viral infections like hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) are a potential risk (though steps are taken to screen for and inactivate such pathogens). In addition, there is a theoretical risk, although deemed very low, that hIVIG administration may be capable of transmitting other known or unknown infectious agents other than viruses, such as infectious prions (e.g., the agent of Creutzfeldt-Jakob disease).

Immune globulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella.

The safety of human IV immunoglobulins is well established. As described in the Investigational Brochures (IBs), a number of adverse events have been associated with the use of IVIG in both children and adults. In the range of 1 to 15%, usually less than 5%, of recipients experience some type of reaction, with the severity ranging from mild to severe. Most reactions occur during the initial 30 to 60 minutes of the infusion and are mild and self-limited.

Pyrogenic Reactions

- These reactions are marked by a significant rise in temperature and are usually accompanied by systemic symptoms.

Allergic Reactions

- Allergic reactions often present with an uncomfortable feeling, especially a tightening around the neck, chest, or abdomen. There may be difficulty swallowing, a choking sensation, or difficulty breathing. Other symptoms of anaphylaxis include wheezing, rash, hives, rapid or weak pulse, hypotension, sweating, or an upset stomach with or without nausea, vomiting or diarrhea. Other more serious allergic reactions are rare, and include hemolysis and aseptic meningitis.

Vasomotor Symptoms

- These can occur with or without additional cardiac manifestations.
- Blood pressure can either increase or decrease, and may be accompanied by flushing or tachycardia.
- Patients experiencing such reactions may report shortness of breath or tightness in the chest.

Non-allergic Systemic (Anaphylactoid) Reactions

- These reactions most commonly include headache, dizziness, or lightheadedness.
- Patients can also experience chills, nausea, vomiting, back or hip pain, malaise, myalgia and arthralgias.
- Rigors are a rare infusion reaction that is an extreme form of chills that affects the whole body with vigorous shaking.
- The most frequent cause of such reactions is infusion at an excessively rapid rate.
- These types of reactions are more common in a patient naïve to IgG treatment and/or who harbor chronic infection. These reactions may be marked by flushing and warmth of the skin, chills, headache, dizziness, nausea, vomiting, and muscle aches.
- Frequently the patient reports anxiety and in some cases, “a sense of impending doom.” Often, the patient will have elevated blood pressure rather than hypotension, distinguishing this type of reaction from true anaphylaxis.

Post-infusion Reactions

- These reactions can occur immediately or up to 48 to 72 hours following the infusion.
- Symptoms associated with post-infusion reactions are usually less severe in nature, but can interfere with a patient's quality of life.
- Common post-infusion reactions may include headache, low-grade fever, nausea, arthralgias, and generalized malaise.

Other Reactions

- Renal dysfunction, acute renal failure, and osmotic nephropathy may occur with immune globulin intravenous products in predisposed patients. Renal dysfunction and acute failure occur more commonly in patients receiving IVIG products containing sucrose. The hIVIG products in this study do not contain sucrose.
- Transfusion-related acute lung injury (TRALI), although very rare, may occur and is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever.
- The infused volumes of study product may be as high as 200 mL, so there is the risk of volume overload in the recipient which could cause pulmonary edema. Transfusion-associated circulatory overload (TACO) has been associated with plasma infusion and may be clinically indistinguishable from TRALI even though the physiologic mechanisms differ. TACO is hydrostatic, not permeability, edema and more responsive to diuresis when it occurs. Patients with pre-existing conditions who may not tolerate the volume of hIVIG/placebo to be given will be excluded from this study, but this condition could still occur in recipients.
- There are case reports of pulmonary emboli occurring after administration of IVIG and plasma therapy, though definitive studies assessing risk are lacking.[72] Pulmonary emboli have been shown to develop in approximately 10-15% of critically ill adults.[73] Other thrombotic events, including myocardial infarction, cerebral vascular accident, and deep vein thrombosis may also occur.

Specific Considerations in COVID-19

There is potentially a slight elevation in the risk of thrombosis with standard IVIG therapy, and in some cases COVID-19 is associated with thrombotic complications. Hence participants with pre-existing prothrombotic tendencies will not be included and any thrombotic events will form part of the primary endpoint assessment and be monitored during interim safety analyses by the DSMB.

There is a theoretical risk the antibody infusion may worsen the disease course of COVID-19 via antigen-dependent enhancement (ADE). It is unclear if this phenomenon is relevant and clinically significant in COVID-19, but to ensure detection of any such phenomenon (which could be manifested by disease progression soon after hIVIG infusion) close monitoring of clinical disease outcomes will be maintained in the randomized groups, including in the days prior to the primary endpoint assessment at Day 7.

3.1.3 Confidentiality and Privacy

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

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

Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publication from this trial will not use information that will identify study participants. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the IRB, NIAID and applicable regulatory agencies (e.g. US Food and Drug Administration [FDA]).

3.2 Known Potential Benefits

While the trial is conducted to test the hypothesis that hIVIG will reduce the risk of further disease progression, hIVIG may or may not prevent this outcome in any individual who participates in this trial. However, there is benefit to society from their participation in this trial resulting from insights gained about the therapeutic agent under study as well as the natural history of the disease. While there may not be benefits for an individual, there will be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

4 OBJECTIVES AND ENDPOINTS

4.1 Primary Objectives and Primary Endpoint

The primary objective is to compare the clinical status of participants in the hIVIG + SOC and placebo + SOC groups on Day 7 using an ordinal outcome with 7 mutually

exclusive categories. On Day 7, the worst of the 7 categories the participant was in that day will constitute the primary outcome. The 7 categories are:

7. Death

6. End-organ failure

5. Life-threatening end-organ dysfunction

4. Serious end-organ dysfunction

3. Moderate end-organ dysfunction

2. Limiting symptoms due to COVID-19

1. No limiting symptoms due to COVID-19

Appendix F provides clinical definitions of each category. In addition to the overall summary odds ratio (OR) that will be estimated as described in Section 11.1, ORs will be estimated for the 6 dichotomized definitions of improvement that can be formulated from the categories of the ordinal outcome.

4.1.1 Rationale for Primary Endpoint at Day 7

The goals of this study are to assess the safety, tolerability and efficacy of a single infusion of hIVIG in preventing further progression and mortality related to COVID-19 when administered at the onset of clinical progression, with the aim of improving the long term outcome of the disease process. There is as yet no consensus on the optimal endpoint for determining clinical benefit from COVID-19 therapies, including the constituent elements of the endpoint and the timing of its assessment after randomization. Both may differ depending on the target population and the nature of the treatment studied.

The primary ordinal outcome captures the range of severity experienced by hospitalized patients with COVID 19, recognizing that end-organ manifestations in addition to pneumonia and ARDS are increasingly emerging as significant contributors to morbidity. The ordinal outcome includes 7 well-defined mutually exclusive categories that assess further progression of disease as well as recovery from COVID-19.

The ordinal outcome includes both pulmonary manifestations as assessed in prior COVID-19 trials and additional components representing key non-pulmonary outcomes; the latter are highlighted as *“extra-pulmonary”* in the guidance table (Appendix F). The primary endpoint will include both pulmonary and extra-pulmonary components, while the pulmonary manifestation scale only will be reported as a secondary endpoint.

Day 7 was chosen for the timing of the primary endpoint for several reasons based on the following assumptions. The impact of hIVIG on disease progression may not

be immediate; a few days may be needed to see the effects on clinical outcomes as measured by the ordinal outcome. Also, transient treatment effects that are no longer present at Day 7 may be clinically less relevant. Assessment of the ordinal outcome at a later time point may result in a diminished treatment difference because spontaneous recovery from COVID-19 may have begun in many participants. Also, antibody differences between the treatment groups, an important biologic mechanism for observing a clinical benefit, are assumed to be greatest during the first week after infusion.

Lastly, use of Day 7 to characterize the clinical severity of participants in 7 categories as studied here, results in a distribution of participants in the placebo group for the ordinal outcome that is sufficiently granular and not overly skewed to the most severe or least severe categories and, therefore, provides good power for comparing the two treatment groups with a feasible sample size given the difficulty in producing large quantities of hIVIG (see Section 5.5).

4.2 Secondary Objectives

Secondary objectives will be assessed by comparing hIVIG + SOC with placebo + SOC over the 28 day follow-up period for outcomes listed below. Because there is no established endpoint for evaluating the clinical efficacy of treatments for COVID-19, other clinically relevant outcomes, including outcomes used in other COVID-19 treatment trials, will be recorded. Thus, the randomized groups can be compared for multiple outcomes, and results can be compared or combined with other trials. Many of the endpoints used in other trials are ordinal outcomes or are defined based on a dichotomy of an ordinal outcome and assessed at a single follow-up time point or as a time-to-event outcome.

1. All-cause mortality through Day 28.

2. The primary ordinal outcome on Days 3, 5, 14 and 28.

3. Change in National Early Warning Score (NEWS) (see Appendix G) from baseline at Day 3.

4. Time to the 3 least favorable categories of the primary outcome measure.

5. Time to the 2 most favorable categories of the primary outcome measure.

6. Hospitalization status (a binary outcome, alive and discharged from the hospital to home or rehabilitation versus dead or hospitalized) at Days 7, 14 and 28.

7. Time to discharge (this is similar to the recovery outcome used in the ACTT-1 trial[40])

8. Days alive outside of a hospital through Day 28

9. Pulmonary only components of the primary outcome measure at Days 3, 5, 7, 14 and 28

10. Thrombotic components of the primary outcome measure (stroke, myocardial infarction, venous and arterial thrombosis or embolism, plus disseminated intravascular coagulation) at Days 3, 5, 7, 14, and 28.

11. Outcomes assessed in other treatment trials of COVID-19 for hospitalized participants in order to facilitate cross trial comparisons and overviews, e.g., 6-, 7- and 8- category ordinal scales at days 7, 14 and 28; and binary outcomes defined by improvement or worsening based on the primary ordinal outcome and ordinal outcomes used in other trials.

12. Clinical organ dysfunction defined by *new onset* of any one or more of the following conditions (or requirement for the following therapies) through Day 28:
    a. Respiratory:
        1. Extracorporeal membrane oxygenation (ECMO)
        2. Invasive ventilation
        3. Non-invasive ventilation or high flow oxygen
    b. Cardiac and vascular:
        1. Myocardial infarction
        2. Myocarditis or pericarditis
        3. NYHA Class III/IV congestive cardiac failure
        4. Vasopressor therapy
    c. Renal:
        1. Renal replacement therapy (dialysis)
    d. Hepatic:
        1. Hepatic decompensation
    e. Neurological
        1. Cerebrovascular event (stroke)
        2. Encephalitis, meningitis or myelitis
        3. Acute delirium
    f. Hematological:
        1. Disseminated intravascular coagulation
        2. New thrombotic events, including pulmonary embolism, deep venous thrombosis, or arterial thrombosis
    g. Infective:
        1. Microbiologically-proven severe infection (not including SARS-CoV-2)

13. Safety and tolerability will be assessed using outcomes described above (e.g., mortality and thrombotic outcomes) and also assessed by the following outcomes:

a. A composite of incident grade 3 and 4 events (not limited to a laboratory abnormality), SAEs (see Section10.1.2), or death through Day 7 (primary safety endpoint)
b. Infusion reactions of any grade severity during the infusion and 2 hours post-infusion, and percentage of participants for whom the infusion was interrupted or stopped prior to completion
c. SAEs or deaths through Day 28
d. Prevalence of adverse events of any grade on Days 1, 3, 7 and 28.

14. Change in immunoglobulin levels (IgG, IgG subclasses, IgM, IgA) and neutralizing antibody titers from baseline to Days 1, 2, 3, 7, 28 and 90.

