PROTOCOL TITLE: **Open, non-comparative pilot study to provide access to treatment with investigational convalescent plasma and measure antibody levels in patients hospitalized with COVID-19**

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VERSION NUMBER:

Version 1.0

DATE:

05.04.2020

REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☐	FDA (Food and Drug Administration)
☐	HHS (Department of Health and Human Services)
☐	VA
☒	Other:

FUNDING:

No funding available

CLINICAL TRIALS

Is this a clinical trial per the NIH definition of a Clinical Trial? ☒ Yes ☐ No

NIH Definition of a Clinical Trial:

A research study in which one or more human subjects are prospectively assigned to

one or more interventions. An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Use the following four questions to determine the difference between a clinical study and a clinical trial:

1) Does the study involve human participants? ☒ Yes ☐ No
2) Are the participants prospectively assigned to an intervention? ☒ Yes ☐ No
3) Is the study designed to evaluate the effect of the intervention on the participants? ☒ Yes ☐ No
4) Is the effect being evaluated a health-related biomedical or behavioral outcome? ☒ Yes ☐ No

Note that if the answers to the 4 questions are yes, your study meets the NIH definition of a clinical trial, even if…

- You are studying healthy participants
- Your study does not have a comparison group (e.g., placebo or control)
- Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Your study is utilizing a behavioral intervention

If yes to all 4 questions, please confirm that the research team is familiar with and agrees to comply with the investigator requirement to register the study on the ClinicalTrials.gov database. Additionally, the approved consent document(s) must be uploaded to the ClinicalTrials.gov database ☒ Yes ☐ No

For any assistance with registration of your trial or the requirements, please contact HSC-CTSCResearchConcierge@salud.unm.edu

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1. Objectives

1.1. Primary

1.1.1. To provide access to treatment with investigational convalescent plasma to inpatients with documented COIVD-19 infection

1.1.2. To measure NAb titers in an aliquot of the CP administered, to measure the volume of CP administered, and determine whether there is a correlation between the NAb dose (in NAb units/kg body weight, where a unit is the reciprocal of the endpoint NAb titer in the CP multiplied by the volume in ml) and change or lack of change when comparing pre-treatment and day one NAb titers.

1.2. Secondary, exploratory objectives

1.2.1. To evaluate the safety of convalescent plasma (CP) administration in hospitalized COVID-19 patients

1.2.2. To evaluate viral shedding of SARSCoV-2 in nasopharyngeal or nasal samples before and on days 3, 7, and 14 after CP transfusion

1.2.3. To perform genomic analysis of the SARS-CoV-2 from patients before and after treatment with CP transfusion

1.2.4. Determine cumulative incidence of disease severity (transfer to ICU, type of respiratory support, LOS, and mortality)

2. Background

Passive antibody treatment involves the administration of antibodies against a specific infection to a susceptible individual to treat or ameliorate the severity of the disease caused by the infectious agent. Plasma from patients that have recovered from the infection is harvested and administered to the non-immune. The use of this modality of treatment dates back to the 1890´s, but it popularity decreased during the antibiotic era.(Casadevall, 2020)

During the current SARSCoV-2 pandemic, with its associated high mortality and morbidity and the lack of demonstrated and effective treatment or vaccine, the induction of immunity with the transfusion of convalescent plasma offers a therapeutic alternative.

Convalescent plasma was studied during the SARS epidemic in 80 patients in Hong Kong.(Cheng 2005) Those treated before day 14 from had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. There is also anecdotal information on the use of convalescent serum in seriously ill individuals. Three patients with SARS in Taiwan were treated with 500 mL convalescent serum, resulting in a reduction in serum virus titer, and each survived (Yeh 2005)

There are reports that convalescent serum was used for therapy of patients with COVID-19 in China during the current outbreak. In an open label study, 5 patients received transfusion with convalescent plasma with a SARS-CoV-2– specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay [ELISA]) and a neutralization titer greater than 40 (end point dilution titer) that had been obtained from 5 patients who recovered from COVID-19 (Shen 2020). Convalescent plasma was administered between 10 and 22 days after admission. In this preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status.

In another study, 10 patients were treated with one dose of 200 mL convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above 1:640 in addition to maximal supportive care and antiviral agents Duan 2020). The clinical symptoms were significantly improved along with increase of oxyhemoglobin saturation within 3 days. Several parameters tended to improve as compared to pre-transfusion, including increased lymphocyte counts (0.65×10^9/L vs. 0.76×10^9/L) and decreased C-reactive protein (55.98 mg/L vs. 18.13 mg/L). Radiological examinations showed varying degrees of absorption of lung lesions within 7 days. In none of these two trials serious adverse events associated with the use of CP were reported.

More recently, the FDA has endorsed the use of CP under an emergency IND, specific guidance on donor and potential recipient selection has been published. (https://www.fda.gov/media/98616/download)

Little is known about how the treatment with CP affects the recipient's immune response to the infection with SARS-CoV-2. What levels of neutralizing antibodies (NAbs) are obtained in patients transfused? Is there association between neutralizing antibody titers and clinical outcomes? In the study by Duan et al, with 10 patients treated with CP, the neutralizing antibody titers of five patients increased and four patients remained at the same level after CP transfusion. However, neither study performed a comparison between the NAb dosing adjusted for body weight versus resulting NAb levels in recipients.

