

Partners Protocol #: 2020P001215

TITLE: ESCAPE (Evaluation of SARS-CoV-2 Antibody-containing Plasma thErapy): A Prospective, Randomized, Double-Masked, Placebo-Controlled Trial of High-Titer COVID-19 Convalescent Plasma (HT-CCP) for the Treatment of Hospitalized Patients with COVID-19 of Moderate Severity.

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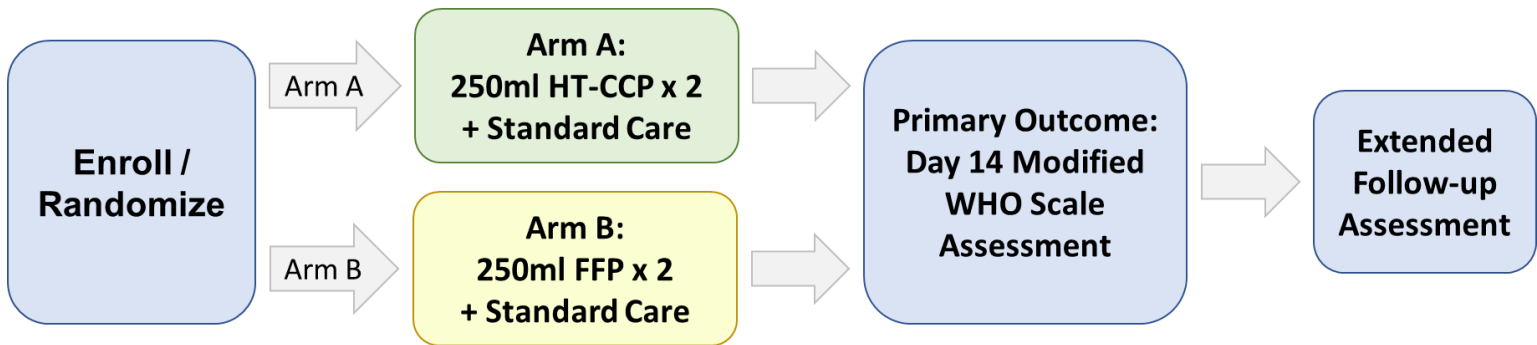
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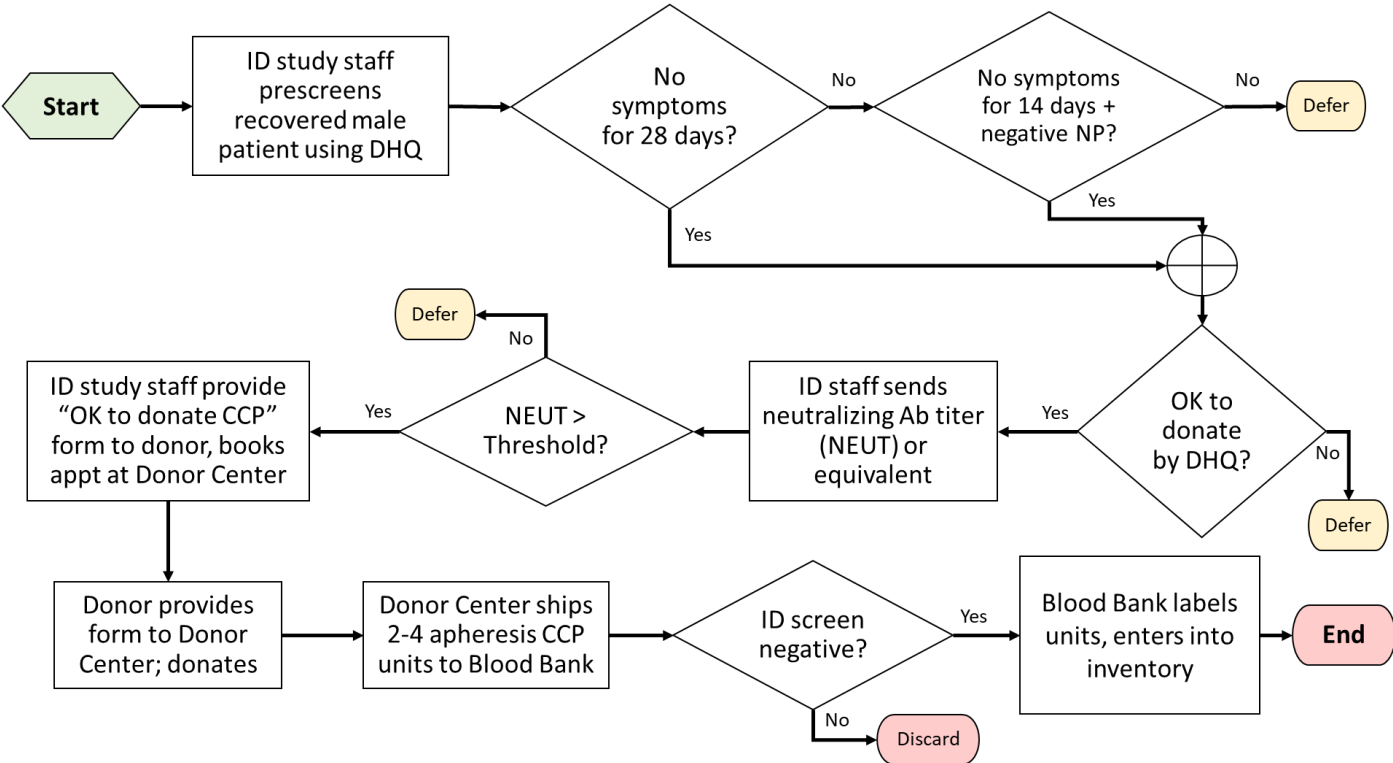
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STUDY SCHEMA



HT-CCP COLLECTION SCHEMA



ABBREVIATIONS

ACEI	Angiotensin-Converting-Enzyme Inhibitor
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
ARDS	Acute Respiratory Distress Syndrome
CCP	COVID-19 Convalescent Plasma
CoV	coronavirus
COVID	Coronavirus Disease
CVA	Cerebro-Vascular Accident
DM	Diabetes Mellitus
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
ED	Emergency Department
FFP	Fresh Frozen Plasma (frozen within 8 hrs)
FP24	Frozen Plasma (frozen within 24 hrs)
FiO ₂	Fraction of Inspired Oxygen
HLA	Human Leukocyte Antigen
HT	High-Titer
HTN	Hypertension
ICU	Intensive Care Unit
LAR	Legally Authorized Representative
MERS	Middle East Respiratory Syndrome
MI	Myocardial Infarction
MOS	Modified Ordinal Scale
NEUT	Neutralizing Antibody Titer
NSAID	Non-Steroidal Anti-Inflammatory Drug
PaO ₂	Partial Arterial Pressure of Oxygen
PE	Pulmonary Embolism
PI	Principal Investigator
RCT	Randomized Controlled Trial
SAE	Severe Adverse Event
SARS	Severe Acute Respiratory Disease
SOFA	Sequential Organ Failure Assessment
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-Associated Lung Injury