15. The primary endpoint by duration of symptoms at study entry. This is a key subgroup analysis. For those with shorter duration of time since symptom onset, the treatment effect is hypothesized to be greater than among participants who have had symptoms for a longer period of time. This hypothesis assumes that disease progression among those with longer duration of symptoms at study entry will be primarily determined by organ damage that has already occurred instead of ongoing viral replication. In addition, it is assumed that the natural antibody response to SARS-CoV-2 infection is likely to be greater at entry for those with longer symptom duration, and this would diminish the treatment difference between the hIVIG and placebo groups over the week following infusion. Given the inclusion criteria of ≤ 12 days, we anticipate the upper quartile will be 8-10 days (75% of participants will have symptom duration < 8 to 10 days). In ACCT-1, a more severely ill target population than studied here, there was no limit to the duration of symptoms and the median was 9 days (interquartile range, 6 to 12).[40] The quartile definitions for duration of symptoms will be determined following the completion of enrollment, and will be stated in the data analysis plan.

16. The primary endpoint for other subgroups defined by the characteristics measured at baseline will also be assessed:
    - Age
    - Biological sex
    - Race/ethnicity
    - BMI
    - Presence of selected chronic medical conditions (cardiovascular disease, diabetes, asthma, chronic obstructive pulmonary disease, hypertension, cancer)
    - Geographic location
    - hIVIG product administered
    - hIVIG lot potency of administered product
    - Upper respiratory SARS-CoV-2 viral load
    - Neutralizing antibody level

- Oxygen saturation level
- Dyspnea severity
- Organ/respiratory dysfunction category based on ordinal primary outcome
- NEWS
- Disease progression risk score (defined using pooled treatment groups with the following baseline predictors of the day 7 ordinal outcome: age, gender, duration of symptoms, oxygen saturation level, ordinal outcome category at entry, NEWS, and chronic health conditions).

5 STUDY DESIGN

5.1 Overall Study Design

This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of hIVIG in consenting hospitalized patients with COVID-19 who have had COVID-19 symptoms ≤ 12 days, and who do not have life-threatening organ dysfunction or organ failure. Remdesivir will be provided to participants in both the hIVIG and placebo groups as SOC unless contraindicated for an individual participant.

Participants may co-enroll in INSIGHT observational studies (e.g. INSIGHT 004 Genomics, FLU-003+) or have been previously enrolled in such studies prior to hospitalization (e.g. ICOS).

5.2 Randomization

Randomization will be stratified by site pharmacy (clinical sites may share a pharmacy). Participants will be randomized in a 1:1 ratio to receive a single infusion of hIVIG or placebo.

Hyperimmune IVIG will be manufactured by multiple groups and the specific hIVIG distributed to each site will be determined in a way that considers factors discussed in Section 5.4.

Within each stratum permuted block randomization will be used to generate treatment assignments.

5.3 Blinding

Hyperimmune IVIG or placebo will be prepared by a pharmacist who is unblinded to the treatment assignment.

Blinding of the participant and clinical staff will be achieved by placing a colored sleeve over the infusion bags used for hIVIG and placebo. Placebo will consist of normal saline.

In the event that the blind is broken for safety reasons, this will be recorded, and the protocol co-chair(s) will be notified. In that situation, every attempt will be made to minimize the number of people unblinded.

5.4 Distribution of Anti-Coronavirus hIVIG to Clinical Sites

It is critical to establish whether Anti-Coronavirus hIVIG is safe and effective as rapidly as possible. To accomplish this, hIVIG will be manufactured for use in this trial by 3 different groups. Four hIVIG products, two produced by an Alliance of several companies including Takeda Pharmaceuticals and CSL Behring, and one each produced by Emergent BioSolutions and Grifols Shared Services North America, Inc., will be used. No single group can prepare sufficient quantity of hIVIG product to rapidly complete this trial. Thus, for practical reasons, the primary analysis (see Section 11.1) which compares the hIVIG and placebo groups on Day 7 for the primary ordinal endpoint will pool the outcome results for the 4 different hIVIG products and matching placebos.

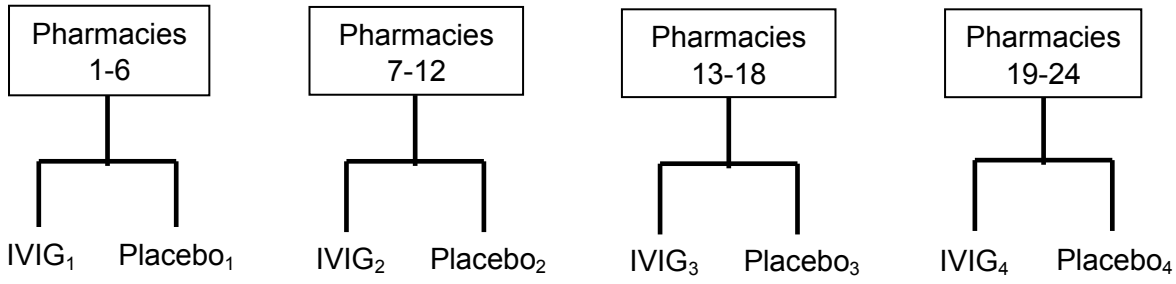
To simplify logistics related to the supply of hIVIG to clinical sites and to take advantage of the randomization, which is stratified by site pharmacy, the same hIVIG product will be provided to a given site pharmacy for the duration of the trial to the extent possible. This is illustrated in Figure 2 with an example that assumes that there are 24 site pharmacies and the supply of each of hIVIG products will be the same.

The site pharmacy allocation of hIVIG will take into account estimates of the number of participant doses each manufacturer will provide and estimates of the number of participants to be enrolled by sites using each site pharmacy (i.e., it may not be an equal number of site pharmacies or participants for each hIVIG product).

It is likely that the hIVIG provided by each manufacturer will be from more than one lot during the study. For each individual participant, all hIVIG vials used will come from the same lot. This plan for distributing the hIVIG will simplify the tracking of lots used by each site pharmacy. This plan also simplifies the pharmacy plans prepared for each site pharmacy.

More generally, with this plan, one can consider this as parallel multi-center trials of different hIVIG products for which planned analyses that compare the hIVIG and placebo groups for primary and secondary outcomes will be pooled across the hIVIG products used. With such a plan, depending on the number of doses of each hIVIG product provided, there may be adequate power to compare each hIVIG product with matching placebo for some outcomes other than the primary efficacy outcome, including potentially change in anti-SARS-CoV-2 IgG levels from baseline (Day 0), safety outcomes, such as AEs and infusion interruptions, and selected secondary efficacy outcomes.

FIGURE 2. EXAMPLE OF ALLOCATION OF HIVIG TO 24 SITE PHARMACIES



5.5 Sample Size Assumptions

5.5.1 Primary Analysis

The planned sample size for the trial is 500 participants (250 in each group). The following assumptions were made in estimating the required sample size.

a. The primary analysis will be intention to treat.
b. A proportional odds model with indicators for the six cut-offs corresponding to using any of categories 1 to 6 as cut-offs for determining clinical improvement, treatment group (hIVIG versus placebo), baseline severity of illness as defined by the ordinal outcome, two-way interactions between baseline severity of illness and the six cut-offs, hIVIG product/matching placebo used, and two-way interactions between hIVIG product/matching placebo used and the six cut-offs will be used to estimate the OR.
c. Type 1 error = 0.05 (2-sided) and power = 0.80.
d. The clinical status (% distribution) of participants in the placebo group at Day 7 is assumed as shown in the 3rd column in Table 1. Since both randomized treatment groups will receive remdesivir as SOC (unless contraindicated), these percentages were estimated using Day 7 data from the ACTT-1 trial for a subgroup of patients similar to ours (the subgroup of participants who entered ACTT-1 in categories 4+5 of their 8-category ordinal outcome for disease severity and were randomized to the remdesivir group).
e. We assumed an OR (hIVIG/placebo) of 1.61 for a more favorable outcome. This corresponds to the % distribution of the clinical status of participants in the hIVIG group at Day 7 shown in the 2nd column in Table 1 below. For example, the percentage of participants in the 2 most favorable categories would be increased to 65.4% in the hIVIG group from 54.0% in the placebo group (an 11.4% increase from the placebo group). Conversely, the percentage of participants in the 4 most severe categories would decrease to 19.4% from 28.1% in the placebo group. The same proportional improvement was assumed across the ordinal scale.
f. Sample size depends on a number of assumptions, including the hypothesized odds ratio, the number of categories in the ordinal outcome, and the distribution of responses for the placebo group.[74] Hypothesized odds ratios closer to 1.0 correspond to a smaller treatment effect, and require a larger sample size to

maintain 80% power. The final sample size was chosen after consideration of a range of odds ratios and of category percentages for the placebo group.

g. Based on the category percentages in Table 1, the estimated sample size is 494. This was increased to 500 to allow for a small number of participants who may be randomized but not receive the study infusion or be lost to follow-up.

We are planning a *blinded* sample size re-estimation using pooled data (both the hIVIG and placebo groups combined) for the primary endpoint that will be made after approximately 150 participants have completed the Day 7 follow-up assessment. The goal of the re-estimation is to retain 80% power to detect the hypothesized summary odds ratio of 1.61. The re-estimation will use the observed (pooled) distribution of the ordinal outcome at day 7, pooled across study arms.

TABLE 1. HYPOTHESIZED PERCENTAGE OF PARTICIPANTS IN EACH CATEGORY ON DAY 7 IN THE HIVIG AND PLACEBO GROUPS BASED ON AFOREMENTIONED ASSUMPTIONS

Category	hIVIG + SOC Group	Placebo + SOC Group
7. Death	0.6	1.0
6. End-organ failure	4.0	6.3
5. Life-threatening end-organ dysfunction	4.2	6.3
4. Serious end-organ dysfunction	10.6	14.5
3. Moderate end-organ dysfunction.	15.1	17.9
2. Limiting symptoms due to COVID-19	57.6	49.0
1. No limiting symptoms due to COVID-19	7.8	5.0
Total	100.0	100.0

5.5.2 Key subgroup analysis

For the key subgroup defined according to duration of symptoms at entry, 375 participants will be in the lower 3 quartiles. Assuming the category percentages in Table 1, with 375 participants, an OR of a more favorable outcome on hIVIG compared to placebo of 1.61 can be detected with 70% power. For this subgroup, an OR of 1.73 can be detected with 80% power and type 1 error = 0.05 (2-sided).

5.5.3 Key secondary outcomes

The study is not powered to detect treatment differences in mortality, because the mortality is expected to be low given the eligibility criteria.

The following outcomes are defined as key secondary outcomes:

Composite of death, end-organ failure, or life-threatening end-organ dysfunction (categories 5-7 of the ordinal outcome) at Day 7: This composite outcome comprises the most severe three categories of the ordinal outcome. Decreasing the probability that a participant enters one of these disease states and remains there through Day 7, has high clinical significance. Comparing the hIVIG+SOC versus the placebo+SOC groups for the proportion of participants in the three worst categories on Day 7, a total sample size of 500 participants is sufficient to detect a decrease to 6.1% in the hIVIG group compared with 13.6% in the placebo group (difference 7.5%, OR=2.4) with 80% power, under the following assumptions:

a. The analysis will be intention to treat.
b. Type 1 error = 0.05 (2-sided) and power = 0.80.
c. The proportion of participants who are in categories 5-7 of the ordinal outcome on Day 7 in the placebo + SOC group is 13.6% (Table 1). In the ACTT-1 study, the proportion was 10.8%, among participants in baseline categories 4+5 of the ACTT-1 ordinal outcome who were randomized to the remdesivir group (confidential data, personal communication).

