VA CoronavirUs Research and Efficacy Studies-1 (VA CURES-1)

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Sponsor:
Office of Research and Development
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PRIVILEGED AND CONFIDENTIAL

1 TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and applicable VA policies, regulations and procedures. The Study Chairs will assure that no deviations from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the VA Central Institutional Review Board (CIRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study will have completed Human Subjects Protection and ICH GCP Training prior to participation in study activities.

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the VA CIRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the VA CIRB before the changes are implemented to the study. All changes to the consent form will be VA CIRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

EXECUTIVE SUMMARY

The very acute onset and rapid dissemination of SARS-Coronavirus-2 (SARS-COV-2) across the world over several months precluded the early availability of effective preventive and therapeutic interventions. The impact of SARS-CoV-2 is substantial with hospitalization of about 20% of those infected, half of whom require intensive care due to respiratory failure from which death may ensue. Prominent among those who preferentially experience this high incidence of morbidity and mortality are men over age 65 years with underlying comorbidities such as hypertension, diabetes, lung, heart, kidney or liver disease, obesity and immunocompromise[1; 2], clinical features commonly shared by the Veteran population. Effective therapies are currently quite limited. We propose to bolster immune defense against the virus with convalescent plasma that contributes antiviral antibodies and, potentially, non-antibody factors to its therapeutic activity.

Hospitalized Veterans with documented SARS-CoV-2 infection and evidence of early respiratory compromise (hypoxemia and requirement for oxygen) will be randomized to receive convalescent plasma or a masked saline placebo. The primary outcome is the rapidity and frequency of progression to respiratory failure or death in the two groups. The randomized, double-blind placebo-controlled design is essential to confirm the utility or the futility of convalescent plasma, building on mostly promising safety and outcomes with convalescent plasma in 6 anecdotal and case series of 56 patients with SARS-CoV-2[3-8] and a small non-randomized trial with retrospective controls [9]. However, observational and non-randomized studies may miss systematic bias and are not always confirmed with controlled randomized trials for other viral infections[10,11-15], thus the rigorous controlled trial of convalescent plasma proposed in VA **C**oronavir**U**s **R**esearch and **E**fficacy **S**tudies-1 (VA CURES-1).

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title

VA **C**oronavir**U**s **R**esearch and **E**fficacy **S**tudies-1 (VA CURES-1).

Study Description

The full VA CURES program is a newly initiated series of adaptive, double-blind placebo-controlled, randomized clinical trials (RCTs) to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19. This framework will permit multicenter trials to be conducted in VA Medical Centers to compare different investigational therapeutic agents to a single contemporaneous control arm consisting of best supportive care (BSC). Interim monitoring will allow early stopping for futility, efficacy, or safety. After VA CURES-1 testing convalescent plasma vs saline is launched, new arms or new trials can be introduced according to scientific and public health needs. If one therapy proves to be efficacious, this treatment may become the control arm for comparison(s) with new experimental treatment(s). Any such change would be accompanied by an updated sample size and an amended protocol.

This adaptive platform is used to rapidly evaluate different therapeutics in a population of those hospitalized with moderate to severe COVID-19. The platform will provide a common framework sharing a similar population, design, endpoints, and safety oversight. New stages with new therapeutics can be introduced and will be described in a stage-specific appendix. One independent Data and Monitoring Committee (DMC) will actively monitor interim data in all stages to make recommendations about early study closure or changes to study arms.

This VA CURES adaptive design RCTs may involve multiple stages, each investigating different interventions. To convey clearly the protocol elements, interventions, objectives and endpoints for each stage, common elements are described in the main protocol document while each stage is noted in a stage-specific appendix.

The first stage in the clinical trial (VA CURES-1) is:

Stage 1: Convalescent Plasma vs Saline

If convalescent plasma is shown to be beneficial in Stage 1, we may proceed to the next stage (VA CURES-1a) under amended design and subsequent approval:

Stage 1a: Convalescent Plasma vs Fresh Frozen Plasma

If convalescent plasma is shown not to be beneficial in Stage 1, we will design a RCT testing an alternative agent.

Study Objectives

The primary objective of the VA CURES program is to evaluate the clinical efficacy of different investigational therapeutics compared with the control arm by binary analysis of the composite primary outcome of acute hypoxemic respiratory failure or all-cause death by Day 28. Acute hypoxemic respiratory failure is defined as the initiation of mechanical ventilation [either via

endotracheal intubation or as non-invasive positive pressure ventilation (NIPPV) for an indication other than for pre-diagnosed sleep apnea at outpatient settings] OR extracorporeal membrane oxygenation (ECMO).

The secondary objectives are to evaluate the clinical efficacy and safety of different investigational therapeutics compared to the control arm as assessed by the secondary efficacy outcomes and the safety outcomes defined in the stage-specific Objectives and Endpoints. Each stage may prioritize different secondary endpoints for the purpose of multiple comparison analyses.

Study Outcomes

Primary efficacy outcome: Proportion of participants developing acute hypoxemic respiratory failure or all-cause death up to day 28.
Key secondary efficacy outcome: Time to recovery (as determined by attaining a score of 1,2 or 3 on the World Health Organization (WHO) 8-point ordinal scale).

Study Population

This trial will study putative therapeutics in a hospitalized adult population (≥18 years old) with moderate to severe COVID-19. The trial will have common inclusion and exclusion criteria but may be modified for each stage for the unique risk of the study product in that stage.

Inclusion Criteria

1) Age 18 or older.
2) Confirmed acute SARS-CoV-2 infection.
3) Requirement for supplemental oxygen therapy that is either new or at least 2 Lpm greater than previous outpatient chronic therapy.
4) Ability to provide written informed consent from patient or legally authorized representative (LAR).

Exclusion Criteria

1) anticipated hospitalization <48 hours.
2) anticipated respiratory failure (as defined above) or death within 48 hours.
3) Septic shock or multiple organ dysfunction or failure.
4) Current or anticipated participation in another randomized trial for SARS-CoV-2.

Study Phase

Phase 3

Study Sites

VA CURES-1 will initially engage 25 VA Medical Centers nationally. Site selection will be determined by presence of: 1) sufficient numbers of cases of COVID-19; 2) a committed local site investigator (LSI); 3) established infrastructure for clinical trials (study coordinator(s), research pharmacist, blood bank); 4) onsite clinical laboratory; and 5) laboratory facilities for study sample processing, labeling and storage. Multiple sites will be IRB-approved via VA CIRB, but site activation will be dependent on the incidence of SARS-CoV-2 at that site.

Study Intervention

Study interventions will vary depending on the stages or trials under VA CURES. VA CURES-1 compares convalescent plasma versus saline.

Study Duration

The series of studies comprising the full VA CURES adaptive study will last for up to 60 months. This specific protocol (VA CURES-1) will have a specific timeline (20 months) within the full VA CURES adaptive protocol. The study can be terminated early if the target number of participants is met or if the interim analysis demonstrates efficacy, harm or futility accordingly to protocol-specified stopping boundaries.

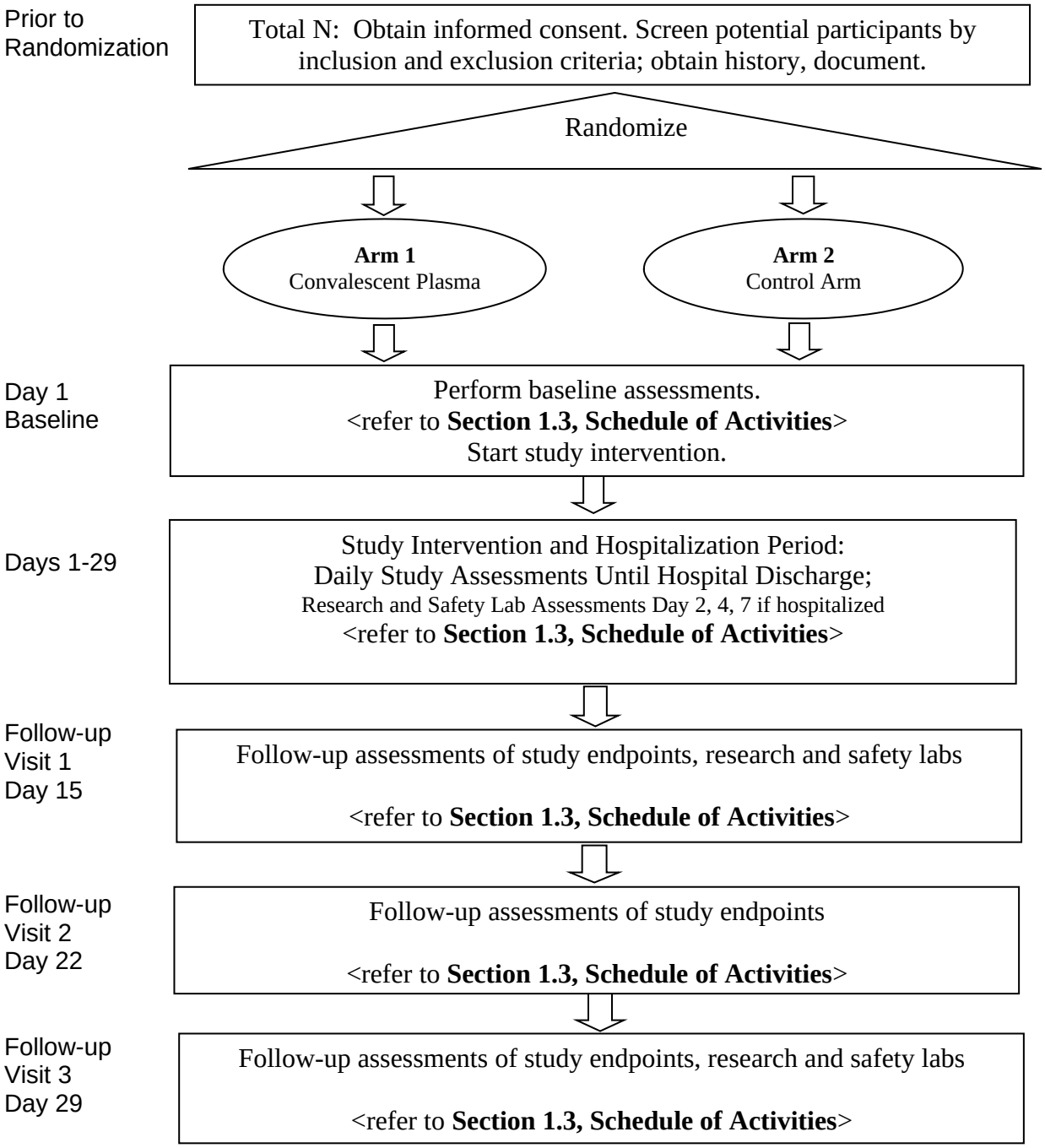
Participant Duration

An individual subject will complete the study in up to 35 days, from screening and randomization at Day -3 to 0, to follow-up on Day 29 + 3 days.

1.2 STUDY SCHEMA

This adaptive design clinical trial may involve multiple stages each investigating different interventions. In order to clearly convey the protocol elements, interventions, objectives and endpoints for each stage, common elements are described in the main protocol document while each stage is noted in a stage-specific appendix. Below is the study schema for Stage 1.

Figure 1. Study Schema



1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1. Schedule of Assessments

Day ± Window	Up to 72 hrs. prior to Randomization Time	Day 1	Up to 36 hrs. after Randomization Time	Day 2 - Hospital Discharge		Day 15 ±2	Day 22 ±3	Day 29 +3[15]
Procedures	**Eligibility**	**Randomization/ Baseline**	**Product Administration**	**Hospitalization[14] Period**	**Initial Discharge**	**Follow-up Visit 1 (15d)**	**Follow-up Visit 2 (22d)**	**Follow-up Visit 3 (29d)**
Obtain signed Informed Consent[1]	X							
Obtain Demographics & Medical History data	X							
Perform physical exam	X							
Review -SARS-CoV-2 results	X							
Administer pregnancy test for females	X							
Review Eligibility	X							
Randomize participant		X[3]						
Assess Admission Signs and Symptoms		X[4]						
Collect Vital Signs[2] (NEWS2)		X[4]		X[9]		X[13]		X[13]
Collect Clinical status data[2]		X[4]		X[9]		X	X	X
Evaluate Adverse Events		X[4]	X	X[9]	X	X	X	X
Review Concomitant Medications		X[4]	X[7]		X	X	X	X
Obtain Safety Labs[5] -Hematology, chemistry, liver tests		X[4]		X[10,12]		X[13]		X[13]
Obtain Exploratory Research Labs[6] -Blood -Respiratory sample		X[4]		X[11,12]		X[13]		X[13]
Administer Study Product			X[8]					
Obtain Discharge info					X			
Collect Readmission data, if applicable						X	X	X

Notes:

[1] This form is completed by the participant or legal representative.

[2] Refer to Section 8.1 of the protocol for details of clinical data to be collected including WHO ordinal score, National Early Warning Score (NEWS2), oxygen requirement, mechanical ventilator requirement, etc.

[3] Randomization must occur within 72 hours of initial hospital admission.

[4] Baseline assessments should be performed before the first study product administration:

- *Day 1 safety labs and Day 1 exploratory research specimens can be collected up to 24 hours prior to randomization and before the first study product administration.*
- *Laboratory tests performed as part of routine clinical care up to 24 hours before randomization will be accepted for the baseline safety laboratory tests.*
- *See Visit Schedule Grid for more details.*

[5] Safety laboratory tests include WBC with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and prothrombin time (PT).

[6] Research Specimens include respiratory samples and 30mL of blood for research studies (2 tablespoons) as feasible. Nasopharyngeal (NP) swabs are preferred, but if these are not obtainable, oropharyngeal (OP), saliva (S) or anterior nares swabs (AN) may be substituted.

[7] If product administration starts on day of randomization (Day 1), then concomitant medications only need to be reviewed one time, at day of randomization

[8] Ideally, product administration should start on the same day as randomization (Day 1) but may be started up to 36 hours after randomization.

[9] Obtain clinical status data, vital sign data (for NEWS2), and assess adverse events daily during hospitalization, both during initial hospitalization and for readmissions.

[10] Obtain safety labs only on Days 2, 4, and 7 if hospitalized, including readmissions. Any laboratory tests performed as part of routine clinical care within the visit windows specified in Table 5 can be used for safety laboratory testing.

[11] Blood for research studies only on Days 2, 4, and 7 and swabs for RT-PCR only on Days 4, and 7, if hospitalized (includes readmissions).

[12] If not hospitalized at study site on Day 2, 4 or 7, no need to collect any labs or specimen on that day.

[13] For Day 15, 22, and 29 follow-up visits:

- *If not hospitalized and have an in-person visit on Day 15 and 29: collect NEWS2, safety laboratory tests, and research laboratory samples.*
- *If discharged, collect hospital readmission data at each subsequent visit.*
- *Day 22 visit (after discharge) is generally done by phone or telehealth.*
- *<u>In-person</u> visits (after discharge) are preferred and strongly encouraged for <u>Days 15 and 29</u>. However, when quarantine and other factors limit the participant's ability to return to the site for the visit, they may be performed by telehealth or by phone.*

[14] Hospitalization period includes initial hospitalization and readmissions.

[15] The final visit cannot occur before Day 29.

2 INTRODUCTION

2.1 STUDY RATIONALE

Since December 2019, SARS-Coronavirus 2 (SARS-CoV-2; COVID-19) infections are over 6 million persons and approaching 200,000 deaths in the US with a continually rising rate of infection. Of the ≈20% of patients admitted to hospital, up to half progress to ICU admission, respiratory failure or death. Prominent among these progressors are older men, particularly those with underlying comorbidities (e.g., hypertension, diabetes, lung, heart, kidney or liver disease, obesity and immunocompromised)[1], all common among Veterans. Effective interventions are few, other than recently-approved remdesivir, which shortened hospital stay but did not decreased overall mortality[16]. Convalescent plasma from persons recovered from SARS-CoV-2 infection is readily available for treatment.

