Regulatory Documents for Sites Participating in the National Expanded Access Program (IND 19832) for the Use of COVID-19 Convalescent Plasma in the Treatment of COVID-19 Disease

Assembled 9/1/2020
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1. Executive Summary

The intent of this EAP document packet is to provide to the participating sites and treating physicians, the primary regulatory documents used throughout the lifecycle of the National Expanded Access Program for the Use of COVID-19 Convalescent Plasma in the Treatment of Patients with COVID-19.

This program was initiated on April 3, 2020 and enrollment was closed on August 21, 2020.

This program was funded by BARDA, conducted under FDA oversight for IND 19832 and had the Mayo Clinic IRB serve as the IRB of record for all sites participating in the program.

In accordance with 45 CFR 46.103(e), by agreeing to participate in the trial which included signing up on the website, which served as documentation of each participating institution’s reliance on Mayo’s IRB. A separate IRB reliance agreement was not required for each site.

Only the approved versions of the documents which were posted on the website are included in this packet. Other documents which were not approved or not posted on the website are not included in the packet.

This packet should contain the essential documents necessary to satisfy the needs of the treating physician participating in a program which is FDA regulated.

Key Program Identifiers

IND #19832  
NCT# 04338360  
IRB # 20-003312

The Regulatory Sponsor and overall PI is Michael J. Joyner, MD.

The primary objectives of this program were to provide access to COVID-19 Convalescent Plasma and establish the initial safety determination and profile for COVID-19 Convalescent Plasma. Additionally the program helped establish, standardize and qualify the supply chain throughout the United States for COVID-19 Convalescent Plasma.

Based on the published results of the program on August 21, 2020 the Secretary of Health and Human Services issued an Emergency Use Authorization for COVID-19 Convalescent Plasma.

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2. Background

Few treatments beyond supportive measures are currently available for patients critically ill with COVID-19. However, infusions of convalescent donor plasma have demonstrated improvement in patient outcomes for illnesses like Ebola, Influenza, MERS and SARS. Mayo Clinic along with other academic medical centers and offices within the United States government set up an expanded access program to study treatment of COVID-19 with convalescent plasma.

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.1 In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.

One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19. Convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic.

Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials.

FDA guidance (https://www.fda.gov/media/136798/download) provides recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. FDA guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

Severe morbidity and mortality is occurring during this COVID-19 Pandemic. Since there is no currently recognized effective standard of care treatment for patients infected with SARS-CoV-2, multiple investigational agents are being tested. These include antivirals marketed or approved for other indications or being developed specifically for SARS-CoV-2 and other immunotherapies.

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.
The collection and transfusion of convalescent plasma as a treatment was first used in the 1890s and helped reduce the severity of a number of infectious disease outbreaks prior to the development of antimicrobial therapy in the 1940s.

In the early 20th century, convalescent plasma treatment was used during outbreaks of various infectious diseases, including measles, mumps and influenza. More recently, it was used during the H1N1 influenza pandemic in 2009, and again in 2013 during the Ebola outbreak in West Africa.

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19. [Roback JD 2020, Joyner MJ 2020, Shen C 2020]

The FDA is permitting the use of convalescent plasma as an investigational treatment for patients with moderate or severe COVID-19 infection. It is considered an investigational treatment because clinical studies have started but have not yet been completed. We know there is evidence that convalescent plasma has helped patients with other illnesses, but doctors and researchers will not know how effective convalescent plasma will be in treating COVID-19 patients until more studies are completed.

While additional treatment options are evolving, convalescent plasma can be considered and may help some moderately or severely ill patients. The idea to use this treatment for the new coronavirus was suggested by Arturo Casadevall, MD, PhD, from Johns Hopkins University; and Liise-anne Pirofski, MD, from the Albert Einstein College of Medicine. [Casadevall A 2020]
3. Introduction

This expanded access program will provide access to investigational COVID-19 convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

Plasma has been and is being collected by registered or licensed blood banks, including the American Red Cross. Collection of plasma will be done using the guidelines from AABB, the FDA, and the American Red Cross or as contained in the COVID-19 Convalescent Plasma Collection Protocol, and using otherwise standard operating procedures at the blood establishments.

Plasma from patients who have recovered from a documented SARS-CoV-2 infection may contain high titer anti-SARS CoV-2 antibodies which may be able to modify the course of the infection and decrease morbidity and mortality associated with SARS-CoV-2 infection when transfused into hospitalized patients in a serious or life-threatening situation or at high risk for progression of severe disease.

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4. FDA

**IND Acknowledgement letter from FDA dated 4/2/2020**

- The initial IND for the EAP was submitted to and received by the FDA on 4/1/2020.
- The routine standard acknowledgement letter was received from the FDA on 4/2/2020.
- This was followed on 4/2/2020 with a letter from the FDA allowing the EAP to proceed.

The FDA allowed a modification to the manner in which the Statement of Investigator was completed for this EAP. So rather than having each treating physician complete the Form FDA 1572, the commitments of this form for the Statement of Investigator were incorporated into a REDCap form which could be completed electronically.

There were two versions of this form:

- The initial version of the form was sent out separately after the REDCap physician registration form. This process was used from 4/3/2020 to 4/23/2020.
- The second version of the form was incorporated into the physician registration process and REDCap form. This was used from 4/23/2020 to present/end of the program.

**Statement of Investigator (Form FDA 1572) Version 1**

- [Version 1 Blank Form](#)
- [Version 1 Example Form](#)

**Statement of Investigator (Form FDA 1572) Version 2**

- [Version 2 Blank Form](#)
- [Version 2 Blank Form Full Abridged (with participating site choices)](#)
- [Version 2 Example Form](#)

Completed 1572s are maintained on file by the sponsor and are not required to be maintained by each site or participating physician. There was the option in the second version of the form for the treating physician to print or save a copy of the form right after it was initially completed.
Mayo Clinic
Attention: Michael J. Joyner, MD
200 First Street SW
Rochester, MN  55905

Dear Dr. Joyner:

The Center for Biologics Evaluation and Research (CBER) has received your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). We assigned the following biologic product name and IND number to this application. They serve only to identify your IND and do not imply that we endorse your application.

IND #: 19832

Sponsor: Michael J. Joyner, MD

Biologic Product Name: Convalescent Donor Plasma

Submission Date: April 1, 2020

Receipt Date: April 1, 2020

Primary Point of Contact: Michael J. Joyner, MD

You must not initiate studies in humans until 30 days after the date of receipt shown above. If we notify you verbally or in writing of serious deficiencies that require correction before human studies can begin, you must continue to withhold such studies until we notify you that the material you have submitted to correct the deficiencies is satisfactory. If we place a clinical hold on this file, we will provide you as soon as possible, and no more than 30 days after imposition of the hold, with a written explanation of the basis for placing the IND on hold (21 CFR 312.42(d)).

You are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations (Title 21 of the Code of Federal Regulations [CFR]). Those responsibilities include:

1. Reporting to this office any unexpected fatal or life-threatening suspected adverse reaction associated with use of this product as soon as possible, but no
later than seven (7) calendar days after initial receipt of the information (21 CFR 312.32(c)(2));

2. Notifying this office and all participating investigators in a written IND safety report of potential serious risks associated with the use of the product from clinical trials or any other source, as soon as possible, but no later than fifteen (15) calendar days after initial receipt of this information (21 CFR 312.32(c)(1));

3. Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (21 CFR 312.33);

4. Obtaining prior written approval from FDA to charge for an investigational product in a clinical trial under IND (21 CFR 312.8); and,

5. Conducting all laboratory or animal studies intended to support the safety of this product in compliance with the regulations for “Good Laboratory Practice for Nonclinical Laboratory Studies” (21 CFR Part 58). If you have not conducted these studies in compliance with these regulations, please provide a statement describing in detail all differences between the practices used and those required in the regulations (21 CFR 312.23(a)(8)(b)(iii)).

In addition, please provide the following:

1. For each new lot of the investigational biologic used in clinical trials, the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results) (21 CFR 312.23(a)(7)).

2. If not included in your submission copies of the consent forms for each clinical study (21 CFR 50.20). Also, please provide documentation of the Institutional Review Board approval(s) for each clinical study (21 CFR 312.23(a)(1)(iv)).

Please note that you are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) (42 U.S.C. §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 U.S.C. 282(j)) which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under sections 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 U.S.C. 282(j) have been met. Where available, the certification must
include the appropriate National Clinical Trial (NCT) control numbers (42 U.S.C. 282(j)(5)(B)).

You did not include such certification when you submitted this application. You may use Form FDA 3674 Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j)) to comply with the certification requirement. The form can be found at https://www.fda.gov/media/69901/download.

In completing Form FDA 3674, you should review 42 U.S.C. 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Please note that FDA published a guidance Certification To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of the Public Health Service Act, Added by Title VIII of the Food and Drug Administration Amendments Act of 2007 that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm. Additional information regarding Title VIII of FDAAA is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System (PRS) website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, do not include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission, clearly identify the submission it pertains to and that it contains the FDA Form 3674 that was to accompany that application.

SUBMISSION REQUIREMENTS

You should use this IND number to identify all future correspondence and submissions, as well as telephone inquiries concerning this IND.

Please review the sponsor and primary point of contact (PPOC) information in this letter. CBER tracks one sponsor name and address and one PPOC and address per IND in our database. Because the PPOC is the individual with whom we will generally communicate regarding this IND, it is essential that we have current and correct PPOC information. If the sponsor or PPOC information is not accurate, or if it changes, please send an amendment containing the updated information.
If you have any questions, please contact the Regulatory Health Project Manager, LT Kimberly Bissohong at Kimberly.Bissohong@fda.hhs.gov or (301) 796-5350.

Sincerely,

Sonday L. Kelly, MS, RAC, PMP
Chief, Regulatory Project Management Staff
Office of Blood Research and Review
Center for Biologics Evaluation and Research
Thank you for your participation in the US Expanded Access Program (EAP) for Convalescent Plasma for the Treatment of Patients with COVID-19.

You are required by the FDA to complete Form 1572 to meet regulatory requirements. For this EAP protocol, the FDA has allowed use of this Data Capture Form in place of the actual FDA Form 1572.

You only need to complete FDA Form 1572 once, even if you enroll multiple patients. However, if you are registered at more than one hospital/medical center you will receive a 1572 for each site after you enroll a patient.

Information, protocol, consent forms and site registration, enrollment and followup forms are available at www.USCOVIDplasma.org.

If you have any questions or difficulties please email USCOVIDplasma@mayo.edu, which will be monitored from 7am-7pm CST.

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Form FDA 1572 Commitments

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to personally conduct or supervise the described investigation(s). I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met. I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments. I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68. I agree to report adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met. I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments. I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

☐ I agree
☐ I do not agree (this may limit participation eligibility)

I attest to follow the protocol and submitting this form equates to my signature on the form

Date of Agreement

(MM-DD-YYYY (ex. 04-02-2020))
Thank you for your participation in the US Expanded Access Program (EAP) for Convalescent Plasma for the Treatment of Patients with COVID-19.

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Information, protocol, consent forms and site registration, enrollment and followup forms are available at www.USCOVIDplasma.org.

If you have any questions or difficulties please email USCOVIDplasma@mayo.edu, which will be monitored from 7am-7pm CST.

Response was added on 04/09/2020 7:44am.

### Local Physician/PI Information

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Regulatory Documents for National EAP (IND 19832) Participating Sites – 9/2/2020
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Form FDA 1572 Commitments

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to personally conduct or supervise the described investigation(s). I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met. I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments. I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68. I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

☑️ I agree
☐ I do not agree (this may limit participation eligibility)

I attest to follow the protocol and submitting this form equates to my signature on the form

Date of Agreement 04-09-2020
(MM-DD-YYYY (ex. 04-02-2020))
Physician/PI Registration and FDA 1572 for US Expanded Access Program for Convalescent Plasma for the Treatment of Patients with COVID-19

Thank you for your desire to participate in this program!

**Mayo Clinic will serve as the IRB of record.**

The Mayo Clinic IRB serves as the central IRB for this study in the United States at the request of the U.S. Government.

To participate, you and your hospital need to rely on the Mayo Clinic IRB for the Expanded Access Program (EAP) protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the program by registering on [https://USCOVIDplasma.org](https://USCOVIDplasma.org) serves as documentation of each participating institution's reliance on Mayo's IRB.