A decrease from 13.6% to 8% (OR 1.8) could be detected with power of 47%.

Time to discharge from hospital, time to the 2 most favorable categories of the primary ordinal outcome: We expect that by Day 28, almost all participants will be discharged from the hospital. Similarly, we expect most participants will be in in one of the 2 most favorable categories of the primary ordinal outcome by Day 28. In the ACTT-1 trial, in the subset of participants who entered the trial with disease severity similar to our eligibility criteria (ACTT-1 ordinal outcome categories 4+5), 94.7% had been discharged from the hospital by Day 28. This percentage was similar for the ACTT-1 definition of “recovery” that include a small percentage of participants who were hospitalized but no longer requiring medical care. Comparing the hIVIG versus placebo groups for time to hospital discharge, our study is powered to detect a relative rate ratio (RRR) of 1.3 with 80% power and a significance level of 0.05. The power calculations assume that the RRR is approximately constant to Day 28, the overall cumulative percentage discharged (pooled across treatment groups) by Day 28 is 94% and that between 2.5 and 3% withdraw consent or are lost to follow-up by Day 28. We assume power is similar for time to the 2 most favorable outcomes of the primary ordinal outcome.

Hospitalization status: Comparing the hIVIG versus the placebo+SOC groups for the hospitalization status (a binary outcome, alive and discharged from the hospital to home or rehabilitation versus dead or hospitalized) on Day 7, the total sample size of 500 participants is sufficient to detect an increase in the proportion discharged to

58% in the hIVIG group from 45% in the placebo group (OR=1.7), with 80% power. Similarly, the study has 80% power to detect an increase to 81% in the hIVIG group compared with 70% in the placebo group (OR=1.85) at Day 14. Corresponding estimates from the ACTT-1 trial were 51% discharged on Day 7, and 77% on Day 14, for participants that were similar to ours and randomized to the remdesivir arm (confidential data; personal communication). Our hypothesized percentages are slightly lower, because our eligibility criteria allow for use of high-flow oxygen, in addition to the ACTT-1 ordinal categories 4+5. Power calculations assume that the treatment groups are compared by intent-to-treat.

5.6 Schedule of Assessments

Participants will be randomized and given their infusion of study drug/placebo on Day 0, in addition to standard of care therapy. All participants will be followed through 28 days. Consenting participants at selected sites will return for a visit 90 days after randomization to obtain a blood draw; this subset will comprise all participants at selected sites where return for a later visit is practical for participants. While in the hospital, evaluations will be made each day (Appendix B). SAEs and deaths should be immediately reported. Participants who are discharged will be asked to return to the site at Day 1, 2, 3, 7 and Day 28 (if already discharged) for a blood draw and health status assessment. Additional visits after discharge at Days 5 and 14 can be completed by telephone contact.

5.7 Approach to Intercurrent Therapies and Clinical Trial Co-enrollment

In general, the study will take a pragmatic approach to the use of intercurrent, concomitant medications. With the exception of convalescent plasma or IVIG (hyperimmune or standard, other than study drug) which is not permitted prior to entry or through Day 7, there are few restrictions.

Participants will be asked at screening to agree to refrain from participation in other clinical trials until after the assessment of the primary endpoint (Day 7). However, it is recognised that, in the case of progression to life-threatening disease and end-organ failure (broadly categories 5 and 6 of the outcome measure) there will be considerable clinical concern, and participation in an additional clinical trial at that time will not be restricted.

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

The planned analyses are by intention to treat. All participants will be compared at Day 7 irrespective of use of concomitant treatments. Concomitant treatments at baseline and Day 7 will be recorded. The study randomization and site stratification will balance the use of concomitant medications on average at baseline and these will be summarized with other baseline characteristics. Follow-up use of concomitant

treatments may differ by treatment group reflecting different efficacy/safety of the study treatments. Use of concomitant treatments will be summarized at Day 7 by treatment group.

6 SCIENTIFIC RATIONALE FOR THE STUDY

The clinical course of SARS-CoV-2-infected individuals tends to diverge around day 3 to 8, with a fraction of patients showing progression (most notably pneumonia) while others recover. A proportion of those progressing then further progress to end-organ failure, including respiratory failure, and in some cases death. Humoral immunity to SARS-CoV-2 is not yet well understood, and may be variable or delayed in some individuals (including potentially those progressing). Augmentation of the antibody response using passive immunotherapy with hIVIG to SARS-CoV-2 around the onset of clinical progression but before end-organ failure has developed may reduce the subsequent risk of further disease progression and death.

7 STUDY POPULATION

The total sample size is projected to be 500 adults ≥18 years of age with COVID-19 and who meet all eligibility criteria. These participants will be enrolled at clinical trial sites globally. Each site pharmacy may supply several clinical sites; approximately 20-30 site pharmacies will participate (see Section 5.4). The estimated time from screening (Day -1 or Day 0) to the end of the study for an individual participant is approximately 28 days. Consenting participants at selected sites will return at Day 90 for a final blood draw.

Patient eligibility must be confirmed by a study clinician named on the delegation log. There is no exclusion for receipt of SARS-CoV-2 vaccine (experimental or licensed).

7.1 Inclusion Criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

1. SARS-CoV-2 infection documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection

2. Symptomatic COVID-19 disease

3. Duration of symptoms attributable to COVID-19 ≤ 12 days

4. Requiring inpatient hospital medical care for clinical manifestations of COVID-19 (admission for public health or quarantine only is not included)

5. Age ≥ 18 years

6. Willingness to abstain from participation in other COVID-19 treatment trials until after study Day 7

7. Provision of informed consent by participant or legally authorized representative

7.2 Exclusion Criteria

1. Prior receipt of SARS-CoV-2 hIVIG or convalescent plasma from a person who recovered from COVID-19 at any time

2. Prior receipt of standard IVIG (not hyperimmune to SARS-CoV-2) within 45 days

3. Current or predicted imminent (within 24 hours) requirement for any of the following:

    - Invasive ventilation
    - Non-invasive ventilation
    - Extracorporeal membrane oxygenation
    - Mechanical circulatory support
    - Continuous vasopressor therapy

4. History of allergy to IVIG or plasma products

5. History of selective IgA deficiency with documented presence of anti-IgA antibodies

6. Any medical conditions for which receipt of the required volume of intravenous fluid may be dangerous to the patient

    - Includes New York Heart Association Class III or IV stage heart failure

7. Any of the following thrombotic or procoagulant disorders:
    - Acute coronary syndromes, cerebrovascular syndromes and pulmonary or deep venous thrombosis within 28 days of randomization
    - History of prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome

8. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments

7.3 Costs to Participants

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

8 STUDY PRODUCT

8.1 hIVIG and Placebo

8.1.1 hIVIG Description

Summary characteristics of the individual hIVIG products and placebo are summarized in Section 2.2.9, with information on handling and preparation found in the Study Procedure Modules

8.1.2 hIVIG Dose

The hIVIG product is administered as a single dose of 400 mg/kg (or 0.4 g/kg) body weight, to a maximum dose of 40 g or 400 mL (i.e. capped at a body weight of 100kg).

The safety profile of hIVIG is anticipated to be comparable to licensed IVIGs for which doses of well above 400 mg/kg are safe and well tolerated. Licensed IVIGs are used with doses up to 400mg/kg for immune replacement and up to 2 g/kg for immunomodulatory induction, with an established favourable safety profile in which adverse events are not closely dose related.

The selected dose is derived from measures of anti-SARS-CoV-2 neutralizing potency from hIVIG, in comparison with that observed in convalescent plasma pools. Convalescent plasma pools used to produce hIVIG contain approximately 10 mg/mL of IgG immunoglobulin. Analysis of hIVIG shows an expected 10-fold increase in anti-SARS-CoV-2 binding IgG, but a lower than expected (5-fold) enrichment in anti-SARS-CoV-2 neutralizing potency. This suggests that only 50% of anti-SARS-CoV-2 neutralizing potency of plasma pools utilized to produce hIVIG is associated with IgGs. Based on this comparison, the neutralizing potency associated with the selected dose of 400 mg/kg hIVIG is significantly higher than in a fixed dose of 400 mL of convalescent plasma (3.5-5 fold higher than that dose of plasma when administered to 70-100 kg). This dose was therefore selected as providing an appreciable dose margin over convalescent plasma (in addition to the other advantages of hIVIG versus plasma), while remaining well within the accepted safe dose range for other IVIG products, and observing the limitations of hIVIG product supply.

There are no data so far to define target therapeutic titers for anti-SARS-CoV-2 antibody which would support dose derivation from target titers rather than the approach to dose selection described above. Although not considered for dose selection in the present study, the hIVIG products' potencies, and circulating levels of immunoglobulins (IgG, IgG subclasses, IgM, IgA) and neutralizing antibody titers following treatment will be measured. The analysis of the relationship between neutralizing titers and clinical outcomes may help to define a target therapeutic neutralizing titer for hIVIG+SOC and therefore may support dose optimization for future clinical investigations.

8.1.3 hIVIG Administration

The hIVIG product is administered as a single dose of 400 mg/kg (or 0.4 g/kg) current actual (not ideal) body weight, to a maximum dose of 40 g or 400 mL (i.e. capped at a body weight of 100 kg). The product as supplied should not be diluted. The infusion line may be flushed with normal saline.

Infusion of hIVIG/placebo should commence at an infusion rate of 0.5 mg/kg/minute for approximately 30 minutes. If the infusion is well tolerated, the rate of administration may be increased to a maximum of 4 mg/kg/minute as follows: the rate may be increased by doubling the infusion rate after intervals of not less than 30 minutes, so long as the infusion remains well tolerated. Participants should remain under close clinical observation during the infusion and for at least 60 minutes following completion of the infusion.

For participants judged to be at risk for volume overload (including but not limited to those with pre-existing cardiac failure), or who have for renal dysfunction (estimated creatinine clearance <60ml/min), administer hIVIG at the minimum infusion rate practicable.

For all participants, use of diuretics may be considered as clinically appropriate to avoid or treat fluid overload, with the goal of maintaining participants in a euvolemic state following completion of the infusion.

If adverse events occur, such as flushing, headache, nausea, changes in pulse rate or blood pressure, the rate of infusion should be slowed or infusion should be temporarily stopped. When events resolve, the infusion may be resumed at a rate that is comfortable to the participant (start at half of the last tolerated rate and increase gradually).

The hIVIG treatment should be immediately stopped should new onset or worsening of any of the following occur:

• Profound hypotension (systolic blood pressure < 80 mmHg)

• Severe shortness of breath, wheezing, or sustained (i.e., ≥ 10 seconds) new decrease in oxygen saturation to < 90% on room air

• Severe (Grade ≥ 3) local infusion site reactions, including pain, tenderness, erythema, or swelling as defined in the protocol-specified toxicity grading scale

• Sustained body core temperature exceeding 38.5°C or increase in body core temperature >2.0°C from baseline prior to infusion

• Suspected intercurrent sepsis (not manifestations of COVID-19)

• Severe chest pain

• Suspected anaphylaxis

8.1.4 Preparation/Handling/Storage/Accountability

This information is found in the Study Procedure Modules.

8.2 Remdesivir Background Therapy

8.2.1 Rationale

The antiviral drug remdesivir is being provided to all participants in this study, unless contraindicated. Remdesivir was shown to improve time to recovery in moderately-to-severely ill individuals hospitalized with COVID-19[40]. It is being provided to standardize background therapy in this study; while considered standard of care in hospitalized patients, due to shortages and regulatory status the drug may not be available at some participating sites during the study period.

