The COVID-IG trial: intramuscular (IM) injection of COVID-19-convalescent hyperimmune immunoglobulin (COVID-IG) to prevent SARS-CoV-2 infection in high-risk persons

Study Design: A randomized, placebo-controlled trial to determine whether immunoglobulin prepared from the pooled plasma from COVID-19 convalescent donors (COVID-IG) prevents infection with SARS-CoV-2 after IM administration. COVID-IG will be compared to immunoglobulin prepared from pooled plasma from donors never infected with SARS-CoV-2 (Control-IG).

Population: Healthcare workers involved in direct patient care; residents of nursing homes; military personnel or other high-risk groups in congregate settings with high rates of infection; susceptible persons in low-income developing countries.

Regimen: Participants will be randomized 1:1 to receive intramuscular injections of COVID-IG or placebo CONTROL-IG every 2 months for 12 months.

Monitoring Plan: Intensive (every two week) monitoring of participants for the incidence of infection with SARS-CoV-2 and their levels of neutralizing antibodies to SARS-CoV-2.

Rationale:

Need: Measures to prevent the transmission of COVID-19 are needed now, especially in high-risk populations.

Choice of intervention: Administration of SARS-CoV-2 neutralizing antibodies is the only form of immunization available in the absence of vaccines or humanized monoclonal antibodies, which are on the horizon. COVID-IG can be prepared from the sera of thousands of convalescent persons now – if the requisite effort and resources are made available. The administration of immune IG to prevent viral diseases in susceptible persons has a 100-year history of safety and efficacy.

Choice of therapeutic route: Intramuscular (IM) injections can be delivered by persons with a minimum of training. It does not require administration in a healthcare setting, such as a hospital or clinic. These features render IM injection of COVID-IG ideal for use in high-risk congregate groups and in resource limited healthcare settings.

Deliverables:

Clinical deliverable: The prevention of SARS-CoV-2 infection is of paramount importance for susceptible individuals and society. This trial aims to demonstrate a 50% or greater reduction in the incidence of infection over a 1-year period in the recipients of COVID-IG. This will protect the recipients and reduce transmission to their susceptible contacts, cutting the R_0 by half or more.

Scientific deliverable: In addition to demonstrating therapeutic efficacy and safety, this trial will provide quantitative data on the level of neutralizing antibody required to prevent infection. This information will facilitate the interpretation of serologic studies of naturally acquired infections. Very importantly, it also will provide a clear target for vaccines and monoclonal antibody preparations that will permit prediction of their efficacy in advance of any large controlled trials.

TABLE 1. SCHEDULE OF EVENTS

Study period	Screen	Start	Follow-up					
Day	-1 to 0	0	3	7	14	28	Every 2 weeks through 12 months	Every 2 months through 12 months
Informed consent	X							
Demographic and Medical history	X							
Pregnancy test [1]	X							
Vital signs	X	X						
Concomitant medications	X							
Randomization		X						
Immunoglobulin Injections (IM)		X						X
CBC and CMP		X						
COVID-19 Symptom screen	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	
Adverse event monitoring		X	X[3]	X[3]	X[3]			X[3]
Nasopharyngeal swab for SARS-CoV-2 RT-PCR	X	X	X	X	X	X	X	
Sample of venous blood for antibody testing and future research	X	X	X	X	X	X	X	

[1] Urine or serum pregnancy test for women of childbearing potential

[2]To be assessed via text messaging

[3]This will be performed daily for 14 days following each injection every 2 months by text messaging

Safety and Efficacy of Intramuscular COVID-19 Convalescent Immunoglobulin Prophylaxis in Healthcare Personnel at Risk of SARS-CoV-2 Infection as a Result of their Patient-Care Activities

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Table of Contents

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ADR: Adverse Drug Reaction
ADE: Antibody-mediated enhancement of infection
AE: Adverse Event/Adverse Experience
CFR: Code of Federal Regulations
CLIA: Clinical Laboratory Improvement Amendment of 1988
CMP: Complete Metabolic Panel
COI: Conflict of Interest
Control-IG: Immunoglobulin isolated from donors who never have been infected with SARS-CoV-2
COVID-19: Coronavirus Disease
COVID-IG: Immunoglobulin treatment isolated from donors who have recovered from SARS-CoV-2 infection
CRF: Case Report Form
CURB-65: score for pneumonia severity
DMC: Data Management Center
DSMB: Data and Safety Monitoring Board
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
GCP: Good Clinical Practice
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HTLV: Human T-cell lymphotropic virus
IB: Investigator's Brochure
ICF: Informed Consent (Informed Consent Form)
ICH: International Conference on Harmonization
ICU: Intensive Care Unit
IEC :Independent ethics committee
IM: Intramuscular
IG: Immunoglobulin
IND: Investigational New Drug Application
IRAE: immune related adverse event
IRB: Institutional review board
ISBT: International Society of Blood Transfusion
ISM: Independent Safety Monitor
IWRS :Interactive web response system
MERS: Middle East Respiratory Syndrome
OP: Oropharyngeal
RT-PCR: Reverse Transcriptase Polymerase chain reaction
PER: protocol event report
PK: Pharmacokinetic
PPE: Personal Protective Equipment

SAE: Serious adverse event
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SOFA: sequential organ failure assessment
TRALI: Transfusion-related acute lung injury
UP: Unanticipated Problem
UPnonAE: Unanticipated Problem that is not an Adverse Event
WNV: West Nile virus
ZIKV: Zika virus

PROTOCOL SUMMARY

Long title: SAFETY AND EFFICACY OF INTRAMUSCULAR COVID-19 CONVALESCENT IMMUNOGLOBULIN PROPHYLAXIS IN HEALTHCARE PERSONNEL AT RISK OF SARS-CoV-2 INFECTION AS A RESULT OF THEIR PATIENT CARE ACTIVITIES

Short title: The COVID-IG trial

Clinical Phase: II/III

IND Sponsor:

Conducted by: UCSD and San Diego VAMC

ClinicalTrials.gov Registration:

Sample Size: 2014

Study Duration: May 1, 2020 to May 1, 2021

Study Design: A randomized, placebo-controlled trial to assess the efficacy of immunoglobulin prepared from pooled plasma from COVID-19 convalescent donors (COVID-IG) compared to immunoglobulin pooled from donors never infected with SARS-CoV-2 (Control-IG) as prophylaxis against SARS-CoV-2 infections.

Population: Healthcare workers 18 years of age and older involved in direct patient care

Regimen: Participants will be randomized 1:1 to receive intramuscular injections of COVID-IG or placebo CONTROL-IG every 2 months for 12 months.