In light of limited availability of CP and the urgent need for promising therapies for COVID-19, it will not be initially feasible to measure NAb titers in the convalescent plasma (CP) prior to plasma administration or to adjust the volume of CP to be administered based on NAb titer in the CP or the body weight or plasma volume of the recipient. However, while this study does not involve administration of plasma with known NAb titer, information gained from the current study may help inform dosing in the future, including in potential dosing modifications that could be submitted via a protocol modification.

The correlation between the levels or titers of neutralizing antibodies after CP transfusion and viral shedding has not been sufficiently explored. Are certain levels of neutralizing antibodies associated with viral clearance? In the study by Duan et al., the viral load was undetectable after transfusion in seven patients who had previous viremia (Duan et al.) We propose to monitor viral shedding in respiratory secretions after CP transfusion. The presence of the virus is relevant for transmission, especially in the hospital setting.

3. Study Design

This is an open label pilot study designed to provide access to treatment with investigational convalescent plasma and assess the relationship between NAb titers in the investigational convalescent plasma compared to changes in NAb levels in the recipient in hospitalized patients with COVID-19.

4. Inclusion and Exclusion Criteria

Inclusion Criteria for Enrollment

1. Patients must be 18 years of age or older.
2. Hospitalized with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR testing. If COVID-19 test results are pending or done at enrolment, test results must be positive prior to administration of convalescent plasma.
3. Patient (or legally authorized representative, LAR) is willing and able to provide written informed consent and comply with all protocol requirements.
4. For patients unable to consent, consent by the legally authorized representative (LAR) may be obtained by phone.

Exclusion Criteria

1. Female subjects with positive pregnancy test or breastfeeding.
2. Receipt of pooled immunoglobulin in past 30 days.
3. Contraindication to transfusion or history of prior severe allergic reactions to transfused blood products
4. On ECMO or in refractory shock at entry

5. Number of Subjects

This pilot aims to explore safety and measure antibody levels in patients treated with CP. We aim to enroll 30 subjects to ensure the estimate of *neutralizing antibodies* to be within 20% margin of error.

6. Study Timelines

Hospitalized patients will be enrolled as soon as their COVID-19 diagnosis is confirmed, using approved diagnostic methods, and will be followed until hospital discharge or death. Patient enrollment will start immediately after IRB approval. We anticipate a 3-month enrollment. The study will continue for another 24-months after the last enrollment during which we will be able to process and analyze data, and disseminate findings.

7. Study Endpoints

7.1. Primary endpoint:

7.1.1. Titers of SARS-CoV-2 neutralizing antibodies measured by focus reduction neutralization test (FRNT) at days 0 (pre-transfusion), 1, 3, 7 and 14 days of CP transfusion.

7.1.2. Availability of convalescent plasma

7.2. Secondary endpoints:

Clinical outcomes:

7.2.1 Serious adverse events
7.2.2 SARCoV-2 viral shedding in nasopharyngeal samples determined by RT-PCR
7.2.3 Genomic variations of SARS-CoV-2 before and after CP transfusion
7.2.4 Transfer to ICU
7.2.5 Type and duration of respiratory support (and other ICU support including ECMO, CRRT) in ICU
7.2.6 Cardio-circulatory arrest (at any time)
7.2.7 ICU mortality and LOS
7.2.8 Hospital mortality and LOS
7.2.9 Ventilator-free days
7.2.10 In hospital mortality
7.2.11 Titer of other functions of antibodies, including antibody-dependent cell-mediated and complement-dependent cytotoxicity

7.3. Safety Endpoints:

7.3.1 Rapid deterioration of respiratory or clinical status on transfusion of SARS-CoV-2 convalescent plasma.

7.3.2 Cumulative incidence of serious adverse events during the study period: febrile non-hemolytic transfusion reaction, allergic transfusion reaction, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO),

transfusion related infection, hemolytic transfusion reaction or evidence of antibody dependent enhancement of infection (ADE).

8. Research Setting

The study will be conducted in the University of New Mexico Hospital. Patients admitted to the COVID-19 units including the emergency department, regular wards and intensive care units will be enrolled. Patients will be identified from the TriCore Laboratory testing result portal available to the research team or upon notification by providers in the participating institutions. Approval by the treating provider will be requested before patient enrollment and consent.

There is no external sponsor for this research. Immune assays and genomic studies will be performed utilizing existing resources within the Bradfute and Domman laboratories in the Center for Global Health.

SARS-CoV-2 neutralizing antibody titers will be measured using the focus reduction neutralization test (FRNT) in Dr. Steven Bradfute's Laboratory, Center for Global Health (CGH), UNMHSC. Neutralization assays will be conducted using methods already established in the Bradfute laboratory. Briefly, serial dilutions of plasma will be incubated with 50-100 pfu of SARS-CoV-2 at equal volumes for 1 hour and added to Vero E6 cells, followed by overlaying with agarose. Two days later cells will be fixed with 4% formaldehyde, stained with crystal violet, and plaques will be counted. Other functions of antibody, including antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity, will be ascertained using established methods.