Convalescent plasma therapy is being used empirically, although only five of six small uncontrolled case series (total n=56) in SARS-CoV-2[3-8] and a recent study with non-randomized controls[9] suggest improved selected clinical, virologic and laboratory outcomes and outcomes in another small randomized trial were equivocal[17]. For other infections, such as influenza and Ebola virus, promising observational studies were not reliably confirmed by controlled trials [10,11-15]. In multiple infections, use of convalescent plasma has been distinguished by its safety profile but not by the consistency of its benefit. The current double-blind, placebo-controlled RCT is designed to determine definitively whether this intervention is effective in a population at high risk of complications and death from SARS-CoV-2 infection. We compare the effect of convalescent plasma vs. saline placebo with a robust study design, adequate sample size and statistical and logistical rigor to assure that the interventions we make to treat serious disease are well-validated to support its use or to move on to test other potentially safe and effective treatments.

2.2 BACKGROUND

Purpose of the Study

The newly emergent coronavirus SARS-CoV-2 has exceeded two earlier highly fatal species—severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS) in 2012 in the speed and breadth of its transmission worldwide and four common upper respiratory coronavirus species in its virulence and associated mortality. Described initially in Wuhan, China, the infection has already spread to infect over 25 million persons worldwide with 860,000 deaths as of September 1, 2020, and over 6 million infected in the U.S. and approaching 200,000 deaths. Although the majority of persons infected recover naturally based on their own innate and adaptive immune responses, up to 20% are ultimately hospitalized with an increased risk of respiratory failure and death. Persons age 65 years or older represent a minority of infections but comprise the majority of those with complications, hospitalization and death[1,18]. These outcomes are most prominent among older persons with comorbidities, e.g., chronic lung, cardiac and renal disease, as well

as hypertension, diabetes, obesity and immunosuppression[1; 2], conditions common among veterans.

In the absence of an effective vaccine or other biologic preventive measures, treatment options for those with serious disease are also limited. To date, only one antiviral medication (remdesivir) has shown efficacy to shorten time to recovery but not decrease mortality[16]. Multiple medications to limit viral replication, minimize inflammation, modulate immune responses are in broad empiric use and testing[19], but none other has been proven to be effective[20-23] and a number have untoward side effects[22].

Convalescent plasma from persons recovered from SARS-CoV-2 is being used to treat hospitalized individuals with complicated COVID-19 infection. Although relatively safe and widely used, only sparse data support the efficacy of this intervention to limit respiratory failure and death. With other infections (SARS, influenza, Ebola), initiation of plasma therapy early in hospitalization was variably associated with improved outcomes[14,24,25], outcomes that may not be consistently confirmed in randomized controlled trials[26,27]. Validating the efficacy of convalescent plasma therapy for COVID-19 is an important goal, given the contradiction between results of ad hoc versus controlled evaluations of convalescent plasma for other acute viral infections. We will determine the ability of convalescent plasma initiated early in the course of hospitalized disease to decrease respiratory failure and death from SARS-CoV-2 with a robust prospective, randomized, placebo-controlled study protocol. In the context of an acute threatening pandemic, we are compelled to intervene; we propose to determine whether we are using an effective intervention and doing no harm.

Study Design

The parent VA CURES study is an adaptive set of randomized double-blind placebo-controlled trials to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19; VA CURES-1 determines the impact of convalescent plasma vs. saline on critical clinical outcomes. The study is a multicenter trial that will be conducted at VA Medical Centers to compare different investigational therapeutic agents to a control arm. New arms can be introduced according to scientific and public health needs. There will be interim monitoring to allow early stopping for futility, efficacy, or safety. If one therapy proves to be efficacious, then this treatment may become the control arm for comparison(s) with new experimental treatment(s). Any such change would be accompanied by an updated sample size. This adaptive platform is used to rapidly evaluate different therapeutics in a population of those hospitalized with moderate to severe COVID-19. The platform will provide a common framework sharing a similar population, design, endpoints, and safety oversight. New stages with new therapeutics can be introduced and will be described in a stage-specific appendix. One independent Data and Monitoring Committee (DMC) will actively monitor interim data in all stages to make recommendations about early study closure or changes to study arms.

This adaptive design clinical trial may involve multiple stages each investigating different interventions. In order to clearly convey the protocol elements, interventions, objectives and endpoints for each stage, common elements are described in the main protocol document while each stage is noted in a stage-specific appendix.

The first stage in the clinical trial is:

Stage 1: Convalescent Plasma vs Saline (VA CURES-1)

If convalescent plasma is shown to be beneficial in Stage 1, we may proceed to the next stage (Stage 1a) under separate review and protocol:

Stage 1a: Convalescent Plasma vs Fresh Frozen Plasma (VA CURES-1a)

Participants will be assessed daily while hospitalized with a series of efficacy, safety, and laboratory assessments. See stage-specific schedule of assessments for details.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Reported risks with convalescent plasma have been very few, despite its broad use in patients with influenza, SARS-CoV, MERS and Ebola virus. Among 5,000 patients with SARS-CoV-2, serious adverse events in the first 4 hours after transfusion were <1%, but included death in 0.3% in these very ill patients[28]. Based on an extensive clinical experience with fresh frozen plasma, infrequent reactions include pulmonary edema from transfusion-associated circulatory overload (TACO). There may be a possibility of mild transfusion reactions with urticaria or more severe reactions such as transfusion-related acute lung injury (TRALI) occurring shortly after transfusion in the following circumstances: ABO blood group incompatibility, highly or less reactive transfused anti-human leukocyte antigen (HLA) Class II antibody, anti-human neutrophil antigen (HNA) antibody and antibodies to IgA among IgA-deficient recipients. Fresh frozen plasma overall is associated with 1:9,500 risk of incompatible plasma-related hemolysis. Most hospitals have a daily maximum amount of allowable transfusion of incompatible plasma[29,30]. The hemolysis risk with transfusion of incompatible plasma is ~1:12,000 for TRALI in HLA Ab-tested platelet/plasma units (only previously pregnant females tested).

Passive administration may inhibit subsequent antibody production and subsequent protection from disease, as reported for Respiratory Syncytial Virus (RSV). Although the U.S. blood supply is screened for all known transmissible pathogens, there is also a potential risk for the transmission of currently unrecognized pathogens.

2.3.2 KNOWN POTENTIAL BENEFITS

The possibility that use of convalescent immune plasma may be associated with benefits is supported by a limited number of small case series [3,5-7] and a non-randomized controlled study with SARS-CoV-2[9, and] few prospective randomized trials with SARS-CoV [24], MERS[25,31]. These benefits have included decreased oxygen requirement, improved pulmonary infiltrates, decreased duration of hospitalization, more rapid resolution of viral detection, improvement in inflammatory laboratory parameters and, in some cases, mortality[3,24,32]. More substantial results support the use of convalescent plasma with influenza with decreased mortality and length of hospital stay[10,25,33], particularly in very early studies and when administered earlier in the course of disease and hospitalization (≤4 days for influenza).

Mechanistically, the potency of convalescent plasma is thought to be due to neutralizing antibodies, particularly to the surface S spike and receptor binding domain of the virus[34] that prevent binding to epithelial and other target cells as well as cell-to-cell spread. However, antibodies may also enhance virulence mechanisms as well as neutralize [35-37]. Antibodies in convalescent plasma may facilitate clearance of bacterial and viral coinfections and modify inflammation and modulate T cell function[38], limit neutrophil adhesion to and activation of endothelial cells and support antigen-presentation to facilitate immune responses.

It is also possible that non-convalescent plasma would have some benefit. Polyclonal antibodies in plasma likely avoid selection of viral escape mutants that can accompany therapy with monoclonal antibodies. Non-neutralizing antibodies may serve a range of Fc-mediated protective effects[39,40] by supporting antibody-dependent cellular cytotoxicity (ADCC) by natural killer (NK) and cytotoxic lymphocytes to kill infected cells and supporting phagocytosis of virus and infected cells (ADCP). Non-antibody protective functions of plasma may mediate inhibition of inflammation and cytokine production and regulate complement-dependent lung epithelial and vascular endothelial damage[41] with regulatory proteins such as CD55[42]. The volume of plasma infused is unlikely to modify clotting parameters.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The safety of fresh frozen plasma, including convalescent immune plasma from persons with SARS-CoV-2, given to persons with active disease is high. The potential benefits, as above, include decreased mortality, decreased hospital length of stay and improvement in hypoxemia, pulmonary infiltrates and overall clinical status by a range of mechanisms. All of these outcomes are based on very sparse case series and almost all studies are of low or very low quality, lacked controls groups, and were at moderate to high risk of bias[25]. Hence, we believe that equipoise about the risks and benefits exist. A prospective randomized placebo-controlled study provides credible and actionable results to support or negate the use of this intervention. The results also provide a solid rationale for more selective and effective interventions with antibody alone (purified polyclonal or monoclonal), non-immune plasma alone, or specific plasma components that may be more readily accessible and affordable to persons within the VA and worldwide.

3 OBJECTIVES AND ENDPOINTS

Table 2. Objectives and Endpoints.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: • Proportion of patients who died from any cause or had respiratory failure by Day 28	• Died from any cause; • Respiratory failure is defined by requiring mechanical ventilation, with or without endotracheal intubations, or extra-corporeal membrane oxygenation. This is evaluated up to and including Day 28.
Key Secondary	
To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm, as assessed by: • Time (in days) to recovery (as defined by attaining stages 1, 2 or 3 on the WHO 8-point ordinal scale)	Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the WHO ordinal scale: • Hospitalized, not requiring supplemental oxygen; • Not hospitalized, limitation on activities and/or requiring home oxygen; • Not hospitalized, no limitations on activities. This is evaluated up to and including Day 28.
Additional Secondary	
1. To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: • Time (in days) to death or respiratory failure by Day 28	Time to death or respiratory failure is defined as the first day on which the subject died from any cause or had respiratory failure (defined above). This is evaluated up to and including Day 28.
2. To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: • Proportion of patients who died from any cause, had respiratory failure or required humidified heated high-flow nasal cannula (HHHFNC) at ≥ 15 Lpm by Day 28 • Time (in days) to death or respiratory failure or HHHFNC at ≥ 15 Lpm by Day 28	This is evaluated up to and including Day 28.

3. To evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: • **Mortality** o 28-day all-cause mortality	• Date and cause of death (if applicable)
• **Clinical Severity** *1) 8-point ordinal scale: (WHO)* ▪ Time to an improvement of one category from Day 1 (baseline) using the WHO ordinal scale. ▪ Time to an improvement of two categories from Day 1 (baseline) using the WHO ordinal scale. ▪ Subject clinical status using ordinal scale at Days 2, 4, 7, 11, 14, 21, and 28. ▪ Mean change in the WHO ordinal scale from Day 1 (baseline) to Days 2, 4, 7, 11, 14, 21, and 28.	• WHO ordinal scale (See Table 3) Clinical outcome assessed using ordinal scale daily while hospitalized and on Days 14, 21, and 28.
2) National Early Warning Score (NEWS2)[43,44]: ▪ Time to discharge from initial hospitalization or to a NEWS2 of ≤ 2 and maintained for 24 hours, whichever occurs first. ▪ Change from Day 1 (baseline) to Days 2, 4, 7, 11, 15, and 29 in NEWS2.	• NEWS2 assessed daily while hospitalized and on Days 15 and 29 (if the participant attends an in-person visit or still hospitalized)
• **Hospitalization** ▪ Duration of initial hospitalization (days). ▪ Number of hospitalizations related to COVID-19	• Number and days of hospitalizations up to and including Day 28

4. To evaluate the safety of different investigational therapeutics as compared to the control arm as assessed by: • Cumulative incidence of SAEs through Day 29. • Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs through Day 29. • Discontinuation or temporary suspension of study product administrations (for any reason) • Changes in complete blood count with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and prothrombin time (PT) reported as international normalized ratio (INR) over time (analysis of lab values in addition to AEs noted above).	• SAEs • Grade 3 and 4 AEs • Change in total WBC number, neutrophil number, lymphocyte number, hemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, AST, and PT/INR from Day 1 to Days 2, 4, and 7 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).
Exploratory	
1. To examine if the effect of convalescent plasma is associated with the days of symptoms at time of plasma administration	• Plasma administered on day ≤7 vs. >7 days of symptoms on primary outcome
2. To examine if effect of convalescent plasma differs by comorbidities	• Primary outcome in persons with ≤2 or ≥3 comorbidities **(**age ≥65 years, chronic lung, cardiac and renal disease, hypertension, diabetes, obesity and immunosuppression)
3. Research sample collection and management for future investigations: Respiratory samples on days 1, 4, 7, 15, 29 and 30 mL of blood on days 1, 2, 4, 7 in hospital and days 15 and 29 in- or outpatient.	• Sample Collection (Research lab draw with routine labs), preparation, labeling, shipping, storage and monitoring will be addressed in a future amendment.
4. Impact of donor convalescent plasma parameters on the activity of administered plasma	• Donor plasma samples retained by Vitalant Blood services and provided to CURES-1 investigators will be tested for antibody levels, neutralization against SARS-CoV2, inflammatory and other mediators in relation to clinical and laboratory outcomes in study subjects.

World Health Organization (WHO) Ordinal Scale

WHO 8-point ordinal scale for clinical improvement, modified for use in this study, is described in ***Table 3***. Note that this scale is being calculated to permit comparability of VA CURES-1 to other studies of experimental therapies for COVID-19, although a clinical score of "5" by the WHO scale differs from the operational definition of acute hypoxemic respiratory failure for use in determining this study's primary outcome.

Table 3. Modified WHO 8-point Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Clinical Score
Uninfected	No clinical or Virologic evidence of infection	0
Ambulatory	No limitation of activity	1
	Limitation of activity and/or home oxygen	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prong	4
Hospitalized Severe disease	Humidified high-flow oxygen	5a
	Non-invasive ventilation	5b
	Intubation and mechanical Ventilation	6
	Ventilation + additional organ support—pressors, RRT, ECMO	7
Dead	Death	8

National Early Warning Score-2

NEWS2 has demonstrated an ability to discriminate subjects at risk of poor outcomes[43]. This score is based on seven clinical parameters (see **Table 4**). The NEWS2 is being used as an efficacy measure. The NEWS2 Score should be evaluated daily while hospitalized and on Days 15 and 29. It can be performed concurrently with the Ordinal Scale. NEWS2 should be evaluated at a consistent time for each applicable study day, if possible. The seven parameters can be obtained from the hospital chart or electronic medical record (EMR) using the last measurement prior to the time of assessment. A numeric score is given for each parameter (e.g., a RR of 9 is one point, oxygen saturation of 92 is two points). This value is recorded for the day obtained (i.e., on Day 3, the vital signs and other parameters from Day 3 are used to obtain NEWS2 Score for Day 3). ECMO and mechanically ventilated subjects should be assigned a score of 3 for RR (RR <8) regardless of the ventilator setting. Subjects on ECMO should get a score of 3 for heart rate since they are on cardiopulmonary bypass.

Table 4. The NEWS Scoring System [43]

Physiological parameter	Score						
	3	2	1	0	1	2	3
Respiration rate (per minute)	≤ 8		9-11	12-20		21-24	≥ 25
SpO_2 Scale 1 (%)	≤ 91	92-93	94-95	≥ 96			
SpO_2 Scale 2[1] (%)	≤ 83	84-85	86-87	88-92 ≥ 93 on air	93-94 on oxygen	95-96 on oxygen	≥ 97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤ 90	91-100	101-110	111-219			≥ 220
Pulse (per minute)	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Consciousness[2]				Alert			CVPU
Temperature (C)	≤ 35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥ 39.1	

[1]*SpO_2 Scale 2 is used only for participants with history of pre-existing suspected or confirmed hypercapnia.*
[2]*Level of consciousness = alert (A), conscious but non-alert (C) and arousable only to voice (V) or pain (P), or unresponsive (U).*

4 STUDY DESIGN

4.1 OVERALL DESIGN

The VA CoronavirUs Research and Efficacy Study-1 (VA CURES-1) is designed to determine the safety and efficacy of convalescent plasma to prevent progression to respiratory failure and death among persons hospitalized with SARS-CoV-2 and who require supplemental oxygen.

This adaptive design clinical trial may involve multiple stages each investigating different interventions.