A separate IRB reliance agreement is not required. The Mayo Clinic IRB is a nationally recognized IRB that is accredited by the Association for the Accreditation of Human Research Protection Programs.

**Link to IRB Protocol:** [Protocol](#)

**Link to Consent Forms:** [English](#), [Spanish](#), [Arabic](#)

**Instructions:**

You must complete this form to register as a local physician/PI including the Statement of Investigator FDA 1572, and the Patient Enrollment Form before your patient can receive convalescent plasma.

**NOTE:** Your site/medical center can designate one physician/PI for this Expanded Access Program OR multiple physicians/Pis can register for each site.

Information, protocol, consent forms and site registration, enrollment and followup forms are available at [www.USCOVIDplasma.org](http://www.USCOVIDplasma.org).

If you have any questions or difficulties registering please email [USCOVIDplasma@mayo.edu](mailto:USCOVIDplasma@mayo.edu), which will be monitored from 7am-7pm CST.

### Site/Medical Center Information

**Select Registered Site/Medical Center**

- Mayo Clinic Rochester, Rochester, MN

If your site is not listed, click this link to fill out the **site registration form**.

If your site was recently registered (24hrs), select "SITE RECENTLY REGISTERED" from drop down menu.

* must provide value

### Local Physician/PI Information

**Local Physician/PI Last Name**

* must provide value

**Local Physician/PI First Name**

* must provide value

**Local Physician/PI ID Number (Select one: only one ID type is need per physician)**

- NPI number
- DEA number

reset
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<th><strong>Local Physician/PI NPI Number</strong></th>
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<td><strong>Local Physician/PI Email Address</strong></td>
<td><a href="mailto:wentworth.mark@mayo.edu">wentworth.mark@mayo.edu</a></td>
</tr>
<tr>
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<tr>
<td><strong>Confirm your email address</strong></td>
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<tr>
<td><strong>Local Physician/PI Cell Phone Number (for study related matters)</strong></td>
<td>* must provide value</td>
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</table>

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to adhere to the protocol, to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.

* must provide value

**Statement of Investigator FDA 1572 Commitments**

- I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation(s).
- I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
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- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study (es) are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

* must provide value

- I agree
- I do not agree (this may limit participation eligibility)

Submit
Physician/PI Registration and FDA 1572 for US Expanded Access Program for Convalescent Plasma for the Treatment of Patients with COVID-19

Thank you for your desire to participate in this program!

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Link to IRB Protocol: Protocol

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If you have any questions or difficulties registering please email USCOVIDplasma@mayo.edu, which will be monitored from 7am-7pm CST.

| Site/Medical Center Information |
Select Registered Site/Medical Center

If your site is not listed, click this link to fill out the site registration form.

If your site was recently registered (24hrs), select "SITE RECENTLY REGISTERED" from drop down menu.
Whittier Hospital Medical Center, Whittier, CA
Wichita County Health Center, Leoti, KS
Wilkes Barre General Hospital, Wilkes Barre, PA
Williamette Valley Med Ctr, McMinnville, OR
Willapa Harbor Hospital, South Bend, WA
William Beaumont Hospital-Grosse Pointe, Grosse Pointe Farms, MI
William Beaumont Hospital-Royal Oak, Royal Oak, MI
William Beaumont Troy, Troy, MI
William Newton Memorial Hospital, Winfield, KS
Williamsburg Regional Hospital, Kingstree, SC
Williamson Med Ctr, Franklin, TN
Williamson Memorial Hospital, Williamson, WV
Williamsport Hospital, Williamsport, PA
Willow Creek Womens Hospital, Johnson, AR
Wilmington Hosp C.C. System, Wilmington, DE
Wilmington Surgery Center, Wilmington, NC
Wilson Medical Center, Neodesha, KS
Winchester Hospital, Winchester, MA
Winchester Medical Center Winchester, Winchester, VA
Windber Hospital & Wheeling Clinic, Windber, PA
Windham Comm Memorial Hospital, Willimantic, CT
Wing Memorial Hospital, Palmer, MA
Winona Health Services, Winona, MN
Winthrop University Hospital-Mineola, Mineola, NY
Wise Regional Medical Center, Decatur, TX
Wm Middleton Mem Veterans, Madison, WI
Woman And Children’S Hospital, Buffalo, NY
Women And Infants Hospital, Providence, RI
Women’S & Children’S Hospital, Columbia, MO
Womens Health Care Services, Wichita, KS
Womens Healthcare Associates, Santa Monica, CA
Women’S Hospital Of Greensboro, Greensboro, NC
Womens Hospital Of Texas, Houston, TX
Wood County Hospital, Bowling Green, OH
Woodland Heights Medical Center, Lufkin, TX
Woodlawn Hospital, Rochester, IN
Woodward Hospital & Health Center, Woodward, OK
Woodwinds Health Campus, Woodbury, MN
Wooster Community Hospital, Wooster, OH
Wright-Patterson Air Force Base, Wright Patterson Afb, OH
Wrmc Medical Complex Laboratory, Batesville, AR
Wvu Hospitals Inc, Morgantown, WV
Wyandot Memorial Hospital, Upper Sandusky, OH
Wyoming County Community Hosp, Warsaw, NY
Wythe County Comm Hospital, Wytheville, VA
Yakima Valley Memorial Hospital, Yakima, WA
Yale New Haven Hospital, New Haven, CT
Yale-New Haven Hospital-Chapel Campus, New Haven, CT
York General Hospital, York, NE
York Hospital, York, ME
York Hospital, York, PA
Zablocki VA Medical Center, Milwaukee, WI
Zeeland Community Hospital, Zeeland, MI

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**Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to adhere to the protocol, to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.**

- I agree
# Statement of Investigator FDA 1572 Commitments

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to personally conduct or supervise the described investigation(s). I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met. I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments. I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68. I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

- [ ] I agree
- [ ] I do not agree (this may limit participation eligibility)

---

**I attest to follow the protocol and submitting this form equates to my signature on the form**

Date of Agreement

_________________________________________
Thank you for your desire to participate in this program!

Mayo Clinic will serve as the IRB of record.

The Mayo Clinic IRB serves as the central IRB for this study in the United States at the request of the U.S. Government.

To participate, you and your hospital need to rely on the Mayo Clinic IRB for this Expanded Access Program protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the program by registering on https://USCOVIDplasma.org serves as documentation of each participating institution’s reliance on Mayo’s IRB.

A separate IRB reliance agreement is not required. The Mayo Clinic IRB is a nationally recognized IRB that is accredited by the Association for the Accreditation of Human Research Protection Programs.

Link to IRB Protocol: Protocol

Link to Consent Forms: English, Spanish, Arabic

Instructions:

You must complete this form to register as a local physician/PI including the Statement of Investigator FDA 1572, and the Patient Enrollment Form before your patient can receive convalescent plasma.

NOTE: Your site/medical center can designate one physician/PI for this Expanded Access Program OR multiple physicians/Pis can register for each site.

Information, protocol, consent forms and site registration, enrollment and followup forms are available at www.USCOVIDplasma.org.

If you have any questions or difficulties registering please email USCOVIDplasma@mayo.edu, which will be monitored from 7am-7pm CST.

Response was added on 08/14/2020 2:38pm.

Site/Medical Center Information

Select Registered Site/Medical Center

Example Site Name - City, State

If your site is not listed, click this link to fill out the site registration form.

If your site was recently registered (24hrs), select "SITE RECENTLY REGISTERED" from drop down menu.
Local Physician/PI Information

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☐ I agree
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I attest to follow the protocol and submitting this form equates to my signature on the form
4.1 Emergency Use Authorization


Today (8/23/2020), the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency’s ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum, this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.

Today’s action follows the FDA’s extensive review of the science and data generated over the past several months stemming from efforts to facilitate emergency access to convalescent plasma for patients as clinical trials to definitively demonstrate safety and efficacy remain ongoing.

The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19.

Listing of documents and links associated with the EUA:

- EUA Request 26382 Packet
  - https://www.fda.gov/media/141481/download

- EUA Decision Letter
  - https://www.fda.gov/media/141477/download

- Clinical Memorandum
  - https://www.fda.gov/media/141480/download

- EUA of COVID-19 Convalescent Plasma Fact Sheet for Health Care Providers
  - https://www.fda.gov/media/141478/download

- EUA of COVID-19 Convalescent Plasma Fact Sheet for Patients and Parents/Caregivers
  - https://www.fda.gov/media/141479/download

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For Immediate Release:
August 23, 2020

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency’s ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum, this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.

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The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19.

Alex Azar, Health and Human Services Secretary:
“The FDA’s emergency authorization for convalescent plasma is a milestone achievement in President
Trump’s efforts to save lives from COVID-19,” said Secretary Azar. “The Trump Administration
recognized the potential of convalescent plasma early on. Months ago, the FDA, BARDA, and private
partners began work on making this product available across the country while continuing to evaluate
data through clinical trials. Our work on convalescent plasma has delivered broader access to the
product than is available in any other country and reached more than 70,000 American patients so
far. We are deeply grateful to Americans who have already donated and encourage individuals who
have recovered from COVID-19 to consider donating convalescent plasma.”

Stephen M. Hahn, M.D., FDA Commissioner:
“I am committed to releasing safe and potentially helpful treatments for COVID-19 as quickly as
possible in order to save lives. We’re encouraged by the early promising data that we’ve seen about
convalescent plasma. The data from studies conducted this year shows that plasma from patients
who’ve recovered from COVID-19 has the potential to help treat those who are suffering from the
effects of getting this terrible virus,” said Dr. Hahn. “At the same time, we will continue to work with
researchers to continue randomized clinical trials to study the safety and effectiveness of convalescent
plasma in treating patients infected with the novel coronavirus.”

Scientific Evidence on Convalescent Plasma

Based on an evaluation of the EUA criteria and the totality of the available scientific evidence, the
FDA’s Center for Biologics Evaluation and Research determined that the statutory criteria for issuing
an EUA criteria were met.

The FDA determined that it is reasonable to believe that COVID-19 convalescent plasma may be
effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized
patients. The agency also determined that the known and potential benefits of the product, when used
to treat COVID-19, outweigh the known and potential risks of the product and that that there are no
adequate, approved, and available alternative treatments.

The EUA is not intended to replace randomized clinical trials and facilitating the enrollment of
patients into any of the ongoing randomized clinical trials is critically important for the definitive
demonstration of safety and efficacy of COVID-19 convalescent plasma. The FDA continues to
recommend that the designs of ongoing randomized clinical trials of COVID-19 convalescent plasma
and other therapeutic agents remain unaltered, as COVID-19 convalescent plasma does not yet
represent a new standard of care based on the current available evidence.

Terms of EUA

The EUA requires that fact sheets providing important information about using COVID-19
convalescent plasma in treating COVID-19 be made available to health care providers and patients,
including dosing instructions and potential side effects. Possible side effects of COVID-19
convalescent plasma include allergic reactions, transfusion-associated circulatory overload, and
transfusion associated lung injury, as well as the potential for transfusion-transmitted infections.
Mayo Clinic Expanded Access Program

The FDA initially facilitated access to convalescent plasma for treating COVID-19 by using pathways that included traditional clinical trials and emergency single-patient investigational new drug (IND) applications.

An Expanded Access Program for convalescent plasma was initiated in early April to fill an urgent need to provide patient access to a medical product of possible benefit during a time that the FDA was working with researchers to facilitate the initiation of randomized clinical trials to study convalescent plasma. As the number of single patient IND requests started to number in the hundreds on a daily basis, the FDA worked collaboratively with industry, academic, and government partners to implement an expanded access protocol to provide convalescent plasma to patients in need across the country via the national expanded access treatment protocol. The program was developed with funding from the HHS’ Biomedical Advanced Research and Development Authority (BARDA), with the Mayo Clinic serving as the lead institution. To date, the program has facilitated the infusion of over 70,000 patients with convalescent plasma.

The EUA was issued to the HHS Office of the Assistant Secretary for Preparedness and Response.

The EUA remains in effect until the termination of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19. The EUA may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation’s food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

###

Inquiries

**Media:**
- □ FDA Office of Media Affairs
- □ 301-796-4540

**Consumer:**
- □ 888-INFO-FDA

Content current as of:
FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement in Administration’s Fight ...
EMERGENCY USE AUTHORIZATION REQUEST FOR

CONVALESCENT PLASMA FOR THE TREATMENT OF PATIENTS WITH COVID-19

SPONSORED BY:
THE OFFICE OF THE ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

EUA 26382
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1. DESCRIPTION AND ITS INTENDED USE

1.1. Name of Product

COVID-19 convalescent plasma

1.2. Description of Product

COVID-19 convalescent plasma, an unapproved biological product, is human plasma collected by FDA registered or licensed blood establishments from individuals whose plasma contains antibodies to SARS-CoV-2. These individuals must also meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and be qualified to donate. COVID-19 convalescent plasma for use under this EUA is collected and manufactured as described in section 8 below.