Virus sequencing will be performed in the laboratory of by Dr. Daryl Domman in the Center for Global Health using the PCR-based NGS sequencing protocol described by the ARTIC Network https://artic.network/ncov-2019

9. Resources Available

9.1. Principal investigator and co-investigators are experienced Pulmonary, Critical Care, Infectious Disease ID Pharmacists, Virologist or Transfusion Medicine specialists with ample experience in conducting clinical trial and with the use of CP in previous clinical studies (GM):

9.1.1. Michelle Harkins, MD, is a Pulmonary and Critical Care Medicine specialist and is the Chief of the Division of Pulmonary at UNMH

9.1.2. Nestor Sosa, MD, is an Infectious Disease Attending and is the Chief of Infectious Diseases at UNMH.

9.1.3. Gregory Mertz, MD, is an infectious diseases specialist at UNM with a history of NIAID-sponsored research (GMertz, PI) involving collection of plasma from survivors of hantavirus cardiopulmonary syndrome (HCPS) in New Mexico and Chile, development and evaluation of FRNT and BSL-2 based pseudovirion assays for measurement of ANDV neutralizing antibody titers, and evaluation of the safety of immune plasma administration for HCPS (Vial P, 2015),

9.1.4. Steven Bradfute, PhD, is a basic scientist whose research area is viral infections and immune response.

9.1.5. Jay Raval, MD, is a Transfusion Medicine specialist and is Senior Director of Transfusion Medicine and Therapeutic Pathology at UNM.

9.1.6. Daryl Domman, PhD, is an Assistant Professor at CGH with expertise in infectious disease genomics, bioinformatics, and genomic epidemiology.

9.1.7. Douglas J Perkins, PhD, is a Professor of Medicine and Director, Center for Global Health, University of New Mexico. Dr. Perkins has studied the pathogenesis of infectious diseases for the past 23 years, including in Kenya for the last 18 years, and sub-Saharan Africa for the 23 years.

9.1.8. Keenan Ryan PharmD, is an Infectious Diseases trained pharmacist at UNM

9.1.9. Yiliang Zhu, PhD, professor at the Division of Epidemiology, Biostatistics and Preventive Medicine is a biostatistician and data scientist.

9.2. The treating provider (Hospital Medicine or Pulmonary Critical Care) in the respective COVID-19 units will be responsible for medical decision-making, ordering and evaluating the participants.

9.3. Prior to enrollment, availability of the study product (SARS-CoV-2 convalescent plasma) will be verified by the study team in collaboration with our blood bank.

9.4. Study agents will be procured and stored at UNMH blood banking the participating hospitals. Donor selection and harvest, labeling and shipment of the study agent will be performed by Vitalant.

9.5. The subjects will receive the study agent while hospitalized in our institutions.

9.6. All research specified laboratory testing will be performed in CGH laboratories.

10. Prior Approvals

10.1. Departmental Scientific Review is attached.

11. Multi-Site Research:

11.1. **Not Applicable t**his trial will be conducted at UNMH**.**

12. Study Procedures

12.1. Potential subjects will be identified by reviewing the registry of +SARSCoV2 RTPCR testing (at TRICORE laboratory) in hospitalized patients.

12.2. Eligibility of the potential study participants will be identified by their treating providers (Hospital Medicine and Intensive Care Unit). The treating providers will notify representatives of the research team. Members of the research team will verify the eligibility of the potential subjects and will obtain informed consent from them or their LAR.

12.3. Once the participant or their LAR gives their written informed consent, the research team will notify the treating provider so they can place the medical order for the investigational products. If LAR consented via phone, a copy of the consent form will be mailed to LAR.

12.4. The protocol specific activities are detailed in Table 1

12.5. Treatment

Subjects will receive the convalescent plasma.

Study drug: The investigational product is anti-SARS-CoV-2 convalescent plasma obtained from former patients identified as having recovered from COVID-19 and obtained by Vitalant from local and national donors following national blood donation guidelines. These donors will be cleared for blood donation like any other volunteer blood donor and samples will have been screened for transfusion-transmitted infections (e.g. HIV, HBV, HCV, WNV, HTLV-I/II, T. cruzi, ZIKV) both through the use of the uniform donor questionnaire and FDA mandated blood donor screening tests. This single-donor plasma product will have been collected using apheresis technology and in accordance with standard FDA and blood bank protocols.

A 1ml of aliquot of anti-SARS-CoV-2 plasma will be saved for NAb titer measurement by FRNT (as mention in section 8.) in the CGH laboratory and the total volume of plasma administration will be recorded.

12.5.1. Study subjects will receive 1 unit (200mL) of SARS-CoV-2 convalescent plasma collected from a single donor who recovered from COVID-19.

12.5.2. The anti-SARS-CoV-2 convalescent plasma will be in standard plasma blood unit bags, anticoagulated with a citrate-based anticoagulant (ACD-A, CP2D, et cetera), labeled with a specific ISBT product code, and stored in the UNM Blood Bank per FDA, AABB, and CAP protocols. Plasma transfusion will be administered over no more than four hours.