1. STUDY SUMMARY

Title	ESCAPE (Evaluation of SARS-CoV-2 Antibody-containing Plasma therapy): A Prospective, Randomized, Double-Masked, Placebo-Controlled Trial of High-Titer COVID-19 Convalescent Plasma (HT-CCP) for the Treatment of Hospitalized Patients with COVID-19 of Moderate Severity.
Background	COVID-19 is a global pandemic for which effective treatments are desperately needed. It is possible that convalescent donor plasma may confer therapeutic benefit in SARS-CoV-2 infection, however this remains unknown and randomized controlled trials are needed to evaluate the safety and efficacy of this approach.
Study Design	Prospective, randomized, double-masked, placebo-controlled, multi-center clinical trial.
Study Population	Hospitalized patients with COVID-19 but without moderate or severe ARDS.
Investigational Arm	250mL HT-CCP x2 doses given sequentially.
Control Arm	250mL FFP or FP24 x2 doses given sequentially.
Sample Size	Up to 220 subjects.
Inclusion Criteria	<ol style="list-style-type: none"> 1. Age >1 year. 2. Active COVID-19 infection confirmed by positive SARS-CoV-2 PCR. 3. Meets institutional criteria for admission to hospital for COVID-19. 4. Admitted to hospital within 5 days of enrollment. 5. PaO₂/FiO₂ >200 mmHg if intubated. 6. SpO₂ ≤ 93% and bilateral pulmonary infiltrates if on room air. 7. Patient or surrogate able to provide informed consent.
Exclusion Criteria	<ol style="list-style-type: none"> 1. Previous treatment with convalescent plasma for COVID-19. 2. Current use of investigational antiviral therapy targeting SARS-CoV-2. 3. History of anaphylactic transfusion reaction. 4. Clinical diagnosis of acute decompensated heart failure. 5. Objection to blood transfusion.
Randomization	Randomization will be blocked and stratified by institution, and level of severity at entry. Within each stratum, subjects will be randomized 1:1 to investigational treatment or control arm.
Masking	Patient and treating physician will not know whether administered study agent is HT-CCP or FFP/FP24.
Primary Endpoint	MOS score at day 14.
Secondary Endpoints	<ol style="list-style-type: none"> 1. 28-day mortality. 2. Time to hospital discharge. 3. Time to viral clearance. 4. Ventilator-free days through day 28. 5. Incidence of secondary COVID-19.
Safety Endpoints	<ol style="list-style-type: none"> 1. Respiratory decompensation after administration of study agent. 2. Incidence of TRALI, TACO, and allergic reaction.
Statistical Analysis	The primary test of treatment effect will use ordinal logistic regression to test the treatment effect and to assess the influence of clinically important covariates on the relative odds of progression. Pearson's chisquared test comparing day-14 score counts in the two treatment groups will be employed as a backup because it is robust to non-proportional odds and can detect mean differences of 2+ units in average outcome scores. This analysis is a 2×10 table and will also yield a valid test of the null hypothesis. Fisher's exact test will be used if the expected count in at least one table cell is less than 5. Event time comparisons of secondary outcomes will use the logrank statistic. Influence of clinical covariates on secondary outcomes will be assessed using restricted mean survival time regressions.

2. OBJECTIVES

2.1 Study Design

This study is a randomized, double-masked, placebo-controlled trial evaluating the safety and efficacy of High-Titer COVID-19 Convalescent Plasma (HT-CCP) for the treatment of hospitalized patients with COVID-19 of moderate severity.

2.2 Primary Objective

- To determine whether the early addition of HT-CCP to standard treatment improves the clinical outcome (as assessed by the Modified WHO Ordinal Scale) of patients with COVID-19 who are hospitalized but not yet in moderate or severe ARDS.

2.3 Secondary Objectives

- To assess whether time to viral clearance differs between study arms.
- To assess whether time to hospital discharge differs between study arms.
- To assess whether 28-day mortality differs between study arms.
- To assess whether the number of ventilator-free days differs between study arms.
- To assess for incidence of secondary infection with SARS-CoV-2.

2.4 Safety Objectives

- To assess for incidence of respiratory decompensation immediately after infusion of study agent.
- To assess for incidence of TRALI, TACO, and allergic reaction to study agent.
- To assess for any unexpected side effects of study agent.

2.5 Correlative Science Objectives

- To analyze antibody profiles of HT-CCP/FFP donor units and recipients (including but not limited to antibody titer, antibody characteristics, and antibody functions) and assess for possible correlates with clinical outcome.
- To analyze other markers of immune function and assess for possible correlates with clinical outcome.

3. BACKGROUND

3.1 The magnitude of the COVID-19 crisis.

The current outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel virus that causes the clinically variable but often severe viral respiratory syndrome now known as COVID-19, is now a global pandemic that threatens the lives of millions of people across the world. As of April 16th, 2020, there have been 632,548 confirmed cases and 31,071 deaths due to COVID-19 in the United States alone, with the former likely being a gross underestimate of the actual incidence and prevalence (U.S. Centers for Disease Control and Prevention [CDC] 2020). Reported mortality rates have demonstrated some variability between countries, however all data to date indicate that SARS-CoV-2 is a highly infectious and lethal virus in the elderly population, as well as in patients with comorbidities that are exceedingly common in the U.S., and can in fact be fatal in patients of any age.

Compounding the formidable natural course of SARS-CoV-2 is the absence of any pre-existing immunity to it in the human population and the resulting exponential growth of clinically severe infections that is

now increasingly straining healthcare systems across the country. There is now a consensus among medical and epidemiological experts that a lack of adequate medical resources, including intensive care and mechanical ventilation capabilities, may further worsen the lethality of the virus as the crisis reaches its peak over the coming weeks.

3.2 Current options for treatment.

Currently, the treatment of patients with COVID-19 is supportive in nature, ranging from symptomatic self-treatment at home to hospitalization for patients requiring oxygen to invasive ventilation for upwards of 75% of those who require ICU-level care (Bhatraju 2020). Multiple investigational therapies are currently under study, including the RNA-dependent RNA polymerase inhibitor, remdesivir. Although the hypothesized efficacy of this drug is based on strong biological rationale and pre-clinical data (Wang 2020), it is not an agent that was developed to target SARS-CoV-2 specifically or the immune response to it, and even if ultimately proven to be efficacious is unlikely to be immediately available to the majority of the population. Likewise, chloroquine phosphate and hydroxychloroquine are currently being evaluated in multiple studies of SARS-CoV-2-infected/exposed individuals and may ultimately prove to have some degree of efficacy via inhibition of endosomal-mediated viral cellular entry (Liu 2020), however clinical data to date have been conflicting and largely anecdotal, and again the proposed mechanism does not purport to enhance the innate or adaptive immune response to the virus.

3.3 Rationale for use of CCP for the treatment of COVID-19.

COVID-19 convalescent plasma (CCP) represents perhaps the only therapeutic modality against SARS-CoV-2 that has the potential to both augment the virus-specific immune response and be immediately deployable and scalable during and immediately after the imminent peak of the pandemic when the majority of deaths are expected to occur, as well as during the hypothesized second peak that may occur later in 2020 after initial relaxing of social distancing measures. The hypothesis for its efficacy is based partially on our routine clinical experience with intravenous immune globulin (IVIg), a passive antibody therapeutic modality for which there is an abundance of data demonstrating both preventive and therapeutic activity against viral and bacterial infections via augmentation of the humoral immune response (Falsey 2017, Lejeune 2017, Raanani 2009). The use of CCP for COVID-19 is further supported by historical data on utilization of convalescent donor plasma (CP) during past respiratory virus outbreaks such as those of SARS-CoV-1 and influenza A (H1N1) (Hung 2011, Cheng 2005).