1.3. Intended Use

Under this Emergency Use Authorization (EUA) request, the Office of the Assistant Secretary for Preparedness and Response (ASPR) is proposing the use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. This EUA request is based on: 1) historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, 2) certain preclinical evidence; 3) results from small clinical trials and observational studies of convalescent plasma conducted during the current outbreak; and 4) data obtained from the ongoing National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.

Data suggest that use of COVID-19 convalescent plasma with high antibody titer may be effective in reducing mortality in hospitalized patients with COVID-19. COVID-19 convalescent plasma units containing anti-SARS-CoV-2 antibodies but not qualified as High Titer COVID-19 Convalescent Plasma by the test used in its manufacture described in section 8.2 are considered Low Titer COVID-19 Convalescent Plasma and must be labeled accordingly. These units are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of patient benefit:risk. Current evidence suggests benefit is most likely in patients treated early in the course of the disease. FDA will continue to evaluate this authorized use based on additional data that become available.

Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs are needed. Convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Ongoing clinical trials of convalescent plasma should not be amended based on the issuance of the EUA. Providers are encouraged to enroll patients in those ongoing clinical trials.

2. UNMET NEED ADDRESSED BY THE EUA

On February 4, 2020, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak.

Currently, although there are only a few other products available under EUA, there are no drugs or other therapeutics approved by the FDA to prevent or treat COVID-19 infection that is affecting millions of individuals in the nation. Remdesivir and dexamethasone may have benefit
in specific populations, but the former is in limited supply at this time. Convalescent plasma has been requested for nearly 100,000 individuals as part of the National Expanded Access Treatment Protocol, indicative of the large unmet medical need for safe and effective therapeutic agents against COVID-19.

3. APPROVAL/CLEARANCE STATUS
FDA has not approved COVID-19 convalescent plasma for any indication.

4. MANUFACTURING SITE/CGMP STATUS
COVID-19 convalescent plasma under this EUA will be obtained from FDA-registered or licensed blood establishments that collect plasma for transfusion according to the blood donor eligibility criteria and donor qualifications described at 21 CFR 630.10 and 21 CFR 630.15. Section 8 details the manufacturing process for the product.

5. ADEQUATE, APPROVED AND ALTERNATIVE PRODUCTS
There are no drugs or other therapeutics approved by the FDA to prevent or treat COVID-19.

6. SAFETY AND EFFICACY INFORMATION
The sponsor has pointed to four lines of evidence in support of the potential effectiveness of COVID-19 convalescent plasma in the treatment of hospitalized patients with COVID-19: 1) the history of convalescent plasma for respiratory coronaviruses, 2) evidence of preclinical safety and efficacy in animal models, 3) recently published studies of the safety and efficacy of COVID-19 convalescent plasma, and 4) data on safety and efficacy from the U.S. EAP.

6.1. History of Convalescent Plasma in Prior Outbreaks

Published Studies of Convalescent Plasma for Respiratory Infections
A systematic review of passive antibody therapy for SARS coronavirus and severe influenza found a trend towards reduction in mortality, but noted that studies were commonly of low or very low quality, lacked control groups, and were at risk of bias.

An uncontrolled study involved the treatment of 80 patients in Hong Kong with SARS-CoV-1. A higher day-22 discharge rate was observed among patients who were given convalescent plasma before day 14 of illness (58.3% vs 15.6%; P<0.001) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; P=0.001). A small retrospective nonrandomized study of patients with progressive SARS after ribavirin and pulse methylprednisolone treatment, the plasma-treated group had a shorter hospital stay and lower mortality than the group that continued treatment with pulse methylprednisolone. These reports followed a single case report of successful convalescent plasma therapy in a 57-year-old woman with SARS in Hong Kong. A case series of three patients with SARS in Taiwan were treated with convalescent plasma, resulting in a reduction in viral load; all three
recipients survived. Treatment with convalescent plasma use was also reported in three patients in South Korea with MERS, but researchers found only a subset of convalescent plasma showed neutralizing activity. A group in Saudi Arabia reported on the feasibility of collecting convalescent plasma for passive immunotherapy of Middle East respiratory syndrome coronavirus (MERS-CoV) infection by using ELISA to screen serum samples from 443 potential plasma donors. They found only a small subset (9 patients) showed neutralization activity and concluded trials would be challenging because of the small pool of donors with sufficiently high titers.

6.2. Preclinical Safety and Efficacy

SARS-CoV-2 replicates efficiently in the lungs of Syrian hamsters and causes severe pathological lesions in the lungs of these animals following intranasal SARS-CoV-2 infection. Micro-CT analysis revealed that severe lung injury occurs in infected hamsters and that the severity of the lung abnormalities is related to the degree of infectious dose. Commonly reported imaging features of COVID-19 patients with pneumonia such as severe, bilateral, peripherally distributed, multilobular ground glass opacity, and regions of lung consolidation were present in all infected animals but not in mock-infected control animals. Computational modeling suggests that ACE2 from Chinese hamster could interact with the S glycoprotein of SARS-CoV-2. SARS-CoV-2–infected hamsters mounted neutralizing antibody responses and were protected against subsequent rechallenge with SARS-CoV-2. Postinfection sera were collected from hamsters that had been infected with the high or low dose of virus and then pooled. The pooled serum was then transferred intraperitoneally to three hamsters on day 1 or 2 after infection with $10^3$ PFU of the virus. Normal uninfected hamster serum was injected intraperitoneally into three naïve hamsters as a control. Virus titers in the nasal turbinates and lungs of the animals that received postinfection serum on day 1 postinfection were statistically significantly lower than the virus titers in those organs of animals that received normal serum at the corresponding time point postinfection. Viral titers trended lower in animals administered convalescent plasma on day 2 after infection. These data suggest that earlier administration of convalescent plasma is more effective than later administration.

Mice are resistant to SARS-CoV-2. Providing hACE2 by adenovirus transduction leads to expression of the encoded protein and sensitizes a broad range of immunocompetent and immunodeficient mice for SARS-CoV-2 infection without development of severe disease or extrapulmonary manifestations of disease. When 6- to 8-week-old BALB/c mice were transduced intranasally with $2.5 \times 10^8$ PFU Ad5-hACE2, hACE2 expression was observed predominantly in the alveolar epithelium and in occasional airway epithelial cells. Control mice received an Ad5-empty vector. Five days after transduction, mice received $1 \times 10^5$ PFU of SARS-CoV-2 and were monitored over a 10-day time course. Ad5-hACE2 transduced BALB/c mice infected with SARS-CoV-2 showed ruffled fur, hunching, and difficulty breathing beginning 2 days post infection (d.p.i.). The mice lost up to 20% of their body weight in the first 4–6 days of infection, and virus grew to high titers in lung tissue and gradually declined over the course of the infection. Robust viral antigen was detected in the lungs of mice transduced with Ad5-hACE2 but not Ad5-empty control. Lung tissues demonstrated a variety of lesions including perivascular to interstitial inflammatory cell infiltrates, necrotic cell debris, and alveolar edema. Gross lung specimens from infected Ad5-hACE2-transduced mice revealed increased vascular congestion and hemorrhage, with the most severe changes observed at 5 d.p.i. In experiments of adoptive
plasma transfer, Ad5-hACE2-transduced mice were injected with 150 μL of plasma i.v. from a healthy donor or COVID-19, MERS, or SARS convalescent patients one day prior to infection. Weight and virus titers in lung tissues were monitored and expressed as FFU/g tissue (n = 4 mice per group per time point). Pooled plasma from 3 patients who recovered from SARS-CoV-2 infection (FRNT50 titer = 1:1,000) as well as plasma from a healthy donor, 3 SARS survivors (PRNT50 titer against SARS-CoV = 1:140), and 2 MERS convalescent patients (FRNT50 titer against MERS-CoV = 1:2,183) were evaluated. Administration of 150 μL of SARS-CoV-2 plasma one day prior to SARS-CoV-2 infection prevented weight loss and lung tissue histological changes, and accelerated the rate of virus clearance. More rapid clearance was not observed after treatment with pooled plasma from SARS-CoV-1 survivors or MERS survivors.2

6.3. Clinical Trials Conducted Using COVID-19 Convalescent Plasma

Early data on the use of convalescent plasma came in the form of two case series from the initial outbreak in China10 11. These studies in patients with very severe illness found that patients showed improved viral load, symptoms, and radiographic findings. The case series studies suggested COVID-19 Convalescent Plasma may be helpful but were limited by their small size and lack of controls. A large number of clinical trials have been initiated, but most have not yet reported results. Available data generally fall into one of four categories: randomized controlled trials, controlled trials based on availability of plasma but not truly randomized, retrospective matched cohorts (e.g., propensity score matched), and case series. Several reports remain in pre-print status and have not been peer-reviewed at the time of this submission.

Randomized controlled trials

The two randomized controlled trials reported to date were both stopped early, resulting in trials that may have been underpowered to detect clinically meaningful differences. The first study by Li et al. in Wuhan, China12, was in patients with severe to life-threatening COVID-19 who were transfused with 4-13 mL/kg COVID-19 Convalescent Plasma with ELISA titer >1:640. The primary outcome was time to clinical improvement within 28 days and the study found clinical improvement in 27/52 (51.9%) in the COVID-19 Convalescent Plasma arm, and 22/51 (43.1%) in the control arm (p=0.26). When examining subgroups by disease severity they found that in severe disease 21/23 (91.3%) in the COVID-19 Convalescent Plasma arm and 15/22 (68.2%) in the control arm [p=0.03] showed clinical improvement. In life-threatening disease, 6/29 (20.7%) in COVID-19 Convalescent Plasma and 7/29 (24.1%) in control (p=0.83) showed clinical improvement. However, there was a non-significant test for interaction (p=0.17), so the results in the subgroups should not be interpreted differently. Of note, the median duration of symptoms at the time of transfusion was 30 days. The study was stopped early due to low enrollment as a result of improved case rates in the Wuhan region.

The second RCT by Gharbharan et al. in the Netherlands13 examined patients with clinical COVID-19 as determined by a positive test in the previous 96 hours (most patients met criteria for severe disease, median of 10 days of symptoms at transfusion) who were treated with 300 mL of plasma with a neutralization titer of at least 1:80. The primary outcome was overall mortality until discharge. The trial was stopped early because they observed that antibody titers in the recipients were already high at the time of transfusion, and therefore, they made a decision to halt and redesign the trial because the presumed benefit would be in patients earlier in disease. At the time of study stopping, 6 of 43 COVID-19 Convalescent Plasma patients (14%) had died.
and 11 of 43 control patients (26%) had died. The prespecified comparison of adjusted mortality showed no difference (aOR 0.95 [0.2-4.67]), but the study was underpowered to detect clinically meaningful differences at study stopping.

**Controlled trials**

In addition to the randomized controlled trials, two studies from the Middle East\(^1\) \(^4\) \(^5\) reported prospective trials in which the control patients were those who were not transfused due to a lack of plasma availability\(^1\) \(^4\) or “As a result of ABO compatibility and limited plasma…randomly chosen to take CP”\(^1\)\(^5\).

The study by Rasheed et al\(^1\)\(^5\) examined COVID-19 Convalescent Plasma transfusion in patients admitted to the ICU for less than 3 days (mean of 14-16 days of symptoms) and found that 1 of 21 COVID-19 Convalescent Plasma patients (4.8%) died within the observation period, and 8 of 28 (28.6%) control patients died within the observation period, with only one patient experiencing a mild allergic reaction. This study is limited by the lack of formal reporting of statistical approaches.

A study by Abolghasemi et al\(^1\)\(^4\) likewise compared COVID-19 Convalescent Plasma transfused patients to controls who were not transfused due to plasma availability within 3 days of enrollment. Patients had severe disease and were enrolled if they were within 7 days of illness onset. Patients were transfused with 500-1000 mL of plasma confirmed anti-SARS-CoV-2 by semi-quantitative ELISA. The primary outcomes were described as survival and hospital length of stay. All-cause mortality was 17/115 (14.8%) in the COVID-19 Convalescent Plasma arm versus 18/74 (24.3%) in the control arm [p=0.09]. The mean hospital length of stay was 9.5 days in COVID-19 Convalescent Plasma arm versus 12.9 in the control [p=0.002]. 107 (93%) COVID-19 Convalescent Plasma patients were discharged versus 59 (79.7%) in the control [p=0.006].