Table 1: Schedule of Events

Study period	**Screen**	**Baseline**	**Transfusion**	**Follow-up**				
Day	**-1 to 0**	**0**	**0**	**1**	**3**	**7**	**14**	
Eligibility								
Informed consent	**x**							
Demographic and Medical history	**x**							
SARS-CoV-2 RT-PCR for eligibility	**x**							
Pregnancy test	**x**							
Type and screen	**x**							
Study Agent Administration								
Plasma Transfusion			**x**					
Study Procedures								
Vital signs	**x**	**x**	**xxxx**[1]	**x**	**x**	**x**	**x**	
Physical assessment	**x**		**x**	**x**		**x**		
Symptom screen	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Concomitant medications	**x**	**x**	**x**					

Adverse event monitoring		**x**	**x**	**x**	**x**	**x**	**x**	
Laboratory testing								
SARS-CoV-2 RT-PCR[2] and Genomic analysis		**x**			**x**	**x**	**x**	
SARS-CoV-2 neutralizing antibody		**x**		**x**	**x**	**x**	**x**	
Secondary End point registration (clinical outcome)								

1. Vital sign testing: Immediately prior to infusion, 10-20 minutes after start of infusion, at completion of infusion and 30-60 minutes after the end of the infusion
2. Sampling can include nasopharyngeal, nasal or oropharyngeal swabs.

13. Data Analysis

13.1.1. We will determine whether there is a correlation between the NAb dose (in NAb units/kg body weight, where a unit is the reciprocal of the endpoint NAB titer in the CP multiplied by the volume in ml) and change or lack of change when comparing pre-treatment and day one NAb titers. We will also compare changes in pre- and post-treatment NAb titers based on NAb dosing calculated in units/BSA and units/calculated plasma volume to see if either measurement provides a better prediction of changes in NAb titers in recipients.

13.2. Data analysis will be limited to hospitalized subjects with respiratory symptoms and laboratory confirmation of SARS-CoV-2 infection by detection RNA in upper or lower respiratory samples (nasal or oral swabs or endotracheal fluid) or blood or by detection of NAb in serum. Subjects without laboratory-confirmed COVID 19 will be excluded from analysis.

Neutralizing antibody titers in the patient's first blood sample (day 0) will be compared by rank sum (Wilcoxon) test between patients who develop any of the secondary

clinical end-points and patients who do not develop these secondary endpoints. The same comparison will be performed to evaluate NAb titers with other parameters such as age ≥65 and <65, presence or absence of diabetes, or presence or absence hydroxychloroquine therapy. These analyses of day 0 Nab titers aim to characterize patient heterogeneity in Nab titers in relationship to patient demographic and clinical characteristics.

We will also analyze the association between NAb titers at day 0 with duration of viral shedding, duration of hospitalization and duration of intubation and other clinical parameters.

Our primary endpoint for statistical analysis is changes in NAb titers at day 1, 3, 7, and 14 from the entry level (day 0). Our primary hypothesis is that Nab titers will increase post-transfusion in positive correlation with transfused volume of convalescent plasma when adjusted for NAb titer in the convalescent plasma. We will use repeated measurements analysis of variance (ANOVA) or analysis of covariance (ANCOVA) when controlling for other factors (e.g. use of hydroxychloroquine) for initial exploration of the association with the transfusion volume of convalescent plasma. A more advanced approach is to use nonlinear regression models with random effects to characterize the trajectory of Nab titers over the course of 14 days. This latter approach can effectively characterize individual-specific trajectory in Nab titers in relation to convalescent plasma, and at the same time quantify between-patients variation, thereby improving statistical power. This mixed-effects nonlinear regression modeling approach is also capable of adjusting for other factors as appropriate (e.g. patient age). We will also conduct post-hoc analysis of change in Nab titers from day 0 to a specific day (day 1, 3, 7, or 14) post transfusion of convalescent plasma when appropriate. Better understanding and better characterization of the relationship between Nab titers and amount of convalescent plasma transfusion adjusted for NAb titer in the convalescent plasma will inform standardized dosage for future study.

In the absence of a comparison group, we will use descriptive statistics to report other parameters of interest (e.g. secondary outcomes), including the use of mean (SD), frequency (%) and their confidence interval. When appropriate, we will also report association between a parameter of interest and a factor of clinical relevance (e.g. duration of shading and underlying comorbidities, Nab titers at a specific post-transfusion day and underlying comorbidities, Nab titers at a specific post-transfusion day and secondary outcomes such as transfer to ICU or hospital death). This analysis will utilize odds ratio and Fisher's test for dichotomous variables, and Wilcoxon test a continuous variable.

We will conduct interim analysis after the first 10 patients complete the study. Based on the interim analysis results we may consider submitting a protocol amendment requesting adjustment our patient recruitment or CP dosing.

Given that we have a large number of clinical parameters of potential interest and a small sample of 30 patients, we do not have the statistical power or data depth for all analyses. The focus of our analysis is on the primary outcome and primary hypothesis. Much of the analyses of secondary outcomes are of the nature of exploration. We will adjust for multiplicity of comparisons (e.g. associations) using False Discovery Rate (FDR) in reporting our findings.