1) BACKGROUND AND SCIENTIFIC RATIONALE

No proven pharmacologic options currently exist to prevent COVID-19, the disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The scientific community aims to develop effective vaccines, but success is not assured and, even in the best-case scenario, vaccines will require a year or more to develop. Alternative measures to prevent the transmission of COVID-19 are needed now, especially in high-risk populations such as health care workers (HCW). This protocol will test the hypothesis that passive immunization using intramuscular (IM) administration of immunoglobulin (IG) containing a high titer of antibody to SARS-CoV-2 is an effective and safe method of preventing COVID-19. This immune IG is called COVID-IG.

Rationale for Passive Antibody Therapy

Passive immunization is the transfer of antibodies to a recipient to provide protection from infection. Passive immunization has been used for decades to prevent diseases such as hepatitis A, hepatitis B, varicella, rubella, and measles (*1*). Unlike vaccination, which requires an immune response that takes time to develop, passive immunization takes effect almost immediately after administration. More importantly, passive immunization can be the only form of immunization available in the absence of a vaccine; this is the case with COVID-19. Passive immunization is also the only form of immunization available to immunocompromised patients who cannot be safely immunized with many live attenuated vaccines.

To provide passive immunization for COVID-19, we propose to use a preparation of concentrated IG purified from pooled plasma from donors who have recovered from COVID-19. This type of preparation, also known as hyperimmune globulin or hyperimmune IG, has been used to prevent or mitigate many other infectious diseases, including botulism, cytomegalovirus, hepatitis A, hepatitis B, rabies, tetanus, vaccinia, and varicella (*2*).

Rationale for Prophylaxis of SARS-CoV-2 infection (COVID-19) with COVID-IG

No vaccine or pharmacologic intervention currently exists to prevent COVID-19. While humanized monoclonal antibodies to SARS-CoV-2 may prove to be effective for passive immunization, these reagents are very early in development and, like vaccines, cannot meet the current clinical need. In contrast, COVID-IG can be produced now using plasma from thousands of donors who have recovered from COVID-19. Unlike the individual plasma samples from which it is made, COVID-IG will have known and standard properties. Most important among these is its ability to neutralize viral infectivity, that is, COVID-IG will contain a known amount of SARS-CoV-2 neutralizing antibody.

Although hyperimmune IG has not been studied for prevention of COVID-19, passive immunization has been used in the form of single-donor convalescent plasma for the treatment of patients who already suffer from COVID-19 (*3*)(*4*). Due to the absence of well-matched no-treatment or placebo controls in these studies, the therapeutic benefits and risks of COVID-19 convalescent plasma is unclear. Nonetheless, the FDA has approved the use of COVID-19 convalescent plasma for treatment in critically ill patients with COVID-19 in the United States.

An important general principle regarding passive immunization is that it is more effective when used for prophylaxis than for treatment. Prevention of SARS-CoV-2 infection is of paramount importance in the fight against this pandemic, and it is the key to allowing our society to begin functioning normally again. Prevention of SARS-CoV-2 infection is also of utmost importance in protecting healthcare workers, who are at relatively high risk of SARS-CoV-2 infection due to their exposure to persons shedding infectious SARS-CoV-2. Such persons may be ill with COVID-19, or they may be pre-symptomatic (infectious before the onset of symptoms) or asymptomatic (infectious without any symptoms). Thus, healthcare workers have continual exposure to infected persons, many of whom are unrecognized as such. They are a high-risk group that might benefit from this study if COVID-IG is effective as prophylaxis, and their risk is sufficient to enable the study to reach its primary endpoints of efficacy and safety.

Finally, COVID-IG given by the IM route is convenient and practical. It minimizes time in the healthcare setting. The COVID-19 pandemic has created a new environment in which admission to the hospital or an infusion center must be minimized to avoid the risk of exposure to SARS-CoV-2. Intramuscular COVID-IG, as opposed to intravenous COVID-IG, can be administered outside of hospitals and clinics by trained healthcare personnel other than nurses. It can even be administered in drive through stations. IM COVID-IG can be given at an outpatient facility as a single injection, and the subject must be monitored for no longer than 30 minutes before being allowed to return home or to work. No IV access or pretreatment is needed

Rationale for Dosing Interval

The half-life of IgG is approximately 3-4 weeks (*5*). This protocol will provide COVID-IG or non-immune CONTROL-IG by IM injection every two months. This interval is chosen so that the antibodies transferred by injection will decline only by 4- to 8-fold (2-3 half-lives) before the next dose. The intention is to maintain a protective level antibody throughout the 12 month period of treatment and observation in the subjects in the COVID-IG arm of the trial.

Rationale for Testing Interval

A primary endpoint of the study is the prevention of infection with SARS-CoV-2. Because a substantial fraction of infections are asymptomatic, we cannot rely solely on a symptom-screen to identify them. In addition to a symptom screen, we will test for infection by PCR for SARS-

CoV-2 viral RNA in nasal pharyngeal swabs every two weeks. We anticipate that this will enable us to detect all new SARS-CoV-2 infections in the study participants.

At the same time (and interval) we will test the serum of each participant for neutralizing antibody titer, or we will use a surrogate test such as a quantitative ELISA for antibody to SARS-CoV-2 protein(s). In the subjects treated with normal CONTROL-IG (the placebo group), the detection of these antibodies (absent from all study participants at enrollment) will permit detection of all new SARS-CoV-2 infections. In the subjects treated with COVID-IG, the detection of these antibodies will reflect the antibodies in the administered COVID-IG and/or an increase in titer that could occur as a result of a "breakthrough-infection" (i.e., an infection that occurs despite the presence of antibody to SARS-CoV-2). Levels of antibody observed in breakthrough-infections, if they occur, together with levels observed in the same participants two weeks earlier, would permit us to determine the minimal levels of antibody to SARS-CoV-2 required to prevent infection.

Overview of the Potential Risks

Intramuscular immunoglobulin is considered extremely safe. The most common side effect is a local reaction at the injection site (pain and tenderness, swelling, redness, or bruising) which is usually minor and resolves spontaneously in 1-3 days (*6*). The product is contraindicated in people with severe thrombocytopenia or coagulation disorders because of the potential for hemorrhage into the injected muscle. Systemic side effects following injection include fatigue, fever, malaise, headache, muscle aches, and nausea. Rare or theoretical side effects include anaphylaxis, hypersensitivity reactions, blood clotting, hemolysis, renal dysfunction or failure, acute lung injury, and sterile abscess at the infection site (*7*). People with IgA deficiency are thought to be at increased risk of anaphylaxis.

Hyperimmune IG is derived from human serum. The serum is subjected to testing protocols that are similar to those used by blood banks and transfusion services. Nonetheless, as is the case with any biological product, there is a very small risk of allergy/anaphylaxis, transfusion related acute lung injury (TRALI), or passive transfer of unknown infectious agents.