These studies provide encouraging signs of effectiveness but are limited due to their nonrandomized design, and in the case of Rasheed et al\(^1\)\(^5\), low quality of the methods and report.

**Retrospective matched cohort studies**

Several reports of retrospective matched cohort studies of COVID-19 Convalescent Plasma have been made publicly available\(^1\)\(^6\) \(^7\) \(^8\).

In severe to life-threatening COVID-19 Liu et al\(^1\)\(^8\) found that convalescent plasma transfusion was significantly associated with improved survival in non-intubated patients (hazard ratios: 0.19 (95% CI: 0.05 ~0.72); p=0.015), but not in intubated patients. Convalescent plasma recipients were more likely than controls to remain the same or have improvements in supplemental oxygen requirements at day 14 (OR 0.86, p =0.028).

Using a propensity score matching algorithm, Salazar et al\(^1\)\(^6\) found 28-day mortality was 3.7% in 136 COVID-19 Convalescent Plasma transfused subjects with severe COVID-19 versus 7.6% in 543 non-transfused controls, although the difference was not significant in the overall population (p=0.13). In those transfused within 72 hours of admission and with high-titer units, there was a significant difference in 28-day mortality (1.2% in COVID-19 Convalescent Plasma vs 7.0% in control). The authors concluded that transfusion of high anti-RBD IgG titer COVID-19 convalescent plasma early in hospitalization reduces mortality.
In smaller studies, Perotti et al and Hegerova et al found similar trends toward benefit but noted that trends would need confirmation in well-controlled randomized trials.\(^\text{17} 19\).

**Case Series**

Several investigators have reported case series ranging in size from 5 to 20,000 patients and across several countries \(^\text{10} 11 20 21 22 23\). This includes the early reports described above in the early pandemic in China.\(^\text{10} 11\). The largest series are those reported out of the Expanded Access Program by Joyner et al.\(^\text{21} 22\). These data demonstrated a low rate of adverse events observed with COVID-19 Convalescent Plasma transfusion, with 7-day mortality rate of 8.6% overall (12.1% in non-ventilated subjects, 6.2% in ventilated subjects). The authors concluded that COVID-19 Convalescent Plasma is safe in hospitalized patients with COVID-19. Additional case series similarly showed that most patients improved following COVID-19 Convalescent Plasma but were of limited interpretability in the absence of controls.\(^\text{20 23 24}\)

### 6.4. Clinical Safety and Efficacy

**Protocol 20-003312, Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19**

The National Expanded Access Treatment Protocol, sponsored by the Mayo Clinic, was initiated in early April 2020 to provide broad access to convalescent plasma. This expanded access program provided access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who had severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. The protocol had a single arm with sites across the US. COVID-19 convalescent plasma was obtained from the American Red Cross or America’s Blood Centers. The study design included capture of demographics and endpoints of safety, 7-day- and 30-day survival. As a tertiary objective exploring efficacy, dose response by titer or the plasma administered was explored.

**Objective**

The primary objective of the expanded access program was to make COVID-19 convalescent plasma broadly available. The secondary objective was to assess the safety of patient transfusion with COVID-19 convalescent plasma. Tertiary endpoints included the assessment of healthcare outcomes at 7 and 28 days after treatment as well as the retrospective determination of COVID-19 neutralizing antibody titers in transfused units and their correlation with clinical outcomes.

**Patients and Methods**

As of August 4, 2020, there were 85,719 patients enrolled and 56,472 patients reported to have been treated at 2738 clinical sites enrolled in the EAP located across all 50 states and the District of Columbia. For the purposes of the safety analysis, a convenience sample drawn from 20,000 consecutive patients enrolled in the EAP from April 3 to June 2, 2020, was used. Exploratory efficacy analyses correlating neutralizing antibody titers to observed clinical outcomes have been undertaken on 4330 patients administered convalescent plasma. Different assays were used for determination of these antibodies, including the 1) Mayo Clinic pseudovirus neutralization assay, 2) Ortho VITROS total IgG assay, and 3) Broad Institute SARS-CoV-2 neutralization assay.

**Results**
Demographic data showed that recipients were broadly representative of the US population in terms of race and ethnicity. Disease severity and concomitant medications changed over time with enrollment of less sick patients as the pandemic progressed over time and with reduced use of hydroxychloroquine/azithromycin and increased use of remdesivir and steroids at later times.

**Safety**

Safety data are presented for a convenience sample of 20,000 recipients. The incidence of all serious adverse events was low; these included transfusion reactions (n=89; <1%), thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680; -3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were judged to be unrelated to the convalescent plasma transfusion per se. The seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).

Overall mortality was higher in patients admitted to ICU (10.48%; 95% CI 9.99%, 11.06%) than in patients not admitted to ICU (6.02%; 95% CI, 5.53%, 6.55%), and in patients with mechanical ventilation (12.10%; 95% CI, 11.32%, 12.93%) than in those not on mechanical ventilation (6.17%; 95% CI, 5.75, 6.61%).

**Efficacy**

Survival and 7-day mortality were evaluated according to neutralizing antibody titers assessed by various methodologies, including a pseudovirus neutralization assay developed at the Mayo Clinic, a commercial assay from Ortho Diagnostics (Ortho VITROS total IgG) and a SARS-CoV-2 BSL-3 neutralization assay developed at the Broad Institute. Data demonstrating the correlation between these assays are provided in Figure 1. Based on the available evidence, it was determined that the Broad Institute titers would serve as the reference standard for diagnostic accuracy to which the others would be compared. Note that while these assays generally correlated with each other, precise performance characteristics based on a reference panel or gold-standard methodology (plaque reduction neutralization titer) were not available at the time of this determination.

Using the Broad neutralization titers with a cutoff value of an ID\textsubscript{50} of 250, which corresponds to an Ortho VITROS IgG S/C level of 12 as determined by a cross-laboratory titer comparison study, there was no difference in 7-day survival noted in the overall population of treated patients, nor was there any difference in this parameter for the pre-specified subset of patients who were intubated at the time of treatment. However, in the prespecified subset of patients who were not intubated at the time of treatment (approximately 2/3 of those analyzed), comparing patients treated with plasma with a neutralizing antibody titer greater than an ID\textsubscript{50} of 250 to those patients treated with lower titers there was a 21% reduction in 7-day mortality from 14% to 11% (p=.03).
Figure 1: Comparison of Assay Performance

The Broad ID50 was determined using a BSL-3 neutralization assay, the Mayo Titer level was obtained using a pseudo-neutralization assay, and the Ortho IgG was determined using the Ortho Vitros IgG antibody assay.

Additionally, in a subset analysis that was not included in the original analysis plan, those patients not intubated at the time of treatment, less than 80 years of age, who were treated within 72 hours of diagnosis, comparing those treated with plasma with a neutralizing antibody titer greater than an ID50 of 250 to those patients treated with lower titers there was a 45% reduction in 7-day mortality from 11.3% to 6.3% (p=0.008)

In additional analyses of survival using a Kaplan-Meier approach, the survival trends observed at 7 days persisted over a longer time period, with significantly improved survival in non-intubated patients (Figure 2, p=0.032) and a larger benefit in the subset of patients not intubated at the time of treatment, less than 80 years of age, who were treated within 72 hours of diagnosis (Figure 3, p=0.0081)
Figure 2: Kaplan-Meier plot of survival following the administration of convalescent plasma in patients not on ventilators.

Figure 3: Kaplan-Meier plot of survival following the administration of convalescent plasma in patients in the subset of patients not on ventilators, less than 80 years of age who received plasma within 3 days of diagnosis.

Additional analyses of data from the EAP were posted publicly by Mayo Clinic investigators and collaborators. In their analyses, the investigators observed an association between reductions in adjusted 7-day and 30-day mortality and earlier transfusion (<=3 days) of COVID-19 Convalescent Plasma and high antibody levels. Antibodies were measured using the Ortho VITROS IgG assay. Low, medium, and high antibody levels were defined as <4.62, 4.62-18.45, and >18.45 (S/C ratio), respectively.27
Conclusion
These data provide evidence to support the conclusion that transfusion of convalescent plasma to treat hospitalized patients with COVID-19 meets the “may be effective” criterion for issuance of an EUA. The data are consistent with earlier findings suggesting that administration of convalescent plasma to hospitalized patients, particularly with units containing higher titers of SARS-CoV-2 antibodies, and early on during the disease course, may be effective in reducing mortality in hospitalized patients with COVID-19.

7. POTENTIAL RISKS AND BENEFITS

7.1. Risk-Benefit Assessment

7.1.1. Risks
Known risks associated with plasma transfusion include transfusion-transmitted infections (e.g. HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and posttransfusion purpura have also been described.

FDA guidance issued April 2020 and updated on May 1, 2020 indicate that the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information. FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.25

A theoretical risk of administration of convalescent plasma is the phenomenon of antibody-dependent enhancement of infection (ADE). ADE has been described in other viral infections, such as dengue, and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms of ADE have been proposed, including the theoretical concern that antibodies to one type of coronavirus could enhance infection to another strain. Preparations with high titers of antibody against the same virus strain are thought to be less likely to cause ADE.

Another theoretical risk is that antibody administration may attenuate the immune response and make patients more susceptible to re-infection. There are no such reports in the literature at this time.

7.1.2. Benefits
COVID-19 is a serious and potentially fatal or life-threatening human disease. The potential benefits of COVID-19 convalescent plasma therapy could include improvement in symptoms, reduced need for supplemental oxygen and mechanical ventilation, and possibly reduced mortality. Data suggest that use of COVID-19 convalescent plasma with high antibody titers is more likely to be effective in reducing mortality in hospitalized patients with COVID-19, the use of low titer units also may be effective. Current evidence suggests benefit is most likely in patients treated early in the course of the disease. Units containing anti-SARS-CoV-2 IgG
antibodies but not qualified as High Titer COVID-19 Convalescent Plasma by a test found acceptable for this purpose as part of the manufacture of COVID-19 Convalescent Plasma by FDA (see section 8.1), are considered Low Titer COVID-19 Convalescent Plasma units and are authorized for use and will be labeled as “Low Titer.” Health care providers can decide whether to use such units based on an individualized assessment of patient benefit/risk.

7.1.3. Risk-Benefit Assessment
Based on the totality of scientific evidence available at this time, it is reasonable to conclude that the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks.

Information derived from ongoing clinical trials of COVID-19 convalescent plasma, particularly randomized, controlled trials, as well as clinical trial results from studies of other investigational medical products to treat COVID-19, will continue to inform this risk benefit assessment.26

7.2. Contraindications
COVID-19 convalescent plasma may be contraindicated in patients with a history of severe allergic reactions or anaphylaxis to plasma transfusion.

7.3. Use in Specific Populations

Pediatric
The safety and effectiveness of COVID-19 Convalescent Plasma has not been evaluated in pediatric patients. The decision to treat patients <18 years of age with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

Geriatric
In the ongoing National Expanded Access Treatment Protocol sponsored by the Mayo Clinic, 56,472 patients were treated as of August 5, 2020. Preliminary analyses of the first 20,000 patients indicated that 5,423 (27.1%) were 60-69 years of age, 4,114 (20.6%) were 70-79 years of age, and 2,568 (12.8%) were 80 year of age or older. Although adverse event rates in the geriatric subgroup have not yet been provided, the rates in the overall population for the individual events of mortality within 4 hours, transfusion-associated circulatory overload (TACO), Transfusion related acute lung injury (TRALI), severe allergic transfusion reaction, thrombotic/thromboembolic complication, sustained hypotension, and cardiac events were ≤ 0.37%.

Pregnancy
The safety and effectiveness of COVID-19 convalescent plasma in pregnancy has not been evaluated. It should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. The decision to treat pregnant women with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

Nursing Mothers
It is not known whether or not transfused anti-SARS-CoV-2 antibodies are excreted in human milk. The safety and effectiveness of COVID-19 convalescent plasma in nursing mothers has not
been evaluated. The decision to treat nursing mothers with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

8. CHEMISTRY, MANUFACTURING, AND CONTROLS

The manufacture of COVID-19 Convalescent Plasma requires qualification of the donor and assessment of the donated plasma for appropriate antibody titers.