13.3. Sample size. A sample size determination is less plausible for this pilot study since we aim to establish the effect size of convalescent plasma transfusion on Nab titers. However, we will conduct a post-hoc statistical power analysis to determine the actual power with the sample we obtain.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

14.1. A DSMB will be convened to include clinicians specializing in clinical trials, transfusion medicine and biostatisticians. The roster will be provided in a Modification for HRRC approval once the DSMB has been created.

14.2. The safety information that will be collected and monitored as follows: reports of rapid deterioration of respiratory or clinical status on transfusion of SARS-CoV-2 convalescent plasma and cumulative incidence of serious adverse events during the study period: febrile non-hemolytic transfusion reaction, allergic transfusion reaction, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infection, and hemolytic transfusion reaction.

14.3. Review of data after 10 participants have been enrolled.

14.4. Considering the novelty and rapidly changing situation of the COVID-19 pandemic, the investigators will review relevant publications that may help inform decisions related to the efficacy and safety of the investigational products.

14.5. The occurrence of any serious adverse event will be notified to the HRRC in accordance with GCP regulations. An analysis of all adverse events will be presented with the analysis of the first 10 patients enrolled and periodically thereafter.

14.6. The conditions that would trigger a suspension or termination of the research (i.e., stopping rules), are as follows:

a. If available published information convincingly reports non-efficacy or significant safety concerns with the use of SARS-CoV-2 convalescent plasma.

b. If an unexpectedly high incidence of serious adverse events judged to be related to SARS-CoV-2 convalescent plasma is detected in these critically ill COVID-19 patients during the trial in the clinical judgetment of the investigators compared to that expected in similarly ill patients receiving normal donor plasma in the clinical judgement of the investigators.

c. If there is an unanticipated safety signal, stopping the study will be considered.

14.7. Findings will be reported to the HRRC within 5 business days and to the FDA accordingly. A preliminary analysis of the study end points will be performed after 10 patients have been enrolled and end-points reached. The results will be presented to the HRRC and investigators.

15. Withdrawal of Subjects

15.1. Subjects will be withdrawn if the PI determines, in consultation with the treating clinician(s) that continuation in the study is not in the participant's best interest. Subjects may also withdraw (or be withdrawn by their LAR at their request at any time during their participation in the study by contacting a member of the study team.

15.2. If a patient develops a serious adverse event that may be probably or definitely related to the CP, during the infusion, that may trigger the discontinuation of the offending drug.

15.3. If a participant is withdrawn from the study, chart review will continue to be performed to track the participant's clinical outcomes.

15.4. Data and specimens collected before withdrawal will not be removed from the study.

16. Data Management/Confidentiality

16.1. Participants will be assigned a randomly generated study ID that will be linked to identifiers (MRN, DOB) in a linking table to be kept separate from the research data. Data and specimens will be labelled with the study ID only.

16.2. Only HRRC-approved members of the study team who have the appropriate training will have access to the data and identifiers.

16.3. Data will be entered into REDCap on a password-protected computer using a secure network.

16.4. Any hard copy records/data will be kept in a locked file cabinet in the locked office of a designated member of the study team

16.5. Once data collection is complete, data will be de-identified by destruction of the linking table. Study records will be kept for 6 years past study closure.

17. Data and Specimen Banking

Not Applicable

18. Risks to Subjects

18.1 Published data on convalescent antibody administration in SARS (Cheng 2005 and Yeh 2005) and SARS and MERS (Mair-Jenkins 2015), and preliminary data on convalescent plasma administration in COVID-19 (Shen 2020 and Duan 2020), also suggests that CP is safe and well tolerated.

18. 2 One theoretical risk involves the phenomenon of antibody-mediated enhancement of infection (ADE). ADE can occur for several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain (Casadevall, 2020). It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as proposed for MERS. Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. The available evidence from the use of convalescent plasma in patients with SARS1 and MERS and anecdotal evidence of its use in patients with COVID-19 (Casadevall 2020), suggest it is safe. Nevertheless, caution and vigilance will be required in for any evidence of enhanced infection. Both COVID-19 and ADE may cause ARDS, and we recognize that this will be very difficult to attribute etiology in this small pilot study. None-the-less, we will pay particular attention to the incidence of ARDS in study subjects without comorbidities predicting risk of progression to severe disease, and we will closely follow any reports suggesting ADE that emerge from multicenter, placebo-controlled trials of CP, including two proposed CTSC-based RCTs for outpatient PrEP and outpatient treatment of early COVID-19 with CP, and we will forward any reports suggesting ADE to the IRB.

18.2 Another theoretical risk is that antibody administration to those infected by SARS-CoV-2 may avoid disease but modify the immune response such that those individuals mount attenuated immune responses, thereby leaving them vulnerable to subsequent re-infection. It will not be feasible to assess this risk in data collected in this hospital-based treatment study, but we will monitor the emerging scientific literature and report any concerning findings to the IRB.

18.3 There are risks associated with any transfusion of plasma including transmission of transfusion transmitted viruses (e.g. HIV, HBV, HCV, etc.), allergic transfusion reactions, anaphylaxis to transfusion, febrile transfusion reaction, transfusion related acute lung injury (TRALI), transfusion associated cardiac overload (TACO), and hemolysis should ABO incompatible plasma be administered. In order to minimize the risks of disease transmission, donors will fulfill donor requirements for blood donation with the exception of recent illness, in this case COVID-19 infection.