The risk of transmitting a pathogen is reduced by (1) epidemiological screening of donors; (2) testing of plasma for HIV, HAV, HBV, HCV, West Nile virus and human parvovirus B19 genomic material; and (3) manufacturing procedures that have demonstrated the capacity to inactivate/remove pathogens. Based on screening, this risk is thought to be less than one in a million(*8*).

IG has a theoretical risk of transmitting the prions causing Creutzfeldt-Jacob disease (CJD), but no cases of transmission of CJD have ever been identified for IG manufactured by the processes used to manufacture COVID-IG or NORMAL-IG.

Passive immunotherapy entails a theoretical risk of antibody-mediated enhancement of infection (ADE). ADE has been described for several viral diseases and is due to an enhancement of disease in the presence of non-neutralizing antibodies. For coronaviruses, potential mechanisms of ADE include a theoretical concern that antibodies to one type or strain of coronavirus could enhance infection by another type or strain(*9*). The available evidence from the use of convalescent plasma in patients with SARS1 and MERS(*10*), and evidence of its use in COVID-19 thus far, suggest that passive immunotherapy is safe. Nevertheless, vigilance is required for evidence of ADE in this protocol.

Another theoretical risk is that passive immunotherapy for SARS-CoV-2 might not prevent infection but, instead, reduce or eliminate the symptoms of COVID-19 and attenuate the immune response so that the individual remains vulnerable to re-infection.

Overview of Potential Benefits

A benefit to the individual of immunotherapy intramuscular COVID-IG is that it could prevent infection and subsequent disease. Another potential benefit is societal: if the frequency with which exposed persons become infected is decreased, the risk of further transmission decreases and the epidemic will slow. With regard to the healthcare workers, who are the subjects of this protocol, prevention of infection will help preserve hospital and clinic staffing levels during the COVID-19 pandemic. It will also prevent nosocomial SARS-CoV-2 infection transmitted by healthcare personnel.

2) STUDY HYPOTHESES

PRIMARY HYPOTHESES

1. Healthcare workers who receive injections every 2 months of intramuscular immunoglobulins isolated from the plasma of COVID-19 convalescent individuals (COVID-IG) will have a 50% lower rate of acquiring SARS-CoV-2 infection (based on new nasopharyngeal RT-PCR swab positivity) over a 12-month period compared to healthcare workers who receive injections every 2 months of immunoglobulins obtained from individuals never infected with COVID-19 (Control-IG).
2. Healthcare workers who receive COVID-IG injections and those that receive Control-IG injections will not have a significant difference in their number of adverse events of grade 3 or greater over a 12-month period.

SECONDARY HYPOTHESES

1. Antibodies against SARS-CoV-2 will become detectable in the bloodstream of those in the COVID-IG group by day 3 of the study and will persist for the 12-month study period, whereas these antibodies will not be detectable throughout the study period in those who receive Control-IG.

EXPLORATORY HYPOTHESES

1. Among participants who **do** develop breakthrough COVID-19 during the study period:
    a. Those infected in the COVID-IG group will have less severe infection compared to those infected in the Control-IG group, based on categorization of disease as Mild (not requiring hospitalization), Moderate-Severe (requiring hospitalization but not resulting in ICU care or death), or Critical (resulting in ICU care or death).
    b. The infected individuals in the COVID-IG group who do not require hospitalization will have significantly lower CURB-65 scores than the infected individuals in the Control-IG group who do not require hospitalization.
    c. The infected individuals in the COVID-IG group who require hospitalization will have lower SOFA scores than the infected individuals in the Control-IG group that require hospitalization.
    d. The infected individuals in the COVID-IG group will have lower levels of inflammatory markers (CRP, ferritin, LDH, d-dimer, and IL-6), and higher levels of lymphocytes than the infected individuals in the Control-IG group.

3) STUDY OBJECTIVES

PRIMARY OBJECTIVES:

1. EFFICACY: Compare the incidence of confirmed SARS-CoV-2 infection based on new nasopharyngeal PCR positivity between those receiving intramuscular COVID-19 convalescent immunoglobulin (COVID-IG) or placebo control immunoglobulin (standard immunoglobulins prepared from plasma of individuals who have not been infected with SARS-CoV-2), also referred to herein as Control-IG over a 12-month period
2. SAFETY: Compare the incidence of Grade 3 or 4 or serious adverse events in participants receiving COVID-IG compared to participants receiving Control-IG over a 12-month period

SECONDARY OBJECTIVES

1. Study the presence, titer, and persistence of antibodies to SARS-CoV-2 in peripheral blood in COVID-IG vs. Control-IG recipients.

EXPLORATORY OBJECTIVES

1. In participants who develop COVID-19 infections during the study, compare disease severity between the COVID-IG and Control-IG groups using the following:
    a. Categorization of disease as: Mild (symptoms not requiring hospitalization); Moderate-Severe (infection requiring hospitalization); or Critical (infection requiring ICU care or resulting in death)
    b. CURB-65 Score in participants not requiring hospitalization
    c. SOFA Score in participants requiring hospitalization
    d. Levels of inflammatory markers (CRP, LDH, ferritin, d-dimer, IL-6, CBC) on presentation of illness

4) STUDY POPULATION

Inclusion Criteria for Enrollment

1) 18 years of age or older
2) All healthcare workers with direct patient contact in emergency rooms or inpatient hospital settings (e.g., nurses, doctors, respiratory therapists)
3) Available for clinical follow-up for 12 months after enrollment
4) English speaking
5) Able to consent
6) Not currently participating or planning to participate in other COVID-19 clinical trials involving pre- or post-exposure prophylaxis

Exclusion Criteria

- Confirmed active or past COVID-19 infection (detectable by nasopharyngeal SARS-CoV-2 RNA levels or serum antibody)
- Symptoms consistent with COVID-19 infection (fevers, acute onset cough, shortness of breath, anosmia, or dysgeusia) at time of screening
- Receipt of any approved or investigational drug with established activity against SARS-CoV-2 in the last 3 months
- Positive serum or urine pregnancy test for women of childbearing potential
- Women who are breastfeeding or anticipate pregnancy within 6 months
- History of allergic reaction to immunoglobulin or to blood products

- Known IgA deficiency
- Current active febrile illness
- History of venous or arterial thrombosis
- Receipt of any blood product in past 120 days
- Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigators would adversely affect participant safety and/or compliance
- Inability to comply with the study plan and follow-up schedule

5) STUDY PROCEDURE

Randomization

Participants enrolled in the study will be randomized using an interactive web response system (IWRS) to receive COVID-IG vs CONTROL-IG at a 1:1 ratio, stratified by age and gender. The age strata will be dichotomized as 18 through 49 years of age, and 50 years of age and older. The randomization list (using permuted blocks) will be generated by the UCSD Biostatistician using R (version 3.6.1). Study personnel and subjects will be blinded throughout.