Although there is a paucity of randomized controlled trials evaluating CP in the context of past outbreaks and pandemics, the data are nonetheless encouraging. A prospective cohort study in Hong Kong during the 2009 H1N1 pandemic, for example, demonstrated an 80% reduction in risk of death in severely ill patients who received CP versus controls who refused it (OR: 0.2, 95% CI: 0.06-0.69, $P = 0.011$) (Hung 2011). Moreover, CP-treated patients in this study were found to have lower levels of IL-6, IL-10, and TNF α compared to controls at corresponding timepoints, suggesting that CP could potentially exert a dampening effect on the cytokine release syndrome (CRS) suspected to be involved in the pathogenesis of severe COVID-19 (Mehta 2020). Likewise, a systematic review and exploratory meta-analysis of CP use in severe acute respiratory infections that was performed in the aftermath of the H1N1 pandemic identified 32 studies between 1919 and 2011 that collectively suggested a similar reduction in risk of death with this approach (OR: 0.25, 95% CI: 0.14-0.45, $I^2 = 0\%$). However, this analysis included only two comparative studies of CP in SARS-CoV-1 (69 patients total), neither of which were randomized, and both of which were deemed to be at medium-to-high risk of bias (Mair-Jenkins 2015).

Regarding SARS-CoV-2 specifically, only two uncontrolled case series of 15 CCP-treated patients in total have been published, although both reported signs of clinical improvement (e.g. defervescence and increased blood oxygen saturation) within days after CCP transfusion (Duan 2020, Shen 2020). Additionally, the Chinese government issued a press release in February 2020 reporting that 245 patients had been offered CCP and that 91 had demonstrated evidence of clinical improvement. No other clinical data on CCP exist currently, although this will soon change with the recent establishment of the National Convalescent Plasma Project and hopefully this protocol.

3.4 **Justification for a double-masked, placebo-controlled, RCT design.**

Taken together, the available data on past CP use call not only for the immediate investigational use of CCP for our hospitalized patients, but also for well-designed RCTs to ultimately validate or refute this approach. Given the severity of the current crisis and the absence of proven therapeutic options beyond supportive and intensive care, the argument that compassionate use CCP should be offered to as many COVID-19 patients as possible is an understandable one. However, we feel that there is enough potential for both futility and unintended harm with this approach to establish equipoise and justify an RCT.

Beyond the poor quality of prior CP studies which limits interpretation of the available data, allogeneic plasma transfusions are known to carry risk of adverse events such as transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and allergic reactions that may include bronchospasm and, rarely, anaphylaxis. There is also a likely minimal but potential risk of viral transmission from newly convalescent donor to recipient, including transmission of a different strain of SARS-CoV-2, which could in theory worsen the severity of disease. Additionally, plasma transfusions are known to contain complement, a known mediator of cytokine release, thus making it possible that CCP could either trigger or exacerbate CRS in a COVID-19 patient.

The phenomenon of antibody-dependent enhancement of infection (ADE), whereby the presence of cross-reacting antibodies or low levels of neutralizing antibody against a viral pathogen can paradoxically worsen the viral syndrome, is also a risk that needs to be considered (Halstead 2010). The clinical relevance of ADE has been best elucidated in dengue disease, wherein secondary infection by the dengue flavivirus can be considerably more severe than primary infection due to the enabling of viral entry into FcγR-expressing cells by antibodies generated against the initial viral serotype. A recent study of a long-term pediatric cohort in Nicaragua suggests that this process occurs within a narrow window of pre-existing antibody levels, above which the patient is protected from clinically significant ADE (Katzelnick 2017). Human coronavirus infection is not known to be clinically exacerbated by ADE, although ADE has been demonstrated to occur in a feline coronavirus model (Vennema 1990). ADE has been demonstrated to occur in both SARS-CoV-1 and MERS-CoV infection *in vitro* via conformational change of the spike protein induced by neutralizing antibody ligation that triggers antibody-dependent and non-endosomal viral entry into FcγR-expressing cells. In this model, enhanced viral entry can be overcome by higher antibody levels that saturate the FcγRs (Wan 2020). Although the historical data on CP use during past viral outbreaks do not suggest that ADE-mediated worsening of COVID-19 severity is likely to occur, these data nevertheless suggest that it remains a possibility, especially at the lower end of convalescent donor antibody titers, which adds further justification for both the selection of high-titer donors and an RCT design.

Conversely, it is also possible that components of HT-CCP other than the neutralizing antibodies themselves could exert a therapeutic effect, which could favorably impact clinical outcomes. Both coagulation factors and complement, for example, could confer benefit to subjects in terms of lowering risk of bleeding and augmenting the immune response, respectively. If HT-CCP ultimately proves to

improve clinical outcomes in the study population, it is critical that this benefit has been convincingly determined to be attributable to the convalescent donor source and not to components common to all donor plasma. Otherwise the considerable time and resource utilization within the medical community that is likely to result from a positive study (e.g. donor screening and PCR/antibody testing) will be, in truth, unnecessary. The only way to eliminate this possibility is to use standard, non-convalescent plasma (FFP) as a placebo.

Likewise, without blinding both the subject and investigator/care team to study arm, there would be considerable risk of bias that could affect outcome. A hospital physician who knows that the subject did not receive HT-CCP, for example, could become more concerned about mild worsening of clinical or laboratory parameters and act on them when the same parameters would not have altered the therapeutic plan for a subject who was known to have received HT-CCP. Likewise, a patient's own knowledge that they have not received an investigational therapy that could ultimately prove to be lifesaving may cause severe emotional distress that could negatively impact clinical outcome, as well as inflict undue suffering upon the subject.

3.5 Rationale for study population and primary endpoint.

Multiple RCTs should and will be performed during the COVID-19 crisis to identify the conditions under which CCP confers both safety and the greatest benefit so that resources can be utilized with optimal efficiency and outcome. Our rationale for focusing on patients who require hospitalization and possibly intubation, but who have not yet progressed to the point of critical illness, is twofold. First, as the majority of cases are mild and do not progress to the point of hypoxia, devoting a finite number of CCP units to outpatients who are statistically likely to survive with supportive measures alone would not be the most efficient utilization of limited resources during a pandemic; the potential exceptions here would include exposed or infected health care workers for whom clinically severe and/or slowly resolving infection would have direct impact on the functionality of the U.S. healthcare system, as well as elderly patients for whom the projected risk of mortality at the time of diagnosis is exceptionally high. Second, in the setting of active clinical infection, passive antibody therapy may be most beneficial when given earlier in the disease course. In a case series of 80 patients hospitalized with SARS-CoV-1 and given CP after failure of ribavirin and methylprednisolone, for example, those who received CP more than 14 days after onset of symptoms had a significantly longer time to recovery and a higher mortality compared those who were treated within two weeks of symptom onset (Cheng 2005). Accordingly, this study is designed to focus on those patients who are within five days of hospital admission and whose pulmonary disease has progressed to mild ARDS at worst, as we believe these patients have both a demonstrated need for efficacious therapy beyond supportive care alone as well as a relatively high likelihood of benefiting from passive antibody therapy.