18.4 Venipuncture can cause bruising, bleeding and mild discomfort. It is infrequently associated with infection. To minimize the risk of phlebotomy, only adequately trained

study personnel or hospital personnel will draw blood. Blood volumes to be obtained fall within OHRP guidelines for minimal risk studies. Alternative procedures are not feasible.

18.5 Breach of confidentiality from data obtained during the enrollment interview or clinical charts. Subject confidentiality will be maintained by the following methods: All records will be kept in a locked file. All computer entry and networking will be performed with coded numbers only. Clinical information will not be released without written permission from the subject. Access to identified, source records will be limited to the local site principal investigator and study personnel.

18.6. 1.1.1. Mild to discomfort from obtaining NP. Nasal swabs can be performed without discomfort or risk. To minimize discomfort from obtaining nasal or NP swabs, these will be obtained by trained medical personnel, and subjects who cannot tolerate NP swabs will only have nasal swabs obtained.

19. Potential Benefits to Subjects

A key potential benefit is treatment for established infection. Convalescent plasma would be administered to those with clinical disease in an effort to reduce their symptoms and mortality. Based on the historical experience with antibody administration, it can be anticipated that *antibody administration relatively early in the course of disease would be more effective in preventing disease progression than in the treatment of established severe disease.*

Given that historical and current anecdotal data on use of convalescent plasma suggest it is safe in coronavirus infection, the high mortality of COVID-19, particularly in elderly and vulnerable persons, suggests that the benefits of its use in those at high risk for or with early disease outweigh the risks. However, for all cases where convalescent plasma administration is considered, a risk-benefit assessment must be conducted to assess individual variables.

20. Recruitment Methods

Members of the research team will review the list of admitted or hospitalized patients with a positive SARSCoV-2 test. Alternatively, treating providers may also notify the research team of the admission of SARSCoV-2 patients or the positive result of a suspected COVID-19 patient.

21. Provisions to Protect the Privacy Interests of Subjects

21.1. Only members of the research team will access trial related documents.

21.2. All study procedures will be conducted in the participant's room or other private area of the hospital.

22. Economic Burden to Subjects

22.1. The study is responsible for the cost of any research-related procedures. The participant and/or third party payer is responsible for any standard of care procedures.

22.2. Investigators do not anticipate any additional costs.

23. Compensation

No compensation will be given to study participants.

24. Compensation for Research-Related Injury

The University of New Mexico does not have funds set aside to pay for the cost of any care or treatment that might be necessary or for any wages lost as a result of participating in this study. Medical costs to care and treatment of study related harm will be billed to the participant and/or third party payer.

25. Consent Process

25.1. An approved member of the study team will conduct the consent process with the participant and/or their LAR in a private area of the hospital or by phone if needed. If applicable, impartial witness will be utilized as needed (witness/translator for Spanish speaking participant and impartial witness for phone consent).

25.2. It may not be possible to have an in-person discussion of the study with participants or their LAR. Documenting written informed consent in these instances must involve a process as follows: the participant or their LAR receives a copy of the informed consent document in advance of a telephone discussion. The investigator obtains consent over the telephone with the participant or their LAR. If LAR consented via phone, a copy of the consent will be mailed to LAR.

25.3. The informed consent form may be mailed, emailed or faxed to the participant or their LAR. The consent discussion may then be conducted by telephone or in person when the subject or subject's LAR can read the consent form during the discussion.

25.4. Investigators will explain the study to the potential participant or their LAR by reading the informed consent document to the participant and/or LAR, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation), and allowing the potential participant or their LAR ample opportunity to ask questions. This can be done by phone or in person.

25.5. Investigators will ensure a thorough verbal discussion by phone or in person of the consent form. Investigators will allow the potential participant or LAR time to read the consent form and allow the participant or their LAR sufficient time to consider whether or not to participate in the research.

25.6. Investigators will ensure the potential participant or their LAR additional questions s/he may have are addressed.

25.7. Participants and/or their LAR will be asked to explain the purpose of the study, procedures involved, and/or conditions for participation to confirm understanding.

25.8. If the participant or LAR agrees to participation, s/he signs the consent form and returns it to the investigator for signature and date. The signed and dated consent form can be returned to investigators by mail, facsimile, or by scanning the consent form and returning it through a secure e-mail account.

25.9. Once the signed form is received, the investigator who conducted the informed consent will sign and date the consent and will ensure the participant or their LAR receives a copy of the fully signed consent form. The fully signed original consent form will be filed with the participant's study records.

25.10. Ongoing consent from participants and and/or their LAR will be ascertained as research procedures are being conducted.

25.11. Alternately, on a case-by-by case basis, and per the FDA regulation 21 CFR 50.23 Exception from general requirements, the following will be done:

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent

determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the HRRC as a Reportable New Information (RNI) within 5 working days after the use of the test article. The documentation to be used within the RNI is titled "Informed Consent Exception from General Requirements". The form can be completed via eSignatures by utilizing the fillable form or hand written signatures by utilizing the non-fillable form.

Subjects not fluent in English

25.12 Given the public health emergency surrounding this research, non-English speaking patients may be included in the study, and this will only include Spanish speaking individuals.