8.2.2 Description

Remdesivir is a single diastereomer monophosphoramidate prodrug designed for the intracellular delivery of a modified adenine nucleoside analog GS-441524. In addition to the active ingredient, the lyophilized formulation of remdesivir contains the following inactive ingredients: water for injection, sulfobutylether-β-cyclodextrin (SBECD), and hydrochloric acid and/or sodium hydroxide.

8.2.3 Administration

Remdesivir will be administered as a 200 mg IV loading dose (100 mL volume) on the first day of its infusion followed by 100mg daily for the course described below; remdesivir may have commenced prior to randomization. For participants starting remdesivir after randomization to hIVIG/placebo, the loading dose should be given immediately after the infusion of hIVIG/placebo, once any infusion reactions from that infusion have resolved; for those who commenced remdesivir prior to randomization, the usual maintenance dose of 100 mg can be given after the hIVIG/placebo infusion on Day 0 in the same manner. After the first remdesivir infusion, a 100 mg once-daily IV maintenance dose (also 100 mL volume) is given each day while hospitalized for

up to a 10 day total course; shorter durations of 5 days may be considered by the clinical investigator as appropriate in patients who are not ventilated. Infusions will not be given to participants after discharge. The total treatment course should not exceed 10 calendar days even if an infusion is missed.

The dose should be given at approximately the same time each day (+/- 2 hours for medication scheduling).

Any dose that is delayed may be given later that calendar day. Any dose that is missed (not given that calendar day) is not made up. The treatment course continues as described above for hospitalized patients even if participants become PCR negative.

8.2.4 Contraindications

Remdesivir is contraindicated in participants with a history of hypersensitivity to remdesivir or any ingredient of the solution for injection.[75] Clinical caution should be exercised in individuals with hepatic or renal dysfunction, and hepatic and renal function should be checked prior to dosing and monitored during therapy.[75] Remdesivir has not been studied in pregnancy, and use in pregnancy should be based on an individual assessment of risk/benefit by the treating physician.

8.2.5 Dose Modification

If the estimated glomerular filtration rate (eGFR) decreases to < 25 mL/min, the remdesivir infusion should not be given on that day. The infusion may be resumed on the next day if the eGFR returns to ≥ 30 mL/min. If the participant's renal function worsens to the point that they require hemodialysis or hemofiltration, remdesivir will be discontinued.

If the ALT and/or AST increases to > than 5 times the upper limit of normal, the dose of remdesivir should be withheld and not be restarted until the ALT and AST reduces to ≤ 5 times the upper limit of normal.

8.2.6 Preparation/Handling/Storage/Accountability

This information is found in the Study Procedure Modules.

8.3 Standard of Care Therapy

8.3.1 Thromboprophylaxis and diagnosis of thrombotic complications

Consideration should be given to the use of pharmacological thromboprophylaxis (thrombosis prevention) in line with local clinical guidelines as appropriate for an individual participant, in addition to approaches to maintain mobility and minimize other thrombotic risks. Standard approaches to thromboprophylaxis supported by high quality evidence include the use of low molecular weight heparin (for example, enoxaparin 0.5m/kg daily; high quality evidence), which is the preferred agent in

some COVID-19 treatment guidelines.[76,77,78] However other standard approaches in accordance with local and institutional guidelines and the medical circumstances of an individual participant may also be considered, including the use of low (prophylactic) dose unfractionated heparin (high quality evidence), or higher doses than prophylactic doses as judged appropriate (low quality evidence). Specialist advice should be sought for participants who are pregnant.

An appropriate degree of clinical suspicion should be maintained for the development of new thrombotic complications, including deep venous thrombosis, pulmonary embolism, and other vascular events. Use of laboratory testing such as D-dimer may be confounded in the presence of acute COVID-19 infection. Consideration should be given to use of definitive imaging strategies for diagnosis wherever possible (for example, limb ultrasonography, computed tomography pulmonary angiograms), as appropriate for an individual participant.

8.3.2 Other Standard Supportive Care

Participants will be offered supportive care of complications of COVID-19 as clinically appropriate for the individual.

This includes appropriate management of pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy. Such care includes treatment with anti-bacterial agents for patients believed to have bacterial infection (high quality evidence), and guidelines-compliant management of sepsis when it is present (moderate quality evidence).

For participants requiring intensive care measures, consideration should be given to supportive care measures including lung-protective ventilation for patients who require invasive ventilation (high quality evidence) and prone positioning for mechanically ventilated patients with more than moderate ARDS (high quality evidence).[79,80]

As noted in section 8.1.3, hIVIG administration, use of diuretics may be considered as clinically appropriate to avoid or treat fluid overload.

Links to details of such care can be found in Appendix D.

8.3.3 Cautions and Contraindications

It is not recommended to use high dose chloroquine (600 mg twice daily) due to studies showing excess harm and no demonstrable benefit. (Hydroxy)chloroquine has no documented clinical benefit, and hence should not be used as part of SOC for COVID-19. Of note, the effectiveness of remdesivir may also be reduced if combined with (hydroxy)chloroquine, and hence it is not advisable to combine these two drugs;

in patients who are on pre-existing hydroxychloroquine for therapy of other diseases such as systemic lupus erythematosus, specialist advice should be sought.[81]

8.3.4 Infection Control Measures

Minimum standards of protection to *reduce the risk of SARS-CoV-2 transmission* from trial participants to research personnel, participants in other trials, or patients treated in the same facility can be found in links displayed in Appendix D.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening/Baseline, Follow-up and Endpoint Assessments

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

9.1.1 Screening/Baseline Assessments

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

- Confirm EITHER:
  - the positive SARS-CoV-2 test result (PCR or other NAT) was performed within 3 days prior to randomization or,
  - if more than 3 days prior to randomization, the prospective participant demonstrates progressive disease suggestive of ongoing SARS-CoV-2 infection
- Take a focused medical history, including the following information:
  - Demographics including age, biological sex
  - Day of onset of COVID-19 signs and symptoms
  - History of chronic medical conditions, including targeted conditions for outcome analysis
  - Medication allergies
  - Current use of targeted concomitant medications
  - Prior use of monoclonal antibody treatment or SARS-CoV-2 vaccine trial participation
- Perform a focused physical examination:
  - Height and weight;
  - Vital signs: Blood pressure, heart rate
  - Respiratory rate, oxygen requirements and saturation
- Obtain blood for local laboratory evaluations:

- White blood cell count
- Hemoglobin
- Platelets
- Lymphocytes
- C-reactive protein (CRP)
- Serum creatinine
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)

- Determine disease status at entry (includes SpO2, oxygen requirements) for the constituents of the ordinal outcome categories.

- Plasma and serum specimens for central testing for immunoglobulin levels, SARS-CoV-2 neutralizing antibody determination and storage for future COVID-19 related research (four [4] 1 mL aliquots of serum and four [4] 1 mL aliquots of plasma). Two 9mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

- Mid-turbinate swab for determination of SARS-CoV-2 viral load in central laboratory

- Urine or serum pregnancy test (in women of childbearing potential) (not an exclusion criterion but performed to ensure any pregnancy is recognized at entry)

Note: If a woman is either postmenopausal (i.e., is age ≥ 45 years and has had ≥12 months of spontaneous amenorrhea) or surgically sterile (i.e., has had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation), she is not considered to be of childbearing potential.

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

Participants who qualify will be randomized within 24 hours of obtaining the baseline assessments. Post-randomization on Day 0 the following will be recorded:

- Adverse events of any grade severity prior to starting the infusion
- Start and stop times of the infusion of hIVIG/placebo and remdesivir
- Infusion related reactions
- Whether the completion of the infusion was as planned
- Medication used prophylactically or therapeutically to manage infusion-related reactions
- Adverse events (AEs) of any grade severity during and for 2 hours after the infusion

9.1.2 Follow-up assessments

Participants will be followed through Day 28 following randomization for collection of study data. Clinical data targeted to components of the primary and secondary endpoints will be collected daily during hospitalization, and at scheduled visits to day 28 after discharge. This will include discharge status, development of key medical conditions, vital signs including SpO_2. On Day 7, interim targeted physical exam and concomitant medications will be collected along with the results of blood tests for serum creatinine, ALT or AST, white blood cell count, hemoglobin, platelets, lymphocytes, and C-reactive protein (CRP).

AEs of any grade severity will be collected on Day 0 prior to infusion and on Days 1, 3, 7, and 28 (AEs present on those days). Incident AEs of grade 3 or 4 severity will be collected through Day 7 and all SAEs will be collected through Day 28.

The primary ordinal outcome measure will be assessed daily while the participant is hospitalized and on Day 3, 5, Day 7 (primary endpoint), Day 14 and Day 28 for all participants. Items necessary for determination of NEWS will be collected on Day 3. The Borg dyspnea score will be evaluated at baseline and day 7.

For participants who are no longer hospitalized, in-person visits will be done on study days where blood is collected (Days 1, 2, 3, 7, and 28). For other visits (Day 5 and Day 14), contact with the participant for the purpose of study data collection may be performed by telephone, recognizing that certain components of the endpoints (e.g. SpO_2) are not likely available from outpatients. Other information as possible will be gathered.

On Days 1, 2, 3, 7, and 28, plasma and serum samples (four 1 mL aliquots of both plasma and serum at each visit) will be obtained for central testing of antibody levels (including neutralizing antibodies) to SARS-CoV-2 and for storage for future related research. Two 9 mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

In consenting participants at selected sites (determined at site level prior to opening; selected sites will endeavor to follow all participants to day 90), plasma and serum samples (four 1 mL aliquots of both plasma and serum) will be obtained at Day 90 for central testing of antibody levels (including neutralizing antibodies) to SARS-CoV-2 and for storage for future related research. Two 9mL tubes, SST and EDTA, of blood (18 mL total) will be drawn in order obtain the 8 aliquots.

For patients co-enrolled on INSIGHT 004 Genomics, where genomics samples have not already been collected prior to enrollment in this protocol they may be collected at any time during follow-up.

9.1.3 Stored Samples and Future Research

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

10 SAFETY REPORTING

The safety evaluation of the study intervention includes several components, all of which will be regularly reviewed by the independent DSMB. For this protocol, the term “study intervention” refers to the hIVIG/placebo and to remdesivir.

With the exception of infusion related reactions of any grade, which are only collected for the hIVIG/placebo, all other AEs are collected for the study intervention (either the hIVIG/placebo or study-provided SOC treatment). Selected events will be reported to regulators and IRBs/ethics committees in addition to being regularly reviewed by the DSMB.

The following information will be collected to evaluate safety:

- Infusion-related reactions of any grade severity during and within 2 hours post-infusion of the hIVIG/placebo.
- Clinical AEs of any grade severity will be collected on Days 0, 1, 3, 7, and 28 (AEs present on those days).
- Targeted laboratory abnormalities of any grade severity at Day 7.
- Incident grade 3 and 4 clinical adverse events occurring through Day 7 (isolated laboratory abnormalities that are not associated with signs or symptoms are not recorded).
- Clinical events that are collected as part of the primary ordinal outcome or as secondary outcomes through Day 28. These are protocol exempt events and are not reported as SAEs unless they are considered as related to the study intervention.
- Serious adverse events, including laboratory-only serious events, considered related to the study intervention (either the hIVIG/placebo or a study-provided SOC treatment) through Day 28.
- Serious adverse events that are not collected as part of the primary ordinal outcome or as a secondary outcome through Day 28.
- Unanticipated problems through Day 28.
- Deaths through Day 28.

An overview of safety data collected during the study is given in Table 2.