8.1. Donor Eligibility and Donation Suitability

a. COVID-19 convalescent plasma must only be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15). Note the additional donor eligibility requirements for the collection of plasma by plasmapheresis in 21 CFR 630.15(b). Donation testing for relevant transfusion-transmitted infections must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

b. COVID-19 convalescent plasma must be collected from individuals who meet the following qualifications:

- Evidence of COVID-19 documented by an FDA-authorized diagnostic test (e.g., nasopharyngeal swab) at the time of illness, or

  Individuals who did not have a prior diagnostic test and/or never had symptoms of COVID-19 may be qualified to donate if they have reactive (positive) results in two different tests authorized by FDA to detect SARS-CoV-2 IgG antibodies

- Complete resolution of symptoms (if present) at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.

- Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

8.2. SARS-CoV-2 Antibody Testing

a. Plasma donations should be tested for SARS-CoV-2 IgG antibodies as a manufacturing step to determine suitability before release. Units tested by the Ortho VITROS SARS-CoV-2 IgG test and found to have a signal-to-cutoff (S/C) ratio of 12 or greater qualify as High Titer COVID-19 Convalescent Plasma. If a blood establishment is considering using an alternative testing assay in manufacturing in order to qualify High Titer COVID-19 Convalescent Plasma, it should contact CBER to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA.
b. Units containing anti-SARS-CoV-2 antibodies but not qualified as High Titer COVID-19 Convalescent Plasma by the test described above, are considered Low Titer COVID-19 Convalescent Plasma units and must be labeled accordingly. These units are authorized for use. Healthcare providers can decide whether to use such units based on an individualized assessment of benefit:risk. FDA will continue to evaluate this authorized use based on additional data that become available.

8.3. **Other Considerations**

Blood establishments should be aware of the following considerations:

- a. Registered-only or licensed blood establishments that collect plasma intended for transfusion do not need to request a supplement to their license to collect and manufacture COVID-19 convalescent plasma for the authorized use provided they 1) follow their standard operating procedures for plasma collection and all applicable regulations, and 2) collect plasma from individuals that meet the donor qualifications specified above.

- b. Once manufactured, COVID-19 convalescent plasma may be distributed for use under the EUA.

- c. Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.120(a) to collect COVID-19 convalescent plasma.

8.4. **Labeling**

The requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.

- a. FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.


- c. The manufacturing process used and the expiration date on the label for COVID-19 convalescent plasma should be the same as for other plasma products that are of the same type. For example, COVID-19 Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection, stored at -18°C or colder and have an expiration date one year from the date of collection.

- d. Convalescent plasma units should be clearly labeled, based on the test results that are used as part of manufacturing, as being High Titer COVID-19 Convalescent Plasma or Low Titer Convalescent Plasma based on the level of SARS-CoV-2 antibodies.

- e. Convalescent plasma container label must not indicate a license number.
9. FACT SHEET FOR HEALTHCARE PROVIDERS

Refer to Attachment 1.

10. FACT SHEET FOR RECIPIENTS

Refer to Attachment 2

11. PROGRAM SCHEMA

COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States or its territories in accordance with applicable regulations, policies and procedures. Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable (21 CFR 630.30). Units of COVID-19 convalescent plasma under this EUA will be documented to contain antibodies to SARS-CoV-2 and labeled according to Section 8.4.

12. INSTRUCTIONS FOR USE

12.1. Dosage of COVID-19 Convalescent Plasma

Health care providers will administer COVID-19 convalescent plasma with neutralizing SARS-CoV-2 according to standard hospital procedures and institutional medical and nursing practices. Clinical dosing may first consider starting with one convalescent plasma unit (about 200 mL), with administration of additional convalescent plasma units based on the prescribing physician’s medical judgement and patient’s clinical response. Patients with impaired cardiac function and heart failure may require a smaller volume or more prolonged transfusion times.

12.2. Administration of COVID-19 Convalescent Plasma

Health care providers will administer COVID-19 convalescent plasma infusion through a peripheral or central venous catheter according to standard institutional medical and nursing practices for the administration of plasma. (http://www.aabb.org/tm/coi/Documents/coi1017.pdf)

12.3. Storage and Packaging

COVID-19 Convalescent Plasma, may be stored frozen at -18C or colder, and has an expiration date one year from the date of collection. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.
13. **ADVERSE EVENT MONITORING**

Healthcare Providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required blood or blood components under 21 CFR 606.170.

14. **LABELING**

Please refer to Attachment 2 for additional patient information that will be provided to recipients.

15. **RECORD KEEPING, REPORTING, AND RECORD ACCESS BY FDA**

Record keeping, reporting and record access must be maintained per 21 CFR 606.100.
16. REFERENCES

1. Imai, M et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. PNAS | July 14, 2020 | vol. 117 | no. 28 | 16587–16595


August 23, 2020

Robert P. Kadlec, MD, MTM&H, MS
Assistant Secretary for Preparedness and Response
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Dear Dr. Kadlec:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with Coronavirus Disease 2019 (COVID-19), as described in the Scope of Authorization (Section II) of this letter, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19 (the virus was later named SARS-CoV-2).1 On March 27, 2020, on the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act, subject to the terms of any authorization issued under that section.2

COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. It is an investigational product and is not currently approved or licensed for any indication. Based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the ongoing National Convalescent Plasma Expanded Access Protocol (EAP)

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sponsored by the Mayo Clinic,\(^3\) it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks of the drug for the treatment of patients hospitalized with COVID-19.\(^4\)

Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of disease. COVID-19 convalescent plasma units containing antibodies to SARS-CoV-2 but not qualified as high-titer by a test found acceptable for this purpose by FDA (see Section II) are considered Low Titer units and are acceptable for use based on an individualized assessment of patient benefit-risk. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of COVID-19 convalescent plasma efficacy and to determine the optimal product attributes and appropriate patient populations for its use. Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs are needed. COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Additional data will be forthcoming from other analyses and ongoing, well-controlled clinical trials in the coming months. These ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on the issuance of this EUA; providers are encouraged to enroll patients in those trials.

Having concluded that the criteria for issuance of this authorization under 564(c) of the Act are met, I am authorizing the emergency use of COVID-19 convalescent plasma for treatment of hospitalized patients with COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. **Criteria for Issuance of Authorization**

I have concluded that the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19 when administered as described in the Scope of Authorization (Section II) meet the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause COVID-19, a serious or life-threatening disease or condition, including severe respiratory illness, in humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that COVID-19 convalescent plasma may be effective in treating COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of COVID-19 convalescent plasma when used to treat COVID-19 outweigh the known and potential risks of such products; and

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\(^3\) A national expanded access protocol (EAP) sponsored by the Mayo Clinic was established in April 2020 and has enrolled >90,000 subjects as of August 13, 2020. The goal of this uncontrolled, single-arm study is to provide access to COVID-19 convalescent plasma in hospitalized subjects with severe or life-threatening COVID-19 or judged by the treating provider to be at high risk of progression to severe or life-threatening disease.

\(^4\) Information derived from ongoing clinical trials of COVID-19 convalescent plasma (particularly randomized controlled trials), as well as clinical trial results from studies of other investigational medical products to treat COVID-19, will continue to inform the risk-benefit assessment for this EUA.
3. There is no adequate, approved, and available alternative to the emergency use of COVID-19 convalescent plasma for the treatment of COVID-19.5

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The emergency use of the authorized COVID-19 convalescent plasma under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below.

The Authorized COVID-19 Convalescent Plasma (Product Description):

I am authorizing the use of COVID-19 convalescent plasma, a biologic product to be used for the treatment of hospitalized patients with COVID-19.

COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains SARS-CoV-2 antibodies and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. Under this EUA, authorized COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States or its territories in accordance with applicable regulations, policies, and procedures. Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable (21 CFR 630.30).

Plasma donations must be tested by registered or licensed blood establishments for anti-SARS-CoV-2 antibodies as a manufacturing step to determine suitability before release. Units tested by the Ortho VITROS SARS-CoV-2 IgG test and found to have a signal-to-cutoff (S/C) value of 12 or greater qualify as high titer COVID-19 convalescent plasma. If a blood establishment is considering using an alternative test in manufacturing in order to qualify high titer COVID-19 convalescent plasma, they should contact the FDA Center for Biologics Evaluation and Research (CBER) to determine acceptability of the proposed test, which if accepted, would require an amendment to this EUA.

Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by the test described above are considered low titer units and must be labeled accordingly. The health care provider may assess whether units with a S/C value of less than 12 are acceptable for use based on an individualized assessment of benefit-risk. FDA will continue to evaluate this recommendation based on additional data that become available.

Health care providers will administer the authorized COVID-19 convalescent plasma with anti-SARS-CoV-2 antibodies according to standard hospital procedures and institutional medical and nursing practices. Clinical dosing may first consider starting with one COVID-19 convalescent plasma unit (about 200 mL), with administration of additional COVID-19 convalescent plasma units based on the prescribing physician’s medical judgment and the patient’s clinical response.

5 No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
COVID-19 convalescent plasma is authorized to be accompanied by the following product-specific information pertaining to emergency use, which is required to be made available to health care providers and patients respectively:


Changes to the authorized Fact Sheets may be requested by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and are authorized to be made in consultation with, and with concurrence of, the Office of Blood Research and Review (OBRR)/Center for Biologics Evaluation and Research (CBER), Counterterrorism Office (CT)/Office of the Center Director (OD)/CBER, and Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC), as appropriate.

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma, when used for the treatment of hospitalized patients with COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that COVID-19 convalescent plasma may be effective for the treatment of hospitalized patients with COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that COVID-19 convalescent plasma (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS’s determination under Section 564(b)(1)(C) described above and the Secretary of HHS’s corresponding declaration under Section 564(b)(1), COVID-19 convalescent plasma is authorized for the treatment of hospitalized patients with COVID-19 as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization
Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

**ASPR**

A. ASPR will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, registered or licensed blood establishments, hospitals, health care providers) involved in distributing or receiving authorized COVID-19 convalescent plasma. ASPR will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

B. ASPR may request changes to this authorization, and such changes may be permitted without amendment of this EUA upon concurrence of OBRR/CBER, CT/OD/CBER, and OCET/OCS/OC.

C. ASPR may request changes to the authorized Fact Sheets for COVID-19 convalescent plasma, and such changes may be permitted without amendment of this EUA upon concurrence of OBRR/CBER, CT/OD/CBER, and OCET/OCS/OC.

D. ASPR will report to FDA serious adverse events and all medication errors associated with the use of the authorized COVID-19 convalescent plasma that are reported to ASPR, or of which ASPR otherwise becomes aware, during the pandemic.

E. ASPR will make available to FDA upon request any records maintained in connection with this EUA.

**Registered or Licensed Blood Establishments**

F. Registered or licensed blood establishments will ensure that the authorized COVID-19 convalescent plasma, accompanied with the authorized labeling (i.e., Fact Sheets), is distributed to hospitals consistent with the terms of this letter, and that such hospitals are aware of the letter of authorization.

G. Registered or licensed blood establishments will ensure that appropriate storage and cold chain is maintained. The authorized COVID-19 convalescent plasma should be frozen after collection and stored at -18°C or colder. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.

H. Through a process of inventory control, registered or licensed blood establishments will maintain records regarding distribution of the authorized COVID-19 convalescent plasma (i.e., donor records, quantity, receiving site, receipt date).

I. Registered or licensed blood establishments will make available to FDA upon request any records maintained in connection with this EUA.
Hospitals to Whom the Authorized COVID-19 Convalescent Plasma Is Distributed, and Health Care Providers Administering the Authorized COVID-19 Convalescent Plasma

J. Hospitals and health care providers receiving authorized COVID-19 convalescent plasma will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to health care providers and to patients and caregivers, respectively, through appropriate means.

K. The authorized COVID-19 convalescent plasma must be stored frozen at -18°C or colder. Once thawed and refrigerated, the authorized COVID-19 convalescent plasma must be used within 5 days for patient transfusion.

L. Hospitals and health care providers administering COVID-19 convalescent plasma will track serious adverse events that are considered to be potentially attributable to COVID-19 convalescent plasma use and must report these to FDA in accordance with the Fact Sheet for Health Care Providers. Health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required under 21 CFR 606.170.