Intervention

I. Participants will be randomized in a 1:1 ratio to receive either intramuscular COVID-IG or CONTROL-IG every 2 months
II. Study drugs: The investigational drug (COVID-IG) consists of immunoglobulin prepared from pooled plasma from donors who have recovered from SARS-CoV-2 infections. The placebo control drug (CONTROL-IG) consists of immunoglobulin prepared from pooled plasma from donors who have never been infected SARS-CoV-2. All immunoglobulin products will be screened for transfusion-transmitted infections (e.g., HIV, HBV, HCV, WNV, HTLV-I/II, ZIKV, *Trypanosoma cruzi, syphilis*). This is consistent with standard blood banking protocols.
III. The Intervention arm will receive 5.0 ml intramuscular injections of COVID-IG
IV. The control arm will receive 5.0 ml intramuscular injections of CONTROL-IG
V. Both active and control drugs will be in standard vials, with a study-specific ISBT label. Study products will be labeled with the following statement: “Caution: New Drug--Limited by Federal law to investigational use." [see 21 CFR 312.6 (a)].
VI. Study injections can be administered by any trained study personnel

6) EVALUATIONS AND MONITORING

Study Schedule

Screening (Day -1 to 0)

- Informed consent
- Demographic and medical history
- Pregnancy test
- Vital signs
- Concomitant medications
- COVID-19 symptom screen
- Nasopharyngeal swab to screen for SARS-CoV-2 by PCR
- Venous blood draw for antibody screen and future research

Start (Day 0)

- COVID-19 symptom screen
- Vital signs
- Randomization
- Administration of intramuscular study IG
- Adverse event monitoring** (**this will be performed in-person on the injection day and then for 14 consecutive days every 2 months following each injection by text messaging)**
- CBC and CMP
- Nasopharyngeal swab SARS-CoV-2 PCR testing
- Venous blood draw for antibody monitoring and future research

Days 3, 7, 14, 28, and every 2 weeks thereafter for 12 months

- COVID-19 symptom screen (text message)
- Nasopharyngeal swab for SARS-CoV-2 PCR testing
- Venous blood draw for antibody monitoring and future research

Every 2 months from day 0 through 12 months

- Study injections
- Adverse event monitoring (as indicated above, **this will be performed in-person on the injection day and then for 14 consecutive days every 2 months following each injection by text messaging)**

TABLE 1. SCHEDULE OF EVENTS

Study period	Screen	Start	Follow-up					
Day	-1 to 0	0	3	7	14	28	Every 2 weeks through 12 months	Every 2 months through 12 months
Informed consent	X							
Demographic and Medical history	X							
Pregnancy test [1]	X							
Vital signs	X	X						
Concomitant medications	X							
Randomization		X						
Immunoglobulin Injections (IM)		X						X
CBC and CMP		X						
COVID-19 Symptom screen	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	
Adverse event monitoring		X	X[3]	X[3]	X[3]			X[3]
Nasopharyngeal swab for SARS-CoV-2 RT-PCR	X	X	X	X	X	X	X	
Sample of venous blood for antibody testing and future research	X	X	X	X	X	X	X	

[1] Urine or serum pregnancy test for women of childbearing potential

[2]To be assessed via text messaging

[3]This will be performed by text messaging daily for 14 days following each injection every 2 months by text messaging

Additional Information on Monitoring and Evaluations

- To monitor for adverse reactions to the study IG injections, participants will be required to respond to text messaging asking them about adverse reactions. **This will occur daily for the 14 days following each IG injection**.

- Participants will be monitored for SARS-CoV-2 infection (the primary study endpoint) by serial testing for SARS-CoV-2 RNA by PCR and for antibody to SARS-CoV-2 (please see Table 1).

- Participants will be monitored for signs and symptoms of COVID-19 by text messaging on designated days (see above). However, they will also be instructed to report the onset of any symptoms suggestive of COVID-19 throughout the study, whether or not these occur on the designated reporting days. These symptoms include: fever, shortness of breath, cough, anosmia, or dysgeusia. If any of these occur, they are instructed to contact the study team immediately.

- If a participant reports symptoms suspicious for COVID-19, he/she will undergo additional evaluation and additional laboratory testing with nasopharyngeal SARS-CoV-2 RT-PCR (in addition to the scheduled lab evaluations). If there is confirmation of COVID-19 by laboratory testing or if clinical judgment deems participant to have COVID-19 in the context of false negative testing, then severity assessment will be performed and additional labs will be obtained that will include CRP, ferritin, LDH, d-dimer, IL-6 and a CBC with differential.

- In all circumstances in which text messaging is required, the study team will be responsible for contacting participants if they do not respond to text messages.

7) ACCRUAL, RETENTION, AND WITHDRAWAL

To ensure the trial accrues and retains the number and diversity of participants required to assess the primary and secondary endpoints, a recruitment and retention risk assessment will be conducted at least monthly. We will use an ongoing evaluation process, which will include iterative feedback from recruitment reports and study participants, and will guide implementation activities.

Recruitment methods will include:

- Broad targeted advertisements at the medical center (e.g., brochures/flyers, web advertisements, and media)
- Mail, email, telephone messages
- Social, professional and community networks (e.g. co-workers)

Study coordinators will maintain Screening Logs based upon information obtained from:
Pre-Screen/Screening

- Phone calls made to potential participants
- Potential participants contacted using MyChart (an Epic EHR product) pending IRB approval.
- Encouraging potential participants share study information and study contact phone numbers with friends who may be interested in participating in the study
- Potential participants will be invited to register on ResearchMatch
- Potential participants will be asked “how did you hear about the study”

Consenting

- Potential participants will be given opportunities to ask questions about the study
- Participation in the study will be recorded in their electronic health record

Retention

In addition to visits where lab tests are performed, participants will be sent daily text messages for the first 14 days of the study to ensure that they report via text message whether or not they experience adverse events related to the study injections, and this series of text messages will be repeated following each injection of the study drug (i.e., every 2 months). Study participants will also be sent texts periodically throughout the study monitoring for symptoms of new COVID-19 infection. The study team will be responsible for contacting these participants if they do not respond to these text messages. The study team will also be responsible for participant attrition and missed visits. Team leaders will provide missed visit status reports, including the reason why the visit was missed, to the Data Coordinating Center (DCC). The DCC will compile reports to generate a master log of participant attrition and missed visits. This log will be monitored to guide and inform continuous process improvement.