Table 2. Adverse Event Data Collection Overview

	Day 0*	Infusion +2 hrs	Day 1	Day 3	Day 5	Day 7	Day 14	Day 28
Infusion-related reactions and symptoms		X						
Incident Grade 3 and 4 clinical AEs**			Collected through day 7					
Clinical AEs of any grade severity	X	X	X	X		X		X
Targeted laboratory abnormalities of any grade						X		
Targeted clinical events collected as study endpoints***				Collected through Day 28				
Serious clinical AEs not reported as a study endpoint***				Collected through Day 28				
Unanticipated problems				Collected through Day 28				
Any serious adverse event related to study-provided treatment				Collected through Day 28				

* pre-infusion AE collection
** Incident grade 3 and 4 AEs are *new* (not present at baseline) AEs or AEs that have *increased in grade*
*** see section 10.2.5 for specific events

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

10.1 Definitions

10.1.1 Adverse Event (AE)

An adverse event is any untoward or unfavorable medical occurrence in a study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with their participation in

research, whether or not considered related to the research. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE. AEs are reported on the appropriate case report form (CRF) when prompted.

10.1.2 Criteria for Seriousness

Events are serious if they lead to one of the following outcomes:

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

10.1.3 Unanticipated Problems

An unanticipated problem (UP) is any incident, experience or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to:
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure (IB) or other study documents; and
   b. the characteristics of the population being studied; and
2. Possibly, probably, or definitely related to participation in the research; and
3. Places study participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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

10.1.4 Severity

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

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

TABLE 3. GENERIC AE GRADING SCALE

Grade 1	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Symptoms causing inability to perform usual social and functional activities
Grade 4	Symptoms causing inability to perform basic self-care functions, or medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5	Events resulting in death

10.1.5 Causality

Causality refers to the likelihood that the event is related to the study intervention. It will be assessed for SAEs and UPs. This assessment will be made for both the agent under investigation (hIVIG) and the study-provided background therapy of remdesivir using the following guidelines:

- Reasonable possibility – There is a clear temporal relationship between the study intervention and the event onset, and the AE is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- No reasonable possibility – There is no evidence suggesting that the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

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

10.1.6 Expectedness

Expectedness will be assessed for SAEs using the Reference Safety Information section of the IBs for the hIVIG and remdesivir.

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

10.2 Schedule for Data Collection and Reporting of Specific Events

10.2.1 Infusion-related reactions

Infusion related signs/symptoms of any grade that are new or have increased in grade compared to their pre-infusion level are reported for the hIVIG/placebo if they occur during or within 2 hours post infusion. Any infusion related reaction assessed as meeting SAE criteria will be reported as an SAE. Similarly, any grade 3 or 4 infusion related reaction will be reported as an AE.

10.2.2 Targeted Laboratory abnormalities

Selected laboratory tests are performed prior to infusion and on Day 7. These values are associated with a severity grade centrally using the laboratory test results reported on the eCRFs with normal ranges, and with the DAIDS AE Grading Table.

Other laboratory abnormalities identified in the course of the participant's clinical care are not reported as AEs (e.g., an isolated elevated glucose level) unless they are associated with a specific clinical diagnosis/syndrome, in which case they are reported if they meet the reporting criteria of one of the other safety outcomes. In addition, if an isolated laboratory test result meets SAE reporting criteria (e.g., a serious event related to the study intervention), it should be reported as an SAE.

10.2.3 Clinical adverse events of any grade severity on Days 0, 1, 3, 7 and 28

On Day 0 prior to infusion and on Days 1, 3, 7 and 28 the prevalence of AEs of any grade severity that the participant reports that day will be collected. This information supplements the information on grade 3 and 4 events through Day 7 that is collected.

10.2.4 Incident Grade 3 and 4 clinical adverse events through Day 7

From the time of randomization on Day 0 through Day 7, clinical events reaching Grade 3 or 4 severity level will be reported as AEs unless they are a protocol-specified exempt event (see below).

Any medical condition of grade 1 and 2 that is present at Day 0 will be reported as an AE if it increases to Grade 3 or 4 by Day 7.

Isolated laboratory abnormalities will not be recorded on the eCRF for grade 3 and 4 events. However, as noted above, if an isolated laboratory result meets SAE criteria, it should be reported as an SAE.

10.2.5 Protocol-specified exempt events

These events are listed in sections 4.1 and 4.2 and are collected systematically during study follow-up on eCRFs. These events will not be reported as Grade 3 or 4 AEs even if they occur at that severity grade. They also will not be reported as SAEs, even if they meet one or more of the criteria for seriousness, ***unless the investigator considered that there was a reasonable possibility that the study intervention caused the event***. These events may occur during the initial hospitalization, lead to a re-admission, or occur in a later hospitalization during follow-up.

The following are **protocol-specified exempt events**:

- Death
- Stroke
- Meningitis
- Encephalitis
- Myelitis
- Myocardial infarction
- Myocarditis
- Pericarditis
- New onset of worsening of CHF (NYHA class 3 or 4)
- Arterial or deep venous thromboembolic events
- Respiratory failure defined as receipt of high flow nasal oxygen, noninvasive ventilation, or invasive ventilation
- Hypotension requiring vasopressor therapy
- Renal dysfunction requiring renal replacement therapy
- Hepatic decompensation
- Acute delirium
- Disseminated intravascular coagulation
- Microbiologically-proven severe infection (not including SARS-CoV-2)

10.2.6 Reportable SAEs

Reportable SAEs for this study are:

- Serious clinical AEs not reported as a study endpoint; and
- Any serious AE related to the study intervention

Deaths, life-threatening events, and others SAEs considered related to the investigational agent, irrespective of whether the event is mentioned above as a protocol-specified exempt event, that occur from the time of infusion of the hIVIG/placebo begins through the Day 28 visit must be reported by sites on the SAE eCRF to the sponsor via the INSIGHT Safety Office. These events must be reported **within 24 hours of site awareness.** All other SAEs must be reported within 3 days of site awareness.

SAEs are followed until the outcome of the SAE is known. If the outcome of an SAE is still unknown at the time of the final follow-up visit (Day 28), the outcome will be entered in the database as "unknown."

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

Safety reports for SUSARs indicate the study intervention (i.e., are unblinded).

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

10.2.7 Unanticipated Problems (UPs)

UPs must also be reported via the appropriate eCRF to the INSIGHT Safety Office no later than 7 calendar days after site awareness of the event. Investigators are responsible for submitting UPs that are received from the sponsor to their overseeing IRB/EC. Investigators must also comply with all reporting requirements of their overseeing IRB/EC.

10.2.8 Deaths

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

10.3 Medical Monitor

A Medical Monitor appointed by the sponsor will be responsible for reviewing all SAEs, making an independent assessment of causality and expectedness, preparing sponsor safety reports, and communicating as needed with the DSMB and the Investigational New Drug (IND) holder.

10.4 Treatment Interruption or Discontinuation

An infusion may be interrupted or discontinued at any time at the participant's request or at the discretion of the Investigator or Sponsor. Reasons for interruption or discontinuation and the total volume administered will be recorded.

10.5 Halting Rules

The sponsor medical monitor or the DSMB may request that enrollment be halted for safety reasons (e.g., unacceptably high rate of infusion-related reactions or other unanticipated AEs). As a guideline, the DSMB will be asked to consider halting enrollment if more than 5% of participants experience a grade 3 or 4 infusion AE or if more than 10% do not complete the infusion due to an AE(s). This will be informed by the lower bound of the confidence interval. If the study is temporarily halted or stopped for safety reasons, IRBs/ethics committees will be informed.

The IND holder and sponsor, in collaboration with the protocol chair and the DSMB will determine if it is safe to resume the study. The sponsor will notify the Site Investigators of this decision. The conditions for resumption of the study will be defined in this notification. The Site Investigators will notify their local IRBs/ethics committees of the decision to resume the study.

11 EVALUATION

11.1 Data Analysis

A brief summary of the statistical considerations is provided here, full details will be described in a statistical analysis plan (SAP) that will be finalized prior to unblinding of the data. Data unblinding will either occur after a recommendation from the independent DSMB or after all participants complete the Day 28 follow-up visit.

The primary analysis will be by intention to treat comparing all participants randomized to hIVIG with those randomized to placebo. The different hIVIG products will be pooled for this analysis.

This analysis plan applies to the primary efficacy and safety outcomes, and important secondary outcomes.

For the primary endpoint, the percent of participants in the 7 categories of the ordinal outcome will be compared. A proportional odds model will be used to estimate a summary OR.[82] The model will include a single indicator for treatment, indicators for the participant's clinical state at entry (categories of ordinal outcome), and its two-way interactions with the six cut-offs. The model will also include indicators for which of the four hIVIG product/matching placebo product was used and their two-way interactions with the six cutoffs for each of the six cumulative odds of improvement. A test for the proportional odds assumption will be carried out. Even if the proportional odds assumption is violated, the overall summary OR will be the basis for inference based on the primary analysis. In order to further characterize the summary OR and any deviations from proportional odds, separate ORs will be estimated for each of the six dichotomized definitions of improvement that can be formulated from the components of the ordinal outcome.

For the primary endpoint analysis only, multiple imputation based on baseline and follow-up data will be used to estimate participant status at day 7 for participants with missing follow-up data. For this imputation the following baseline covariates will be considered in addition to an indicator for treatment group: age, geographic region, clinical status based on the ordinal outcome at enrollment, presence of comorbidities, NEW score, and oxygen saturation. In addition to these baseline covariates, the last NEW score and the last value of the ordinal outcome measured will be used in the imputation.

We will impute ten data sets; parameter estimates (e.g., the summary odds ratio) from the 10 multiply imputed datasets will be combined using Rubin's combining rules. The imputation will take into account whether partial information concerning the ordinal outcome at Day 7 is known (e.g., it is known that the patient is alive and no longer hospitalized and receiving supplemental oxygen and only which of the best 2 categories the patient is in is unknown).

Categories 3 and 4 of the primary ordinal outcome differ in part by the amount of supplemental oxygen required, and a single cut point (4 liters/minute) defines the difference. Since, together, these 2 categories of the ordinal outcome are expected to include approximately 30% of participants, an analysis that combines these two categories (a 6-category ordinal outcome) will be carried to supplement the primary analysis using the same methods described above.

SAEs and grade 3 and 4 events (excluding isolated laboratory abnormalities) will be classified by system organ class according to MedDRA®. The composite of incident grade 3 or 4 events, an SAE or death over 7 days of follow-up will be summarized with Mantel Haenszel chi-square tests stratified by hIVIG/matched placebo group. Time to event methods (e.g., Kaplan-Meier estimates and Cox regression) will be used to summarize deaths and SAEs through Day 28.

Safety analyses will also include infusion reactions collected during or within 2 hours after the infusion of hIVIG/placebo. Percentages of participants who experience infusion reactions or prematurely terminated infusions will be summarized by treatment groups, and Cochran Mantel Haenszel tests will be used to compare groups.

For secondary endpoints such as time to discharge and time to the 2 most favorable categories of the primary ordinal outcome, time to event methods that take into account the competing risk of death will be used. Specifically, Gray's test with rho=0, the Fine-Gray model, and the Aalen-Johansen estimator for the cumulative incidence curve are the competing risk equivalents to the log-rank test, Cox proportional hazards model, and the Kaplan-Meier estimator for the cumulative proportion of participants with the event, respectively.[83,84,85]

Longitudinal random effects models will be used to summarize log-transformed antibody level differences between the hIVIG and placebo groups at Days 1, 3, 7 and 28 of follow-up. Baseline antibody levels will be included as a covariate in these

models. For the subset of participants for whom blood is collected at Day 90, antibody levels will be compared.