The goal for any COVID-19 therapeutic trial should ultimately be to save lives. However, given the known mortality rate of this infection as well as the high quality of medical care within the Harvard Medical School-affiliated hospitals and the state of Massachusetts, we estimate that it would take upwards of a 1000-subject RCT to demonstrate a 28-day survival advantage in favor of HT-CCP. Within the accrual limitations of a multisite or even statewide study, establishing 28-day mortality as the primary endpoint would thus likely necessitate a period of several months or longer before completion of accrual, which would significantly reduce the potential for practice-changing impact of the study results in the context of the current crisis. Instead, we propose to use a modified ordinal scale (MOS) score at 14 days post-randomization as our primary endpoint. This scale is based on the 7-point ordinal scale endorsed by the WHO for COVID-19 clinical trials, but with more detailed stratification of disease severity which we feel will be better able to detect a clinically meaningful therapeutic effect if one is truly present. This

endpoint is easily measurable, applicable to the entire study population (both floor and ICU patients), and less likely than 28-day mortality to be confounded by other off-label or investigational therapies that the subject may receive in the event of clinical decline. Detection of a significant difference in this primary endpoint between study arms in favor of HT-CCP would provide support for the immediate off-protocol use of this form of therapy for moderately ill patients with COVID-19, while failure to meet this endpoint would provide the greater medical community with a note of caution against devoting time and resources to this modality of therapy for patients with COVID-19 of moderate severity.

3.6 Rationale for longitudinal study design.

There are many aspects of SARS-CoV-2 that remain unknown, among them the degree of immunity versus susceptibility of convalescent patients to secondary SARS-CoV-2 infection. Although the likelihood of newly convalescent individuals succumbing to a secondary SARS-CoV-2 infection is probably low, we do not know this as a certainty, and there are in fact early reports from South Korea of convalescent patients who are now testing positive for SARS-CoV-2 by PCR after previously testing negative. Thus, absent a highly efficacious vaccine, there may in fact be a long-term risk of secondary COVID-19 for some patients should the virus enter an endemic phase after resolution of the current pandemic. Along the same lines, it is possible that passive antibody therapy with HT-CCP could weaken the patient's own innate and/or adaptive immune response, which could leave them with lower long-term cellular and/or humoral immunity to SARS-CoV-2. Given the enormity of the current crisis, this theoretical risk is worth taking for our hospitalized patients, however it also warrants careful assessment by extended follow-up.

4. PARTICIPANT SELECTION

Patients with COVID-19 will be eligible for this trial if they meet the following eligibility criteria:

4.1 Inclusion Criteria

- 4.1.1 Age >1 year
- 4.1.2 Active COVID-19 infection confirmed by positive SARS-CoV-2 PCR.
- 4.1.3 Meets institutional criteria for admission to study site inpatient service for COVID-19.
- 4.1.4 Hospitalized ≤ 5 days prior to enrollment.
- 4.1.5 If on room air, must have $SpO_2 \leq 93\%$ and bilateral pulmonary infiltrates.
- 4.1.6 If intubated, PaO_2/FiO_2 ratio must be greater than 200 mm/Hg at time of enrollment.
- 4.1.7 Is able to understand and willing to provide informed consent. In the event the patient lacks capacity to make medical decisions, the patient's LAR or child's parent or guardian may provide informed consent.

4.2 Exclusion criteria

- 4.2.1 Previous treatment with convalescent plasma for COVID-19.
- 4.2.2 Current use of investigational antiviral therapy targeting SARS-CoV-2.
- 4.2.3 History of anaphylactic transfusion reaction.

4.2.4 Clinical diagnosis of acute decompensated heart failure.

4.2.5 Objection to blood transfusion.

4.3 **Inclusion of women and minorities**

Both males and females of all races and ethnic groups are eligible for this trial.

5. **DONOR SELECTION AND PLASMAPHERESIS**

5.1 **Initial Donor Screening**

Study staff will perform initial screening of prospective male donors (or nulliparous females, or females screened negative for HLA antibodies) in order to reduce the likelihood that the donated plasma will contain HLA antibodies, a major risk factor for the development of transfusion-related acute lung injury (TRALI) in recipients of plasma transfusions. Prospective donors will move on to neutralizing antibody titer testing once they are confirmed appropriate for donation by an abbreviated Donor History Questionnaire (DHQ; please see attached COVID-19 Convalescent Plasma Pre-Screening Form).

5.2 **Donor Neutralizing Antibody Titer (NEUT) Testing**

Upon passing the initial donor screening, the prospective donor will have a blood sample drawn by study staff and sent for neutralizing antibody testing (most likely by a pseudoviral neutralizing antibody assay) to confirm the presence and titer of anti-SARS-CoV-2 neutralizing antibodies.

5.3 **Convalescent Plasma Donation, Shipment, and Screening**

Once the antibody assay has confirmed a NEUT of greater than 1:160, study staff will provide the donor with an “OK to donate CCP” form and schedule the donor an appointment at the Kraft Family Blood Donor Center (KFBDC) or an alternate donor center. If multiple HT-CCP donors are available to donate at any given time, study staff will, whenever possible, preferentially schedule donors who have the highest NEUTs in coordination with the donor center while also ensuring adequate availability of ABO type-specific donor units.

At the time of their appointment at the donor center, the donor will present their form to donor center staff and undergo apheresis collection of two-four 250 mL units of HT-CCP according to standard donor center protocol. Donor center staff will then ship the HT-CCP units to the study site hospital blood bank. The blood bank will quarantine the units until all standard viral marker screening test results are returned. Units cleared for transfusion will be labeled as CCP and entered into inventory. Units will be stored at ≤ -18 °C with continuous temperature monitoring. Upon receiving an approved transfusion order for a consented subject, the blood bank will thaw a unit of CCP. Units will be ABO identical with the recipient whenever possible; ABO non-identical but compatible units will be issued if necessary, depending on inventory. Thawed CCP units will be stored for up to 5 days at 1-6 °C with continuous temperature monitoring.

6. **TREATMENT PLAN**

6.1 **Treatment Regimen**

Two 250 mL units (500 mL total) of HT-CCP that have been collected from the same donor (whenever possible) will be administered sequentially over no greater than a 24-hour period to participants

randomized to arm A. Two 250 mL units (500 mL total) of FFP or FP24 will be administered sequentially to participants randomized to arm B. Both the subject and the treating physician will be blinded to the identity of the infused agent.

6.2 Pre-Treatment Criteria

In order to receive study treatment, participants must not have acquired a diagnosis of acute decompensated heart failure since study enrollment.

6.3 Agent Administration

- 6.3.1 Each unit of study agent will be infused intravenously at a rate of ≤ 500 mL/hr within four hours of release by the blood bank.
- 6.3.2 The second unit of study agent will be given no greater than 24 hours after completion of the first dose.
- 6.3.3 In the event of a sudden respiratory and/or hemodynamic compromise during the transfusion of study plasma, the transfusion will be stopped immediately and the patient will receive appropriate acute supportive care. For reactions limited to urticaria (i.e. no hypotension or bronchospasm), the transfusion may be paused, the urticaria treated with antihistamine, and the transfusion restarted with approval of the covering clinician. The HT-CCP unit will be returned to the blood bank, and a transfusion reaction workup will be initiated per standard procedure.
- 6.3.4 In the event of a transfusion reaction to the first dose of study agent, the subject may receive the second dose after resolution of symptoms if the investigator deems the reaction to be non-severe.
- 6.3.5 In the event of any other AE during or after the first dose of study agent, the subject may receive the second dose after resolution of symptoms if the investigator deems the AE to be non-severe.