Participant Withdrawal

- Participants can terminate study participation and/or withdraw consent at any time without prejudice.
- Randomized participants who withdraw from the study will not be replaced.
- The investigator may withdraw participants without their consent if they are lost to follow up, non-compliant with study procedures or if the investigator determines that continued participation in the study would be harmful to the participant or to the integrity of the study data.
- Discontinuation of the study: The study sponsor, FDA and IRB all have the right to terminate this study at any time.

8) STATISTICAL CONSIDERATIONS

The primary outcome is to compare the incidence rate of developing SARS-CoV-2 infection between the two study arms over a 12-month period. It is hypothesized that the rate will be at least 50% less in the intervention arm. Based on estimates of infection rates in healthcare workers that we have compiled from around the country, including at our institution, we estimate that the incidence ofSARS-CoV-2 infection in our control NORMAL-IG population over a 12-month period will be roughly 5%. Based on our prediction that the COVID-IG group should have at least a 50% decrease in the incidence of SARS-CoV-2 infection, we predict that 2.5% or less of this cohort will become infected over the 12-month study period.

Statistical power is based on a two-sided, two sample binomial test for proportions, and a two-sided overall alpha=0.05 was used. Assuming a 5% control (placebo) rate and 2.5% intervention rate, to achieve 80% power and overall 2-sided alpha=0.05, assuming 10% attrition, we will need to enroll 2014 subjects to obtain 1812 evaluable patients (906 per study arm) .

Interim Analysis Statistical Analyses

One interim analysis and one final analysis for efficacy are planned for this trial. In order to maintain the overall two-sided type I error rate of 0.05, the Lan-DeMets (O'Brien-Fleming) α-spending function will be used.

The table below shows the critical values and other design characteristics used in this analysis. Specifically, a z-statistic greater than the critical value of 2.963 will provide evidence of early stopping for efficacy.

Table 2. Critical values and design operating characteristics.

	Information Rate	Critical Value	Nominal P-value	Sample Size
Interim	0.5	2.96259	0.00305	906
Final	1.0	1.96857	0.04695	1812

Hence, with an overall type I error of 0.05, a sample size of 906 subjects in each treatment arm (1812 overall), this trial is designed to have 80% power to detect a 2.5% difference in infection rates between the two arms. The interim analysis for efficacy will be done when 906 evaluable patients have completed the study, while the final analysis will be done when all 1812 evaluable patients have completed the study.

Additionally, at this mid-point assessment, futility analysis will be conducted through the use of conditional power calculations under a series of alternatives (design effect size, observed effect size, and an intermediate effect size). Subject to the approval of the DSMB, a worst case conditional power value of less than 10% will indicate evidence in favor of early stopping for futility.

Statistical Analysis Plan

General Considerations.

In general, analyses will incorporate the modified intent-to-treat (mITT) principle. Participants who are “randomized” and administered study medication will be included in the mITT population. All results will be reported as point estimates (odds ratios) and interval estimates (95% confidence intervals). All tests of significance for the secondary outcomes will be 2-sided with no adjustments for multiple comparisons. A p-value of 0.05 will be considered statistically significant. Statistical analysis will be conducted using R v.3.6.1. Demographic and baseline characteristics will be compared between study arms using Fisher’s exact test for categorical variables, and a 2-sample t-test for continuous variables. Appropriate non-parametric alternatives will be considered, if parametric assumptions fail.

Analysis of Primary Outcome.

The primary outcome of the study is the SARS-CoV-2 infection rate, which is a binary variable measured over a 12-month period. Fisher's exact test will be used to compare infection rates between study arms. Multivariable logistic regression modeling will be used to assess the association between incidence of infection (yes/no) and study arm, adjusting for other potential covariates, such as age, gender, and presence of cardiopulmonary comorbidities, that are simultaneously unbalanced at baseline (univariate $p < 0.10$) and associated with the outcome (univariate $p< 0.15$). Missing data will be evaluated. If the missingness is not random (non-ignorable), multiple imputation or propensity weighting will be considered.

Analysis of Safety Primary Outcome.

All subjects who receive any intervention will be included in a safety analysis. Adverse Events (AEs), Serious AEs (SAEs), and vital sign data will be listed by subject. AEs will be summarized by method of collection, type, frequency, severity, relationship to study intervention, any change in study intervention, and number of subjects per treatment arm. Severity of AEs in terms of incidence of Grade 3 or 4 or serious adverse events will be compared in COVID-IG and CONTROL-IG recipients. Changes in PE that are expected will be excluded as AEs. Frequency of AEs and SAEs will be described by intervention group and compared using Fisher's exact test.

Analysis of Secondary Outcomes.

(i) Detectable Antibodies. Presence of antibodies starting at Day 3 to the end of the study period (12 months) will be measured and compared between study arms via methods analogous to those used to assess the primary outcome. Titers and length of persistence will be compared between study arms via t-tests and multiple regression modeling.

Analysis of Exploratory Outcomes. In the subgroup of subjects that develop COVID-19, the severity of disease will be compared between study arms. Measurements include severity of disease, CURB-65 score, SOFA score, and levels of inflammatory markers. Methods analogous to those used to assess the primary and secondary outcomes will be applied here, namely Fisher's exact test and t-tests (or Wilcoxon rank sum test if parametric assumptions fail) for categorical and continuous outcomes, respectively. Potential confounders and covariates of interest will be included in a multivariable model (logistic or multiple linear regression) if appropriate.

9) RISKS AND BENEFITS

Potential Benefits of the Study

The potential benefits of administering COVID-IG to healthcare workers at high risk for developing SARS-CoV-2 infection are unknown. However, it is anticipated that this intervention will decrease the risk of developing SARS-CoV-2 infection and decrease the severity of illness should it develop.

Potential benefits of clinical monitoring and virologic testing

Participants enrolled in the study will undergo close clinical and virologic monitoring that could facilitate earlier diagnosis of SARS-CoV-2 infection, with benefits to the individual, to their family, to their patients and to fellow healthcare workers, and to the community at large.

Potential risks

- Risks of IG administration: pain redness, bruising, and swelling at the injection site; fever, chills, rash, headache, serious allergic reactions; transmission of infectious agents, which is exceedingly rare.
- Risks of phlebotomy: local discomfort, bruising, hematoma, bleeding, fainting
- Risks of nasopharyngeal swab: local discomfort

Alternatives

The alternative to participation in this study is to use routine, non-pharmacologic SARS-CoV-2 infection prevention measures, and careful monitoring following close contact with an individual with COVID-19

Safety measures

Participants will be required to take their own temperature (thermometer will be provided by study group if they do not own one) daily for the first 14 days. They will be sent daily text message reminders during this time reminding them to take their temperature and asking them to report any of the following:

- Other new symptoms possibly attributable to the study injection, which could include, but are not limited, to rash, chills, and malaise, and any severe adverse events

If participants respond "Yes" to any of these questions, they will receive a follow-up telephone call from the study team within 24 hours with a decision about how to proceed

Adverse Event (AE)

Any unfavorable medical occurrence in a study participant who has received a study intervention, even if the study physician believes that it is not causally related to the study intervention is considered an AE. This includes any unfavorable and unintended sign (including, for example, an abnormal laboratory finding), symptom, or disease temporally associated with the administration of the study drug.