The first stage in the clinical trial is:

Stage 1: Convalescent Plasma vs Saline

If convalescent plasma is shown to be beneficial in Stage 1, we will proceed to Stage 2:

Stage 2: Convalescent Plasma vs Fresh Frozen Plasma

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma contains SARS-CoV-2-specific antibodies that support neutralization and other antiviral activities that will inhibit viral replication and lyse infected cells to limit underlying tissue damage and inflammation. Administration of convalescent plasma early in the course of infection in the hospital will increase the days to and prevent respiratory failure and death before irreversible lung and vascular damage ensues.

4.3 JUSTIFICATION FOR DOSE

The planned plasma volume for this study is 400-600 mL. Plasma is collected in ~200-250 mL units. All studies to date using convalescent plasma have used 200-600 mL (1-2 units) of plasma. This dose typically provides sufficient antibodies to maintain or increase virus-specific levels in plasma of recipients and is generally well-tolerated for volume. If 400-600 mL volume is deemed excessive due to e.g., congestive heart failure or oliguria, then 200-250 mL will be given if deemed safe by the primary clinicians and study staff.

4.4 END OF STUDY DEFINITION

The study is completed for each subject on day 29 (+3 days) after administration of convalescent plasma or on the day of death.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Veterans must meet ALL of the following criteria to be eligible to participate:

1. Admitted to a participating VA clinical site with symptoms suggestive of SARS-CoV-2 infection.
2. Participant (or legally authorized representative) provides informed consent prior to initiation of any study procedures.
3. Participant (or legally authorized representative) understands and agrees to comply with planned study procedures.
4. Veteran ≥ 18 years of age at time of screening.
5. Has laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or antigen test, as documented by either of the following:
    (1) RT-PCR or antigen positive (nasopharyngeal, oropharyngeal, saliva, lower respiratory) in sample collected ≤ 72 hours prior to screening;
    (2) RT-PCR or antigen positive in sample collected > 72 hours but ≤ 168 hours (i.e. 7 days) prior to screening, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc.), AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
6. Requiring oxygen by nasal cannula or by face-mask as a new treatment (or if previously on home oxygen, at a liter flow at least 2 Lpm greater than home prescription), but not on humidified heated high-flow nasal cannula (HHHFNC) at ≥ 15 Lpm.
7. Can be randomized within 72 hours of initial hospital admission.
8. Agrees not to participate in another therapeutic clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 29 without approval from the investigator(s). Taking part in other research studies, including those unrelated to SARS-CoV-2, without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other study.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Respiratory failure requiring mechanical ventilation, non-invasive ventilation including CPAP (for an indication other than previously diagnosed sleep apnea and maintained on outpatient settings), or extra-corporeal membrane oxygenation or anticipated to require any of those treatments or to die within 24 hours.
2. Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 hours.
3. History of previous transfusion reaction.
4. Previously documented serum IgA deficiency (<7 mg/dL)
5. Documented to have received convalescent plasma in the last 60 days.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Avoid participating in another interventional clinical trial for the treatment of SARS-CoV-2 or SARS-CoV-2. Co-enrollment for natural history studies of SARS-CoV-2 is permitted or studies unrelated to of SARS-CoV-2 can be considered if PI of both studies agree.

5.4 SCREEN FAILURES.

Following Consent and after screening evaluations have been completed, the LSI or designee will review the inclusion/exclusion criteria and determine the subject's eligibility for the study. If there is any uncertainty, the Local Site Investigator (LSI) should make the decision on whether a potential subject is eligible for study enrollment.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients recruited to the study will be from those admitted to acute inpatient medical services. Research staff will employ several strategies to identify potentially eligible subjects. No external recruitment methods are anticipated.

Materials summarizing the purpose and design of the study, key interventions, and key inclusion and exclusion criteria will be made available to clinical providers caring for patients hospitalized with SARS-CoV-2.

Potential participants will be identified by IRB-approved review of CPRS charts and hospital admission logs under a HIPAA waiver. Pre-screening for preliminary eligibility will be performed by a member of the site research team, usually the Site Coordinator, who will complete a checklist of key inclusion and exclusion criteria. If *a priori* requirements for enrollment are met, permission will be obtained, if not previously granted, from the patient's clinical provider to seek informed consent for participation in the study from the patient or his/her authorized healthcare proxy.

Over 30 VA Medical Centers have expressed interest in participating in this study. In the last three months of the epidemic, 1,890 patients with SARS-CoV-2 were admitted to the top 25 VA

medical center targeted for inclusion in this study. The study is proposed to require approximately 702 participants admitted with SARS-CoV-2, assuming a 30% primary event frequency in the study sample, to have 85% power for detecting a 10% absolute reduction in the primary event with convalescent plasma (i.e., hazard ratio 0.7). Among 568 patients admitted with SARS-CoV-2 to the Detroit VA, 69% achieved the primary endpoint of respiratory failure or death, although these frequencies may decrease with less ill patients admitted and more skilled management over time. Proactive and consistent team management and communication will be required for effective ongoing recruitment.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Patients will be randomized within 72 hours of admission to receive 1) 400-600 mL of ABO compatible convalescent plasma from the hospital blood bank or 2) sterile saline, each wrapped in non-disclosing paper with translucent tubing over approximately 4 hours. If volume overload is a concern, 200-300 mL will be infused by pump over 2 hours.

6.1.2 DOSING AND ADMINISTRATION

The dose of convalescent plasma, or placebo, that will be utilized in this study is consistent with the April 8, 2020 published by the FDA (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma). We will utilize a target dose of two units of plasma with antibodies to SARS-CoV-2, based on previously studied dosing established in SARS1, in which a weight-based dose of 5 mL/kg has been utilized.

Study intervention will be started within 36 hours of randomization, at a rate of 150 mL per hour or less. The administration of each unit should last approximately up to 2 hours, and the elapsed time between each transfusion should not exceed 12 hours. Time at start and end of transfusion should be recorded. Vital signs will be measured prior to transfusion, 10-20 minutes after start of transfusion, at completion of transfusion or if discontinued and 30-60 minutes after the end of the transfusion.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Convalescent plasma is obtained from contracted blood service providers, either locally or shipped overnight to requesting centers. Plasma is obtained from veterans and others who have no symptoms for 28 days after recovery from SARS-CoV-2 infection or who have no symptoms for 14-27 days and have a negative nasopharyngeal swab for SARS-CoV-2 RNA. Plasma units are stored in designated areas in the local VA Blood Bank.

Detailed information about drug handling procedures can be found in the Drug Treatment & Handling Procedures (DTHP).

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Blinded study intervention will be supplied to the research staff in a manner that does not identify the active versus placebo. The research staff will remain blinded to the treatment group assignment. Detailed information about drug handling procedures can be found in the Drug Treatment & Handling Procedures (DTHP).

6.2.3 PRODUCT STORAGE AND STABILITY

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Sites are responsible for providing secure storage for study drugs in the Pharmacy or elsewhere as directed by federal and local laws, regulations, policies, and procedures. Investigational drugs must be stored separately from non-study drug inventory to avoid co-mingling of investigational and clinical drug products. Site pharmacists should consult VHA Handbook 1108.04 “Investigational Drugs and Supplies” Clinical supplies may not be used for any purpose other than that stated in the protocol. The investigational drug will be dispensed and administered only for the purposes specified in this protocol. The local site investigator (LSI) is responsible for assuring that the investigational product is administered only to study patients by qualified and approved personnel. The LSI is ultimately responsible for all study drug at their clinical site. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

The study product is a commercially available product with expiration dating assigned by the provider. The site will monitor the dating of all study drug to ensure that the drug will not expire through the anticipated administration and use by the patient.

Detailed information about proper storage procedures can be found in the Drug Treatment & Handling Procedures (DTHP).

6.2.4 PREPARATION

Study intervention will be prepared on site consistent with local policies and procedures and started within 36 hours of randomization. The administration of each unit will be performed by qualified individuals, in a blinded fashion.

Detailed information about proper preparation and blinding procedures can be found in the Drug Treatment & Handling Procedures (DTHP).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 RANDOMIZATION

The study will randomize participants in equal probabilities to study treatment arms. Currently there are two study treatment arms: convalescent plasma versus saline. Participants will be randomized in 1:1 ratio to these two arms. If additional arms are added to or dropped from the trial, randomization will proceed with an equal probability to each of the remaining arms. Randomization will be stratified by participating site and by age (≥65 vs. <65 years old).

The IWRS (Interactive Web Response System) will be used by authorized study site personnel to randomize eligible participants. It is an intranet-based application that is hosted behind the VA firewall on a VA server at the CSPCRPCC. It is only accessible on the VA network to authenticated VA personnel. Access to study data is restricted to personnel that have registered in the IWRS and have been authorized by the study team. All communication to or from the IWRS is encrypted using Hypertext Transfer Protocol Secure (HTTPS) and is secured using a VA furnished Secure Sockets Layer (SSL) certificate.

6.3.2 BLINDING

The study interventions will be provided and administered to all participants in a similar fashion to achieve blinding. The participants, site investigators, clinical prescribers, site coordinators, and most other individuals involved in this study will be blinded to the treatment assignment. Furthermore, the blind will not routinely be broken in order to select post-study, pharmacologic treatment for SARS-CoV-2 infection administered by clinical healthcare providers.

Blinding will be maintained except for when knowledge of the study treatment assignment will influence the medical treatment of the participant. There may be cases of breaking the blind for emergency medical necessity (emergency unmasking), where the clinical research pharmacist may access treatment assignment information, as necessary. If emergency unblinding becomes necessary during local business hours, the treating provider should contact the Local Site Investigator. The LSI should then contact the Study Chair to discuss the situation before requesting that a participant be unblinded by the CSPCRPCC. Outside of local business hours, the treating provider should contact CSPCRPCC directly at a number that is available 24 hours per day, 7 days per week to discuss the need for unblinding and to have the unblinding performed if indicated. Efforts should be made to avoid unblinding unless medically necessary for emergency treatment decisions.

Participants who require emergency unblinding for clinical safety will be discontinued from study intervention. Study staff will be provided with training on emergency unblinding procedures.

Participants or their legally authorized representative will be provided with a Participant Identification Card that lists site staff telephone numbers and a 24-hour CSPCRPCC contact number. The research facility's name and the two possible study treatments are also listed on the card. The Participant Identification Card will include the participant's Randomization Number, which can be used to determine the participant's treatment assignment should emergency unblinding be required for patient safety.

6.4 STUDY INTERVENTION COMPLIANCE

The study intervention consists of intravenous administration of 200-600mL of convalescent plasma or an equivalent volume of 0.9% saline administered in two equally divided doses, less than 12 hours apart. The order will be entered by the site LSI or authorized designee and study product will be administered by clinical staff according to standard procedures for transfusion of component blood products.

Compliance with study intervention will be assessed using case report forms entered by local site staff following completed transfusion of study intervention.

The reason for failure or partial administration of study product will be recorded by study staff.

6.5 CONCOMITANT THERAPY

Therapy prior to enrollment with any other experimental treatment or off-label use of marketed medications that are intended as specific treatment for SARS-CoV-2 infection (i.e., post-exposure prophylaxis) are permitted.

Participants who are taking remdesivir for COVID-19 or another antiviral for a concurrent infection (e.g. oseltamivir for an influenza virus, lopinavir/ritonavir for HIV, etc.), or

immunosuppressive drugs for other medical conditions (corticosteroids for an unrelated condition, tocilizumab for rheumatoid arthritis, hydroxychloroquine for lupus, etc.) may continue with the treatment.

Participants entering the trial may be prescribed therapy for SARS-CoV-2 that has received preliminary FDA approval whether available by prescription or under an expanded access program (EAP), e.g. remdesivir or dexamethasone. These medications may be initiated or continued. However, participants may not have previously received or be given SARS-CoV-2 convalescent plasma under the Mayo or any other EAP.

A participant cannot participate in another clinical trial for the treatment of SARS-CoV-2 until after Day 29. However, if the participant has progressed to respiratory failure in the hospital (see definition in *Section 3*), another experimental treatment protocol may be initiated, but only if there is a sponsor-approved agreement between the leadership of both trials. The agreement will consider potential impact of dual enrollment on study outcomes and participant safety and establish procedures to coordinate adverse event monitoring and reporting of dual-enrolled participants.

6.5.1 CONCOMITANT MEDICATIONS

Use of concurrent medications is allowed if they are part of local best supportive care for SARS-CoV-2 infection.

Pretreatment with appropriate medication to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given at the discretion of the local site investigator and consistent with local site's transfusion protocols.

Pre-admission level A medications will be collected by class at baseline. Concomitant medications taken for the prevention and treatment of COVID-19 in the 7 days prior to Study Day 1 (day of randomization) and concomitant medications prescribed from hospital admission through Day 28 will be collected by study site staff using the designated case report form. This information will be collected via chart review, or in person or telehealth/telephone interviews, when appropriate.

6.5.2 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Not applicable

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from full participation in the study at any time upon request, without any consequences.

If a participant requests to be withdrawn from the study, the LSI or delegee may offer the participant an option of limited participation. The two limited participation options that may be offered are:

1. A participant can choose to withdraw from receiving study product, but agree to all other follow-up, including study staff contact and laboratory testing.

   OR

2. A participant may choose to withdraw from direct participation in all study activities but allow ongoing medical records review by study staff (no contact).

A participant may also choose to withdraw completely from all study activities. If a participant fully withdraws consent, no study procedures may be performed, and no more data may be collected as of the time point at which the patient withdrew consent.

In any of the situations above, study personnel will ascertain and clearly document in the EHR any limits to ongoing participation. A participant's usual medical care is not affected by whether study participation continues (fully or to a lesser degree) or ends.

If a participant withdraws consent or is withdrawn from the study by the Local Site Investigator (LSI), an Early Termination Form will be completed. Data collected up to the point of withdrawal will be used in the analyses. If a participant agrees to limited participation the site must complete a Reduced Participation form.

7.3 LOST TO FOLLOW-UP

Every attempt must be made to ensure that the participant attends all study visits and assessment calls. Prior to a visit, the site staff will place reminder telephone calls and/or text messages. If a participant does not show for a visit or misses an assessment call, the site staff will try to re-schedule the contact within the target visit window. Attempts to contact the participant should be documented in the subject's records.

A participant is considered lost to follow-up if he or she fails to appear for all follow-up assessments. If a participant is lost to follow-up, a Study Completion Form will be completed.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 CONSENT AND SCREENING PROCEDURES

8.1.1 CONSENT PROCESS

The consent process can start as soon as the prospective participant is admitted to the hospital. After a prospective participant is admitted to the hospital or transferred from another hospital, the Site Coordinator (SC) reviews Informed Consent Form (ICF) and HIPAA with the prospective participant or his/her legally authorized representative (LAR). Once the prospective participant or LAR signs the ICF/HIPAA (by signing a hard copy or via e-consent, if available), screening can start. Participants who are enrolled based on approval on their behalf by their LAR must be consented for continued participation in the study should they later become competent prior to Day 29. See *Section 10.1.1.2*.

8.1.2 SCREENING PROCEDURES

Participants must be randomized within 72 hours of initial hospital admission. However, in many cases consent and all the screening assessments can be done in less than 24 hours. If that is the case, randomization, baseline assessments, specimen collection, and the study product administration can occur on the same calendar day as the consent and screening procedures.

After the informed consent, the following assessments are performed to determine eligibility and obtain baseline data:

- Confirm the positive SARS-CoV-2 test result via RT-PCR or antigen test (per inclusion criteria).
- Take a focused medical history, including the following information:
  - History of chronic medical conditions including chronic oxygen requirement prior to onset of COVID-19.
  - History of any previous transfusion reactions.
- Whether they are participating in another clinical trial or plan to enroll in another clinical trial in the next 30 days.
- Height and weight (height can be self-reported).
- Results of recent radiographic imaging (x-ray or CT scan).
- SpO_2.
- Urine or serum pregnancy test (in women of childbearing potential).

Clinical screening laboratory evaluations will be performed locally by the site laboratory.

8.2 BASELINE, RANDOMIZATION AND PRODUCT ADMINISTRATION

Baseline assessments should be performed before the first study product administration.