25.13 The consent process will be conducted by a member of the study team fluent in the Spanish language and/or with the assistance of a qualified interpreter.

***Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally* Authorized Representative**

25.14 Some participants are expected to be cognitively impaired, either due to a pre-existing condition, or because of conditions related to their infection with COVID-19. Cognitively impaired participants will be enrolled in the study with the consent of their LAR

The study team, in consultation with the clinical care provider, will determine if a participant has capacity to consent. Specifically, the investigators will utilize the rCapacity to Consent Quiz or the GCP teach back technique with the consent form. After each section of consent form has been discussed with the participant, the investigator will ask the participant to explain their understanding of the content. Based on the results, the investigators will determine if the participant has the ability to consent.

Capacity to consent will be evaluated by the study team, in consultation with the clinical care provider, as part of the ongoing consent process as described above. If the participant regains capacity to consent, a member of the study team will conduct the consent process as described above.

We will obtain evidence of agency under a durable power of attorney or surrogate health decision maker status under the NM Uniform Health Care Decisions Act, NMSA 1978, 24-7A-1 et seq.

Subjects who are not yet adults (infants, children, teenagers)

N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

Waivers of consent and HIPAA authorization are requested for screening/ recruitment purposes. For the waiver of HIPAA authorization, the Data Warehouse will generate a daily list of patients with documented positive COVID-19 with their locations in the hospital. The attending will be contacted via tigerconnect to consent and start the treatment.

26. Documentation of Consent

26.1. For English-speaking participants (or LARs), consent will be documented using an HRRC-approved consent document.

26.2. For Spanish speaking participants (or LARs), a Short Form of Consent in their preferred language will be used to document consent.

27. Study Test Results/Incidental Findings

27.1. **Individual Results:** Results of the titers of neutralizing antibodies and nasopharyngeal SARSCoV-2 will be not be shared with the participants and their providers. The rest of routine laboratory and clinical notes will be available in the electronic medical record patient portal

28. Sharing Study Progress or Results with Subjects

28.1. During the study we do not intend to provide subjects with a summary of the trial. This a short, pilot study and results will be compiled at the end and then results will be informed in writing to the patients at that moment.

29. Inclusion of Vulnerable Populations

Cognitively impaired adults will be included in the study since the disease under investigation disproportionately affects older adults and/or contributes to the temporary cognitive impairment of a significant proportion of patients. To protect their rights and welfare, consent will be sought from competent ;iLAR, and participants who regain capacity to consent as (determined by the study team in consultation with clinical care providers) will be re-consented.

30. Community-Based Participatory Research N/A

31. Research Involving American Indian/Native Populations N/A

32. Transnational Research N/A

33. Drugs or Devices:
See section 12.1

34. Principal Investigator's Assurance

By submitting this study in the Click IRB system, the principal investigator of this study confirms that:

☐ X The information supplied in this form and attachments are complete and correct.

☐ X The PI has read the Investigator's Manual and will conduct this research in accordance with these requirements.

☐ X Data will be collected, maintained and archived or destroyed per HSC Data Security Best Practices, including:

1. **Best Practice for data collection** is for it to be directly entered onto a data collection form that is in a secured access folder on an HS drive behind a firewall, or in a secure UNM Data Security approved system such as RedCap.
2. **Data collection of <u>de-identified data</u>**, if done in a clinical setting or other setting that does not allow direct entry into a secured system, may be done temporarily using a personal or university owned electronic storage device or hard copy document. **The important security safeguard is that no identifiers be included if the data is entered or stored using an untrusted device or storage.**
3. **Permanent (during data analysis, after study closure**) storage must reside on HSC central IT managed storage. Processing of data (aggregation, etc.) are to be carried out in such a way as to avoid creating/retaining files on untrusted storage devices/computers. Trusted devices are HSC managed and provide one or more of the following safeguards: access logs, encryption keys, backups, business continuity and disaster recovery capabilities.
4. **Alternate storage media** must be approved by HSC IT Security as meeting or exceeding HSC central IT provided security safeguards.

35. CHECKLIST SECTION

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

36. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

A. Describe the data source that you need to review (e.g., medical records):

Medical Record

B. Describe the purpose for the review (e.g., screening):

Screening and Recruitment

C. Describe who will conducting the reviews (e.g., investigators, research staff):

Principal Investigator with other members of the study team

D. Do all persons who will be conducting the reviews already have permitted access to the data source?

☒ Yes

☐ No. Explain:

i. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

1. The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

   ☐ True

   ☐ Other justification:

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

☐ True

☐ Other justification:

3. The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

   ☐ True

   ☐ Other justification:

4. Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. (Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)

   ☐ True

   ☐ Other justification:

37. Partial Waiver of HIPAA Authorization for Screening/Recruitment

Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

A. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☐ Yes. Describe:

   ☒ No

B. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

C. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☒ True

☐ False

38. Waiver of Documentation of Consent N/A
39. Alteration of Consent N/A
40. Full Waiver of Consent/Parental Permission N/A
41. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs) : N/A
42. Full Waiver of HIPAA Authorization (Checklist) N/A
43. Other Waiver Types (Checklist):N/A

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44. Vulnerable Populations (Checklist)

A. Adults with Cognitive Impairments
Complete this checklist if the subject population will include adults with cognitive impairments.