M. Through a process of inventory control, hospitals will maintain records regarding the administered authorized COVID-19 convalescent plasma (e.g., donation identification number, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

N. Hospitals will ensure that any records associated with this EUA are maintained until notified by ASPR and/or FDA. Such records will be made available to ASPR, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

O. All descriptive printed matter, including advertising and promotional material, relating to the use of the authorized COVID-19 convalescent plasma shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

P. No descriptive printed matter, including advertising or promotional material, relating to the use of COVID-19 convalescent plasma may represent or suggest that such product is safe or effective.

Q. All descriptive printed matter, including advertising and promotional material, relating to the use of COVID-19 convalescent plasma clearly and conspicuously shall state that:
• COVID-19 convalescent plasma has not been approved or licensed by FDA;

• COVID-19 convalescent plasma has been authorized by FDA under an EUA;

• COVID-19 convalescent plasma is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

/S/

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures
CLINICAL MEMORANDUM

From: (b) (6), OBRR/DBCD/CRS
To: (b) (6), OBRR
Through: (b) (6), OBRR/DBCD
(b) (6), OBRR/DBCD
(b) (6), OBRR/DBCD/CRS

Re: EUA 26382: Emergency Use Authorization (EUA) Request (original request 8/12/20; amended request 8/23/20)

Product: COVID-19 Convalescent Plasma

Items reviewed: EUA request
Fact Sheet for Health Care Providers
Fact Sheet for Recipients

Sponsor: Robert Kadlec, M.D.
Assistant Secretary for Preparedness and Response (ASPR)
Office of Assistant Secretary for Preparedness and Response (ASPR)
U.S. Department of Health and Human Services (HHS)

EXECUTIVE SUMMARY

COVID-19 Convalescent Plasma (CCP), an unapproved biological product, is proposed for use under an Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act), (21 USC 360bbb-3) as a passive immune therapy for the treatment of hospitalized patients with COVID-19, a serious or life-threatening disease. There currently is no adequate, approved, and available alternative to CCP for treating COVID-19. The sponsor has pointed to four lines of evidence to support that CCP may be effective in the treatment of hospitalized patients with COVID-19: 1) History of convalescent plasma for respiratory coronaviruses; 2) Evidence of preclinical safety and efficacy in animal models; 3) Published studies of the safety and efficacy of CCP; and 4) Data on safety and efficacy from the National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.

Considering the totality of the scientific evidence presented in the EUA, I conclude that current data for the use of CCP in adult hospitalized patients with COVID-19 supports the conclusion that CCP meets the “may be effective” criterion for issuance of an EUA from section 564(c)(2)(A) of the Act. It is reasonable to conclude that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA. Current data suggest the largest clinical benefit is associated with high-titer units of CCP administered early in the
course of disease. Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and appropriate patient populations for its use.

**Recommendation**: CCP meets the eligibility criteria for EUA under section 564 of the Act.

**Introduction and Background**

**SARS-CoV-2 and COVID-19**

The novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), identified in December 2019, causes a respiratory illness known as COVID-19. Clinical manifestations of COVID-19 range from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death[1, 2]. The World Health Organization declared COVID-19 a global pandemic on March 11, 2020 and the virus has caused more than 5,000,000 cases and more than 170,000 deaths in the United States as of August 20, 2020.

Frequently reported symptoms in COVID-19 include fever, cough, shortness of breath, myalgia or fatigue, loss of taste or smell, headache, and gastrointestinal symptoms ([https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html)). Severe disease can result in acute respiratory distress syndrome (ARDS), sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and thromboembolic events. Early reports from the outbreak[3] demonstrated that 81% of cases resulted in mild disease (non-pneumonia, or mild pneumonia). 14% of cases resulted in severe disease (dyspnea, RR>30, SpO2<93, PaO2/FiO2<300, lung infiltrates) and 5% resulted in critical illness. Risk factors for severe illness include older age, type II diabetes mellitus, cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, immunocompromised state from solid organ transplant, sickle cell disease, and serious heart conditions such as heart failure or cardiomyopathy ([https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-increased-risk.html](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-increased-risk.html)).

FDA has not yet approved any therapeutics for the treatment of COVID-19. Studies demonstrated improved mortality with use of dexamethasone in hospitalized patients requiring oxygen support of mechanical ventilation[4]. The antiviral agent remdesivir shortened time to recovery in adults hospitalized with COVID-19[5] and was granted emergency use authorization on May 1, 2020. Additional treatment consists largely of supportive care. A variety of therapeutics have been proposed or are currently under clinical investigation including immunomodulatory agents and other antiviral agents ([https://www.covid19treatmentguidelines.nih.gov/](https://www.covid19treatmentguidelines.nih.gov/)).

**Passive antibody therapy and convalescent plasma**

Among the experimental treatment modalities discussed by the scientific community are the use of immune convalescent plasma or serum, and similarly, hyperimmune globulin from recovered COVID-19 patients[6]. This treatment entails the administration (or transfusion) of plasma (or derivatives thereof) from individuals following resolution of infection under the rationale that
antibodies in the plasma that are transferred to recipients (frequently described as passive antibody therapy) are able to neutralize the virus and protect recipients from infection or prevent or mitigate progression of existing infection. While hyperimmune globulin products might be expected to provide such antibodies in a better-characterized and more consistently manufactured product, convalescent plasma is more rapidly available, has been widely used under the EAP (>70,000 transfused at the time of this writing), and is under investigation in several randomized controlled trials in diverse clinical scenarios (e.g. severe disease, early disease, prophylaxis), localities, and with varying controls (e.g., non-immune plasma, colloid, standard of care).

Passive antibody therapy, including convalescent plasma, has been proposed or used to treat a wide variety of infectious diseases for more than a century, including several respiratory viral illnesses such as influenza, Respiratory Syncytial Virus (RSV), Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS)[7-9]. Examples of hyperimmune globulin used to treat post-exposure prophylaxis include Hepatitis B and Rabies. Passive immune therapy has been used to treat patients who are already manifesting symptoms of varying severity, but it is thought to be most effective when administered prophylactically (e.g., prior to clinical or laboratory evidence of infection); when used for treatment of symptomatic disease, immune plasma is thought to be most effective when administered early after the onset of symptoms. However, well-controlled studies in this field are rare.

Declaration of Public Health Emergency

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19. Pursuant to section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564 of the Act, subject to terms of any authorization issued under that section.

Product Description

CCP is human plasma collected by FDA registered blood establishments from individuals whose plasma contains anti SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and are qualified.

The manufacture of CCP includes testing for anti SARS-CoV-2 antibodies as a manufacturing step to determine titer levels before release. Units tested by the Ortho VITROS SARS-CoV-2 IgG test as part of manufacture and found to have a signal-to-cutoff (S/C) ratio of 12 or greater qualify as High Titer COVID-19 Convalescent Plasma. If a center is considering using an alternative test in manufacturing in order to qualify High Titer CCP, they should contact CBER to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA.

Units containing anti-SARS-CoV-2 antibodies but not qualified as High Titer COVID-19 Convalescent Plasma by the test described above are considered low titer units and must be
labeled as “COVID-19 Convalescent Plasma of Low Titer”. These units are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of benefit:risk. FDA will continue to evaluate this authorized use based on additional data that become available.

**Proposed Indication**

Under this EUA request, the Assistant Secretary for Preparedness and Response (ASPR) is proposing the use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19.

**Proposed Dosing**

Health care providers will administer CCP according to standard hospital procedures and institutional medical and nursing practices.

Clinical dosing may first consider starting with one CCP unit (about 200 mL), with administration of additional CCP units based on the prescribing physician’s medical judgement and patient’s clinical response.

Patients with impaired cardiac function and heart failure may require a smaller volume or more prolonged transfusion times.

**Prior Human Experience**

Early data on the use of convalescent plasma came in the form of two case series from the initial outbreak in China[10-12]. These studies in patients with very severe illness found that patients showed improved viral load, symptoms, and radiographic findings. The case series suggested CCP may be helpful but were limited by their small size and lack of controls.

Following these initial reports, a large number of clinical trials have been initiated, but most have not yet reported results. Available data generally fall into one of four categories: randomized controlled trials, controlled trials based on availability of plasma but not truly randomized, retrospective matched cohorts (e.g., propensity score matched), and case series/single-arm studies1. The detailed findings of these studies are described under “Evidence of Effectiveness” below. In brief, the studies include:

**Randomized controlled trials**

The two randomized controlled trials reported to date[13, 14] were conducted in Wuhan, China[13], and the Netherlands[14].

**Controlled trials**

In addition to the randomized controlled trials, prospective trials in which the control patients were those who were not transfused due to plasma unavailability, have also been reported[15-
Some of these studies provide encouraging signs of effectiveness, with limitations based on the not-truly-randomized nature of the study designs.

Retrospective matched cohort studies

Several reports of retrospective matched cohort studies of CCP have been made publicly available. [18-21]. These studies generally found a trend towards improved mortality when patients were treated earlier in the course of disease. One study found an association between antibody titer and clinical response[21]. These studies used varying approaches to matching, and based on the retrospective nature of their designs, may be subject to bias and confounding.

Case Series

Several investigators have reported case series and single arm studies ranging in size from 5 to 31 patients and across several countries, including the reports from the early pandemic in China described above [10, 11, 22-26].

Expanded Access

The EAP sponsored by the Mayo Clinic was established in April 2020 and has enrolled >90,000 subjects as of August 13, 2020. The goal of this uncontrolled, single-arm study is to provide access to CCP in hospitalized subjects with severe or life-threatening COVID-19 or judged by the treating provider to be at high risk of progression to severe or life-threatening disease. Initial reports from this study by Joyner et al described safety findings and outcomes in the first 5,000[23], and then 20,000 subjects[24]. Additional findings from this study are detailed in the next section of this memorandum.

Eligibility for an EUA

FDA may only issue an EUA if several statutory criteria, outlined in section 564(c) of the Act, are met. These criteria are further explained in an FDA guidance document, (https://www.fda.gov/media/97321/download), and with respect to CCP, are listed below in italics followed by this reviewer’s assessment:

a. Serious or life-threatening disease or condition

Severe COVID-19 requiring hospitalization is a serious or life-threatening disease or condition that has resulted in >170,000 deaths in the United States as of August 20, 2020 (www.cdc.gov/coronavirus/2019-ncov/cases-updates/us-cases-deaths.html). Patients have an increased risk of serious events such as thromboembolic events, cardiomyopathy and arrhythmia, renal injury, and stroke, which can result in long-term morbidity (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html).

b. Evidence of Effectiveness

The sponsor has pointed to four lines of evidence in support of the use of COVID-19 convalescent plasma in the treatment of hospitalized patients with COVID-19:
1. History of convalescent plasma for respiratory coronaviruses

A systematic review of passive antibody therapy for SARS coronavirus (SARS-CoV-1) and severe influenza found a trend towards reduction in mortality, but noted that studies were commonly of low or very low quality, lacked control groups, and were at risk of bias[27].

An uncontrolled study involved the treatment of 80 patients in Hong Kong with SARS-CoV-1 infection[28]. A higher day-22 discharge rate was observed among patients who were given convalescent plasma before day 14 of illness (58.3% vs 15.6%; P<0.001) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; P=0.001). A small retrospective nonrandomized study of patients with progressive SARS-CoV-1 infection after ribavirin and pulse methylprednisolone treatment showed that the plasma-treated group had a shorter hospital stay and lower mortality than the group that continued treatment with pulse methylprednisolone[29]. These reports followed a single case report of successful convalescent plasma therapy in a 57-year-old woman with SARS-CoV-1 infection in Hong Kong[30]. In addition, a case series of three patients with SARS-CoV-1 infection in Taiwan were treated with convalescent plasma, resulting in a reduction in viral load; all three recipients survived[31].

Treatment with convalescent plasma was also reported in three patients in South Korea with MERS, but researchers found only a subset of convalescent plasma showed neutralizing activity[32]. A group in Saudi Arabia reported on the feasibility of collecting convalescent plasma for passive immunotherapy of Middle East respiratory syndrome coronavirus (MERS-CoV) infection by using ELISA to screen serum samples from 443 potential plasma donors[33]. They found only a small subset (9 patients) showed neutralization activity and concluded trials would be challenging because of the small pool of donors with sufficiently high titers.

2. Evidence of preclinical safety and efficacy in animal models

In mouse models of SARS-CoV-1 infection, passive transfer of immune serum to naïve mice prevented virus replication in the lower respiratory tract following intranasal challenge[34].