6.4 Criteria for Taking a Participant Off Protocol Therapy

If, after starting HT-CCP infusion, the participant experiences a complication as a result of the transfusion that requires suspension prior to completion, the participant will not resume transfusion if any of the following criteria are met:

- 6.4.1 Transfusion reaction deemed by investigator and/or responsible attending physician to be severe.
- 6.4.2 The patient (or LAR if the patient does not have capacity to provide consent) does not give consent to resume transfusion.

6.5 Criteria for Taking a Participant Off Study

Participants may be withdrawn from the study if any of the following occur:

- 6.5.1 Withdrawal of consent for study participation.
- 6.5.2 Death.
- 6.5.3 The participant becomes lost to follow-up.
- 6.5.4 Discontinuation of the study.
- 6.5.5 The participant has completed long-term follow-up as per protocol.

The reason for taking a participant off study, and the date the participant was removed, must be documented in a case report form (CRF).

7. ADVERSE EVENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (section 7.1) and the characteristics of an observed AE (section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting:

7.1 Adverse Events List

The following adverse events have been observed with plasma transfusions:

- transfusion-associated circulatory overload (TACO)
- transfusion-related acute lung injury (TRALI)
- allergic or anaphylactic reaction (e.g. rash, angioedema, anaphylaxis)
- febrile non-hemolytic transfusion reaction
- transmission of infections (rare)
- hemolytic transfusion reaction (rare)
- hypotensive transfusion reaction (rare)

7.2 Adverse Event Characteristics

7.2.1 CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

7.2.2 For expedited reporting purposes only: AEs for the agent listed above should be reported only if the adverse event varies in nature, or frequency from the expected toxicity information which is provided. Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

7.2.3 attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators must report to the Overall PI any serious adverse event (SAE) that occurs after the study treatment, during treatment, or within 30 days of treatment on the institutional SAE form. This applies to any medical event equivalent to an unexpected Grade 2 or 3 with a possible, probable or definite attribution, unexpected Grade 4 toxicities, and Grade 5 (death) regardless of study phase or attribution.

7.3.2 Expedited Reporting Guidelines

Investigative sites will report AEs directly to the Partners Human Research Committee per policy: <https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf>

Other investigative sites will report AEs to their respective IRB according to the local IRB’s policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Table 7-1 Adverse Event Reporting Guidelines

Attribution	Reportable AEs				
	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study or for AEs occurring within 30 days of intervention, the AE should be reported within one (1) business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the Partners Human Research Committee per policy: <https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf>

7.3.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the Partners IRB. However, they still must be reported through the routine reporting mechanism (e.g. case report form).

Table 7-2 AE excluded from Expedited Reporting

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
skin	urticaria	1-3	n/a	yes	Unless accompanied by hypotension or bronchospasm.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any SAE that meets the FDA’s criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Routine Adverse Event Reporting

All AEs must be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

8. CORRELATIVE AND SPECIAL STUDIES

8.1 Studies of Antibodies to SARS-CoV-2

8.1.1 Studies of HT-CCP Donors

To qualify for apheresis plasma collection, blood samples will be collected from potential donors and these samples may be tested in parallel using different antibody assays.

8.1.2 Studies of Subjects

Study subjects’ blood will be sampled after enrollment and prior to the first transfusion of study agent (day 0 or day 1), as well as immediately after completion of the second transfusion (approximately 6-12 hours after completion on day 1 or day 2). Additional blood samples will be taken on day 7 (+/- 1 day) and every 7 days thereafter (+/- 1 day) until death or discharge from the hospital.

8.2 Studies of Viral Clearance

Starting on day 0-1, after enrollment, an NP swab for SARS-CoV-2 PCR will be performed on a weekly basis until the subject tests negative. If a subject recovers and is discharged from the hospital before testing negative, they may be offered the option of returning to an outpatient testing site at 1-2 week intervals until they test negative. A confirmatory NP swab may also be offered to a subject who tests negative before complete resolution of their symptoms. Additionally, if tracheal suction is clinically indicated, tracheal aspirate samples will be obtained from intubated subjects on a weekly basis for SARS-CoV-2 PCR testing.

8.3 Extended Follow-Up Studies

After discharge, subjects will be asked to return to the outpatient clinic for evaluation and blood sampling intermittently (approximately 3, 6, and 12 months after discharge) for a total of one year or longer if clinically indicated.

9. DATA COLLECTION

9.1 Baseline Data Collection

The following information will be collected at the time of enrollment:

- age
- sex
- ethnicity
- vital signs (to include oxygen requirement)
- PaO₂/FiO₂ (intubated subjects only)
- MOS score
- height and weight
- date of admission
- date of onset of symptoms
- date of first positive SARS-CoV-2 PCR
- comorbidities (to include HTN, DM, CAD, COPD, asthma, cancer, and autoimmune disease)
- recent and/or chronic use of medications of interest (to include ACEIs, ARBs, NSAIDs, corticosteroids, chemotherapy, immunotherapy, statins)
- prior use of any off-label therapies for COVID-19 (to include chloroquine, hydroxychloroquine, azithromycin, lopinavir, ritonavir, tocilizumab, and sarilumab)
- SOFA score (intubated subjects only)
- Day of intubation and number of days intubated

9.2 In-Hospital Data Collection

The following information will be collected after enrollment and until death or hospital discharge:

- MOS score on days 2, 3, 5, 7, 10, 14, and weekly thereafter
- daily ventilation status (intubated or ventilator-free)
- SOFA score on days 2, 3, 5, 7, 10, 14, and weekly thereafter (intubated subjects only)
- date of death
- date of hospital discharge
- oxygenation status at time of discharge (home O₂ versus O₂-independent)
- documented infection other than COVID-19
- documented medical complication to include MI, CM, CVA, and DVT/PE
- other clinical laboratory data of disease severity (to include, ferritin, CRP, coagulation studies, blood cell counts, and d-dimer)
- other therapies for COVID-19

9.3 Short-Term Follow-Up

For subjects discharged prior to day 29, the following information will be collected via phone call with the subject or the subject's LAR:

- modified ordinal scale score on days 7, 14, 21, and 28
- date of and reason for any re-hospitalization or ED visit (if any)
- date and cause of death

9.4 Extended Follow-Up

After day 28, the following information will be collected via in-person visit or phone call with the subject or subject's LAR at approximately 3, 6, and 12 months after hospital discharge (or longer if deemed necessary by the PI):

- Date of and reason for any re-hospitalization or ED visit (if any)
- Date and cause of death
- Date of any confirmed positive test for active SARS-CoV-2 infection

10. REGULATORY REQUIREMENTS

This study will be conducted in accordance with policies established by the Partners Human Research Committee, AABB, and FDA. CCP units will be administered under the FDA's Investigational New Drug (IND) program. <https://www.fda.gov/media/136798/download>.

10.1 Data Reporting

At the time of publication, a de-identified version of the database will be generated and made available to FDA and the public.