Serious Adverse Event (SAE)

- An SAE is any adverse event that results in any of the following outcomes:
- Death
- Life-threatening event (immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

Unexpected Adverse Event (UAE)

An Unexpected Adverse Event (UAE) is an adverse event, the nature or severity of which is not consistent with the normal CONTROL-G and/or COVID-IG Prescribing Information. This is in contrast to expected AEs, which have been previously observed with use of the study agents.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)

Investigators should report SUSARs to UCSD within 5 calendar days. UCSD will submit the SUSARs to the FDA within 15 calendar days. Fatal or life-threatening SUSARs should be reported to UCSD as soon as possible and no later than 3 calendar days. Fatal or life-threatening SUSARs will be reported to the FDA within 7 calendar days.

Adverse Events of Special Interest (AESI)

An AESI (serious or non-serious) is one of scientific and medical concern specific to the product or program for which ongoing monitoring and rapid communication by investigator to the DSMB and IRB/sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the IRB to other parties (i.e., regulators) might also be warranted.

AESIs include all cases of immune related AEs (IRAEs) felt to be related to IG including

- Grade 2 or greater injection related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- All IRAEs regardless of grade

For all AESIs the IRB and DSMB should be contacted immediately via phone.

Unanticipated Problem (UP)

An Unanticipated Problem (UP) that is not an Adverse Event (e.g., a breach of confidentiality, accidental destruction of study records, or unaccounted-for study drug) should be reported to the IRB and DSMB.

Protocol Deviation

Deviation from the IRB-approved study procedures. Designated serious and non-serious

- Serious Protocol Deviation: Protocol deviation that is also an SAE and/or compromises the safety, welfare or rights of participants or others
- Non-Serious Protocol Deviation: Other protocol deviation

Investigator's Assessment of Adverse Events

- The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose adverse event information, provide a medical evaluation of adverse events, and classify adverse events based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.
- Laboratory abnormalities will be reported as AEs if they meet Grade 1 or higher criteria. The grading of the laboratory AEs will be based on the toxicity tables in https://www.niaid.nih.gov/research/dmid-safety-reporting-pharmacovigilance

Investigator's Assessment of Adverse Events

<u>Assessment of Severity</u>:

1 = Mild: Transient or mild discomfort (<48 hours); no medical intervention/therapy required)

2 = Moderate: Mild to moderate limitation in activity-some assistance may be needed; no or minimal medical intervention/therapy required)

3 = Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

4 = Life-threatening: Extreme limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization or hospice care probable

5= Death

<u>The association assessment categories that will be used for this study are:</u>

- Associated – The event is temporally related to the administration of the study product and no other etiology explains the event.

- Not Associated – The event is temporally independent of the study product and/or the event appears to be explained by another etiology.

<u>The investigator must provide an assessment of association or relationship of AEs to the study product based upon:</u>

- Temporal relationship of the event to the administration of study product
- Whether an alternative etiology has been identified
- Biological plausibility
- Existing therapy and/or concomitant medications

10) SAFETY OVERSIGHT

Monitoring Plan

Study Monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the DSMB and the IRB. They will verify that:

AE collection Requirements for This Protocol

Post entry, all AEs must be documented and reported to the DSMB within 3 business days if any of the following criteria have been met

- Grade ≥ 1 AEs
- Suspected or confirmed immune-related adverse events (IRAE)
- Injection reactions
- AEs that led to a change in study intervention
- AEs meeting SAE definition or expedited adverse event reporting requirement

Expedited Adverse Event (EAE) Reporting to the IRB/Sponsor

The following events must be reported to the DSMB and IRB immediately and no later than 3 days.

- All SAEs
- All AESIs felt related to study treatment
- An important medical event that may not be immediately life-threatening, but may jeopardize the patient or may require intervention to prevent serious health outcomes

Other AEs that must be reported in an expedited manner (within 3 business days to the IRB/sponsor) are as follows:

- Pregnancy

Study Reporting Interval

- All AEs and SAEs will be documented from the first administration of study product
- All AEs and SAEs will be followed until resolution even if this extends beyond the study-reporting period
- Resolution of an adverse event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic

- At any time after completion of the study, if the investigator becomes aware of a SAE that is suspected to be related to study product, this will be reported

Halting Criteria for the Study

A primary goal of this study is to assess the safety of COVID-IG compared to CONTROL-IG. Therefore, every effort should be made to retain participants on study to assess safety outcomes. The study may be discontinued at any time by the IRB on the advice of the DSMB.

The study enrollment and dosing will be stopped and an ad hoc review will be performed if any of the specific following events occur or, if in the judgment of the study physician, participant safety is at risk of being compromised:

- Unexpected death of a dosed participant in relation study injection
- Occurrence of a life-threatening IRAE to include but not limited to allergic/hypersensitivity reaction (anaphylaxis), manifested by bronchospasm, with or without urticaria or angioedema, requiring hemodynamic support with pressor medications or mechanical ventilation.
- Two participants with an unexpected SAE associated with one of the study products
- Four participants with a Grade 3 or higher toxicity for the same MEDRA coded event reported as associated with study product
- An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor, ISM, or SMC consider associated with study product and that may appear minor in terms of individual events but that collectively may represent a serious potential concern for safety
- Any other event(s) which is considered to be a serious adverse event in the good clinical judgment of the responsible physician. This will be appropriately documented.

Furthermore, given that antibody-dependent-enhancement (ADE) of infection might be an issue with convalescent or control IG, we will monitor the number of participants in each trial arm who progress to death. Given that we plan to recruit 906 participants in each study arm and with the following assumptions 1) 5% of those the Control-IG arm are expected to progress to symptomatic infection, 2) 2.5% in the COVID-IG treatment arm are expected to progress to symptomatic infection, and 3) up to 3-4% of those with symptomatic infection may progress to death(*11*), the probability of observing one death in either arm is approximately 0.002.

We will monitor the number of participants that die and determine, for each death, whether it is likely due to administration of the study drug (COVID-IG or CONTROL-IG) (definite, probable, possible, or unlikely). These data will be presented to the DSMB and the IRB to determine early discontinuation of the study is warranted due to safety concerns.