The following eligibility/baseline assessments can be done up to 72 hours prior to randomization time: demographic information (age, ethnicity, gender, body mass index), medical history/baseline comorbidities (e.g. obesity, smoking, diabetes, hypertension, cardiac, renal, liver, and lung disease), and physical exam.

Baseline clinical status data are collected right before randomization. Baseline vital signs (NEWS2) should be collected closest to randomization time and must be collected within 24 hours prior to randomization time.

The following additional baseline assessments are collected prior to study product administration:

- COVID-19 signs and symptoms, including day of onset,
- Medications for this current illness taken in the 7 days prior to Day 1 (See *Section 6.5*),
- Designated pre-admission medications by class (See *Section 6.5*),
- Adverse events (See *Section 8.5*),
- Safety and research labs (See *Section 8.4*).

Day 1 safety and research labs should be collected up to 24 hours prior to randomization and before first study product administration. Laboratory tests performed as part of routine clinical care within the same time period will be accepted for Day 1 safety laboratory tests.

Ideally, product administration should start on the same day as randomization (Day 1), but may be started up to 36 hours after randomization.

8.3 EFFICACY AND EXPLORATORY ASSESSMENTS

For all eligibility, baseline, and study intervention assessments and follow-up visits, refer to **Table 1**: *Schedule of Assessments* for procedure to be done, and details below for each assessment.

8.3.1 MEASURES OF CLINICAL SUPPORT AND LIMITATIONS

On each study day through Day 29, the following measures for the previous day will be recorded. That is, on Day 3, Day 2 measures are assessed as occurring anytime in that 24 hours period (12 midnight to 12 midnight):

- Disposition (hospitalized -ICU, hospitalized – non-ICU, not hospitalized, died)
- Additional organ support (e.g., kidneys, blood pressure support)
- ECMO requirement
- Invasive mechanical ventilation (via endotracheal tube or tracheostomy tube) requirement
- Non-invasive mechanical ventilation requirement including CPAP (for an indication other than previously diagnosed sleep apnea)
- Heated high flow nasal cannula ≥ 15 L/min
- Supplemental oxygen requirement
- Limitations of physical activity (self-assessed)

Site staff will record the above measures daily during initial hospitalization. After discharge from initial hospitalization, site staff will collect the above measures via in-person (preferred), telehealth or telephone follow-up on Study Days 15 and 29, and via telehealth/telephone follow-up on Study Day 22. At the time of initial hospital discharge, participants will be provided with a log to help them record the above measures daily and report the data to site staff at follow-up.

8.3.2 WHO ORDINAL SCALE OF PATIENT CLINICAL STATUS

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. From the measures collected in ***Section 8.3.1***, this ordinal scale can be derived. The modified WHO 8-point Ordinal Scale for Clinical Improvement used in this study is provided in **Table 3** (See ***Section 3****, Objectives and Endpoints*).

8.3.3 NATIONAL EARLY WARNING SCORE 2 (NEWS2)

The NEWS2 point score (*https://www.mdcalc.com/national-early-warning-score-news-2*)[43] will be used (see **Table 4**, ***Section 3****, Objectives and Endpoints*):
1) to assess the severity of illness and comparability of subjects in the convalescent plasma and control groups at enrollment, and
2) to compare changes in score over time between the two groups. Patients who die will be coded on their values on the day of death if the values are available.

8.3.4 DEATH AND DURATION OF HOSPITALIZATION

The study will also collect the following information up to Day 29:

- **Death:** Date of death and cause of death
- **Duration of initial hospitalization:** Date of discharge from current hospitalization and discharge location

8.3.5 EXPLORATORY ASSESSMENTS

• To evaluate the impact of onset of symptoms relative to the time of plasma on the effect of convalescent plasma on primary outcome	Plasma administered on day ≤7 vs. >7 days of symptoms on primary outcome
• To evaluate the impact of comorbidity on the effect of convalescent plasma on primary outcome	Primary outcome in persons with ≤2 or ≥3 comorbidities (age ≥65 years, chronic lung, cardiac and renal disease, hypertension, diabetes, obesity and immunosuppression)
• To evaluate the relationship of clinical, immunologic, inflammatory, metabolic, coagulation, endocrinologic and microbiologic outcomes.	Using stored nasal swab fluid, plasma and blood cells, we will test for antibodies, antibody activity, cytokines, RNA transcripts and soluble and cellular markers of COVID-19 perturbations.
• Characterize the impact of specific parameters of convalescent plasma administered to subject on immunologic, inflammatory, metabolic, coagulation, and endocrinologic outcomes in study subjects.	Using samples of administered convalescent plasma, determine specific antibody levels, neutralization, cytokines and other soluble markers in relation to these outcomes in the plasma of study subjects and their outcomes.

8.4 SAFETY AND OTHER ASSESSMENTS

AEs/SAEs will be identified spontaneously through patient reports, actively elicited during study visits through open-ended questioning and examination and gathered at the time of any telehealth or telephone contact and review of the medical record. See ***Section 8.5***.

8.4.1 CLINICAL LABORATORY EVALUATIONS

- Blood will be drawn at the time points indicated in the *Schedule of Assessments* (**Table 1**) and in **Table 5**.
- Blood volumes are indicated in **Table 5**.
- Blood type will be determined on Day 1 before product administration.
- Fasting is not required before collection of laboratory samples.
- Minimal clinical safety laboratory tests include WBC, differential, Hgb, PLT, creatinine, glucose, total bilirubin, AST, ALT, and PT. Sites that do not have access to a test for PT/ INR will be allowed to report an INR.
- Day 1 clinical laboratory evaluations are drawn prior to initial study product administration as a baseline and results do not need to be reviewed to determine if initial study product administration should be given.
- Clinical laboratory testing will be performed at each clinical trial site in real time.

Table 5: Blood volume and collection windows.

	Randomization/ Baseline					
Day +/- Window	**1**	**2 + 1**	**4 + 1**	**7 ± 1**	**15 ± 2**	**29 ± 3**
Safety hematology, chemistry and liver tests	X 14mL[1]	X[2] 14mL[1]	X[2] 14mL[1]	X[2] 14mL[1]	X[3] 14mL[1]	X[3] 14mL[1]
Blood for research	X[4,5] 30mL	X[2,5] 30mL	X[2,5] 30mL	X[2,5] 30mL	X[3,5] 30mL	X[3,5] 30mL
Total blood volume	44mL	44mL	44mL	44mL	44mL	44mL
Total all study days	Up to 264 mL					

1. For Randomization/Baseline visit, total volume calculated assumes there are no laboratory tests done as part of routine clinical care up to 24 hours prior to randomization. For all other visits, total volume calculated assumes there were no laboratory tests performed as part of routine clinical care in the specified visit window for that assessment: Day 2 + 1, Day 4 + 1, Day 7 ± 1, Day 15 ± 2 and Day 29 ± 3, if still hospitalized (this includes initial hospitalization or re-hospitalization to the same VA hospital).
2. Safety laboratory tests and blood for research will be collected on Days 2, 4, and 7 if the participant is hospitalized at these time points (initial hospitalization or re-hospitalization at the study site).
3. Safety laboratory tests and blood for research will be collected on Day 15 and 29 if the participant is still hospitalized at these time points or if they return for an in-person outpatient visit and the site has the capacity to collect blood in the outpatient setting.
4. Collected before participant receives study product.

5. 30 mL (approximately 2 tablespoons) of blood will be collected.

8.4.2 RESPIRATORY SPECIMEN

To measure viral clearance rates following treatment, respiratory samples will be collected at baseline (up to 24 hours prior to randomization and before product administration), on Days 4 and 7 while hospitalized and during in-person visits on Days 15 and 29. This includes initial hospitalization as well as re-hospitalization to the same VA hospital. Because there is controversy over the best sample type and potential difficulty obtaining specific sample types at certain clinical sites, a decision on allowable types (nasopharyngeal vs. oral vs. saliva) will be described in the Operations Manual.

8.4.3 PROCEDURES TO BE FOLLOWED IN THE EVENT OF ABNORMAL CLINICAL FINDINGS

If a physiologic parameter (e.g., vital signs, or laboratory value) is outside of clinically expected range, then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition or was an error. A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

8.4.4 UNSCHEDULED VISIT

If clinical considerations require the subject to be contacted or seen prior to the next scheduled assessment to assure the participant's well-being, it is permissible in this protocol.

8.4.5 CONCOMITANT MEDICATIONS

Concomitant medications will be collected on the day of randomization, the day of study drug administration, the day of discharge or development of a primary outcome event, at days 15, 22 and 29 after enrollment, and during unscheduled visits if applicable.

8.5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Timely and complete reporting of safety information assists study management in identifying any untoward medical occurrence, thereby allowing: a) protection of safety of study participants; b) a greater understanding of the overall safety profile of the study treatments and therapeutic modalities; c) improvements in study design or procedures; and d) consistency with Good Clinical Practice.

All serious adverse events and the following non-serious adverse events will be collected and reported to the sponsor on study CRFs:

- Treatment-related adverse events of any severity: transfusion reaction (fever, rash), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infections.
- Adverse events that have a grade 3 severity, regardless of attribution;

- SARS-CoV-2 related adverse events and have a grade 3 severity, regardless of attribution: cardiac arrythmias, cardiac arrest, need for ECMO or ventricular assistance, thromboembolic or thrombotic complications, need for intensive medical care, need for increased oxygen support or mechanical ventilation, sustained low blood pressure requiring IV pressure support.

These events will be collected and reported on study CRFs from the time of randomization and until becoming lost to follow-up, discontinuing study participation early, or completing the final study visit, whichever occurs first. Details are described below.

8.5.1 DEFINITION OF ADVERSE EVENTS (AE)

An AE is any untoward physical or psychological occurrence in a human participating in research or associated with the use of a drug in a human. An AE can be any unfavorable and unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research or medical investigational test article. (See 21 CFR 312.32(a) and VHA Handbooks 1058.01 and 1200.05).

8.5.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE is considered an SAE if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent, significant, or permanent incapacity or substantial disruption in the participant's body function/structure, physical activities and/or quality of life;
- Congenital anomaly/birth defect; or
- Important medical events that may not be immediately life-threatening, result in death, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Such events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. (See 21 CFR 312.32(a) and VHA Handbooks 1058.01 and 1200.05)

8.5.3 CLASSIFICATION OF AN ADVERSE EVENT

1.1.1.1 SEVERITY OF EVENT

The Common Terminology Criteria for Adverse Events (CTCAE) v5 [*https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf*] will be used to establish the severity of AEs. To determine an AE's severity, the CTCAE v5 will be consulted, and the threshold levels for AEs

listed in the CTCAE v5 will be used. If an AE is not listed in the CTCAE v5, then the following severity definitions adopted from the CTCAE v5 will be applied to determine the severity:

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 (Moderate): minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*.
- Grade 3 (Severe): medically significant but not immediately life-threatening; disabling; limiting self-care ADL**.

Note: A Semi-colon indicates 'or' within the description of the grade.
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

1.1.1.2 RELATIONSHIP TO STUDY INTERVENTION

Relatedness involves an assessment of the degree of causality (attributability) between the study intervention and the event. Site investigators will be asked to provide an assessment of relatedness of the event to the study intervention. The assessment provided by the site investigator is part of the information used by the sponsor to determine if the event represents an alteration in the safety profile of the study intervention. All events with a reasonable causal relationship to the study intervention should be considered "related". A definite relationship does not need to be established. This study will use the following relatedness scale to categorize an event:

- Definitely Related: The event is clearly related to the study intervention – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the participant's clinical state.
- Possibly Related: An event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

Not Related: The event is clearly not related to the investigational agent/procedure, i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

8.5.3.1 EXPECTEDNESS

An AE that is new or greater than previously known, in terms of nature, severity, or frequency of occurrence, or any other unanticipated serious problem associated with the investigation that relates to the rights, safety, or welfare of subjects, as documented in the protocol or other materials approved by the IRB of record or the characteristics of the study population. Such

materials may include but are not limited to: the informed consent form, safety plan, clinical investigator's brochure (or CSPCPRCC's Drug Information Report), and product labeling (see VHA Handbook 1058.01). The Sponsor will concur or disagree with the site investigator's assessment as to whether an adverse event is anticipated or unanticipated (sometimes referred to as expected/unexpected, respectively).

The following AEs are considered uncommon, but **anticipated** in this study population:

- Related to the study intervention: transfusion reaction (fever, rash), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infections.
- Related to COVID-19 disease progression: cardiac arrythmias, cardiac arrest, need for ECMO or ventricular assistance, thromboembolic or thrombotic complications, need for intensive medical care, need for increased oxygen support or mechanical ventilation, sustained low blood pressure requiring IV pressure support.

As these AEs will be considered anticipated, they will not generally require expedited reporting to the CIRB. The frequency of these events will be monitored regularly during aggregate data review. In the event the frequency of any of these events is identified to be greater than anticipated during aggregate analysis, the event will then be reported as a serious unanticipated problem.

8.5.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Timely and complete reporting of safety information assists study management in identifying any untoward medical occurrence, thereby allowing:

- Protection of study participants' safety;
- A greater understanding of the overall safety profile of the study interventions and therapeutic modalities;
- Appropriate modification of the study protocol, if needed;
- Improvements in study design or procedures;
- Compliance with regulatory requirements.

The Site Study Personnel is responsible for the AE and SAE reporting requirements as described in this protocol, including closely monitoring all participants for new AEs and/or SAEs. Data on AEs and/or SAEs will be collected by:

- Spontaneous reports from the participant or participant's family;
- Elicited during the follow-up visits through open-ended questioning and examination;
- Gathered through medical record reviews during the follow-up period.
- Reviewing accuracy and completeness of all AEs and/or SAEs reports.
- Complying with CSP policies for reporting AEs and/or SAEs.
- Complying with local Research & Development Committee (R&DC) policies for reporting AEs and/or SAEs.
- Complying with:
    - VA Central IRB (http://www.research.va.gov/vacentralirb/) requirements.
    - VHA Handbook 1058.01, Research Reporting Compliance Requirements

    - VHA Handbook 1108.04, Investigational Drug and Supplies
- Notifying VA Central and local R&DC of safety issues reported to the investigator by the CSP.
- Managing and reporting AEs or SAEs, and responding when questions arise, in consultation with the Site Physician, Clinical Research Pharmacist, or Study Chair.

The study investigator will assess and record all AEs according to seriousness, expectedness, relatedness to study drug and action taken.

1.1.2 ADVERSE EVENT REPORTING

The following non-serious adverse events will be collected and reported to the sponsor on study CRFs:

- Treatment-related adverse events that are listed in Section 8.5.3.3 at any severity; and,
- Adverse events that have a grade 3 severity, regardless of attribution; and,
- SARS-CoV-2 related adverse events that are listed in Section 8.5.3.3 and have a grade 3 severity, regardless of attribution.

These adverse events will be collected and reported on study CRFs from the time of randomization and until, becoming lost to follow-up, discontinuing study participation early, or completing the final study visit, whichever occurs first.

All unresolved AEs must be followed up, at least every 30 calendar days, until one of the following outcome categories is met: resolved, no further change expected, study discontinuation, or end of study participation with appropriate transfer of care. New information for unresolved AEs will be collected on the AE Follow-up CRF. If a patient receives care at a non-VA facility for an adverse event they experience, research personnel will obtain the requisite release of information form(s) from the patient and once received, acquire the pertinent medical records from the facility.

1.1.3 SERIOUS ADVERSE EVENT REPORTING

All SAEs will be collected and reported to the sponsor on study CRFs. SAEs will be collected and reported on study CRFs from the time of randomization, and until becoming lost to follow-up, discontinuing study participation early, or completing the final study visit, whichever occurs first. All SAEs will also be recorded on the AE Tracking & Evaluation Record and documented in the electronic VA medical record. If a patient receives care at a non-VA facility for a SAE, research personnel will obtain the requisite release of information form(s) from the patient and acquire the pertinent medical records from the facility.

All unresolved SAEs must be followed up, at least every 30 calendar days, until either resolved, no further change is expected, or the participant has reached the end of the study participation with appropriate transfer of care. New information for unresolved SAEs will be collected on the SAE Follow-up CRF.