10.2 Data Safety Monitoring

A Data Safety Monitoring Board comprised of experts not involved in the study will review the data periodically. Interim analyses will be conducted after 50, 100, and 150 subjects have been accrued and their primary outcomes ascertained. Accrual will not be suspended during the interim monitoring period. Very strong evidence would be required to stop this trial for an efficacy signal.

Interim futility decisions will be supported by conditional power calculations. At each interim analysis, a "final" power calculation will be based on the current observed trend extrapolated to the planned end of the trial. If the probability of rejecting the null hypothesis conditional on the current trend falls below 0.2, the trial will be recommended for termination. The original hypothesized effect as well as a hypothetical optimistic effect or trend might also be of interest in such calculations, so the recommendation to use the cutoff of 0.2 power must be flexible. Clinical circumstances will also bear on this decision.

10.3 Multicenter Guidelines

11. DATA QUALITY MONITORING AND STORAGE

Data will only be available to approved study staff. All data will be captured and stored using a PHRC-approved secure online REDCap database.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design and Primary Endpoint

This study is a prospective, randomized, double-masked, placebo-controlled trial of HT-CCP for the treatment of hospitalized patients with COVID-19 of moderate severity as defined by either non-ICU status or PaO₂/FiO₂ >200 mmHg for patients in the ICU. The primary endpoint is a Modified WHO Ordinal Scale (MOS) numerical score on day 14 of the study (Table 12-1). The eligibility requirements for this trial select individuals at level 3 or higher on the modified scale, but the day 14 outcome can be any one of 10 levels. The numerical scores assigned to those levels are immaterial provided that immediately successive scores increase by one-unit. This section will assume the scores are 0-9 (10 levels).

Table 12-1: Modified WHO Ordinal Scale

Score	Definition
0	no clinical evidence of infection
1	no limitation of activities
2	limited activities
3	hospitalized with no oxygen requirement
4	hospitalized with 1-4L NC oxygen requirement
5	hospitalized with >4 L NC oxygen requirement or intubated with PaO ₂ /FiO ₂ >300 mmHg*
6	intubated with PaO ₂ /FiO ₂ 201-300 mmHg*
7	intubated with PaO ₂ /FiO ₂ 101-200 mmHg*
8	intubated with PaO ₂ /FiO ₂ ≤100 mmHg*
9	death

* Mean P/F ratio over a 24-hour period.

12.2 Randomization

Randomization will be blocked and stratified by institution, and level of severity at entry (less than 6 versus 6 or higher). Within each stratum, subjects will be randomized 1:1 to investigational treatment or control arm. The block size will not be revealed to the investigators. Because the treatments are masked, investigator inquisitiveness regarding treatment balance should be eliminated.

12.3 Sample Size and Power

A standard approach to sample size determination for ordinal scales (Whitehead 1993) assumes proportional odds over the outcome scale and uses the formula

$$N = \frac{12(Z_{\alpha} + Z_{\beta})^2}{\log[\theta]^2(1 - \sum_{i=1}^k \bar{p}_i^3)}$$

where N is the total sample size required, Z_{α} and Z_{β} are the usual standard normal quantiles for type I and II errors, θ is the common odds for the treatment effect, the \bar{p}_i 's are the average probabilities of being in each one of k respective outcome categories, and the allocation is 1:1. This power formula corresponds to a Wald test of the regression coefficient for treatment effect in a simple ordinal logistic regression model.

How to model the expected proportion of subjects in each outcome category will be discussed below. But to make use of this formula, consider the results in Table 12-2. It shows several hypothetical outcome

distributions (treatment and control probabilities averaged together at each level, \bar{p}_i as in the formula) and total sample sizes required for a given treatment effect measured by the odds ratio θ . The odds ratio implies that the treatment would reduce the risk of advancing n levels by θ^n . All scenarios have been calculated assuming a one-sided 0.025 type I error and 90% power. It is essential to use 90% power to be certain the trial is robust against deviations from the design assumptions. Because of symmetry around the outcome scale mean, 4.5, results for average scores in the upper half of the scale will mirror those in the lower half with outcome score probabilities reversed. This is illustrated by scenarios #4 and #5 in the table.

Table 12-2 indicates using this standard approach with reasonable assumptions, sample sizes of 100 per treatment group will suffice to detect a 2.2- to 2.5-fold reduction in the risk of progression to the next more advanced outcome category over a range of true outcome frequencies. The specific design assumption for this trial is case #6 which assumes a mean outcome score of 4 (or 5 by symmetry), a risk reduction (odds ratio) of 2.2-fold, and a required sample size of 103 per group (206 total). The risk reduction implied by the odds ratio is strong, representing a balance between what is important clinically and what is achievable relatively quickly and reliably under the circumstances.

Table 12-2. Total Sample Sizes for Different Outcome Probabilities, Mean Scores, and Odds Ratios

#	Outcome Score Average Probabilities, \bar{p}_i										Mean Score	Odds Ratio	Sample Size
	0	1	2	3	4	5	6	7	8	9			
1	.498	.25	.126	.063	.032	.016	.008	.004	.002	.001	1	2.5	176
												2.0	306
2	.314	.218	.151	.105	.073	.051	.035	.024	.017	.012	2	2.5	158
												2.0	276
3	.205	.169	.140	.115	.095	.078	.065	.053	.044	.036	3	2.5	154
												2.0	268
4	.130	.122	.115	.108	.102	.096	.090	.085	.08	.075	4	2.5	152
												2.0	266
5	.075	.08	.085	.09	.096	.102	.108	.115	.122	.130	5	2.5	152
												2.0	266
6	.130	.122	.115	.108	.102	.096	.090	.085	.080	.075	4	2.2	206

12.4 Operating Characteristics

The operating characteristics (OC) of the design tell us how it will perform under various truths of nature, especially ones that might differ from the design assumptions. There are three elements to this method that present design challenges: the overall treatment effect, average outcome probabilities, and the proportional odds assumption. Under the proportional odds assumption, θ represents a shift in the distribution of outcome scores between the treatment groups. An example is shown in Figure 12-1 which shows cumulative distribution curves for an outcome shifted by $\theta = 2.0$, similar to the examples in Table 12-2. The overall distributions are similar, but one has been shifted to less severe (lower) scores. Figure 12-2 shows the same effect for $\theta = 1.5$, lower efficacy than the examples in Table 12-2. This is a more subtle visual effect in terms of cumulative distributions of outcome scores and might not be clinically meaningful.