Animal models of SARS-CoV-2 infection have been established in hamsters susceptible to SARS-CoV-2 infection and in mice transduced with hACE2 to sensitize them to the SARS-CoV-2 infection. Hamster studies found that postinfection sera from hamsters previously infected with the virus administered to other hamsters following infection with SARS-CoV-2 was able to decrease viral loads[35]. A separate study found immunophylaxis with early convalescent serum achieved a significant decrease in lung viral load but not in lung pathology[36]. In mouse studies, administration of 150 μL of human CCP one day prior to SARS-CoV-2 infection prevented weight loss and lung tissue histological changes, and accelerated the rate of virus clearance[37]. More rapid clearance of SARS-CoV-2 infection was not observed after treatment with pooled plasma from SARS-CoV-1 survivors or MERS survivors.

3. Published studies of the safety and efficacy of COVID-19 convalescent plasma
Randomized controlled trials – Results from two RCTs results have been made publicly available.

The first study by Li et al. in Wuhan, China[13], was in patients with severe to life-threatening COVID-19 who were transfused with 4-13 mL/kg of CCP with an ELISA titer >1:640. The primary outcome was time to clinical improvement within 28 days from randomization, and the study found clinical improvement in 27/52 (51.9%) in the CCP arm, and 22/51 (43.1%) in the control arm (p=0.26). When examining subgroups by disease severity they found that, in severe disease, 21/23 (91.3%) in the CCP arm and 15/22 (68.2%) in the control arm [p=0.03] showed clinical improvement. In life-threatening disease, 6/29 (20.7%) in CCP and 7/29 (24.1%) in control (p=0.83) showed clinical improvement. However, there was a non-significant test for interaction (p=0.17), so the results in the subgroups should not be interpreted differently. CCP treatment was associated with higher rates of negative SARS-CoV-2 viral PCR results from nasopharyngeal swabs at 24, 48, and 72 hours. Of note, the median duration of symptoms at the time of transfusion was 30 days. The study was stopped early due to low enrollment as a result of improved case rates in the Wuhan region, and thus may have been underpowered to detect statistically significant clinical benefit.

The second RCT by Gharbharan et al. in the Netherlands[14] examined patients with clinical COVID-19 as determined by a positive test in the previous 96 hours before enrollment (most patients met criteria for severe disease with a median of 10 days of symptoms at transfusion) who were treated with 300 mL of CCP with a neutralization titer of at least 1:80. The primary outcome was overall mortality until discharge. The trial was stopped early because they observed that antibody titers in the recipients were already high at the time of transfusion, and therefore, they made a decision to halt and redesign the trial because the presumed benefit would be in patients earlier in disease. At the time of study stopping, 6 of 43 CCP patients (14%) had died and 11 of 43 control patients (26%) had died. The prespecified comparison of adjusted mortality showed no difference (OR 0.95 [0.2-4.67]), but the study may have been underpowered to detect statistically significant clinical benefit at study stopping.

Controlled trials (non-randomized) – Two studies from the Middle East[15, 16] reported prospective trials in which the control patients were those who were not transfused due to a lack of plasma availability[16] or “As a result of ABO compatibility and limited plasma…randomly chosen to take CP”[15]. A third study where controls were also based on plasma availability was reported out of China[17].

A study by Rasheed et al[15] examined CCP transfusion in patients admitted to the ICU for less than 3 days (mean of 14-16 days of symptoms) and found that 1 of 21 CCP patients (4.8%) and 8 of 28 (28.6%) control patients died within the observation period, with only one patient experiencing a mild allergic reaction. This study is limited by the lack of formal reporting of statistical approaches.

A study by Abolghasemi et al[16] likewise compared CCP transfused patients to controls who were not transfused due to plasma unavailability within 3 days of enrollment. Patients had severe disease and were enrolled if they were within 7 days of illness onset. Patients were transfused
with 500-1000 mL of CCP confirmed to have anti-SARS-CoV-2 antibodies by a semi-quantitative ELISA. The primary outcomes were described as survival and hospital length of stay. All-cause mortality was 17/115 (14.8%) in the CCP arm versus 18/74 (24.3%) in the control arm [p=0.09]. The mean hospital length of stay was 9.5 days in CCP arm versus 12.9 in the control [p=0.002]. 107 (93%) CCP patients were discharged versus 59 (79.7%) in the control [p=0.006].

A third study where controls were also based on plasma availability was reported out of China[17]. Patients treated with CCP showed significantly improved viral clearance (6/6 CCP (100%), 4/15 controls (26.7%), p=0.004). However, no significant differences in mortality were seen (5/6 (83%) died in CCP arm, 14/15 (93%) died in control arm, p=0.5), noting there was high mortality in this very small, critically ill cohort.

Retrospective matched cohort studies – Several reports of retrospective matched cohort studies of CCP have been made publicly available [18-21].

In severe to life-threatening COVID-19, Liu et al[19] found that CCP transfusion was significantly associated with improved survival in non-intubated patients (hazard ratios: 0.19 (95% CI: 0.05 ~0.72); p=0.015), but not in intubated patients. CCP recipients were more likely than controls to remain the same or have improvements in supplemental oxygen requirements at day 14 (OR 0.86, p =0.028).

Using a propensity score matching algorithm, Salazar et al[21] found 28-day mortality was 3.7% in 136 CCP transfused subjects with severe COVID-19 versus 7.6% in 543 non-transfused controls (p=0.13). In those transfused within 72 hours of admission and with high-titer units, there was a significant difference in 28-day mortality (1.2% in CCP vs 7.0% in control, p = 0.047). The authors concluded that transfusion of high anti-RBD IgG titer COVID-19 CCP early in hospitalization reduces mortality.

In smaller studies, Perotti et al and Hegerova et al found similar trends toward benefit but noted that trends would need confirmation in well-controlled randomized trials[18, 20].

These studies are subject to several limitations due to their retrospective nature. For example, the number of variables used for subject-control matching may be insufficient to assure comparability of the treated patients and the untreated controls. If subjects and controls are selected from the same health care facility and they are well matched, it would be unclear whether there were other confounding factors that led to one patient receiving the plasma and the other seemingly comparable patient not receiving the plasma. If the decision to transfuse was based on a clinical condition that is associated with the outcome of interest (survival), but that is not captured in the matching, this can make treated and untreated patients incomparable and bias the studies. Finally, all are subject to a potential period effect because mortality has been observed to decrease generally over the course of the pandemic, for reasons that remain unclear.

Case series - Several investigators have reported case series and single arm studies ranging in size from 5 to 31 patients and across several countries, including the reports from the early pandemic in China described above [10, 11, 22-26]. Some case reports have highlighted patient improvement in patients with impaired humoral immunity such as X-linked agammaglobulinemia[38] and following lymphocyte depleting chemotherapy[39], although the
relative role of B cells in COVID-19 disease remains uncertain[40]. While the remaining case series and reports are encouraging with respect to the improvement seen in these patients, the interpretation of the results of case series are limited by the absence of controls [12, 22, 25, 26, 41].

4. Data on safety and efficacy from the EAP sponsored by the Mayo Clinic.

In section 6.4 “Clinical Safety and Efficacy” of the CCP EUA request, the sponsor has summarized a safety and efficacy analysis of data obtained from the EAP. This reviewer notes that the primary objective of the Mayo Clinic EAP was to provide access to convalescent plasma, with a secondary objective of demonstrating safety of CCP. Efficacy analyses were described in the protocol as exploratory analyses, and no pre-specified analysis plan was included in the protocol. Accordingly, this single-arm open-label protocol was broadly inclusive, and data collection was limited to encourage rapid roll out of the program, minimize administrative barriers to participation of study investigators, and achieve the primary objective of the program.

Safety: A report of adverse events in the initial population of 20,000 subjects in the EAP[24] found low overall rates of serious adverse events (SAEs). These included transfusion reactions (n=89; <1%), thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, 3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were judged to be unrelated to the convalescent plasma transfusion. The seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).

In addition to the published safety information, additional safety reports and a Data Safety Monitoring Board report for the EAP have been submitted to FDA under the IND file for the EAP. In these reports, SAEs and suspected unexpected serious adverse reactions (SUSARs) did not occur at a rate that raised a safety concern beyond the risks known to be associated with plasma transfusion in patients with critical illness (e.g., severe COVID-19)[42-45]. The lack of a control population limits interpretation of the safety data and many of these adverse events may be difficult to evaluate in the context of severe COVID-19.

Efficacy: The sponsor has provided results from an analysis comparing clinical outcomes in subjects enrolled in the EAP who were treated with different levels of neutralizing antibodies, as assessed with three different assays. This analysis was performed in collaboration with the Mayo Clinic and the FDA Center for Biologics Evaluation and Research (CBER), and this reviewer notes that the analysis was provided, in part, by FDA investigators. While a statistical plan was specified prior to analysis of antibody titers with respect to outcomes as part of the FDA analysis, no analysis plan was specified in the original EAP protocol. Because measurement of the neutralizing antibody titer of the CCP was not required under the EAP, it was expected that patients would receive a wide range of neutralizing antibody titers. As neutralizing activity of antibodies in CCP is thought to be the primary mechanism of action for potential efficacy,
demonstration of a dose-response relationship between neutralizing antibody titers and clinical outcomes would provide early evidence of the efficacy of CCP.

At the time of this review, there were no validated assays for quantification of neutralizing anti-SARS-CoV-2 antibodies for measuring titer levels in plasma for the purpose of determining whether units measured meet the standards identified in the EUA for the manufacture of CCP. The assays described in the EUA submission include: a neutralization assay performed by the Broad Institute using native SARS-CoV-2 virus with detection of infected cells by a semiquantitative assay of IgG against spike protein (Ortho VITROS IgG); and a neutralization assay using a pseudo-typed bearing SARS-CoV-2 spike protein (Mayo Clinic). Among these assays, it appears the testing performed by the Broad Institute is the closest to the gold-standard of a plaque reduction neutralization titer in that this assay uses the native SARS-CoV-2 virus to determine the titer required for 50% inhibition of infection of cultured cells (ID50). FDA/CBER separately received data from a set of CCP samples comparing the correlation between these assays. While these assays generally correlated with each other, precise performance characteristics based on a reference panel or gold-standard methodology (plaque reduction neutralization titer) were not available at the time of this review.

In these assays, an ID50 titer cutoff of 250 in the Broad Institute assay was chosen to distinguish between high titer and low titer plasma. This value correlated with an Ortho VITROS IgG assay signal to cutoff (S/C) of 12. Based on titer data using the Broad Institute assay, the data submitted in the EUA demonstrate the following findings:

- There was no difference in 7-day survival in the overall population between subjects transfused with high versus low titer CCP.
- In the subset of non-intubated patients, there was a 21% reduction in 7-day mortality (from 14% to 11%, p=0.03) in subjects transfused with high versus low titer CCP.
- There was no apparent association between neutralizing antibody titers and 7-day mortality in intubated subjects.
- In additional analyses of a post-hoc subgroup of patients less than 80 years of age who were not intubated and who were within 72 hours of diagnosis, a stronger relationship between neutralizing antibody titers and 7-day mortality is observed. When titers are binned to low versus high at a threshold of 250, the sponsor reports a significant reduction in 7-day mortality from 11.3 to 6.3% (p = 0.0008).
- In additional analyses of survival using a Kaplan-Meier approach, the survival trends observed at 7 days persisted over a longer time period, with significantly improved survival in non-intubated patients (Figure 2, p=0.032) and a larger benefit in the subset of patients not intubated at the time of treatment, less than 80 years of age, who were treated within 72 hours of diagnosis (Figure 3, p=0.0081).

In additional analyses performed by FDA of the relationship between antibody titers and outcomes in the EAP data, similar trends were seen across the Broad Institute neutralization assay, a semiquantitative assay of IgG against spike protein (Ortho VITROS IgG), and a neutralization assay using a pseudo-typed bearing SARS-CoV-2 spike protein (Mayo Clinic).
Additional analyses of data from the EAP were posted publicly by Mayo Clinic investigators and collaborators[46]. In their analyses, the investigators observed an association between reductions in adjusted 7-day and 30-day mortality and earlier transfusion (<=3 days) of CCP and high antibody levels. Antibodies were measured using the Ortho VITROS IgG semiquantitative assay. Low, medium, and high antibody levels were defined as <4.62, 4.62-18.45, and >18.45 (S/C ratio), respectively.