A. *Site Expedited Reporting of Serious Adverse Events to the Sponsor*

All SAEs will be reported by submission of the event on a CRF into the reporting system within 3 calendar days of the Study Site Personnel becoming aware of the event.

B. Site Reporting Requirements to the VA Central IRB

Sites are additionally responsible for following the VA Central IRB policy in submitting safety data, unanticipated serious problems, and protocol deviations. The VA Central IRB's most recent policy including a table of reporting requirements, instructions, and forms can be found at *http://www.research.va.gov/vacentralirb/policies.cfm*.

C. Sponsor Reporting of Related and Unexpected Serious Adverse Events

All SAEs will be assessed by the study Sponsor to determine if an event is anticipated or unanticipated. SAEs found by the Sponsor to be both related to the investigational treatment and unexpected will be reported in accordance with requirements outlined in CSP SOP 3.6 and applicable FDA regulations. Any FDA reporting requirements will be handled by the sponsor, not by individual sites

D. Sponsor Reporting of Adverse and Serious Adverse Events to the DMC

The Study Biostatisticians, with coordination from CSPCRPCC, will tabulate and summarize all AEs and all SAEs for the DMC on a schedule set by the DMC, but no less than every 6 months. The DMC will also determine when the committee should be unblinded to treatment assignment in reviewing AE/SAE data. The DMC will advise the CSR&D Director whether the study should continue or be stopped for safety reasons.

1.1.4 REPORTING EVENTS TO PARTICIPANTS

If a safety event experienced by a participant during the trial's conduct provides new safety information involving potential significant risk to current and future participants, participants will be notified of the safety event in compliance with CSP standard operating procedures.

1.1.5 EVENTS OF SPECIAL INTEREST

The following Events of Special Concern will be reported by the Safety Management Team in accordance with CSP standard operating procedures: suicide, a death due to unusual circumstances, a medical error, an overdose of the study drug, or when a participant is responsible for another person's death, great bodily harm, or significant property damage.

1.1.6 REPORTING OF PREGNANCY

As a strategy to mitigate risk to any pregnant or breastfeeding woman, participants who are pregnant or breastfeeding at time of randomization will be followed for any safety outcomes until the end of study participation. Appropriate transition of care will take place at the end of the study in the event any serious adverse events occurred. Sites will notify the Chair's Office and the CSPCC and CSPCRPCC as soon as they become aware of any participant who becomes pregnant during the study, collection of safety data will continue until the end of participation.

1.2 UNANTICIPATED PROBLEMS

1.2.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

1.2.2 UNANTICIPATED PROBLEM REPORTING

Serious Unanticipated Problems require prompt reporting. The Sponsor must be notified within 72 hours of the site investigator becoming aware of the event. Sites will report Ups to the VA Central IRB in accordance with VA CIRB requirements and timeframes, as detailed on the VA CIRB website.

1.2.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed of any important new information that may affect their safety or their willingness to participate.

2 STATISTICAL CONSIDERATIONS

2.1 STATISTICAL HYPOTHESES

The primary null hypothesis tests whether the proportion of death or respiratory failure by Day 28 differs between the experimental arm (convalescent plasma) and the control arm (saline). The key secondary null hypothesis tests whether time to recovery differs between the experimental and control arms.

2.2 SAMPLE SIZE DETERMINATION

Primary endpoint

The Chi-square test will be used to compare treatment arms on the proportion of death from any cause or respiratory failure up to and including Day 28, with two-sided significance level = 0.05.

A meta-analysis of studies of SARS coronavirus infection and severe influenza reported that convalescent plasma led to an absolute reduction in the risk of mortality from 7% to 23% and a 54% greater likelihood of discharge by day 22[25]. These data suggest that the treatment benefit of convalescent plasma in reducing the risk of death and respiratory failure may be substantial, particularly early in hospitalization. For this trial we conservatively assume a 10% absolute reduction (30% in the control group and 20% in the convalescent plasma group) given that this trial allows local standard of care in both arms, which may include effective medications for COVID-19.

Table 6. Required number of participants to have 80%, 85% or 90% power for the primary outcome, assuming no missing data.

Proportion in the control group	Absolute reduction	Corresponding proportion in the plasma group	Number of participants needed		
			80% power	85% power	90% power
35%	11%	24%	532	610	712
	10%	25%	652	746	874
	9%	26%	858	976	1134
	8%	27%	1042	1192	1396
30%	11%	19%	474	542	634
	10%	**20%**	582	**666**	778
	9%	21%	730	834	976
	8%	22%	936	1072	1254
25%	11%	14%	400	458	536
	10%	15%	496	566	662
	9%	16%	624	714	836
	8%	17%	806	922	1080

Table 6 provides the total number of participants needed for 80%, 85% or 90% power to detect a range of differences in the primary outcome, using the z-test with a two-sided significance level = 0.05 and assuming no missing data. A total of 666 participants are needed to have 85% power for a 10% absolute reduction when the proportion of death or respiratory failure is 30% in the control group (**Table 6**). This sample size has 76% power to detect a 9% absolute reduction

when the control rate is 30% and has 90% (81%) power to detect a 10% absolute reduction when the control rate is 25% (35%) (**Table 7**).

Table 7. Power of a study of 666 participants to detect differences in the primary outcome, assuming no missing data.

Proportion in the control group	Absolute reduction	Corresponding proportion in the convalescent plasma group	Power
35%	11%	24%	88%
	10%	25%	81%
	9%	26%	72%
	8%	27%	61%
30%	11%	19%	91%
	10%	**20%**	**85%**
	9%	21%	76%
	8%	22%	66%
25%	11%	14%	95%
	10%	15%	90%
	9%	16%	83%
	8%	17%	72%

We do not plan to inflate the target number of events for the planned interim analysis described in ***Section 9.4.6*** below. The planned early stopping boundaries are conservative and the impact on power is negligible: the power with 666 participants (with no missing data) is 84.0%.

Assuming 5% of participants have missing data on primary outcome (such as due to lost of follow-up or early withdrawal from the study), we plan to randomize **702** (=702/0.95) participants.

Key secondary endpoint

The key secondary endpoint is time to recovery up to and including Day 28. Currently there is limited information about the anticipated effect size or the proportion of participants who will recover by Day 28. A preliminary review of data from ACCT-1 demonstrated a recovery rate ratio of 1.312.

Table 8 gives the power of the study for time to recovery in a study of sample size 702, for a range of treatment to control recovery rate ratio and proportion of recovery by day 28. If approximately 70% of study participants recover by Day 28, a study of 702 participants will have 83% power to detect a recovery rate ratio of 1.3.

Table 8. Power for time to recovery for a study of 702 participants

Recovery rate ratio	Overall proportion of recovery by day 28			
	80%	75%	**70%**	65%
1.20	58%	55%	52%	49%
1.25	75%	73%	70%	66%
1.30	87%	85%	**83%**	80%
1.35	94%	93%	91%	89%
1.40	98%	97%	96%	95%

Number of sites and recruitment period

Based on CDW data, there were over 3000 Veterans admitted to VA Medical Centers for SARS-CoV-2 infections in January-April 2020, and 40-50% of them had respiratory failure or death within 28 days of hospital admission. In March-May 2020, the top 25 VA Medical Centers had on average 29 (median = 24) hospital admissions per month. Conservatively, assuming each participating site can randomize on average 2 participants per month, the target sample size 702 can be achieved by 15 months of recruitment at 25 sites. We estimate up to 2000 patients may be screened before enrollment and up to 1500 patients enrolled/consented in order to have 702 randomizations.

2.3 POPULATIONS FOR ANALYSES

The primary analysis will be based on an intention-to-treat population, including all participants randomized. The safety analysis will be based on a modified intent-to-treat population consisting of all participants who received at least one dose of any study intervention.

2.4 STATISTICAL ANALYSES

2.4.1 GENERAL APPROACH

This is a double-blind controlled randomized trial testing a superiority hypothesis of convalescent plasma versus saline with a two-sided type I error rate of 5%. Secondary hypotheses have been ordered according to relative importance, with one key secondary hypothesis highlighted. These will be described according to the appropriate summary statistics (e.g., proportions for categorical data, means with 95% confidence intervals for continuous data, median for time-to-event data).

A statistical analysis plan will be developed prior to unblinding of study and database lock.

2.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy analysis to compare the proportion of death or respiratory failure by Day 28 will be done by the Chi-square test. Difference in the proportions and the 95% confidence interval will be presented. To account for randomization stratification factors, site and age (≥65 vs <65 years old), we will use a logistic regression model with site and age as covariates, or as random effects in a generalized linear mixed effects model. We will also perform regression analyses to adjust for baseline patient characteristics (including age, sex, race, Hispanic ethnicity, ABO blood type, BMI, hypertension, chronic lung, heart or kidney diseases, diabetes, immunosuppression). Odds ratios and 95% confidence intervals will be provided.

Every attempt will be made to obtain outcome data for all participants. While we anticipate minimum loss of follow-up in this short follow-up study, small amounts of missing primary outcome data may occur. In such cases, subjects without the primary outcome data will be excluded from the primary analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations and use analysis methods such as multiple imputations. These analyses will be defined in the Statistical Analysis Plan.

2.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Key secondary endpoint, time to recovery:

The primary analysis for time to recovery by Day 28 is an unadjusted log-rank test. Deaths will be considered as never recovering and censored at Day 28. Kaplan-Meier curves and 95% confidence bounds will be provided. If data permit, we may perform a stratified log-rank test where stratification is according to participating site and age (≥65 vs <65 years old), i.e. site and age are randomization stratification factors. We will also perform Cox regression to adjust for baseline patient characteristics (including age, sex, race, Hispanic ethnicity, BMI, hypertension, chronic lung, heart or kidney diseases, immunosuppression). Recovery rate ratio and 95% confidence interval will be provided.

Other secondary endpoints:

1) Binary data (e.g., 28-day mortality) will be summarized as a percent with 95% confidence intervals. Comparisons between arms will be presented as differences in proportions with 95% confidence intervals.
2) The ordinal scale of patient clinical status will be used to estimate a proportional odds model. The hypothesis test will perform a test to evaluate whether the common odds ratio for treatment is equal to one. If data permit, a test stratified by site will also be performed. The distribution of severity results will be summarized by treatment arm as percentages. Efforts to minimize loss-to-follow-up will be considerable. However, small amounts of missing data may occur. In such cases, subjects without final outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations. These analyses will be defined in the Statistical Analysis Plan.
3) Differences in time-to-event endpoints (e.g., time to respiratory failure or death and time to at least a one category improvement in the ordinal scale) by treatment will be summarized with log-rank tests, Kaplan-Meier curves and 95% confidence bounds. The same procedure will be used to compare time to at least a two-category improvement. Hazard ratios (for time to respiratory failure or death) or improvement rate ratios (for time to improvement) and 95% confidence intervals will be provided.
4) Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening).
5) Duration of event (e.g., duration of initial hospitalization) will be summarized according to median days with quartiles.
6) Categorical data (e.g., ordinal scale by day) may be summarized according to proportions by category and/or odds ratios with confidence intervals.

We recognize that allowing study participants to participate in another SARS-CoV-2 treatment trial after progressing to respiratory failure (***Section 6.5***) may affect the interpretation of the primary intent-to-treat analyses for secondary outcomes (e.g., time to recovery and all-cause mortality), especially if one arm has a higher proportion of respiratory failures, leading to a higher proportion in that arm receiving other SARS-CoV-2 treatments. We will take caution in

the interpretation of results. We will also conduct sensitivity analyses to assess robustness of results, such as incorporating other trial participation as a (time-varying) covariate in the model, imputation, or inverse probability weighting.

2.4.4 SAFETY ANALYSES

AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), counted both at the patient level and event level. Severity, frequency, and relationship of AEs and SAEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings. We will compare the proportions of participants experiencing an SAE, treatment related non-serious AEs, SARS-CoV-2 related adverse events of grade 3 severity, or non-serious adverse events of grade 3, by Chi-square test or Fisher's exact test, as appropriate.

2.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be summarized by treatment arm. Continuous variables will be summarized by the mean and standard deviation. Categorical variables will be described by the proportion in each category (with the corresponding sample size numbers).

2.4.6 PLANNED INTERIM ANALYSES

9.4.6.1 INTERIM SAFETY ANALYSIS

Summary of safety data (AEs and SAEs) by treatment group will be presented to DMC at the planned interim analyses and at least every 6 months, or at other frequencies if requested by the DMC. AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), counted both at the patient level and event level. Severity, frequency, and relationship of AEs and SAEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings. Safety monitoring will be ongoing (see ***Section 8.3***). The unblinded statistical team will prepare these reports for review by the DMC.

9.4.6.2 INTERIM EFFICACY AND FUTILITY ANALYSIS

We plan to conduct two interim efficacy analyses of the primary efficacy endpoint at 33% and 67% of total information to allow early stopping of the study when there is sufficient evidence that the convalescent plasma group is superior. The ρ-family alpha spending function of ρ=2.5 with a one-sided significance level 0.025 will be used as a guide for the DMC (non-binding). The type I error spent at the interim efficacy analysis will depend on the actual information time of the interim analysis according to the alpha spending function. If the study is not stopped at interim, the remaining type I error will be spent at the final analysis of the primary outcome. For example, if the two interim analyses occur at exactly 33% and 67% information time, the efficacy boundaries in the z-scale are -2.947 and -2.401, respectively, and the cumulative type I error spent at the two looks are 0.002 and 0.009, respectively; the remaining type I error 0.041 will be allocated to the final analysis.

Conditional power will be presented as an additional guide to the DMC for futility stopping (non-binding). Conditional power is the probability of obtaining a statistically significant treatment

benefit of convalescent plasma at the end of the study given the data accumulated thus far and assuming a hypothesized treatment effect thereafter. If the conditional power is less than 10% under the original treatment effect assumption (30% vs. 20%), consideration should be given to stopping the trial.

Table 9 gives the operating characteristics of the early stopping boundaries for a study of 666 participants, assuming no missing data, the interim analyses are performed at 33% and 67% information time (222 and 444 participants, respectively), and true proportion of death or respiratory failure is 30% in the control group. When the plasma group also has 30% death or respiratory failure (that is, no difference between the two groups), the study has 5.2% probability of crossing the futility boundary at the first interim analysis and 59% probability of crossing the futility boundary at the second interim analysis. When the plasma group has a 10% absolute reduction as compared to the control group (that is, 30% vs. 20%), the study has 11% probability of crossing the efficacy boundary at the first interim analysis and 41% probability of crossing the efficacy boundary at the second interim analysis.

The unblinded statistical team will prepare these closed reports for DMC review and recommendations. Analyses will be presented with blinded codes for treatment arms to protect the possibility that the interim report may fall into the wrong hands. A DMC charter will further describe procedures and membership.

Table 9. Operating characteristics of the early stopping boundaries for a study with 666 participants, assuming the proportion of respiratory failure or death on or before day 28 is 30% in the control group and there are no missing data on the primary outcome. Each result is based on 100,000 simulations.

True absolute reduction	Probability of crossing boundaries at the first interim analysis at 33% information time (222 patients)		Probability of crossing boundaries at the second interim analysis at 67% information time (444 patients)	
	Crossing efficacy boundary	Crossing futility boundary	Crossing efficacy boundary	Crossing futility boundary
-10%	<0.001	0.477	<0.001	0.518
-5%	<0.001	0.202	<0.001	0.730
0%	0.002	**0.052**	0.007	**0.591**
5%	0.017	0.007	0.098	0.203
8%	0.056	0.001	0.266	0.060
9%	0.081	0.001	0.339	0.036
10%	**0.112**	<0.001	**0.411**	0.019
11%	0.149	<0.001	0.477	0.010
12%	0.201	<0.001	0.521	0.004

9.4.6.3 ADMINISTRATIVE MONITORING

The DMC will also monitor study progress and conduct. This administrative monitoring will focus on participant intake (overall and within site), adequacy of randomization, adherence to study protocol (e.g., completeness of follow-up, study intervention adherence and withdrawals, study withdrawals, timely submission of data, timely resolution of data queries, randomization of non-

eligible patients), baseline comparability of treatment groups, and other operational aspects of the study.