Subgroup analyses for the primary 7-category ordinal outcome (primary efficacy outcome), as well as for the primary safety outcome (Grade 3 and 4 events, SAE or death through Day 7) will be performed to determine whether the treatment effect (hIVIG versus placebo) differs across baseline-defined subgroups. The key subgroup analysis is by duration of symptoms at study entry. For the subgroup of participants in the lower 3 quartiles, the OR for the primary ordinal outcome at Day 7 is hypothesized to be greater than the overall result and those in the upper quartile (longest duration of symptoms at study entry). The difference in ORs will be compared for those in the lower 3 quartiles versus the upper quartile. In addition, the trend across the four quartiles will be assessed.

The following other baseline-defined subgroups will be considered: age, gender, race/ethnicity, BMI, history of chronic conditions, geographic region, hIVIG product administered, neutralizing antibody level, baseline upper respiratory SARS-CoV-2 viral load, oxygen saturation level, ordinal outcome category at entry, NEWS, dyspnea severity, and a disease progression score. *A priori* we have no reason to believe the clinical efficacy or safety of hIVIG compared to placebo will be substantially different in any of the subgroups considered. These analyses will be approached cautiously because random differences can occur (type 1 error is inflated due to the number of subgroups examined), confounding due to other factors in defining each subgroup is possible, and power is limited. To partially control the inflation of type 1 error and to guide the interpretation of subgroup summaries, an overall test of heterogeneity of treatment effect (treatment by subgroup interaction) will be constructed to assess how strong the evidence is that the treatment effect varies across the baseline subgroups.

In addition to these subgroup analyses, a subgroup analysis by lot potency will be carried out. The aim of this analysis will be to determine if the primary outcome varies by range in potency among the various lots of hIVIG used. The potency of each lot will be measured by a central laboratory. Participants in the placebo group will be classified according the lot potency they would have received had they been randomly assigned to the hIVIG group. The methods used for this subgroup analysis will be as described above.

If there is a beneficial effect of hIVIG compared to placebo, in order to support regulatory claims for each hIVIG product used, sensitivity analyses comparing each hIVIG product to its matched placebo will be carried out for key efficacy and safety endpoints. These analyses will consider that each hIVIG product will be used by a different group of clinical sites (i.e., each comparison will represent a small multi-center trial), and that power will likely be very low for all of the outcomes. These analyses are referred to as sensitivity analyses because overall therapeutic efficacy and safety will be based on the pooled analysis of the four hIVIG products with placebo.

If the hIVIG and placebo groups differ for the primary ordinal outcome at Day 7, the extent to which a favourable treatment difference for hIVIG can be explained by antibody levels measured at baseline and Days 1, 3, 7, and 28 of follow-up will be investigated.

11.2 Ethical Conduct of the Study

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

11.3 Data Monitoring by an Independent DSMB

An independent DSMB will review the study prior to initiation and at frequent intervals during the trial. The DSMB will review safety data for first 20 to 30 participants randomized after they have been followed for 7 days. Thereafter, the DSMB will review safety data at 30 day intervals. Safety summaries will include the safety outcomes in section 4.2. The DSMB may also convene additional reviews as necessary. After each meeting they will recommend continuing the study as planned, modifying the study, or terminating the study.

The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. As a guideline, asymmetric boundaries will be provided to the DSMB to monitor the primary endpoint comparison. For monitoring early benefit of hIVIG, the Lan-DeMets spending function analogue of the O'Brien-Fleming boundary will be used[86,87]; a Haybittle-Peto type boundary using a 2.5 standard deviation (SD) difference for the first 100 participants enrolled and 2.0 SD afterwards will used as a guideline for harm.[88] The Lan-DeMets boundary used will be chosen to preserve a 1-sided 0.025 level of significance. For computing the Lan-DeMets boundary, the information fraction at each interim analysis will be the number of participants who have completed 7 days of follow-up divided by the target sample size (currently 500). With this guideline for early termination, less evidence will be required for crossing a boundary for harm than benefit.

Futility analyses will also be presented to the DSMB for the primary endpoint comparison by the unblinded statisticians based on conditional power estimates. Conditional power incorporates the observed results by treatment group thus far (and uses the originally assumed treatment effect for future data) to calculate the conditional probability of obtaining a significant result by the end of the trial. If conditional power, given the observed data and assuming the originally hypothesized treatment effect thereafter, is less than 20% after 50% of information (primary endpoints) is available, consideration should be given to stopping the trial.

A SAP will be developed to guide DSMB interim analyses. The SAP will include recommended analyses for the DSMB to consider in addition to the primary endpoint analysis in the event early termination for efficacy or futility is considered. For example, the primary endpoint at Day 7 for the key previously defined subgroup of those in the lower 3 quartiles of symptom duration at entry will be routinely summarized in the closed interim report to the DSMB.

All of these analyses will consider the timeliness of reporting primary outcome data, secondary efficacy and safety outcomes, and subgroups.

12 PROTECTION OF HUMAN SUBJECTS AND ETHICAL CONSIDERATIONS

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

This study will be conducted by major medical centers participating in the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). It is anticipated that potential participants will be recruited by the site investigators and/or that positive SARS-CoV-2 laboratory testing will be used to enquire about potential enrollment. Information about this study will be disseminated to health care providers in these settings.

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

12.2 Informed Consent of Study Participants

Informed consent must be obtained (see sample in Appendix A) prior to conducting any study-related procedures. For patients who are incapacitated, informed consent may be obtained from a legally authorized representative. Capacity will be assessed according to local standards and policies. Local standards and policies will also determine who is legally authorized to consent for an individual who is incapacitated. Should the individual regain capacity during the study, their direct consent should be obtained at the earliest opportunity. Electronic consent methods may be used if approved by the IRB/EC. Procedures for recording of written consent may be modified for infection control purposes as approved by the IRB/EC.

12.3 Confidentiality of Study Participants

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

12.4 Regulatory Oversight

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

A specific protocol monitoring plan will be developed. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

APPENDIX A-1 SAMPLE INFORMED CONSENT FORM (FOLLOW-UP ENDING DAY 28)

Short Title: Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)

Sponsored by: The University of Minnesota

A Multicenter Study of the
International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Full Title of the Study: **An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19**

CONSENT FOR PARTICIPATING IN A NATIONAL INSTITUTES OF HEALTH (NIH)-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ PHONE: _____

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

OHRP Requirements to be read by the sites:

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

Key information:

We are asking you to join a research study about COVID-19. It is your choice whether or not you want to join. This form gives you information about the study that will help you make your choice. You can discuss this information with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting for COVID-19.

What is the research question?

We are trying to find out if giving anti-coronavirus hyperimmune intravenous immunoglobulin (hIVIG) can help people in the hospital with COVID-19 have fewer bad effects from COVID-19, get better faster, and get out of the hospital faster. Anti-coronavirus hIVIG contains antibodies against the virus that causes COVID-19. We think this will help your body fight COVID-19 better, but we are not sure and so we are doing this study. We are asking you to join the study because you are in the hospital with COVID-19.

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

The study staff at your hospital will make sure it is safe for you to be in the study. They will check your medical history. They will look at routine medical test results that you are probably already having done regularly in the hospital.

If you agree to be in the study, we will randomize you to one of two study groups. It will be up to chance, like flipping a coin, and you will have an equal chance (50/50) of getting either hIVIG or a saline placebo (a salt solution). Your doctor will not decide which of these you will get, and neither you nor your doctor or study staff will know what treatment you are getting.

You will get the usual supportive care for COVID-19 recommended by your hospital, just as you would if you do not join the study. In addition, the study will supply an antiviral drug called remdesivir, unless there is a medical reason that you should not get remdesivir. Remdesivir has been shown in other studies to improve recovery from COVID-19 in persons who have been hospitalized.

You will get the study treatment (hIVIG or placebo) once, on the day you join the study. You will get it by a drip through a tube attached to a needle in your arm (intravenously). It will take about 1-2 hours, though it may sometimes take longer depending on how your body reacts to the infusion. This is the only thing in the study that is experimental. Everything else is part of routine medical care for someone in the hospital with COVID-19.

You will get remdesivir once a day intravenously for up to 10 days while you are in the hospital, as part of standard care for your COVID-19.

You will also need to agree not to participate in any other COVID-19 study for the first 7 days you are in this study.

You will be in the study for 28 days. We will check on your health every day while you are in the hospital, and at regular intervals once you leave the hospital.

We will collect the following information at these times:

Up to 1 day before you get study treatment	**Day 0 (the day you get study treatment)**	**Day 1, Day 2, and Day 3**	**Day 5 and Day 14**	**Day 7**	**Day 28**
• Informed consent • Blood tests to check your health • Check to see how you are feeling • Pregnancy test • Your medical history	• Infusion of study treatment • If you are taking certain medicines • Blood for future research (18 mL, about 2 tablespoons) • Nasal swab for future research	• How you are feeling • Blood for future research (18 mL, about 2 tablespoons)	• How you are feeling	• How you are feeling • If you are taking certain medicines • Blood tests to check your health • Blood for future research (18 mL, about 2 tablespoons)	• How you are feeling • Blood for future research (18 mL, about 2 tablespoons)

Day 28 is the last day you will be in the study.

We may need to get some information from your medical record. By signing this consent, you also agree to let us get information for this study from your medical record.

We will send the information we collect to the University of Minnesota (UMN) in the US where it will be stored and analyzed. In this information, only a code number, your year of birth, and a 3-letter code that you or the study staff chooses will be used on your information. We never give information that could identify you, such as your name, address, birth date, or medical record number, to anyone outside this site. The study staff at this site is responsible for keeping your identifying information safe from anyone who should not see it. We will send the blood samples to a laboratory in the US for storage. We will keep them for as long as we have the funding and space to do so, which we hope will be many years. We will use the samples in the future for tests to help understand more about COVID-19 and how people respond to treatment for COVID-19. You and your doctor will not get any results from these tests. We will not test your DNA (your genes). We will not sell your samples and they will not be used for research aimed at making money (commercial research). The samples will not have any information connected to them that could identify you.

Why would you want to be in the study?

If you get the hIVIG, it may help you get better faster, although we do not know that for sure. Remember that half (50%) of the people in this study will not get the hIVIG.

By being in this study, you help doctors know more about how to treat COVID-19 in people in the hospital. Because so many people are getting hospitalized with COVID-19, this could be a big impact if a treatment proves to be effective.

Why would you NOT want to be in the study?

Only half (50%) of the people in this study will get the hIVIG. You may not get the hIVIG. If hIVIG turns out to be a good treatment, you would not get that benefit. It's also possible that if you do get hIVIG, it may turn out not to be useful, or may cause side effects that are harmful to you.

What are the side effects of the study hIVIG treatment?

hIVIG is usually very safe to give. Similar immunoglobulin preparations have been used in many different diseases over many years, but immunogloblin prepared solely from individuals who have recovered from COVID-19 has not been studied before. In an earlier study of influenza hIVIG in people in the hospital with the flu, over 150 people got hIVIG. There were no serious problems that occurred in people because they got hIVIG.

All treatments cause side effects, and you may have some side effects from hIVIG. About 1% to 10% (1 in 100 people to 1 in 10 people) who get hIVIG get a fever, chills, nausea, vomiting, dizziness, shortness of breath, rash, hives, or headache, but these are usually not serious. These can happen during the infusion or afterwards and usually go away on their own or with short-term treatment. Although IVIG has been very safe for people with other diseases, less than 0.1% (less than 1 in 1,000) of people taking other types of IVIG for other illnesses have had very serious reactions to it, including a kind of lung injury called TRALI.

People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. This is very rare but is also a possible effect of any drug. Allergic reactions may be severe or life-threatening.

In some laboratory studies, infusions of antibodies have made infections with viruses similar to the virus that causes COVID-19 worse. This is a very unlikely but possible side effect of the treatment infusion in this study, and you will be closely monitored for any signs of this effect.