This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

   COVID-19 infection may affect persons with pre-existing cognitive impairment for whom no SOC treatment exists. COVID-19 infection can cause conditions resulting in cognitive impairment.

2. Describe how capacity to consent will be evaluated.

   By the research team in consultation with clinical care provider, by capacity to consent quiz or by the teach back technique.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

   Capacity to consent will be assessed as part of the ongoing consent process. To protect their rights and welfare, consent will be sought from competent LAR, and participants who regain capacity to consent as (determined by the study team in consultation with clinical care providers) will be re-consented.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

   The investigators will utilize the Capacity to Consent Quiz with the consent form. After the consent form has been discussed with the participant, the investigator will administer the Capacity to Consent Quiz or by teach back technique after each section of the consent. Based on the results, the investigators will determine if the participant or LAR has the ability to consent.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

   There is no SOC treatment for COVID-19 infection

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

   There is no SOC treatment for COVID-19 infection

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

   All COVID-19 patients enrolled in this study will be hospitalized and closely monitored. Treating providers and members of the research team will be attentive to the clinical condition of all subjects.

B. Children N/A
C. Pregnant Women and Fetuses N/A
D. **Neonates of Uncertain Viability or Nonviable Neonates** N/A
E. **Nonviable Neonates** N/A
F. Biomedical and Behavioral Research Involving Prisoners N/A

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45. Medical Devices (Checklist) N/A

46. Export Control (Checklist) N/A
47. Data Transfer/Sharing (Checklist)

Complete this checklist if the research involves transferring/sharing of data with an external entity (institution, company, etc.).

A. Will data be transferred/shared with an external entity (institution, company, etc.)?

☐ Yes

☒ No. **The remainder of this section does not apply.**

B. Indicate if the data is incoming and/or outgoing:
C. Provide the name of the entity that data will be transferred/shared with:
D. Provide the contact name, email and phone number with whom data is being transferred/shared with:
E. Who is responsible for transmission of the data?
F. Who is responsible for receiving the data?
G. Describe how the data will be transferred/shared. Please note data cannot be transferred/shared without assistance from UNM HSC IT. **Requesting HSC Central IT Transfer is detailed on the Sponsored Projects website:**
H. For data being transferred/shared with outside locations or entities, describe the following:
    - Where is data storage and how will it be maintained in a secure manner (i.e. encryption, password protection, use of Qualtrics or REDCap, etc)?
    - What is method in which data will be collected and stored (i.e. electronic, hard copy, etc)?
    - How long will the data be stored?
    - Who will have access to data?
I. Please list all specific data elements, variables, etc. to be sent out and/or received. Indicate if the data contains identifiers and health information. Please note that identifiers that MUST be removed to make health information de-identified are as follows: Names, All geographic subdivision smaller than a State, All elements of year (except year), Telephone, Fax numbers, E-mail addresses, Social Security, Medical record number, Health plan beneficiary, Account numbers, Certificate/license numbers, Vehicle identifiers and serial numbers, Device identifiers and serial numbers, Web URLs, IP address numbers, Biometric identifiers, full face photographic images, and Any other unique identifying number, characteristic or code.)
J. If the research requires the access, use, or disclosure of any of the 18 individually identifiable protected health information (PHI) identifiers that can be used to identify, contact, or locate a person (e.g., name, medical record number, etc.), are the subjects going to consent to or authorize the disclosure of their individually identifiable health information?
    a. **Or** is HIPAA authorization altered or waived?
K. What is the classification of the data (de-identified, limited data set, protected health information, other).

L. Does the request to transfer/share data include clinical data that belongs to the UNM Health Systems?
M. Does the data to be transferred/shared include information about patients seen at external health systems or at a third party medical provider?
N. Is the external entity a "covered entity"?
O. Is the data that is going to be transferred/shared owned or partially owned by another party or have any type of restrictions including regulatory restrictions (i.e. HIPAA, FERPA, etc.)?
P. Is the data publically available? If yes, please provide details:
Q. Does the data include information about substance abuse treatment, sexually transmitted diseases, genetic testing results, HIV/AIDS testing results, and/or mental health?

48. Specimen Transfer/Sharing (Checklist)

Complete this checklist if the research involves transferring/sharing of specimens with an external entity (institution, company, etc.).

A. Will specimens be transferred/shared with an external entity (institution, company, etc.)?

Yes

X No. **The remainder of this section does not apply.**

B. Indicate if the specimens are incoming and/or outgoing:
C. Provide the name of the entity that specimens will be being transferred/shared with:
D. Provide the contact name, email and phone number with whom specimens are being transferred/shared with:
E. Who is responsible for sending out the specimens? Please note specimens cannot be sent out without a fully executed material transfer agreement. Michelle Harkins
F. Who is responsible for receipt of the specimens? Please note specimens cannot be received without a fully executed material transfer agreement.
G. For specimens being transferred/shared with outside locations or entities, describe the following:

- Where is specimen storage and how will it be maintained in a secure manner?
- What is the method in which specimens will be collected and stored? Collected: phlebotomy and stored:
- How long will the specimens be stored?
- Who will have access to the specimens

49. References

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