2.4.7 SUB-GROUP ANALYSES

Subgroup analyses for the primary outcome will evaluate the treatment effect across the following subgroups:

1) Received study product (plasma/saline) ≤7 days vs. >7 days after onset of symptoms
2) Have ≤2 vs. ≥3 comorbidities at baseline (age ≥65 years, underlying chronic lung, heart, kidney disease, hypertension, diabetes, obesity or immunosuppression)
3) Age <65 vs. ≥65
4) BMI <35 vs. ≥35

A forest plot will display point estimates and confidence intervals across subgroups. Interaction tests will be conducted to determine whether the treatment effect varies by subgroup. We may adjust for selected baseline covariates in the assessment of interactions. We anticipate that convalescent plasma has a larger benefit in those treated early (≤7 days after onset of symptoms), having more comorbidities at baseline, or older (≥65 years old), and a smaller benefit in obese individuals.

2.4.8 EXPLORATORY ANALYSES

We will explore if the treatment benefit of convalescent plasma differs by race (White vs. other races) and ethnicity (Hispanic vs. non-Hispanic), after adjusting for demographics (such as age, sex) and social economic status (such as highest attained educational level and income level) and if feasible, air-pollution data from geo-coding. We will also explore if the treatment benefit differs by ABO blood type.

3 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

3.1 Regulatory, Ethical, and Study Oversight Considerations

3.1.1 INFORMED CONSENT PROCESS

3.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant. Written documentation of informed consent is required prior to starting intervention/administering study interventions.

3.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the prospective participant's agreeing to participate in the study and continues throughout the potential participant's study participation. The most current, CIRB-approved version of the consent form must be used.

The prospective participant will be informed of the rationale for the study, follow-up procedures that are required, and potential risks and benefits of participation. Prospective participants have the option of having family and/or anyone else they deem appropriate present during the informed consent process. The site personnel will verbally discuss the study and all elements of the informed consent document. The prospective participant and/or LAR will be informed that he/she may refuse to participate or withdraw from the study at any time without, in any way, jeopardizing his/her medical care or benefits in the VA system.

The prospective participant or LAR will be given the informed consent form and encouraged to carefully read and review the document and ask any and all questions. The site staff will address questions raised. The prospective participant is then given the opportunity to provide informed consent to participate in the study and to sign the Informed Consent Form. If the patient is unable to provide informed consent and there is a LAR, investigators should obtain consent from the patient's LAR. The Informed Consent Form can be signed on a hard copy or signed electronically via approved mechanisms.

If the prospective participant or LAR provides informed consent and signs the form, the original form is filed in the Subject Consent Forms Master File, a copy is sent to the Palo Alto CSPCC, a copy is filed per local site VA policy, and another copy is given to the patient or LAR. No research procedures may be performed prior to obtaining consent. In addition, each consented patient or LAR must sign a VA research HIPAA authorization (on a hard copy or electronically, if available).

Although the consenting process can be done in the patient's room, due to the nature of the risks of exposure to a COVID-19 patient, direct communication with the patient may not be feasible or safe. Accordingly, **the informed consent may be provided by video or phone**:

- Site personnel will obtain the patient's phone number (e.g. bedside phone or cell phone), and arrange a three-way call or video conference with the patient or LAR, an impartial witness, and if desired and feasible, additional persons requested by the patient or LAR (e.g., next of kin).

- To ensure that patients are approached in a consistent fashion, a standard process should be used when contacting the patient remotely that will accomplish the following:
    - Identification of who is on the call.
    - Review of the ICF with the patient by the site personnel and response to any questions the patient may have,
    - Confirmation by the witness that the patient's questions have been answered,
    - Confirmation by the site personnel that the patient is willing to participate in the trial and sign the informed consent document while the witness is listening on the phone,
    - Verbal confirmation by the patient that they would like to participate in the trial and that they have signed and dated the informed consent document that is in their possession.

If the patient/LAR signs a hard copy of the informed consent form, the signed informed consent document can be obtained by the following procedure and included in the study records:

- Full copy of the Informed Consent is provided to patient and/or LAR during consent for review that they keep.
- Signature page given to patient or LAR at the time of consent; the patient or LAR signs the consent using gloves and a pen that stay in the room.
- Signature page placed in a plastic zip-lock bag that is wiped with purple top wipe before leaving room and then again outside of room after provided with fresh gloves.
- Signature page can be scanned while in bag.
- Signature page removed and added to full consent after 1 week.
- Sites can also use UV if that is local procedure.

If a hard copy of signed informed consent document will not be able to be collected from the patient's location and included in the study records, the following two options are acceptable to provide documentation that the patient signed the informed consent document:

• **Option #1:** Attestations by the witness who participated in the call and by the site personnel that the participant or LAR confirmed that they agreed to participate in the study and signed the informed consent,

Please note: It is recommended that the documented verbal confirmation include information on the version of the IRB-approved informed consent document that was used, such as IRB-approval date and version.

• **Option #2**: A photograph of the informed consent document with attestation by the person entering the photograph into the study record that states how that photograph was obtained and that it is a photograph of the informed consent signed by the patient or LAR.

A copy of the informed consent document signed by the site personnel and witness should include a notation by the site personnel of how the consent was obtained, e.g. telephone, photograph, e-consent. The note should document how it was confirmed that the patient signed the ICF (i.e., either using attestation by the witness and investigator, the photograph of the

signed consent, or e-consent). If applicable, the note should include a statement of why the ICF signed by the patient was not retained, e.g., due to contamination of the document by infectious material.

Site personnel will send CSPCC the informed consent document signed by the participant or LAR or obtained via one of the two options described above via netapp share folder within 30 days of consent.

Re-consent

Participants enrolled by their LAR must be consented for continued participation in study should they later become competent prior to day 29. The data and samples collected prior to the point when the participant declines to continue participation can be used in the analysis.

8.5.5 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to ***Section 7****, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal*, for handling of enrolled study participants.

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Study Chairs will promptly inform study participants, the VA CIRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and CIRB.

3.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the CIRB, regulatory agencies or the Cooperative Studies Program Research Pharmacy Coordinating Center (CSPRPCC) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or

hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Palo Alto Cooperative Studies Program Coordinating Center (CSPCC). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by CSPCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Palo Alto CSPCC.

3.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

*See also **Section 10.1.3**, Confidentiality and Privacy and **Section 10.1.11**, Data Handling and Record Keeping, for further information on future use of study records.*

Data collected for this study will be analyzed and stored at the Palo Alto Cooperative Studies Program Coordinating Center (CSPCC). After the study is completed, the de-identified, archived data will continue to be stored at the Palo Alto CSPCC, accessible for use by researchers including those outside of the study with an approved Data Use Agreement. The biospecimens collected in the study for current and future research will be kept at the Cooperative Studies Program Albuquerque Central Biorepository in Albuquerque, NM unless otherwise specified. All stored specimens and data used for current and future experimental analysis, both clinical and laboratory, by laboratories and investigators within and outside the VA system will be linked to study identification number with no direct subject identifiers or PII/PHI. Thus, all subject data will be deidentified and anonymized with demographic but no specific HIPAA-designated variables. The biospecimens will be accessible for future research with an approved Sample Use Agreement. The VA CIRB will oversee the biorepository for this study. All samples will be destroyed by standard practice within 20 years of study completion. Sample destruction will be validated according to the Standard Operating Procedures of the VA Biorepository.

3.1.4 KEY ROLES AND STUDY GOVERNANCE

Position	Name and E-Mail Address	Mailing Address	Phone Number
Study Chairs	Edward N. Janoff, MD *Edward.Janoff@va.gov*	RMR VA Medical Center 1700 N. Wheeling St; 111L Aurora, CO 80045-7211	Cell: 303-437-6400 VA: 720-723-6255

Position	Name and E-Mail Address	Mailing Address	Phone Number
	Sheldon T. Brown, MD *Sheldon.brown@va.gov*	James J Peters VA Medical Center 130 W. Kingsbridge Rd (SUB-J) Bronx, NY 10468	Off: 718-584-9000, Ext. 6666 Cell: 917-842-6989
National Study Coordinator	Ashlea Mayberry, BN *Ashlea.Mayberry@va.gov*	Rocky Mountain Regional VAMC 1700 N Wheeling, A3-317A Aurora, CO 80045	Office: 720 857 5141 Cell: 720 545 8968
Study Biostatisticians	Mei-Chiung Shih, PhD *Mei-Chiung.Shih@va.gov*	VA Cooperative Studies Program Coordinating Center 701-B N. Shoreline Blvd Mountain View, CA 94043	(650) 493-5000 Ext. 22367 (Dial 1, then 2 for Menlo Park)
	Ilana Belitskaya-Levy, PhD *Ilana.Belitskaya-Levy@va.gov*	VA Cooperative Studies Program Coordinating Center 701-B N. Shoreline Blvd Mountain View, CA 94043	(650) 493-5000 Ext. 21009 (Dial 1, then 2 for Menlo Park)
Study Project Manager	Lisa Zehm, MS *Lisa.Zehm@va.gov*	VA Cooperative Studies Program Coordinating Center 701-B N. Shoreline Blvd Mountain View, CA 94043	(650) 493-5000 Ext. 28805 (Dial 1, then 2 for Menlo Park)
Study Pharmacists	Alexa Goldberg, PharmD *Alexa.Argyres@va.gov*	Department of Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center 2401 Centre Ave SE Albuquerque, NM 87106	(505) 248-3203 Ext. 6318
	Elliott Miller, PharmD, MS *Elliott.Miller@va.gov*	Department of Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center 2401 Centre Ave SE Albuquerque, NM 87106	(505) 248-3203 Ext. 6327

The organizational and administrative/monitoring structure of this study will include the following components:

Administrative/Study Management

- Clinical Science Research and Development (CSR&D)
- Cooperative Studies Program Coordinating Center (CSPCC)
- Study Chairs' Office
- CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC)

- Participating VA Medical Centers
- Executive Committee

Monitoring

- Data Monitoring Committee (DMC)
- VA Central IRB (CIRB)
- CSP Site Monitoring, Auditing and Resource Team (SMART)

Clinical Science Research and Development establishes overall policies and procedures that apply to this master protocol through the study Chairs' Office and the CSPCC.

The Palo Alto CSPCC and the Study Chairs' Office jointly will perform the day-to-day scientific and administrative coordination of the study. These include maintaining the study protocol and case report forms; ensuring the appropriate support for the participating centers; scheduling meetings and conference calls; answering questions about the protocol; conducting site visits; and publishing newsletters. The Palo Alto CSPCC will also prepare interim and final progress reports, conduct quality assurance activities, and archive study data at the end of the study.

The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) will manage the patient safety monitoring of this study. CSPCRPCC is responsible for monitoring and reporting the safety of trial participants through the review, assessment, and communication of serious adverse events reported by study personnel. Reviewing responsibilities will occur through ongoing communication with the Study Chairs, Executive Committee, the Palo Alto CSPCC, and CSP Central Office. In conjunction with the Palo Alto CSPCC, the CSPCRPCC trends and analyzes safety data to prepare reports for various committees including the Data Monitoring Committee (DMC), VA IRB of record, Study Executive Committee(s), and Safety and Evidence Efficiency Meetings (SEEM).

Each participating VA medical center will have a local site investigator (LSI) to be responsible administratively and scientifically for the conduct of the study at the center. LSIs will be expected to attend all SEEM meetings (via in-person or online meeting/conference call), as well as to hire and supervise personnel. Consistent with guidance from CSR&D, the LSI should be given adequate protected time to fulfill the responsibilities of that role (typically 1/8 to 2/8 time). Prior to participation, each site's local R&D and the VA CIRB must also review and approve the site's involvement in the study. The Research and Development Committee (R&D) and the VA CIRB may require the participating investigator to submit annual reports concerning the status of the study at the medical center for local monitoring purposes.

The Executive Committee is the management and decision-making body for the operational aspects of the study, including protocol amendments, and will be concerned with overall management of the study. It will be headed by the Study Chairs and will consist of the study biostatistician, clinical research pharmacist, selected participating LSIs, Palo Alto CSPCC Director and outside consultants as needed. This committee will meet regularly to review

blinded data (not broken down by treatment group), decide upon changes in the study, evaluate the performance of the participating medical centers, evaluate sub- study proposals, and discuss publication of the study results. Approval must be obtained from this Committee before any study data may be used for presentation or publication.

The Data Monitoring Committee (DMC) will provide independent and unbiased review of the study's ongoing progress and will monitor patient intake, outcomes, adverse events, and other issues related to patient safety. The DMC will consist of experts in the study's subject matter field(s), clinical trials, biostatistics, and ethics. These experts will not be participants in the study and will not have participated in the planning of the study. The DMC will meet at the planned interim analyses and at least every 6 months or at other frequencies specified by the DMC. The DMC will consider safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or the unfeasibility of addressing the study hypothesis (e.g., poor patient intake, poor adherence to the protocol). The DMC makes recommendations to the Director of CSR&D about whether the study should continue or be stopped. A DMC Charter will be developed to provide more details on DMC responsibilities and monitoring methods.

VA Central IRB will periodically review the study. In addition, any changes to the informed consent form or protocol will be reviewed by the VA Central IRB and must be approved prior to implementation.

The CSP Site Monitoring, Auditing and Resource Team (SMART), located at the CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque, serves as the Quality Assurance arm of CSP and will monitor the trial for compliance with Good Clinical Practices. The SMART team will provide study personnel with 1) a GCP overview at the kickoff meeting, 2) an in-depth GCP online course through the VA learning management system, 3) GCP tools and resources to enhance compliance and to assist study personnel in organizing study files and 4) will be available throughout the trial to advise and assist LSIs regarding GCP issues. SMART will monitor the trial in accordance with the Integrated or risk-based Monitoring Plan as described in ***Section 10.1.7***. SMART will also conduct periodic routine audits throughout the course of the study. In addition, for-cause audits of a participating site may be conducted if requested through Palo Alto CSPCC Director or by VA CSR&D Central Office.

3.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DMC composed of individuals with appropriate expertise and the study-specific Safety Management Team lead by the Study CRP. The DMC will meet at the planned interim analyses and at least every 6 months to assess safety and efficacy data on each arm of the study. The DMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DMC. At that time, each data element that the DMC needs to assess will be clearly defined. The DMC will provide its recommendations to the study sponsor (CSR&D). SMART will monitor all clinical sites and provide its findings to the study sponsor (CSR&D) through the CSPCC. The Safety Management Team will assess all reported protocol-defined serious adverse events in real-time.

3.1.6 CLINICAL MONITORING

This trial will be conducted in compliance with the currently approved protocol, with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). The intent of these regulations is to safeguard participants' welfare and ensure the validity of data resulting from the clinical research. The VA Cooperative Studies Program's Site Monitoring Auditing and Resource Team (SMART) based in Albuquerque, NM will monitor and assist LSIs in complying with the above GCP requirements.

Monitoring

Study site monitoring will be a collaboration of onsite site visits conducted by SMART Clinical Research Monitors; remote (off-site) monitoring performed by SMART and CSPCC Quality Assurance RNs; and centralized statistical monitoring. These visits and activities will be conducted according to the study's risk-based monitoring plan that will include ongoing periodic review of selected site performance indicator(s) as derived from the data submitted by the site, findings identified during onsite or remote visits, and interaction with the study site personnel. All monitoring feedback will be reviewed periodically by the sponsor. The monitoring plan will be assessed for adequacy and effectiveness at least annually and be revised as necessary to reflect the protocol specific risks that are identified.

In addition, the Executive Committee (EC), Data Monitoring Committee (DMC), the Human Rights Committee (HRC) at the Palo Alto CSPCC, and the Study Group will help to monitor individual and aggregate information for the trial. To assist sites SMART will provide GCP orientation at the study organizational meeting, or via computerized educational modules. SMART will also provide training, manuals and materials to assist study personnel in organizing study files and will be available throughout the trial to advise and assist LSIs regarding GCP issues.

Audits

SMART audit program is separate and distinct from the SMART monitoring program. Two types of audits may occur. The first type is **routine audits**. This audit involves independent site visits and are performed at one or more sites after the first year as determined by SMART. The second type is **for-cause audits.** This audit type is independent of a site as requested by study leadership or CSP Central Office.