It is also possible that getting the study treatment infusions could cause problems with your health because of the amount of fluid given to you for the study treatment if you have some other health condition that affects how your body handles fluids. You will get up to about 400 mL of fluid for hIVIG or placebo, and about 100mL each day for remdesivir if you receive it

Some people may have some side effects after the hIVIG infusions. Other people may have no side effects. You will be monitored closely during the infusions, and short-term medical care will be provided if there are side effects from the infusions that can be treated.

What are the benefits and risks or side effects of remdesivir treatment?

Remdesivir was recently shown to help people who are in the hospital with COVID-19 to get better faster than people who got a placebo. You may be given remdesivir to treat your COVID-19 even if you do not join this study. If your doctor considers that remdesivir is not a suitable treatment for you, you can still join this study, and you will receive hIVIG or placebo without remdesivir. For example, remdesivir might be unsuitable for you if you have serious liver or kidney problems or an allergy to it.

The most common side effects of remdesivir include abnormal liver function test results, abnormal kidney function test results, fever, elevated blood sugar, constipation, nausea, vomiting, decreased appetite, and headache. The abnormal liver and kidney function tests may last a few days or longer but came back to normal levels over time.

People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. This is very rare but is also a possible effect of any drug. Allergic reactions may be severe or life-threatening.

Some people may have some side effects after the infusion of remdesivir. Other people may have no side effects. You will be monitored closely during the infusions, and short-term medical care will be provided if there are side effects from the infusions that can be treated.

What are the side effects of the other study procedures?

As shown in the table of what will happen at each visit, you will have some extra blood drawn for laboratory testing and storage. You will also have an extra swab of your nose and throat that would not be done if you are not in the study. The risks and discomforts of these

extra blood draws and swab are no different than what you would have if they were performed as part of your regular hospital care for COVID-19.

Additional information:

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

The US National Institutes of Health (NIH), an agency of the US Federal government, is paying for this study. Because public money is paying for the study, we are required to comply with all rules and regulations about research. We are doing this study according to internationally recognized standards of research as well as the laws of each country where the study is taking place.

This study is taking place in several countries. We expect to enroll about 500 people around the world.

You do not have to join this research study if you do not want to. If you choose to join the study, you can stop at any time by telling someone on the study team that you want to stop being in the study. If you choose not to join or to stop, your regular medical care will not change.

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

Your study participation may be stopped without your consent if:

- The groups overseeing the study decide the study should be stopped;
- Your study team believes that being in the study is no longer in your best interests.

If your participation is stopped, you will still get the usual care given at your hospital for COVID-19.

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

<u>What are the costs to you?</u>

We will give you the study treatment (hIVIG or placebo) at no cost. We will also give you remdesivir at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

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

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

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

Will you be paid to be in the study?

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

What if you are hurt as part of this study?

If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

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

What happens to the blood samples and respiratory swabs?

We will send the blood and respiratory swab samples to a central laboratory in the United States of America. You and your doctor will **not** get the results of any tests done on these samples.

The blood samples will measure how many COVID-19 antibodies are in your blood. This will tell us how your immune system responded to your COVID-19. The nasal swab will measure how much virus you have in your respiratory system.

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

How do we protect your privacy?

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

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

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

These people may see your medical and research information at your site:

- the *[insert the name of the hospital/clinic]* ethics committee (institutional review board [IRB]);
- the sponsor, other study research staff, and study monitors
- US and other participating countries' health regulatory agencies
- the US National Institutes of Health which is funding the study

They are committed to protecting your privacy.

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

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

Your study data will be shared with the regulators that oversee the studies, as required by law. Your study data will also be shared with the drug company that provides the hIVIG to help them develop the drug.

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

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

A description of this clinical trial will be available at http://www.ClinicalTrials.gov as required by U.S. law, and on the EudraCT website (https://eudract.ema.europa.eu/). These websites will not include your name or any other direct identifiers such as your contact information.

These websites will include a summary of the results of this research once the study has been completed. You can search either website at any time.

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

To do this research, we will collect and use your personal data, as described above and in any HIPAA Authorization Form we have given you. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

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

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

It is your choice whether you allow us to collect and use your data. However, you will not be able to be in this research and have a chance to get the experimental treatment if we cannot collect and use your data.

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

What are your rights regarding your data?

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

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

The GDPR gives you additional rights which we would like to inform you about below.

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

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

Right to Erasure/Anonymization

The sponsor is required under both EU and US law to retain data from research studies like this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your study center that

links your identity to the pseudonymized data held by the sponsor. This means that no one would ever be able to link the data held by the sponsor to you personally.

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

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

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

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

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

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

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

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

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

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

What if you have problems or questions?

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

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

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

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

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE INSIGHT 013 STUDY (Inpatient Treatment with Anti-Coronavirus Immunoglobulin, ITAC)

I have read the consent or have had it explained to me. I am satisfied that I understand the information. By signing this consent, I am stating that I want to join this study. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of the signed and dated consent.

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

_____ Date: _____

Signature of participant

_____

Printed name of participant

_____ Date: _____

Signature of investigator/designee

_____

Printed name of investigator/designee

FOR ADULTS NOT CAPABLE of GIVING CONSENT

_____ Date: _____

Signature of Legally Authorized Representative (LAR)

_____

Printed name of LAR

_____

Relationship of LAR to Participant

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

Witness to Consent Interview

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

_____ Date: _____

Signature of witness

_____

Printed name of witness

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

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

APPENDIX A-2 SAMPLE INFORMED CONSENT FORM FOR SITES COLLECTING DAY 90 SAMPLES

Short Title: Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)

Sponsored by: The University of Minnesota

A Multicenter Study of the
International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Full Title of the Study: **An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19**

CONSENT FOR PARTICIPATING IN A NATIONAL INSTITUTES OF HEALTH (NIH)-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ PHONE: _____

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

OHRP Requirements to be read by the sites:

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

Key information:

We are asking you to join a research study about COVID-19. It is your choice whether or not you want to join. This form gives you information about the study that will help you make your choice. You can discuss this information with your doctor or family or anyone else you would like before you make your choice. Your choice will not affect the care you are getting for COVID-19.

What is the research question?

We are trying to find out if giving anti-coronavirus hyperimmune intravenous immunoglobulin (hIVIG) can help people in the hospital with COVID-19 have fewer bad effects from COVID-19, get better faster, and get out of the hospital faster. Anti-coronavirus hIVIG contains antibodies against the virus that causes COVID-19. We think this will help your body fight COVID-19 better, but we are not sure and so we are doing this study. We are asking you to join the study because you are in the hospital with COVID-19.

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

The study staff at your hospital will make sure it is safe for you to be in the study. They will check your medical history. They will look at routine medical test results that you are probably already having done regularly in the hospital.

If you agree to be in the study, we will randomize you to one of two study groups. It will be up to chance, like flipping a coin, and you will have an equal chance (50/50) of getting either hIVIG or a saline placebo (a salt solution). Your doctor will not decide which of these you will get, and neither you nor your doctor or study staff will know what treatment you are getting.

You will get the usual supportive care for COVID-19 recommended by your hospital, just as you would if you do not join the study. In addition, the study will supply an antiviral drug called remdesivir, unless there is a medical reason that you should not get remdesivir. Remdesivir has been shown in other studies to improve recovery from COVID-19 in persons who have been hospitalized.

You will get the study treatment (hIVIG or placebo) once, on the day you join the study. You will get it by a drip through a tube attached to a needle in your arm (intravenously). It will take about 1-2 hours, though it may sometimes take longer depending on how your body reacts to the infusion. This is the only thing in the study that is experimental. Everything else is part of routine medical care for someone in the hospital with COVID-19.

You will get remdesivir once a day intravenously for up to 10 days while you are in the hospital, as part of standard care for your COVID-19.

You will also need to agree not to participate in any other COVID-19 study for the first 7 days you are in this study.

You will be in the study for 90 days. We will check on your health every day while you are in the hospital, and at regular intervals once you leave the hospital.

We will collect the following information at these times:

Up to 1 day before you get study treatment	Day 0 (the day you get study treatment)	Day 1, Day 2, Day 3, Day 28	Day 5 and Day 14	Day 7	Day 90
• Informed consent • Blood tests to check your health • Check to see how you are feeling • Pregnancy test • Your medical history	• Infusion of study treatment • If you are taking certain medicines • Blood for future research (18 mL, about 2 tablespoons) • Nasal swab for future research	• How you are feeling • Blood for future research (18 mL, about 2 tablespoons)	• How you are feeling	• How you are feeling • If you are taking certain medicines • Blood tests to check your health • Blood for future research (18 mL, about 2 tablespoons)	• Blood for future research (18 mL, about 2 tablespoons)

We may need to get some information from your medical record. By signing this consent, you also agree to let us get information for this study from your medical record.

We will send the information we collect to the University of Minnesota (UMN) in the US where it will be stored and analyzed. In this information, only a code number, your year of birth, and a 3-letter code that you or the study staff chooses will be used on your information. We never give information that could identify you, such as your name, address, birth date, or medical record number, to anyone outside this site. The study staff at this site is responsible for keeping your identifying information safe from anyone who should not see it. We will send the blood samples to a laboratory in the US for storage. We will keep them for as long as we have the funding and space to do so, which we hope will be many years. We will use the samples in the future for tests to help understand more about COVID-19 and how people respond to treatment for COVID-19. You and your doctor will not get any results from these tests. We will not test your DNA (your genes). We will not sell your samples and they will not be used for research aimed at making money (commercial research). The samples will not have any information connected to them that could identify you.

Why would you want to be in the study?

If you get the hIVIG, it may help you get better faster, although we do not know that for sure. Remember that half (50%) of the people in this study will not get the hIVIG.

By being in this study, you help doctors know more about how to treat COVID-19 in people in the hospital. Because so many people are getting hospitalized with COVID-19, this could be a big impact if a treatment proves to be effective.

Why would you NOT want to be in the study?

Only half (50%) of the people in this study will get the hIVIG. You may not get the hIVIG. If hIVIG turns out to be a good treatment, you would not get that benefit. It's also possible that if you do get hIVIG, it may turn out not to be useful, or may cause side effects that are harmful to you.

What are the side effects of the study hIVIG treatment?

hIVIG is usually very safe to give. Similar immunoglobulin preparations have been used in many different diseases over many years, but immunogloblin prepared solely from individuals who have recovered from COVID-19 has not been studied before. In an earlier study of influenza hIVIG in people in the hospital with the flu, over 150 people got hIVIG. There were no serious problems that occurred in people because they got hIVIG.

All treatments cause side effects, and you may have some side effects from hIVIG. About 1% to 10% (1 in 100 people to 1 in 10 people) who get hIVIG get a fever, chills, nausea, vomiting, dizziness, shortness of breath, rash, hives, or headache, but these are usually not serious. These can happen during the infusion or afterwards and usually go away on their own or with short-term treatment. Although IVIG has been very safe for people with other diseases, less than 0.1% (less than 1 in 1,000) of people taking other types of IVIG for other illnesses have had very serious reactions to it, including a kind of lung injury called TRALI.

People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. This is very rare but is also a possible effect of any drug. Allergic reactions may be severe or life-threatening.

In some laboratory studies, infusions of antibodies have made infections with viruses similar to the virus that causes COVID-19 worse. This is a very unlikely but possible side effect of the treatment infusion in this study, and you will be closely monitored for any signs of this effect.

It is also possible that getting the study treatment infusions could cause problems with your health because of the amount of fluid given to you for the study treatment if you have some other health condition that affects how your body handles fluids. You will get up to about 400 mL of fluid for hIVIG or placebo, and about 100mL each day for remdesivir if you receive it

Some people may have some side effects after the hIVIG infusions. Other people may have no side effects. You will be monitored closely during the infusions, and short-term medical care will be provided if there are side effects from the infusions that can be treated.