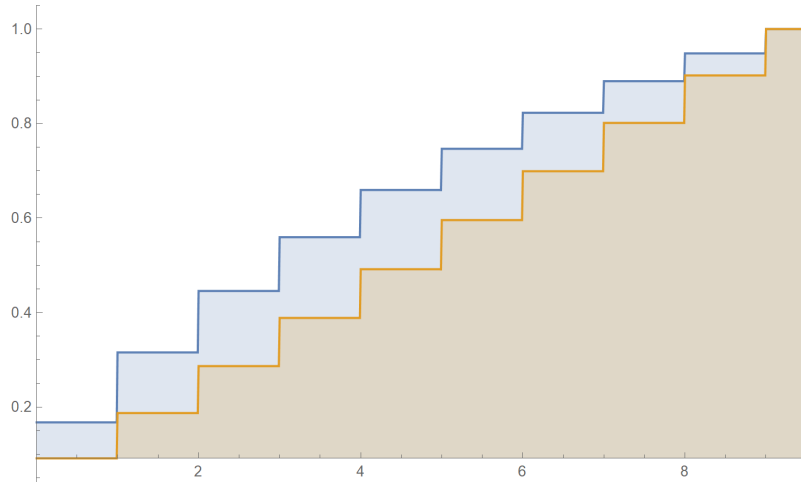


Figure 12-1 Cumulative Probability Distributions Under a Proportional Odds Model With $\theta \approx 2.0$

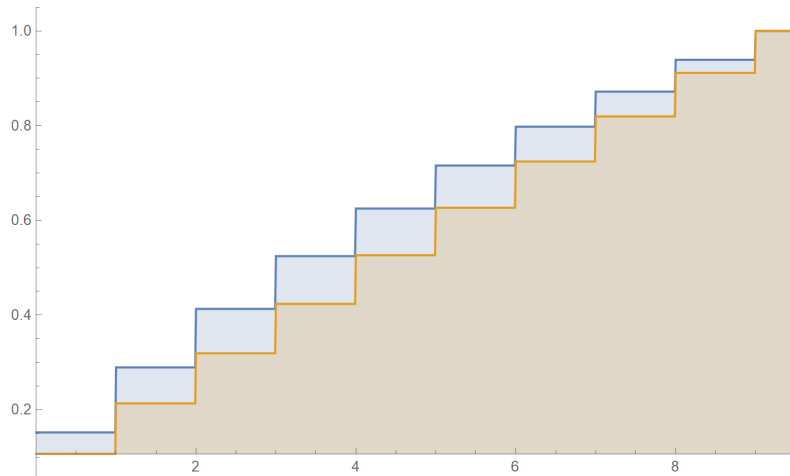


Figure 12-2 Cumulative Probability Distributions Under a Proportional Odds Model With $\theta \approx 1.5$

Figures 12.1 and 12.2 illustrate some good and bad features of the relatively strong proportional odds assumption. The treatment effect is very clean and operates across the entire range of outcomes. A wide spectrum of outcome levels makes it easier to detect a shift. The shift is the same everywhere by definition. This may or may not be biologically plausible, but it simplifies both the analysis of outcomes and yields the tidy sample size approach above. Conversely, if we postulate a modest distributional shift, it likely will correspond to a strong odds ratio reflecting its influence across the outcomes.

We do not have preliminary data on the likely effect size for CCP. We do not know if it will operate uniformly across the severity of disease. A potentially worrisome problem with proportional odds and the use of the sample sizes above is that the analysis is efficient when the assumption is correct but may be under-powered when it is not. This is anti-conservative and runs a risk of sizing the trial too small.

An alternative to proportional odds that does not make any parametric assumptions is to plan for the final analysis using Pearson's chisquared test for a 2 by 10 table. Each cell will contain the count of subjects in

the respective treatment/score based on day 14 assessments. There is no implied ordering or odds ratios. Such an analysis is conservative in that any structure in the data would be detectable using the test with an adequate sample size.

To investigate this, simulations of the trial have been run and analyzed using Pearson’s chisquared test rather than a proportional odds model. Specifying outcome probabilities for this method is a challenge because there is no underlying data structure to govern the arrangement of outcomes. The following minimalist assumptions have been used. For each scenario, the mean outcome score in each treatment group is specified. Once the mean is given, the outcome probabilities are specified by a Gibbs-Boltzmann distribution which has the maximum entropy of any with a given mean. This means that other than the mean, we are as uncertain as possible regarding the outcome probabilities. In very special cases, this distribution yields a proportional odds result, but generally it does not.

Table 12-3 shows the results. In all cases, the trial was simulated 10,000 times with a one-sided 0.025 type I error level. Equal sample sizes in each group were used. Results above and below the middle score, 4.5, would be mirrored for the same difference of means similar to Table 12-2. For example, a mean of 2 versus 4 will yield the same result as 5 versus 7. The results in Table 12-3 indicate that any difference in mean scores of 2 or more units will be detected with very high power using Pearson’s chisquared test. Case #4 shows that the chisquared test will perform poorly on mean differences of only 1 unit.

Additional simulations were run to assess the performance of a Wilcoxon rank sum test and a t-test on simplified summaries of outcomes (data not shown). Those simulations indicate that all these simple and sensible methods of analysis will yield nominal power or greater when the treatment differences are approximately as indicated in Tables 12-2 and 12-3. This suggests that the indicated approach and study size should be adequate to cope with outcome contingencies that do not strictly meet the design assumptions.

Table 12-3. Power for Comparing Treatments Using Pearson’s Chisquared Test

#	Outcome Score Average Probabilities, \bar{p}_i											Mean Score	Power
	0	1	2	3	4	5	6	7	8	9			
1	.498	.25	.126	.063	.032	.016	.008	.004	.002	.001	T	1	1.0
	.205	.169	.140	.115	.095	.078	.065	.053	.044	.036	C	3	
2	.314	.218	.151	.105	.073	.051	.035	.024	.017	.012	T	2	.99
	.130	.122	.115	.108	.102	.096	.090	.085	.080	.075	C	4	
3	.205	.169	.140	.115	.095	.078	.065	.053	.044	.036	T	3	.97
	.075	.080	.085	.090	.096	.102	.108	.115	.122	.130	C	5	
4	.130	.122	.115	.108	.102	.096	.090	.085	.080	.075	T	4	.36
	.075	.080	.085	.090	.096	.102	.108	.115	.122	.130	C	5	
5	.130	.122	.115	.108	.102	.096	.090	.085	.080	.075	T	4	.97
	.036	.044	.053	.065	.078	.095	.115	.140	.169	.205	C	6	

12.5 Accrual and Study Duration

We have no hard data reflecting on the accrual rate for this trial. The current inpatient COVID-19 census at BWH is approximately 150 with a similar number at MGH. Conservatively assuming half of those patients are eligible and half of those will consent, the trial might have accrued 75 individuals by this point in the pandemic. Accordingly, the trial could be completely accrued in 3-4 months. This seems optimistic, but we expect it proceed relatively quickly especially if the local number of cases surges.

12.6 Secondary Endpoints

Key secondary outcomes are:

- 28-day mortality.
- Time to viral clearance.
- Time to hospital discharge.
- Ventilator-free days through day 28.
- Occurrence of SARS-CoV-2 secondary infection at one year.

Among these, the dichotomous outcomes such as 28-day mortality will be determined with a precision of +/- 10% in each treatment group (95% confidence interval). The event time outcomes such as time to viral clearance and time to hospital discharge have precision that depends on the number of observed events. Assuming 50% censoring in such outcomes, the number of observed events is expected to be approximately 50 in each group. This will yield upper and lower relative confidence intervals of 0.76 and 1.32. In other words, the precision on such event rates will be between 25%-32%.

12.7 Interim Monitoring and Analyses

Interim analyses will be conducted after 50, 100, and 150 subjects have been accrued and their primary outcomes ascertained. Accrual will not be suspended during the interim monitoring period. Very strong evidence would be required to stop this trial for an efficacy signal. We will employ a classic Haybittle-Peto interim boundary for efficacy. This is a simple boundary that allows all interim analysis to reference significance levels of 0.001 as the criterion for stopping, and permits the final analysis at 0.025 one-sided, the nominal level. More complex interim boundaries could be employed, but we believe early stopping is unlikely and prefer a simple guideline. Clinical circumstances will also be a major factor in any decision to stop early for efficacy.