Note: Audits may be scheduled or unannounced.

3.1.7 STUDY MONITORING

By agreeing to participate in the study, the participating medical centers delegate responsibility for global monitoring of the ongoing study to the Clinical Science Research & Development (CSR&D) Service, staff at the study site, Palo Alto CSPCC, SMART study monitors, and CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC). However, the local Research and Development (R&D) Committee may require the participating local site investigator to

submit annual and final progress reports concerning the status of the study at the medical center for local monitoring purposes.

Monitoring Performance of Participating Sites

During the study, it may be necessary to drop one or more participating medical centers from the study. Such action must have the prior approval of the CSPCC Director and the Director of VA Clinical Science Research & Development (CSR&D) Service. Early termination is usually based on recommendations from the Executive Committee and the DMC and most often reflects inadequate participant intake or serious noncompliance with GCP. This action should always be based on the best interests of the study and study participants and does not necessarily imply poor performance on the part of the LSI or the medical center. Termination of participating sites will be conducted per CSP guidelines.

Enrollment Issues

The Study Chairs and the Study Biostatistician will monitor the intake rate and operational aspects of the study. Participating medical centers will continue in the study only if adequate participant intake is maintained. If recruitment is not proceeding at an appropriate rate, the Study Chairs and Study Biostatistician will scrutinize the reasons for participant exclusions and other barriers to recruitment. Based on this information, the Executive Committee may choose to drop under-performing sites, add additional sites, make modifications to the inclusion/exclusion criteria, or extend the recruitment period, with the approval/concurrence from the DMC, CSPCC Director, and the Director, CSR&D. Participating sites that enroll below target may be placed on probation and given an opportunity to improve within a reasonable period (e.g. 3 months). If a medical center is placed on probation, the Study Chairs will confer with the site personnel and may visit the site, if necessary, to help improve the rate of recruitment. If there is no improvement in accrual during the probation period, the site may be subject to reduced funding or possible termination as a study site. To prevent the delay in adding new sites and to accommodate potential modification of target sample size accordingly to primary outcome event rate, we plan to start the study with 25 recruiting sites, which is about 5 more than needed from the sample size requirement of 36 participants per year per site. The Executive Committee will take actions leading to discontinuation of a site only with the concurrence of the CSPCC Director. If a site is terminated from the trial, resources will be reallocated to other medical centers or used to start up a back-up site. Central IRB will be informed of all site terminations and probations.

Non-adherence to the protocol and/or Good Clinical Practice (GCP) Guidelines

Strict adherence to the protocol and GCP guidelines will be expected of every participating medical center and monitored by the DMC, the Executive Committee, and the Study Group. Documentation of protocol violations will be required. Protocol violations must be reported to the CSPCC on the appropriate case report form and to the Central IRB to ensure immediate hazard to the participant did not occur. Medical centers with repeated protocol violations or repeated failures to follow GCP Guidelines will be recommended for termination to the DMC, the CSPCC Director, and the Director of CSR&D. If a participating investigator feels that adherence

to the protocol may result in an apparent immediate hazard to the participant, the interest of the participant must take precedence.

By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the Cooperative Studies Program and the Study Committees listed above. However, the Research and Development (R&D) Committee and the VA Central IRB may require the participating investigator to submit annual and final progress reports concerning the status of the study at the medical center for local monitoring purposes.

Study/Site Termination and Close-out Plan

The VA CSR&D, as the sponsor of this study, may stop the trial at any time based on funding issues or internal or external evidence that the study is no longer feasible or unethical to continue. The Data Monitoring Committee (DMC) may recommend to the sponsor that the trial or treatment arms be terminated based on their review of study data for safety, efficacy, futility, study integrity or other reasons. Criteria and procedures for placing a site on probation or terminating a site from participation will be developed. If a site or the entire trial is terminated, participating sites will be notified and given a closeout plan and schedule at that time.

3.1.8 TRAINING AND SUPERVISION

Training for Local Site investigators, Site Coordinators and Research Assistants

Training for the LSIs and SCs will occur at the time of a kickoff meeting and at scheduled conference calls during the start-up period and throughout the study period. Before recruitment starts there will be a kickoff meeting. The attendees will include: Study Chairs, National Study Coordinator, CSPCC staff, PCC staff, SMART staff, LSIs, Site Coordinators and other study personnel. The main goals of the meeting include:

1. Review the structure and objectives of the protocol
2. Review eligibility, recruitment and enrollment strategies
3. Review the rationale and implementation of the procedures and treatments
4. Review assessments and reimbursement
5. Review data management, good clinical practices and adverse event reporting

In case key staff members are not available for this kickoff meeting, a second videoconference meeting will be scheduled at which time the key elements of the kickoff will be presented.

Regular conference calls with LSIs and Site Coordinators will be held to review study progress, address emergent problems, disseminate changes to study procedures and case report forms, and share best practices and lessons learned. Significant publications affecting the understanding of COVID-19 or the study treatments will also be reviewed.

3.1.9 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control checks and study monitoring will enable the Palo Alto CSPCC to examine the database and the clinical sites to ensure data have not been improperly used or accessed. Audit

trails and access logs compliant with 21 CFR Part 11 will be checked routinely, and study monitors will provide continuing education on GCP and check clinical site operations for violations of data security policies and best practices.

Standardization/Validation of Measurements
Details about quality control for assessment procedures are provided in Section 5.5.3 (Procedures to Enhance Completion of Assessment Protocols).

Treatment
Details about quality control for treatment are provided in Section 6.

Blinding
This is a double-blinded placebo-controlled study. Details about blinding procedures are provided in Section 6.3.2.

3.1.10 DATA HANDLING AND RECORD KEEPING

3.1.10.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data Management

The Palo Alto CSPCC will be responsible for the management and quality control of the study data. After the study is approved, data forms will be finalized, and field tested. An Operations Manual with the instructions for data forms will be provided to the LSIs, Site Coordinators and Central RAs to guide the operation and management of the study. A training session at the kickoff meeting is planned prior to the initiation of participant enrollment for all study personnel to assure uniformity in participant management and data collection procedures, and to train all study personnel in study procedures. Training will also be held at subsequent annual Safety and Efficiency Enhancement Meetings (SEEMs) and on an as-needed basis for new study personnel. Site Coordinators and Central RAs will complete data forms promptly and transmit them to the Palo Alto CSPCC. Other personnel may also be involved in data submission, such as LSIs. For the purposes of this section, anyone completing and submitting study data will be considered an end user. If any paper forms are used, the original copies will be kept in the LSI's study files.

DataFax, by DF/Net Research, is the planned clinical data management system (CDMS). Palo Alto CSPCC currently uses DataFax Version 2016 that encrypts data at rest using FIPS 140-2 compliant encryption. It allows for both paper data collection and electronic data capture (EDC). The authorized study personnel will log into DataFax to enter and submit study data directly on electronic case report forms (CRFs), rather than completing and sending a paper CRF. The use of paper CRFs may be reserved as a backup process.

Data management staff at the Palo Alto CSPCC will review data completeness and consistency and add data queries to items that fail these checks. Most data queries will be triggered in real time as study personnel are submitting data. Queries triggered after data submission can be accessed through listings available within the system. Data management staff will work with the authorized study personnel to help resolve queries. Queries will be resolved when the

appropriate corrections to the CRF are made and data resubmitted, or when an explanation is provided to allow data management staff to resolve the query. Corrections and changes to the data will be reviewed by data management staff. Palo Alto CSPCC may generate and distribute targeted data edit reports, as needed.

The Study Chairs, LSIs, Site Coordinators, and Central RAs will receive periodic reports regarding the quality and quantity of data submitted to the Palo Alto CSPCC. Other quality control measures include periodic reports containing participant recruitment information and relevant medical data for review by the Study Chairs. The Palo Alto CSPCC will also prepare summary reports for the Study Chairs, the Executive Committee, the Data Monitoring Committee, and other monitoring groups to track study progress, quality of study conduct and study data, and adverse events.

Study reports will be generated using the CDMS, Statistical Analysis System (SAS) and other tools (e.g., Microsoft Excel and Access). SAS and other statistical software packages will be used to conduct the statistical analysis for the study. The Palo Alto CSPCC is using SAS Version 9.4 and will upgrade to newer versions once they are purchased and validated.

Data Security

The CDMS is fully compliant with US Federal regulations regarding electronic data capture systems established by the Food and Drug Administration (FDA) under 21 Code of Federal Regulations (CFR) 11. Data entered directly into the database provides the official clinical record for data collection. Source documentation is handled in the same manner as a paper-based system. The CDMS is installed on VA servers, which will house the resulting study databases, and are located behind the VA network firewall. Authorized study personnel will use a two-step login process to access the CDMS. They will first need to log into the VA network with their VA credentials and then into the CDMS using a separate login process. The system will be monitored to ensure that all applicable VA regulations and directives are strictly followed.

Access to the study data is restricted by the Palo Alto CSPCC to properly credentialed research staff who have completed required VA security trainings. Only CSP-approved individuals (such as staff at the study site, Palo Alto CSPCC, SMART study monitors, and CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) will have access to the protected health information (PHI) of study participants.

Research data will only be stored on secure VA servers behind the VA firewall. The data will be coded with a unique study identifier for each participant and stored using that study identifier. Identifiable information, such as the participant's name, contact information and SSN, will be collected for participant tracking and safety purposes. This identifiable information will be either encrypted or stored separately from the clinical data. Access to the crosswalk file linking the participant's identifiers and their study data will be restricted to the clinical site, staff at the Palo Alto CSPCC, and study monitors, pharmacists, and staff at the CSPCRPCC.

In case of improper use or disclosure of study data, the facility's Information Security Officer (ISO), Privacy Officer, and the individual's direct supervisor must be notified immediately per VA Directive and Handbook 6500. Records will be maintained and destroyed per the VHA Records Control Schedule (RCS 10-1).

Quality control checks and study monitoring will enable the Palo Alto CSPCC to examine the database and the clinical sites to ensure data have not been improperly used or accessed. Audit trails and access logs compliant with 21 CFR Part 11 will be checked routinely, and study monitors will provide continuing education on GCP and check clinical site operations for violations of data security policies and best practices.

Data Access

Upon final analyses of the stated objectives in this proposal, the study plans to submit results for publication in scientific peer-reviewed journals and provide summary results on ClinicalTrials.gov. After acceptance of the primary and other stated analyses by a journal, CSP will make these publication(s) available via the National Library of Medicine's PubMed Central within a year of the date of publication.

Digital data underlying primary scientific publications from this study will be held as part of a data sharing resource maintained by the CSP. Study data held for this purpose may include data, data content, format, and organization. The data may be available to the public and other VA and non-VA researchers under certain conditions and consistent with the informed consent and CSP policy which prioritize protecting participant privacy and confidentiality to the extent possible. A detailed plan for data sharing will be developed in accordance with current technology, infrastructure, best practices, and policies and procedures in place at the time of oversight committee reviews (e.g., Privacy Board, IRB, Information Security, and IT standards). The plan will include how data will be discovered, retrieved, analyzed, and managed and will note the materials that are available in machine readable formats. This plan may be revised to ensure consistency with VA, including CSP, policies and standards for overall data management and sharing.

3.1.10.2 STUDY RECORDS RETENTION

Research data must be stored for a minimum of 6 years after the end of the study. Records will be destroyed in accordance with the VHA Record Control Schedule. Never destroy or discard records without prior authorization from Palo Alto CSPCC. The CSPCC will ensure that all study related files, including electronic files, are archived and maintained appropriately. Study records must also be available for FDA inspection for a minimum of 2 years following study completion.

3.1.11 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), federal regulations and/or

VHA research requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly.

Strict adherence to the protocol and GCP guidelines, regulatory and VA requirements will be expected of every participating medical center and monitored by the Study Group, the Executive Committee, and the DMC. Medical centers with repeated protocol deviations might be recommended for termination to the DMC, the CSPCC Director, and the Director of VA CSP. If a participating investigator feels that adherence to the protocol may result in an apparent immediate hazard to the participant, the interest of the participant must take precedence.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation. Study personnel can only knowingly deviate from the protocol in an apparent hazard to the participant. All other planned deviations require sponsor and CIRB approval before the deviation can be implemented. All deviations must be addressed in study source documents and reported to the Palo Alto CSPCC. Protocol deviations must be sent to the VA CIRB per their policies. The site investigator is responsible for knowing and adhering to the CIRB requirements.

3.1.12 PUBLICATION AND DATA SHARING POLICY

Publication Policy

All presentations and publications from this study will be done in accordance with the CSP policy as stated in the CSP Guidelines. The presentation or publication of any data collected by participating investigators on patients who enter the VA cooperative study is under the control of the study's Executive Committee. This is true whether the publication or presentation is concerned with the results of the principal undertaking or is associated with the study in some other way. No individual participating investigator is permitted to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices and approval of the Executive Committee. It is the policy of the CSP that outcome data will not be revealed to the participating investigators and Study Chairs until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection.

The Executive Committee has the authority to establish one or more publication committees, usually made up of subgroups of participating investigators and some members of the Executive Committee, to produce presentations and manuscripts for publication. All presentations and publications will be circulated to all participating investigators for their review, comments, and suggestions, at least four weeks prior to submission of the manuscript to the presenting or publication body.

Authorship should include the Study Chairs, the National Study Coordinator, members of the Executive Committee, and Participating Investigators from top recruiting centers and must adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the

International Committee of Medical Journal Editors (as defined by ICMJE standard). The number of authors will not exceed individual journal limitations. All publications must give proper recognition to the study's funding source. If an investigator's major salary support and/or commitment are from the VA, the investigator must list the VA as his/her primary institutional affiliation. Submission of manuscripts or abstracts must follow the applicable VA and VA CSP policies. Ideally, a subtitle is used stating, "A VA Cooperative Study." A copy of the letter to the editor and the manuscript/abstract submitted for publication/presentation should be sent to the CSP Director, and for information purposes, to the members of the study's DMC. The CSP also requires that a copy of every manuscript must be reviewed and approved by the CSPCC Director prior to submission as a last quality control step.

Planned Publications (partial list):

1. A paper describing the use of the adaptive design to test multiple treatments.
2. A paper describing the study methodology useful for the evaluation of emerging COVID-19 treatments.
3. A paper describing the results for the primary outcome and principal secondary outcome measures focused primarily on treatment efficacy and safety.
4. A paper describing the antibody response and neutralization in plasma over time and in relation to outcome.
5. A paper describing correlates of protection, clinical, laboratory, plasma variables

Public Access to Scientific Publications and Research Data

All scientific publications reporting the results of this study will be made publicly available. Final research data from this study will be made publicly available per VA policy under mechanisms that ensure that (i) the release of such data is compliant with all Federal statutes and regulations, and (ii) the privacy of individual participants is assured.

3.1.13 CONFLICT OF INTEREST POLICY

The duties and responsibilities of the Study Chairs and local site investigators, including sub-investigators, require a Research Financial Conflict of Interest Statement to be filed to avoid involvement in a real or perceived conflict of interest. Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In addition, in research a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. This Statement is to assist employees to avoid a conflict between their official duties and private financial interests or affiliations.