11) ETHICS/PROTECTION OF HUMAN PARTICIPANTS

Ethical Standards

UCSD is committed to the integrity and quality of the clinical studies it coordinates and implements. UCSD will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human participants are met. The information provided in this section relates to all UCSD sites participating in this research study

As the Department of Health and Human Services continues to strengthen procedures for human participants' protections via new regulations, UCSD will review these evolving standards in relation to the proposed activities and will advise the investigators on those that may apply.

In addition, UCSD has a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP). The FWA number for UCSD is FWA00004495.

This assurance commits a research facility to conduct all human participants' research in accordance with the ethical principles in The Belmont Report and any other ethical standards recognized by OHRP. Finally, per OHRP regulations, the research facility will ensure that the mandatory renewal of this assurance occurs at the times specified in the regulations.

Institutional Review Board

The UCSD IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before participant enrollment begins, and all safety-related reports and the interim analysis throughout the course of the study. The UCSD IRB currently holds and will maintain a US FWA issued by OHRP for the entirety of this study.

UCSD Medicine IRB Role as the Single IRB for Other Participating Sites

Should other institutions participate in this trial, all UCSD IRB-approved study materials and required local context forms will be distributed to participating sites to complete their local context review. Sites will be immediately notified of changes to the protocol/master consent that may affect local context at their site. Enrollment information will be obtained from sites to include in UCSD IRB continuing reviews. Reporting of any site protocol events or deviations that meet UCSD IRB requirements for prompt reporting will be directed by the coordinating center.

Informed Consent Process

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. The participant will sign the informed consent document before any PHI is collected or any study procedures are

performed. A copy of the signed informed consent document will be given to the participant. The consent will explain that participants may withdraw consent at any time. Extensive explanation and discussion of risks and possible benefits of participation in this study will be provided to the participants in understandable language. Adequate time will be provided to ensure that the participant can consider and discuss participation in this study.
The consent will describe in detail the study interventions/products/procedures and risks/benefits associated with participation. The rights and welfare of the participants will be protected by emphasizing that their access to medical care and its quality will not be adversely affected if they decline to participate in this study.

Participant Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and any sponsors and their agents and the DSMB. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the DSMB and IRB. The results of this research study may be published, but participants' names and other identifiers will not be revealed. Records will remain confidential. To maintain confidentiality, the PIs will be responsible for keeping records in a locked cabinet in a locked area accessible only by authorized personnel. Test results will be coded to prevent association with participants' names. Data entered into computerized files will be accessible only by authorized personnel directly involved with the study and will be coded and password-protected. Participants' records will be available to the FDA, the NIH, the manufacturer of the study product and their representatives, investigators at the site involved with the study, and the IRB.

Prompt Reporting Requirements

Federal regulations require that institutions engaging in human participant research have written procedures to ensure investigators properly report certain events to the Institutional Review Board ("IRB"). This policy defines those events that require prompt reporting the UCSD IRB. The policy applies to all research studies that are overseen by the UCSD IRB.

Reporting Timeframe

For the purposes of this policy, "prompt" means as soon as possible after the event is discovered, but in all cases within 10 working days after discovery of the event. Reportable deaths must be reported within 72 hours after discovery.

What Events Must Be Reported Promptly to the IRB

The following types of events must be promptly reported to the IRB:

1. UPIRSO: All potential "unanticipated problems involving risks to participants or others"(UPIRSO). An event is considered an UPIRSO when it meets all of the following criteria:

a. It is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the population being studied; Unexpected events could be either medical or non-medical events.
b. It is related or possibly related to participation in the research (i.e. there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
c. It places participants or others [e.g. study team members or relatives of a participant] at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

2. POTENTIAL SERIOUS OR CONTINUING NON-COMPLIANCE: Non-Compliance is defined by the Organization as the failure to follow the research protocol, federal, state, or local laws or regulations governing human subjects research, institutional policies, or the requirements or determinations of the IRB. Only incidents that may qualify as serious or continuing non-compliance must be promptly reported:
   a. Serious Non-compliance is defined by the Organization as non-compliance that either (a) significantly harms or poses an increased risk of significant harm to participants or others, or (b) significantly compromises the rights and welfare of the participants or the integrity of the Organization's human research protection program.
   b. Continuing Non-compliance is defined by the Organization as a pattern of non-compliance that significantly compromises the scientific integrity of the study or the rights and welfare of the participants or the integrity of the Organization's human research protection program. When applying this definition, particular consideration may be given by the IRB to activity that recurs after a previous report has been evaluated by the IRB and corrective action has been instituted.
   c. Potential Breaches of Confidentiality: Any unauthorized disclosure of participant's personally identifiable information. Please Note: Potential breaches of confidentiality that involve protected health information (PHI) must also be reported promptly to the HIPAA Privacy Officer. Please see guidance for further detail.
   d. Incarceration of a participant in a study not approved by the IRB to involve prisoners and the study team plans to continue study activities with prisoners while incarcerated.
   e. Unresolved Participant Complaints: Complaints of participants when the complaint indicates unexpected risks or cannot be resolved by the research team.
   f. Other events: There may be other events that should be promptly reportable to the IRB. If you have questions about whether an event is immediately reportable, please contact a Human Research Compliance Associate in the Office of Human Subjects Research.

Events that do not meet the above criteria should be summarized and reported to the IRB at the time of continuing review. Please see the companion reportable event guidance for additional information about the types of events that are reportable under this policy.

Procedure for Reporting to the IRB

The PI has the ultimate responsibility to review each event and determine if it meets any of the above reporting criteria. Events that require prompt reporting shall be reported to the IRB via a Protocol Event Report (PER) in eIRB per the UCSD timelines defined above and/or as defined by the external IRB if applicable. They must also be reported promptly to the DSMB.

Review of Event and Institutional Reporting

Each PER will be reviewed by the DSMB and IRB. Upon receipt, the event will be assessed to determine the level of review required. The IRB is authorized to take any actions necessary to address the event, including but not limited to:

- Requiring modification of the study protocol, informed consent, or other aspects of the study
- Requiring notification of participants
- Requiring monitoring or auditing
- Suspending or terminating the research
- Referring the event to organizational officials for their consideration;
- Requiring further reporting of the event to regulatory agencies or sponsors.

As part of its review, the DSNB and IRB are responsible for determining whether an event qualifies as an UPIRSO, Serious Non-compliance, and/or Continuing Non-compliance. Only a convened IRB may make a formal finding that an event(s) constituted an UPIRSO, Serious Non-compliance, and/or Continuing Non-compliance. Such findings require additional reporting by the Institution.