Interim futility decisions will be supported by conditional power calculations, again in deference to simplicity. At each interim analysis, a “final” power calculation will be based on the current observed trend extrapolated to the planned end of the trial. If the probability of rejecting the null hypothesis conditional on the current trend falls below 0.2, the trial will be recommended for termination. The original hypothesized effect as well as a hypothetical optimistic effect or trend might also be of interest in such calculations, so the recommendation to use the cutoff of 0.2 power must be flexible. Clinical circumstances will also bear on this decision.

12.8 Analysis and Reporting of Primary and Secondary Outcomes

The primary analysis will use all patients randomized to the treatment groups, commonly termed “intention to treat” analysis. In this setting it is unlikely that any trial participant will have a primary outcome that is unknown. In such a circumstance, the “worst case” outcome will be imputed for that subject, i.e., treatment failure. Missing secondary outcomes are more likely, but here again, worst case imputations will assure that every entered study subject contributes to the final analysis.

This trial design facilitates simple valid analyses. The primary test of treatment effect will use ordinal logistic regression stratified by institution and baseline severity per the randomization. The primary test of statistical significance will be the Wald test on the treatment indicator variable. This test exactly parallels the power calculation and design scenario #6 from Table 12-2. A secondary logistic regression analysis will also model the effects of age and sex as covariates to address two well defined and seemingly important risk factors. A third logistic regression will attempt to examine the effects of major comorbidities such as obesity (BMI), diabetes, lung disease, cardiovascular disease, cancer, and immunosuppression. This is an exploratory analysis because it is not straightforward to model this set of complex conditions with a few covariates. Pearson’s chisquared test comparing day-14 score counts in the two treatment groups will be employed as a backup to the primary because it is robust to non-proportional odds and can detect mean differences of 2+ units in average outcome scores. This analysis is a 2×10 table and will also yield a valid test of the null hypothesis. Fisher’s exact test will be used if the expected count in at least one table cell is less than 5. Because the trial employs stratified randomization, it is also simple and valid to stratify the analysis by the same factors. Assuming at least approximate homogeneity of treatment effects across strata, these basic analyses should agree.

Event time comparisons of secondary outcomes will use the logrank statistic. Influence of clinical covariates on secondary outcomes will be assessed using restricted mean survival time regressions.

13. HUMAN SUBJECTS PROTECTION

13.1 Informed Consent

In accordance with federal regulations in 45 CFR § 46.111(a)(5), each patient or LAR must provide written informed consent in order to enroll in the study. Study personnel will carefully explain the study objectives, procedures, risks, and benefits in plain language, and will strive to confirm that the patient or LAR is satisfied with their understanding. Study personnel will answer any questions the subject or LAR may have during the consenting process and during the entire course of the study. Consent can be withdrawn from the subject or LAR at any time. If consent is withdrawn after randomization and transfusion of one or both units of study plasma, all study activities will be suspended, however study personnel will request access to medical records for data related to the study. In cases where consent was initially obtained from an LAR, but the subject regains the ability to independently provide written informed consent, re-consenting of the subject will be conducted and documented by study personnel.

13.2 Minimization of risks to subjects

Federal regulations in 45 CFR § 46.111(a)(1) require that risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk. Accordingly, this trial protocol has been designed to minimize risks to subjects to the extent possible. We have selected that smallest subject sample size that will allow us to rigorously answer critical questions on the safety and efficacy of HT-CCP. By excluding from enrollment individuals with

either: (1) a history of anaphylactic transfusion reaction or (2) acute decompensated heart failure, we will reduce the likelihood of severe allergic reactions or TACO, respectively, in subjects. To further reduce the risk of TACO, each dose of study plasma can be transfused over four hours, and the second dose of study plasma can be transfused several hours after the first dose. (Both units of study plasma must be administered within 24 hours.) Finally, the trial protocol includes monitoring of adverse events, clinical outcomes, and interim analyses by an independent data and safety monitoring board empowered to stop or modify the trial at any time.

45 CFR § 46.111(a)(1) also specifies that risks to subjects are minimized whenever appropriate by using procedures already being performed on the subjects for diagnostic or treatment purposes. Plasma is transfused routinely to hospitalized patients. For example, nonbleeding patients are frequently administered plasma to correct abnormal coagulation test results before minor invasive procedures, albeit without strong supporting evidence for this practice. The risks to subjects of receiving either HT-CCP (intervention arm) or FFP/FP24 (control arm) are low. Per FDA [guidance](#), all donors of convalescent plasma must: (1) have been documented by a laboratory test to have been infected with COVID-19; (2) be >14 days free of symptoms plus have a negative NP swab OR be >28 days free of symptoms; (3) meet all FDA-mandated requirements for donating blood (21 CFR 63.10 and 21 CFR 630.15). All donors of CCP and FFP will have been screened negative using sensitive and specific tests for: HIV 1/2, Hep B, Hep C, HTLV-1/2, ZIKV, syphilis, Chagas, and WNV. (Babesia testing is in the process of being implemented and will likely be in place during this study as well). While the risk of transfusion-transmitted infection from plasma is not zero, the per-unit risks of transfusion-transmitted HIV and hepatitis C are estimated to be lower than 1 per million in the U.S. (Zou 2012). Finally, as with any transfusion, careful monitoring of recipients is required before, during, and after transfusion of plasma in this study.

13.3 Confidentiality

In accordance with federal regulations in 45 CFR § 46.111(a)(7), study personnel will protect the privacy of subjects and maintain the confidentiality of the data. At no time during or after the study will patient identities be disclosed. The minimum protected health information will be collected from subjects. Each subject will be assigned a unique study identification number. All data will be maintained in a secure REDCap database accessible only to study personnel certified by the IRB to have completed appropriate human subjects training.

14. PUBLICATION PLAN

The results of the study should be made public in an open access journal as soon as possible and should also be uploaded to a pre-print archive if the PI considers the findings to be noteworthy.

15. APPENDICES

15.1. Appendix A: Schedule of Events

Evaluation	Day 0-1	Day 1	Day 1-2	Day 7	Day 14	Day 21	Day 28	3/6/12 Months Post-Discharge
Informed Consent ^a	X							
Inclusion/Exclusion Criteria	X							
Baseline Data Collection	X							
Study Treatment	X	X	X					
Research Blood Draw ^b	X		X	X	X	X	X	X
Research NP Swab ^c	X			(X)	X	(X)	X	
Research Tracheal Aspirate ^d				X	X	X	X	
Primary Endpoint Assessment					X			
Short-Term Follow-Up				X	X	X	X	
Extended Follow-Up								X

(X) Optional.

- a) All subjects (or subject's LAR if subject lacks capacity to make medical decisions) must be provided with an IRB-approved informed consent document prior to enrollment and prior to any study related procedures.
- b) Up to 50mL blood will be drawn for research purposes.
- c) Testing will end after a negative result has been obtained.
- d) Only for intubated patients and only if suction of tracheal secretions is clinically indicated on the specified evaluation day.

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