3.2 ABBREVIATIONS

ACOS Associate Chief of Staff

ACP	American College of Physicians
ACR	American College of Rheumatology
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ADL	Activities of Daily Life
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BP	Blood pressure
BRDP	Biostatistical Research Data Processing
CDC	Centers for Disease Control
CDMS	Clinical data management system
CDW	Corporate Data Warehouse
CFR	Code of Federal Regulations
CIRB	VA Central IRB
COVID-19	Infectious disease caused by SARS-coronavirus 2
CPAP	Continuous Positive Airway Pressure
CPRS	Computerized Patient Record System
CPT	Current Procedural Terminology
CRF	Case report form
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSR&D	Cooperative Studies Program Central Office
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
CSR&D	Clinical Science Research & Development
CSSEC	Cooperative Studies Scientific Evaluation Committee
DoD	Department of Defense
DMC	Data Monitoring Committee
ECMO	Extracorporeal Membrane Oxygenation
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EHR	VA electronic health record
EMR	VA electronic medical record
ESC	Event of special concern
FDA	United States Food and Drug Administration
FIPS	Federal Information Processing Standards
GCP	Good clinical practice
HHHFNC	Humidified heated high-flow nasal cannula
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HNA	Anti-human neutrophil antigen
HRC	Human Rights Committee
HSR&D	Health Services Research & Development
HTTPS	Hypertext Transfer Protocol Secure
ICD-10	International Statistical Classification of Diseases, 10th revision
ID	Identification
INR	International normalized ratio
IRB	Institutional Review Board

ISO	Information Security Officer
ITT	Intent to treat
IWRS	Interactive Web Response System
LAR	Legally authorized representative
LSI	Local Site Investigator
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome coronavirus
MVP	Million Veterans Program
NA	Not applicable
NEWS2	National Early Warning Score-2
NIH	National Institutes of Health
NK	Natural killer
ORD	VA Office of Research and Development
PHI	Protected health information
PT	Prothrombin time
RA	Research Assistant
R&D	Research & Development Committee
RCS	VHA Records Control Schedule
RSV	Respiratory Syncytial Virus
SAE	Serious adverse event
SARS	Severe Acute Respiratory Syndrome
SARS-COV	SARS-coronavirus
SARS-COV-2	SARS-coronavirus-2
SAS	Statistical Analysis System
SD	Standard deviation
SE	Standard error
SEEM	Safety and efficiency enhancement meeting
SMART	Site Monitoring, Auditing, and Resource Team
SOP	Standard operating procedures
SpO_2	Peripheral Capillary Oxygen Saturation
SSL	Secure Sockets Layer
SSN	Social Security number
TACO	Transfusion-associated circulatory overload (TACO)
TRALI	Transfusion-related acute lung injury
US	United States
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
VINCI	VA Informatics and Computing Infrastructure
WBC	White Blood Cells
WH-PBRN	Women's Health Practice Based Research Network
WHO	World Health Organization

3.3 Protocol Amendment History

Version	Date	Section(s)	Page Numbers in Version Where changes were	Description of Change

			Implemented	
1.2	08/12/2020	Section 1.3	p.10	Updated Table 1: Schedule of Assessments: - The table now describes study procedures instead of case report forms; - Clarified timing of procedures; - Added Product Administration visit since it occurs within 36 hours of randomization (thus, it might be the next day or even the day after; - Clarified in footnote 3 that randomization should occur within 72 hours of hospital admission; - Removed unnecessary and redundant footnotes; - Clarified acceptable research specimens and corrected amounts; - Clarified that clinical status, vital signs and AE should be obtained daily during hospitalization; - Clarified that Day 15 and 29 visits are preferred to be conducted in person but may be performed by telehealth or by phone if quarantine or other factors limit the participant's ability to return to the site for the visit.
1.2	08/12/2020	Section 1.3.	p.11	Updated notes for Table 1: Schedule of Assessments
1.2	08/12/2020	Section 2.1	p. 12	Updated numbers of coronavirus infections and deaths
1.2	08/12/2020	multiple	multiple	Replaced "subject" with "participant"
1.2	08/12/2020	Section 2.3.1	p.14	Removed "deficiency"

1.2	08/12/2020	Section 3	p.16	Added two secondary outcomes: - proportion of patients who died from any cause, had respiratory failure or required HHHFNC ≥ 15Lpm by Day 28; -Time (in days) to death, respiratory failure or HHHFNC at ≥ 15 Lpm by Day 28.
1.2	08/12/2020	Section 3	p.17	Corrected study days for clinical status assessment: Days 14, 21, and 28 as assessed on Days 15, 22, 29.
1.2	08/12/2020	Section 3	p.18	Removed laboratory assessments on study day 11.
1.2	08/12/2020	Section 3	p.18	Changed amount of blood drawn for research from two 7mL vials to 30mL.
1.2	08/12/2020	Section 5.1.	p.22	IC#4: veterans must be 18 years or older at the time of screening, not enrollment (i.e. enrollment is too vague)
1.2	08/12/2020	Section 5.1	p.22	IC#5: Clarified the acceptable tests for SARS-CoV-2 confirmation: RT-PCR or antigen.
1.2	08/12/2020	Section 5.1	p.22	IC#5: Clarified the acceptable timing of the diagnostic confirmation test (i.e. not more than 168 hours prior to screening)
1.2	08/12/2020	Section 5.1	p.22	IC#6: Corrected the humidified heated high-flow nasal cannula requirement to ≥15 Lpm instead of >15 Lpm.
1.2	08/12/2020	Section 5.1	p.22	EC#1: Added anticipated death within 24 hours to EC#1.
1.2	08/12/2020	Section 5.5	p.23	Specified clinical databases accessed: CPRS charts and

				hospital admission logs.
1.2	08/12/2020	Section 6.3.1	p.25	Added age as a stratification factor for randomization
1.2	08/12/2020	Section 6.5	p.26	Made the following changes to concomitant therapies and medications: - Clarified that off-label use of marketed medications that are intended as treatment for SARS-COV-2 infection is permitted and does not need to be discontinued on enrollment. - Clarified that participant has progressed to respiratory failure in the hospital, another experimental treatment protocol may be initiated if approved by CIRB and if there is an agreement between leadership of both trials; - Clarified that pre-admission level A medications need to be collected by class at baseline; -Clarified that concomitant medications taken for the prevention and treatment of COVID-19 in the 7 days prior to Day 1 and medications prescribed from hospital admission through Day 28 need to be collected.
1.2	08/12/2020	Sections 7.2 and 7.3	p.28	Changed “Study Termination Form” to “Study Completion Form”.
1.2	08/12/2020	Section 7.2	p.28	Replaced “will” with “must”
1.2	08/12/2020	Section 8.1.1	p.29	Added a short description of consent process and referred to Section 10.1.1.2 for details.

1.2	08/12/2020	Section 8.1.2	p.29	Made the following changes to screening procedures: - Clarified that participant must be randomized within 72 hours of hospital admission; - Removed history of medication allergies from screening/baseline procedures; - Moved medications and therapies for this current illness to Section 8.2; - Removed FiO2 assessment.
1.2	08/12/2020	Section 8.2	p.29	Added description and timing of baseline, randomization and product administration procedures.
1.2	08/12/2020	Section 8.3.2	p.31	Updated section number
1.2	08/12/2020	Section 8.4	p.31	Updated safety and other assessments as follows: - Added reference to Table 5; - Changed amount of blood collected from two 7mL vials to 30mL on Days 1, 2-3, 4-5, 7±1, 15±2 and 29±3. - Corrected the blood collection window on Day 29 to 29±3 instead of 29+3; - Corrected the acceptable timing of routine laboratory tests to 24 hours prior to product administration, not 48 hours; - Added Section 8.4.5 to specify when Concomitant Medications should be collected.
1.2	08/12/2020	Section 8.4	p.32	Modified the amounts of blood drawn and collection windows in Table 5
1.2	08/12/2020	Section 9.2	p.42	Changed duration of recruitment from 12 months

				to 15 months and number of participants randomized per month per site from 2.5 to 2.
1.2	08/12/2020	Section 9.4.2	p.42	Updated statistical analysis to account for stratification factors
1.2	08/12/2020	Section 9.4.3	p.43	Added age as a stratification factor
1.2	08/12/2020	Section 9.4.7	p.46	Updated age and BMI limits for subgroup analyses: Age ≥ 65 vs < 65 BMI ≥ 35 vs < 35.
1.2	08/12/2020	Section 10.1.1.2	p.47	Added details of consent procedures and documentation for COVID-19 precautions: - Informed consent may be provided by video or phone; - Photographs of ICF may be accepted; - Signature page of the ICF may be quarantined, then added to the ICF.
1.2	08/12/2020	Section 10.1.3	p.50	Deleted certificate of confidentiality description
1.2	08/12/2020	Section 10.1.4	p.50	Added that CIRB will oversee the biorepository for this study
1.2	08/12/2020	Section 10.1.8	p.54	Removed the wording ‘during the first 12 months of the study’ for site performance evaluation.
1.2	08/12/2020	Section 10.2	p.61	Added abbreviation for Computerized Patient Record System (CPRS); removed abbreviation for fraction of inspired oxygen (FiO_2)
1.2	08/12/2020	Section 10.3	p.63	Added protocol amendment history
1.3	08/25/2020	Section 1.1	p.7	Clarified that the trial will have common inclusion/exclusion criteria but may be modified for each specific stage. Removed reference to

				stage-specific appendix.
1.3	08/25/2020	Section 1.2	p.8	Added reference to study schema for stage 1.
1.3	08/25/2020	Section 1.3	p.11	Clarified that footnote #12 describes follow-up visits on Days 15, 22 and 29 after discharge.
1.3	08/25/2020	Section 5.5	p.23	Corrected that materials summarizing purpose and design of the study, etc. will be made available to clinical providers without IRB or facility approval.
1.3	08/25/2020	Section 6.3.1	p.25	Added description of the randomization procedure (IWRS).
1.3	08/25/2020	Section 8.2	p.30	Corrected that baseline clinical status data are collected right before randomization, not within 24 hours prior to randomization.
1.3	08/25/2020	Section 8.4.1	p.32	Removed sentences about additional laboratory tests that might be required in other study stages.
1.3	08/25/2020	Section 9.2	p.40	Added estimates about the number needed to be screened and consented in order to have 702 randomizations.
1.3	08/25/2020	Section 10.1.4	p.50	Corrected section number for Data Handling and Record Keeping.
1.3	08/25/2020	Section 10.1.4	p.50	Specified that the biospecimens collected in the study for current and future research will be kept at the VA Biorepository in Palo Alto.
1.3	08/25/2020	Section 10.1.4	p.50	Indicated that all samples will be destroyed by standard practice within 20 years of study completion and that sample destruction will be validated according

				to the SOP of the VA Biorepository.
1.3	08/25/2020	Section 10.1.4	p.51	Removed the name of one of the Project Managers who is no longer on the study (Ashley Scales).
1.4	09/02/2020	Section 1.3	pp.10 and 11	Schedule of Activities updated (“Nasopharyngeal swab” was changed to “Respiratory Sample” in the table and footnote).
1.4	09/02/2020	Section 2	p.12	Updated the numbers of SARS-Coronavirus 2 (SARS-CoV-2; COVID-19) infections and deaths.
1.4	09/02/2020	Section 3	p.19	Removed statement about collecting NEWS2 prior to product administration.
1.4	09/02/2020	Section 7.2	p.28	Changed the protocol to allow full or limited study participation.
1.4	09/02/2020	Section 8.5.5	pp.36-37	Corrected section number.
1.4	09/02/2020	Sections 7.2 and 10.1.1.2	pp.28 and 49	Moved the paragraph about the requirement to re-consent the participant if he/she was consented by LAR and later became competent from Section 7.2 to Section 10.1.1.2.
1.4	09/02/2020	Section 10.1.5	p.52	Edited Dr. Janoff’s VA phone number.
1.5	11/09/2020	Section 1.3	p.10	In Table 1, added X for evaluation of adverse events on day of discharge.
1.5	11/09/2020	Section 1.3	p.10	In Table 1, changed “blood for plasma” to “blood”.
1.5	11/09/2020	Section 1.3	p.11	In Table 1, footnote 6, changed “blood for plasma” to “blood for research studies”.
1.5	11/09/2020	Section 1.3	p.11	In Table 1, footnote 6, spelled out “nasopharyngeal”.
1.5	11/09/2020	Section 1.3	p.11	In Table 1, footnote 11, changed “Plasma for

				antibodies" to "Blood for research studies"
1.5	11/09/2020	Section 6.5	p.27	Removed the language about Central IRB needing to approve initiation of another experimental protocol once a participant progresses to respiratory failure.
1.5	11/09/2020	Section 7.3	p.28	Added language to allow site staff to send reminder text messages prior to a visit.
1.5	11/09/2020	Section 8.1.1	p.29	Updated to specify that the ICF can be a hard copy or e-consent.
1.5	11/09/2020	Section 8.3.1	p.30	Added language about a log that will be provided to participants at the time of initial hospital discharge.
1.5	11/09/2020	Section 10.1.1.2	p.47	Added language that the informed consent form can be signed on a hard copy or signed electronically via approved mechanisms.
1.5	11/09/2020	Section 10.1.1.2	p.47	Added language that the HIPAA can be signed on a hard copy or electronically, if available.
1.5	11/09/2020	Section 10.1.1.2	p.48	Specified language that was specific to if a patient/LAR signs a hard copy of the informed consent form.
1.5	11/09/2020	Section 10.1.5	p.51	Added National Coordinator name and contact information
1.5	11/09/2020	Section 10.1.8	p.54	Language that was more relevant to the Monitoring section was moved from the Protocol Deviation section to the Monitoring section
1.5	11/09/2020	Section 10.1.12	pp.59-60	Updated Protocol Deviations section.
1.6	1/20/2021	Sections 1.3, 8.2, 8.4.1 and	p.11, 30 and 32	Increased the timing of Day 1 safety labs and specimen collection (i.e. up to 24

		8.4.2		hours prior to randomization).
1.6	1/20/2021	Section 1.3	p. 11	Added footnote 12 to clarify that if the participant is not hospitalized at study site on day 2, 4 or 7, there is no need to collect labs or specimen on that day.
1.6	1/20/2021	Section 8.4.1	p. 32	Added footnote 2 to Table 5 to clarify that safety labs and blood for research will be collected on Days 2, 4 and 7 if the participant is hospitalized.
1.6	1/20/2021	Section 8.4.2	p. 32	Changed treatment administration to product administration to make it consistent with the rest of the protocol.
1.6	1/20/2021	Section 8.4.3	p. 33	Changed "protocol-specified" range to "clinically expected" range because the protocol does not specify a range.
1.6	1/20/2021	Section 3	p.18	Added Day 1 blood and swab collection to be consistent with other parts of the protocol.
1.6	1/20/2021	Section 4.3, 6.1.1 and 6.4	p.21, 24 and 26	Updated treatment volume limits for consistency.
1.6	1/20/2021	Section 10.1.1.2	p.47	Removed "The consent form will be valid for 90 days post consent. If more than 90 days passes without the participant being randomized, the participant or LAR will need to be re-consented." as this is not applicable to the current study.
1.6	1/20/2021	Section 10.1.1.2	p.49	Added subtitle "Re-consent" in order for the language about re-consent to be searchable in the protocol.
1.6	1/20/2021	Section 10.1.4	p. 50	Changed the Biorepository from VA Biorepository in Palo Alto, CA to the

				Cooperative Studies Program Albuquerque Central Biorepository in Albuquerque, NM.
1.7	3/3/2021	Sections 1.1 and 2.2	p. 6 and 14	Changed the next stage of VA CURES-1 will be VA CURES-1a (rather than VA CURES-2).
1.7	3/3/2021	Sections 1.3, 5.1, and 8.1.2	p. 11, 21, and 29	Changed language to clarify that "Randomization must occur within 72 hours of initial hospital admission".
1.7	3/3/2021	Section 3	p. 20	Added footnote 1 to clarify that the SpO_2 scale 2 should be used for participants with suspected or confirmed history of hypercapnia.
1.8	8/6/2021	Section 8.3.5	p. 31	Added information regarding evaluating the relationship of clinical, immunologic, inflammatory, metabolic, coagulation, endocrinologic and microbiologic outcomes.
1.8	8/6/2021	Section 10.1.4	p. 50	Added the following language, "All stored specimens and data used for current and future experimental analysis, both clinical and laboratory, by laboratories and investigators within and outside the VA system will be linked to study identification number with no direct subject identifiers or PII/PHI. Thus, all subject data will be deidentified and anonymized with demographic but no specific HIPAA-designated variables."
1.9	9/10/2021	Section 3	p. 18	Table 2 was updated to include "Impact of donor

				convalescent plasma parameters on the activity of administered plasma”
1.9	9/10/2021	Section 8.3.5	p. 31	Added information regarding characterizing the impact of specific parameters of convalescent plasma administered to subject on immunologic, inflammatory, metabolic, coagulation, and endocrinologic outcomes in study subjects.

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