What are the benefits and risks or side effects of remdesivir treatment?

Remdesivir was recently shown to help people who are in the hospital with COVID-19 to get better faster than people who got a placebo. You may be given remdesivir to treat your COVID-19 even if you do not join this study. If your doctor considers that remdesivir is not a suitable treatment for you, you can still join this study, and you will receive hIVIG or placebo without remdesivir. For example, remdesivir might be unsuitable for you if you have serious liver or kidney problems or an allergy to it.

The most common side effects of remdesivir include abnormal liver function test results, abnormal kidney function test results, fever, elevated blood sugar, constipation, nausea, vomiting, decreased appetite, and headache. The abnormal liver and kidney function tests may last a few days or longer but came back to normal levels over time.

People can have allergic reactions to drugs, including hives, trouble breathing, or other allergic responses. This is very rare but is also a possible effect of any drug. Allergic reactions may be severe or life-threatening.

Some people may have some side effects after the infusion of remdesivir. Other people may have no side effects. You will be monitored closely during the infusions, and short-term medical care will be provided if there are side effects from the infusions that can be treated.

What are the side effects of the other study procedures?

As shown in the table of what will happen at each visit, you will have some extra blood drawn for laboratory testing and storage. You will also have an extra swab of your nose and throat that would not be done if you are not in the study. The risks and discomforts of these

extra blood draws and swab are no different than what you would have if they were performed as part of your regular hospital care for COVID-19.

Additional information:

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

The US National Institutes of Health (NIH), an agency of the US Federal government, is paying for this study. Because public money is paying for the study, we are required to comply with all rules and regulations about research. We are doing this study according to internationally recognized standards of research as well as the laws of each country where the study is taking place.

This study is taking place in several countries. We expect to enroll about 500 people around the world.

You do not have to join this research study if you do not want to. If you choose to join the study, you can stop at any time by telling someone on the study team that you want to stop being in the study. If you choose not to join or to stop, your regular medical care will not change.

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

Your study participation may be stopped without your consent if:

- The groups overseeing the study decide the study should be stopped;
- Your study team believes that being in the study is no longer in your best interests.

If your participation is stopped, you will still get the usual care given at your hospital for COVID-19.

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

<u>What are the costs to you?</u>

We will give you the study treatment (hIVIG or placebo) at no cost. We will also give you remdesivir at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

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

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

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

Will you be paid to be in the study?

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

What if you are hurt as part of this study?

If you are hurt because of being in this study, *[insert the name of the hospital/clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

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

What happens to the blood samples and respiratory swabs?

We will send the blood and respiratory swab samples to a central laboratory in the United States of America. You and your doctor will **not** get the results of any tests done on these samples.

The blood samples will measure how many COVID-19 antibodies are in your blood. This will tell us how your immune system responded to your COVID-19. The nasal swab will measure how much virus you have in your respiratory system.

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

How do we protect your privacy?

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

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

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

These people may see your medical and research information at your site:

- the *[insert the name of the hospital/clinic]* ethics committee (institutional review board [IRB]);
- the sponsor, other study research staff, and study monitors
- US and other participating countries' health regulatory agencies
- the US National Institutes of Health which is funding the study

They are committed to protecting your privacy.

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

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

Your study data will be shared with the regulators that oversee the studies, as required by law. Your study data will also be shared with the drug company that provides the hIVIG to help them develop the drug.

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

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

A description of this clinical trial will be available at http://www.ClinicalTrials.gov as required by U.S. law, and on the EudraCT website (https://eudract.ema.europa.eu/). These websites will not include your name or any other direct identifiers such as your contact information.

These websites will include a summary of the results of this research once the study has been completed. You can search either website at any time.

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

To do this research, we will collect and use your personal data, as described above and in any HIPAA Authorization Form we have given you. Please tell us whether you agree to have us collect and use your personal data by placing your initials in front of your selection.

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

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

It is your choice whether you allow us to collect and use your data. However, you will not be able to be in this research and have a chance to get the experimental treatment if we cannot collect and use your data.

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

What are your rights regarding your data?

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

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

The GDPR gives you additional rights which we would like to inform you about below.

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

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

Right to Erasure/Anonymization

The sponsor is required under both EU and US law to retain data from research studies like this one for many years. However, you have the right to request that your personal data be completely anonymized. This is done by destroying the information at your

study center that links your identity to the pseudonymized data held by the sponsor. This means that no one would ever be able to link the data held by the sponsor to you personally.

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

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

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

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

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

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

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

Data protection officer responsible for the study center:	
Name:	

Address:	
Phone:	
Email	

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

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

What if you have problems or questions?

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

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

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

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

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE INSIGHT 013 STUDY (Inpatient Treatment with Anti-Coronavirus Immunoglobulin, ITAC)

I have read the consent or have had it explained to me. I am satisfied that I understand the information. By signing this consent, I am stating that I want to join this study. I understand that I do not waive any of my legal rights as a study participant by signing this consent. I understand that I will receive a copy of the signed and dated consent.

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

_____ Date: _____

Signature of participant

_____

Printed name of participant

_____ Date: _____

Signature of investigator/designee

_____

Printed name of investigator/designee

FOR ADULTS NOT CAPABLE of GIVING CONSENT

_____ Date: _____

Signature of Legally Authorized Representative (LAR)

_____

Printed name of LAR

_____

Relationship of LAR to Participant

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

Witness to Consent Interview

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

_____ Date: _____

Signature of witness

_____

Printed name of witness

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

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

APPENDIX B SCHEDULE OF ASSESSMENTS

	Screen or Day 0	Day 0	Follow-up Study Day Shaded columns denote in-person visits								
Day	**−1/0**[1]	**0**[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**28**
Acceptable deviation from day	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**+3**	**+4**
ELIGIBILITY & BASELINE DATA											
Informed consent	X										
Height and weight	X										
Baseline medical history (including day of illness from symptom onset)	X										
Baseline medications	X										
Symptom-directed physical exam	X										
Review SARS-CoV-2 test results	X										
Mid-turbinate swab for central SARS-CoV-2 viral load testing	X										
Urine pregnancy test or other documentation of pregnancy status	X										
STUDY INTERVENTION											
Randomization		X									
Study Drug/Placebo Administration		X									
Assess infusion completion and AEs		X									
STUDY PROCEDURES											
Clinical assessment for ordinal outcomes[2]		X	X	X	X	X	X	X	X	X	X
Vital signs for NEW score assessment[3]	X				X						
Hospitalization status					X		X		X	X	X
Interim medical history									X	X	X
Interim medications									X		
Borg dyspnea scale	X								X		
Clinical adverse events of any grade (present on day of assessment)		X	X		X				X		X
Incident grade 3 and 4 adverse events (all through Day 7)		X	X	X	X		X		X		
Local laboratory testing	X								X		

Research sample storage (plasma and serum) and central testing for immunoglobulin levels and neutralizing antibody titers[4]	X		X	X	X				X		X
SAEs and unanticipated problems	Report as they occur										
Deaths	Report as they occur										
Hospitalization Summary	Report upon hospital discharge										

[1] Screening and randomization can be done in same session.
[2] Collected every day for inpatients and at Days 7, 14 and 28 for outpatients.
[3] Collected while hospitalized only
[4]Consenting participants at selected sites will also be seen at Day 90 (+10 days) to obtain a blood sample for central testing and storage

APPENDIX C INSIGHT 013 PROTOCOL TEAM

To oversee the implementation of this treatment study, membership on the protocol team will include:

- Protocol co-chair(s)
- NIAID, Division of Clinical Research representatives
- INSIGHT University of Minnesota representatives
- INSIGHT International Coordinating Center representatives
- Collaborating laboratory representatives
- Collaborating hIVIG manufacturers
- Site investigators
- Study biostatisticians
- Community representative

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

APPENDIX D REFERENCES ON THE INSIGHT WEBSITE

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the INSIGHT 013 protocol and to other information pertinent to the study:

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

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

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

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

APPENDIX E LIST OF ACRONYMS

µL	microliter
ADE	Antibody-dependent enhancement
AE	adverse event
ACTT	Adaptive COVID-19 Treatment Trial
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
B19V	parvovirus B19
BMI	body mass index
CCP	convalescent plasma containing COVID-19 antibodies
CDC	Centers for Disease Control and Prevention (US)
CI	confidence interval
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CVA	cerebrovascular accident
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DVT	deep vein thrombosis
EC	ethics committee
ECMO	extra-corporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
EU	European Union
FDA	US Food and Drug Administration
g	gram(s)
GCP	Good Clinical Practice

GDPR	General Data Protection Regulation
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hIVIG	hyperimmune intravenous immunoglobulin
HR	hazard ratio
IB	investigator's brochure
ICC	International Coordinating Center
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Institutional Ethics Committee
IgA, IgE, IgG, IgM	immunoglobulin A, E, G, M
IL-6	interleukin 6
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IQR	interquartile range
IRB	Institutional Review Board
IVIG	intravenous immunoglobulin
kg	kilogram
mg	milligram
MI	myocardial infarction
mL	milliliter
mmol	millimole(s)
NEWS	National Early Warning Score
NIAID	National Institute of Allergy and Infectious Diseases, NIH (US)
NIH	National Institutes of Health (US)
nm	nanometer(s)

OHRP	Office for Human Research Protections (US)
OR	odds ratio
PCR	polymerase chain reaction
PHI	personal health information
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury
UMN	University of Minnesota
UP	unanticipated problem
US	United States of America
WHO	World Health Organization
WNV	West Nile virus

APPENDIX F CLINICAL CATEGORICAL DEFINITIONS FOR ORDINAL OUTCOME

Each participant is categorized in the highest applicable category.

Ordinal Category	Categorical Description	Categorical Definition*
7	Death	Death
6	End-organ failure	Currently requiring invasive assisted ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy
5	Life-threatening end-organ dysfunction	Currently requiring non-invasive assisted ventilation or high-flow oxygen or Extra-pulmonary: Symptoms and signs of an acute stroke (NIHSS > 14)
4	Serious end-organ dysfunction	Currently requiring supplemental oxygen (≥ 4 liters/min, or ≥ 4 liters/min above premorbid requirements**) but not high-flow oxygen or Any of symptoms or signs of the following extra-pulmonary conditions: Stroke (NIH Stroke Scale/Score [NIHSS] ≤ 14), meningitis, encephalitis, or myelitis, myocardial infarction, myocarditis, pericarditis, or New York Heart Association Class III or IV congestive heart failure, arterial or deep venous thrombosis including pulmonary embolism.
3	Moderate end-organ dysfunction	Requiring supplemental oxygen < 4 liters/min, or < 4 liters/min above premorbid requirements**
2	Limiting symptoms due to COVID-19	Symptomatic and currently unable to independently undertake usual activities
1	No limiting symptoms due to COVID-19	Can independently undertake usual activities with minimal or no symptoms

***Continued hospitalization or presence in a particular category of inpatient facility (e.g. intensive care or high dependency) is not used to divide these categories, as indication for continued hospitalization among recovering COVID patients is intrinsically subjective, in part determined by social and financial factors, and varies markedly across the globe.*

*** Premorbid requirement refers to requirements prior to the development of COVID-19, for example in patients with chronic obstructive pulmonary disease, other chronic pulmonary diseases, or oxygen requirements related to altitude.*

APPENDIX G NATIONAL EARLY WARNING SCORE (NEWS)

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

≤40	+3
41-50	+1
51-90	0
91-110	+1
111-130	+2
≥131	+3
AVPU	
A	0
V, P, or U	+3

AVPU - Alert, Voice, Pain, Unresponsive.

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