Future Use of Stored Specimens

Participants will be asked for consent to use of their samples for future testing and research prior to study enrollment. Prospective participants who do not consent will not be enrolled. The confidentiality of the participant will be maintained. They will be no plans to re-contact them for consent or to inform them of results. The risk of collection of the sample will be the small risk of bruising or fainting associated with phlebotomy however these samples will be taken at the same time as other protocol required samples. No human genetic testing will be performed on the samples.

Five ml of blood samples will be collected at 10 time points for storage (See Schedule of Events). Serum will be frozen in 1-ml aliquots. These samples will be used to answer questions that may arise while the study is underway or after it is completed. If for instance, there were

unanticipated AEs, serum could be used to run tests that might help determine the reason for the AEs.

Samples would not be shared with investigators other than investigators at UCSD unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at UCSD for 5 years. Any use of these specimens not specified in the current protocol will be reviewed by the UCSD IRB.

Data Management and Monitoring

Source Documents

The primary source documents for this study will be the participants' medical records, laboratory values, and information recorded by the study team that has been provided by the participants. The investigator will retain a copy of source documents. The investigator will permit monitoring and auditing of these data, and will allow the sponsor, IRB and regulatory authorities access to the original source documents. The investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected and be entered into the study database/case report form and must be signed and dated by the person recording and/or reviewing the data. All data submitted should be reviewed by the site investigator and signed as required with written or electronic signature, as appropriate. Data entered into the study database will be collected directly from participants during study visits, through official text-messaging that is part of the study protocol, or will be abstracted from participants' medical records. The participants' medical records must record their participation in the clinical trial as well as any AEs experienced during the trial.

Data Management Plan

Study data will be collected at the study site(s) and entered into the study database. Data entry is to be completed on an ongoing basis during the study.

Data Capture Methods

Clinical data will be entered into a 21 CFR 11-compliant Internet Data Entry System (IDES). The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

Record Retention Guidance

The Principal Investigator (PI) of a study approved by a UCSD IRB is required to retain records associated with a human subjects research project pursuant to Organization Policy 115.2.

UCSD Organization Requirements

Original data must be retained for at least 5 years from the date of publication. Beyond that, where questions have been raised regarding the validity of the published data, investigators must preserve the original data until such questions have been resolved to

the satisfaction of the Organization and any involved government agencies. The director or chair of each department or research unit must decide whether to preserve original data for a given number of additional years or for the life of the unit.

HIPAA

Under the HIPAA Privacy Rule, participants have the right to ask UCSD for an accounting of certain disclosures of their identifiable health information for a period dating 6 years from the date of the last covered disclosure. To ensure that UCSD can meet this accounting requirement, investigators must retain study records, along with records of all disclosures of study information, for at least 7 years after either of the following (whichever is later):

- The last participant has completed his or her participation in the study; or,
- The date of the last disclosure of identifiable health information from study records, if disclosures continue after all participants have completed the study. [45 CFR 164.528]

This requirement to retain study records and to account for disclosures also applies to research that involves the secondary use of medical records or other identifiable health information.

Federally-Funded Research and FDA-Regulated Research

DHHS regulations require that, "records relating to research which is conducted shall be retained for at least 3 years after completion of the research." [45 CFR 46.115(b)]. For Investigational New Drug (IND) research, the FDA requires that sponsors and investigators retain "records and reports required by this part for 2 years after a marketing application is approved for the drug; or if an application is not approved for drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA so notified."

Study Record Retention

The site investigator is responsible for retaining all essential documents listed in the ICH GCP Guidelines. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB/IEC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the site investigator's responsibility to retain copies of source documents until receipt of written notification to the sponsor.

No study document should be destroyed without prior written agreement between the sponsor (IF ANY) and the Principal Investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the site investigator must provide written notification of such intent to sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

REFERENCES

1. M. K. Young, The indications and safety of polyvalent immunoglobulin for post-exposure prophylaxis of hepatitis A, rubella and measles. *Hum. Vaccines Immunother.* **15**, 2060–2065 (2019).
2. Jolles, Stephen. (2018). "Subcutaneous and intramuscular immune globulin therapy." Uptodate. https://www.uptodate.com/contents/subcutaneous-and-intramuscular-immune-globulin-therapy?search=intramuscular%20immunoglobulin&source=search_result&selectedTitle=.
3. L. Chen, J. Xiong, L. Bao, Y. Shi, Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect. Dis.* (2020), , doi:10.1016/S1473-3099(20)30141-9.
4. C. Shen, Z. Wang, F. Zhao, Y. Yang, J. Li, J. Yuan, F. Wang, D. Li, M. Yang, L. Xing, J. Wei, H. Xiao, Y. Yang, J. Qu, L. Qing, L. Chen, Z. Xu, L. Peng, Y. Li, H. Zheng, F. Chen, K. Huang, Y. Jiang, D. Liu, Z. Zhang, Y. Liu, L. Liu, Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. *JAMA - J. Am. Med. Assoc.* (2020), doi:10.1001/jama.2020.4783.
5. S. Mankarious, M. Lee, S. Fischer, K. H. Pyun, H. D. Ochs, V. A. Oxelius, R. J. Wedgwood, The half-lives of IgG subclasses and specific antibodies in patients with primary immunodeficiency who are receiving intravenously administered immunoglobulin. *J. Lab. Clin. Med.* (1988).
6. Public Health Agency of Canada. Canadian immunization guide: part 5 - passive immunization. Ontario, Canada: Government of Canada; 2017.
7. CSL Behring.Product information: Normal Immunoglobulin-VF 2017. Available from: https://www.cslbehring.com.au/-/media/ cslb-australia/documents/aus-pis-and-cmis/normal-immunoglobu lin-au-pi-900.pdf ?la=en-us&hash= 48E460BA88375592764C0AECF0083C074322AABB.
8. Australian Red Cross Blood Service. Residual risk estimates for transfusion-transmissible infections 2018. [accessed 2018 Mar 27]. https://transfusion.com.au/adverse_events/risks/estimates.
9. Y. Wan, J. Shang, S. Sun, W. Tai, J. Chen, Q. Geng, L. He, Y. Chen, J. Wu, Z. Shi, Y. Zhou, L. Du, F. Li, Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. *J. Virol.* (2019), doi:10.1128/jvi.02015-19.
10. J. Mair-Jenkins, M. Saavedra-Campos, J. K. Baillie, P. Cleary, F. M. Khaw, W. S. Lim, S. Makki, K. D. Rooney, J. S. Nguyen-Van-Tam, C. R. Beck, The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis. *J. Infect. Dis.* (2015), doi:10.1093/infdis/jiu396.
11. "Coronavirus disease 2019 (COVID-19) Situation Report – 46. World Health Organization. March 6, 2020."