Summary of Evidence of Effectiveness

Considering the totality of the scientific evidence summarized above, I agree that current data support the conclusion that CCP to treat hospitalized patients with COVID-19 meets the “may be effective” criteria for issuance of an EUA. Adequate and well-controlled randomized trials remain nonetheless necessary for a definitive demonstration of CCP efficacy and to determine the optimal product attributes and the appropriate patient populations for its use.

Current evidence suggests that benefit is most likely in patients treated early in the course of the disease (e.g., prior to intubation). In addition, as outlined in the data reviewed above from different studies, there is a potential benefit of CCP in intubated and non-intubated patients. Considering the absence of a control population in the EAP and that data from randomized trials remain limited, the lack of benefit observed in intubated patients in this study is currently insufficient to exclude potential benefit in this population. Therefore, bearing in mind the safety profile observed to date, inclusion of intubated and non-intubated patients under the EUA appears appropriate at this time.

Current evidence suggests that units with higher antibody content or neutralization activity are more likely to be effective. The identification of effective antibody levels or neutralizing activity levels is limited by the unavailability of validated assays for this purpose as part of the manufacture of CCP. However, if one considers the use of quantitative antibody or neutralization activity tests as a manufacturing test of product potency, the available data support use of the Ortho VITROS IgG assay for this purpose. The sponsor’s recommended S/C cutoff of 12 or greater correlates with a neutralizing antibody titer of 250 in the Broad Institute’s neutralizing antibody assay and accordingly, is acceptable as cutoff to qualify High Titer CCP. Other assays that have been validated to correlate with comparable anti SARS-CoV-2 antibody titers and provide similar quantitative assessment of neutralization activity may be acceptable for this purpose. If a blood establishment is considering using an alternative test in manufacturing in order to qualify High Titer CCP, they should contact CBER to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA.

Although higher titer units appear to be associated with improved survival in the EAP, this reviewer notes that the efficacy analysis of the EAP did not include an untreated (or placebo) control population. The EAP study showed a gradient of mortality in relation to the antibody level in the transfused CCP. This finding of a dose-response between antibody level and reduction in mortality provides evidence that the antibody is the active agent in convalescent plasma for treatment of COVID-19. This is consistent with the long history and biological basis of the use of convalescent plasma in treating infectious diseases.
The minimal antibody titer that would be effective in different patients has not been defined. It is expected to vary based on a number of factors, such as the potency of the antibody (itself dependent on the CCP donor), the volume transfused, the severity of the illness, the duration of the illness, and the time of administration of CCP relative to the patient diagnosis. Furthermore, a trend towards improved outcomes was observed at lower titer thresholds than those proposed in the EUA in some of the analyses of the EAP performed by the Mayo Clinic[46].

Therefore, based on findings which suggest that the antibody is the active agent in convalescent plasma, past experience, and the number of studies described earlier in this memo showing evidence of effectiveness of CCP, CCP not qualified as High-Titer by the Ortho VITROS assay still meets the evidentiary standard of “may be effective”. These units will be labeled as “COVID-19 Convalescent Plasma of Low Titer”. Health care providers will decide whether to use the units based on an individualized determination of potential benefit and risk.

c. Risk-Benefit Analysis

Potential benefits include potential improved survival and viral clearance in hospitalized patients with COVID-19. These potential benefits are based on the summary of effectiveness outlined above.

Risks are expected to include those inherent to plasma transfusion:
- Transfusion related acute lung injury (TRALI)
- Transfusion associated cardiac overload (TACO)
- Allergic/Anaphylactic reactions
- Febrile nonhemolytic transfusion reactions
- Transfusion-transmitted infections
- Hemolytic reactions

Some plasma transfusion risks, such as TRALI and TACO, would be expected to be elevated in patients with baseline pulmonary injury or impaired cardiac function, respectively. However, the actual risks of these events observed in the EAP population[24] were within the expected rates of these events for transfusion of plasma in critically ill patients[43, 45].

Additional risks specific to convalescent plasma include a theoretical risk of antibody-dependent enhancement (ADE) and a theoretical risk of suppressed long-term immunity.

Antibody-dependent enhancement of disease is thought to occur when antibodies to an infectious agent ‘bridge’ the pathogen to Fc receptors on immune cells, leading to increased viral entry and enhancement of infection[47]. The potential for ADE was explored in macaque models of SARS-CoV-1[48] wherein investigators found that passively transferred antibodies could skew inflammatory responses, potentially leading to exacerbation of pulmonary pathology. However, no overt evidence of ADE has been observed in the studies of CCP summarized above. As a result of the lack of adequately powered randomized controlled studies, this theoretical risk cannot be excluded at this time.
The potential of passive immune therapies to suppress long-term immunity in recovered patients has not been evaluated in clinical studies to date. Ongoing trials will evaluate antibody responses following treatment with CCP.

CCP may be contraindicated in patients with a history of severe allergic reactions or anaphylaxis to plasma transfusion.

Summary of Risk-Benefit Analysis

Based on the above, it is reasonable to believe that the known and potential benefits of CCP outweigh the known and potential risks of CCP for the proposed EUA. Information derived from ongoing clinical trials of CCP, particularly randomized, controlled trials, as well as clinical trial results from studies of other investigational medical products to treat COVID-19, will continue to inform this risk benefit assessment.

d. No alternatives

There are currently no adequate, approved, and available alternatives to CCP for the treatment of COVID-19. Remdesivir has been granted emergency use authorization but is not an approved treatment at the time of this writing.

In sum, the proposed EUA for CCP meets the eligibility criteria for Emergency Use Authorization under section 564 of the Act.

Fact Sheets for Healthcare Providers and Recipients

The Fact Sheet for Health Care Providers and Fact Sheet for Recipients were reviewed, and suggested revisions sent to the sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the intended setting.

Conclusions

- COVID-19 Convalescent Plasma may be effective in the treatment of COVID-19 and it is reasonable to believe that the known and potential benefits of CCP outweigh the known and potential risks of the product for the proposed EUA.
- Current evidence suggests clinical benefit is most likely in patients treated early in the course of the disease (e.g., prior to intubation) and with the use of CCP with higher antibody levels or neutralization activity.
- Current data are limited by the unavailability of validated assays of antibody levels or neutralization activity in CCP. Based on the available data, it is reasonable to use the Ortho VITROS IgG assay with an S/C cutoff of 12 or greater as a manufacturing potency test to qualify high titer units of CCP.
• Based on the available evidence, CCP without a result of 12 or greater in the Ortho VITROS assay meets the criteria for issuance of an EUA because, among other things, it is reasonable to believe it may be effective in treating COVID-19 and the known and potential benefits of the product outweigh its known and potential risks. Such units must be labeled as “COVID-19 Convalescent Plasma of Low Titer.” Health care providers can decide whether to use these units based on an individualized determination of potential benefit and risk.

• The Fact Sheet for Health Care Providers and Fact Sheet for Recipients are accurate, not misleading, and appropriate for the intended setting.

• Randomized controlled trials are required to show definitive evidence of safety and efficacy and to determine the optimal product attributes and appropriate patient populations for the use of COVID-19 Convalescent Plasma.
References


FACT SHEET FOR HEALTH CARE PROVIDERS

EMERGENCY USE AUTHORIZATION (EUA) OF COVID-19 CONVALESCENT PLASMA FOR TREATMENT OF COVID-19 IN HOSPITALIZED PATIENTS

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product COVID-19 convalescent plasma to treat hospitalized patients with COVID-19.

INSTRUCTIONS FOR HEALTH CARE PROVIDERS

The information in this Fact Sheet is the minimum information necessary to inform you of the significant known and potential risks and benefits of the emergency use of COVID-19 convalescent plasma.

As the health care provider administering COVID-19 convalescent plasma, you must provide recipients with the Fact Sheet for Patients/Caregivers and must communicate the following information to the recipients:

1. FDA has authorized emergency use of COVID-19 convalescent plasma, which is not an FDA-approved biological product

2. The patient or caregiver has the option to accept or refuse administration of COVID-19 convalescent plasma

3. The significant known and potential risks and benefits of COVID-19 convalescent plasma and the extent to which such risks and benefits are unknown

4. Information on available alternative treatments and the risks and benefits of those alternatives.

If providing this information will delay the administration of COVID-19 convalescent plasma to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after convalescent plasma is administered.

For information on clinical trials that are testing the use of COVID-19 convalescent plasma for COVID-19, please see www.clinicaltrials.gov.

INTENDED USE

The EUA for COVID-19 convalescent plasma authorizes the use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. This EUA is based on historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the ongoing National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.
Data suggest that use of COVID-19 convalescent plasma with high antibody titer may be effective in reducing mortality in hospitalized patients with COVID-19. Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by a test described below are considered “COVID-19 Convalescent Plasma of Low Titer” and are authorized for use (see Product Description). Health care providers can decide whether to use these units based on an individualized determination of potential benefit:risk. FDA will continue to evaluate this authorization based on additional data that become available. Current evidence also suggests that benefit is most likely in patients treated early in the course of the disease.

Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs are needed. Convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Ongoing clinical trials of convalescent plasma should not be amended based on the issuance of the EUA. Providers are encouraged to enroll patients in those ongoing clinical trials.

**PRODUCT DESCRIPTION**

COVID-19 convalescent plasma is human plasma collected by FDA registered blood establishments from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and are qualified. Convalescent plasma is qualified and labeled as having high titer anti-SARS-CoV-2 antibodies based on testing accepted by FDA under this EUA.

Units containing anti-SARS-CoV-2 antibodies but not qualified as High Titer COVID-19 Convalescent Plasma are considered Low Titer COVID-19 Convalescent Plasma and must be labeled accordingly. These units are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of benefit:risk. FDA will continue to evaluate this authorized use based on additional data that become available.

**DOSAGE, ADMINISTRATION, AND STORAGE OF COVID-19 CONVALESCENT PLASMA**

**Dosage**

Health care providers will administer COVID-19 convalescent plasma according to standard hospital procedures and institutional medical and nursing practices.

Clinical dosing may first consider starting with one convalescent plasma unit (about 200 mL), with administration of additional convalescent plasma units based on the prescribing physician’s medical judgment and the patient’s clinical response.

Patients with impaired cardiac function and heart failure may require a smaller volume or more prolonged transfusion times.
Administration
Administer COVID-19 convalescent plasma infusion through a peripheral or central venous catheter according to standard institutional medical and nursing practices for the administration of plasma (http://www.aabb.org/tm/coi/Documents/coi1017.pdf).

Storage
COVID-19 convalescent plasma, may be stored frozen at -18°C or colder, and has an expiration date one year from the date of collection. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.

DRUG INTERACTIONS
COVID-19 convalescent plasma may be contraindicated in patients with a history of severe allergic reactions or anaphylaxis to plasma transfusion.

SIDE EFFECTS, RISKS, BENEFITS, AND RISK-BENEFIT ASSESSMENT

Side Effects
Known side effects and hazards associated with plasma transfusion include transfusion-transmitted infections (e.g. HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and posttransfusion purpura have also been described. Additional information on risks of plasma can be found in the AABB Circular of Information (http://www.aabb.org/tm/coi/Documents/coi1017.pdf).

Risks
A theoretical risk of administration of convalescent plasma is the phenomenon of antibody-dependent enhancement of infection (ADE). ADE has been described in other viral infections, such as dengue, and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms of ADE have been proposed, including the theoretical concern that antibodies to one type of coronavirus could enhance infection to another strain. Preparations with high titers of antibody against the same virus strain are thought to be less likely to cause ADE.

Another theoretical risk is that antibody administration may attenuate the immune response and make patients more susceptible to re-infection.

Benefits
COVID-19 is a serious and potentially fatal or life-threatening human disease. The potential benefits of COVID-19 convalescent plasma therapy could include improvement in symptoms, reduced need for supplemental oxygen and mechanical ventilation, and reduced mortality. Support for the safety and effectiveness of COVID-19 convalescent plasma is derived from past human experience with convalescent plasma, evidence of preclinical safety and efficacy in animal models, published studies on the safety and efficacy of COVID-19 convalescent plasma in COVID-19 patients including from the National Expanded Access Treatment Protocol sponsored by the Mayo Clinic (EAP). A report of adverse events in the initial population of
20,000 subjects in the EAP found low overall rates of serious adverse events. Analysis of over 35,000 transfused patients in the EAP study found a dose-response between antibody level and reduction in mortality. Available evidence suggests that COVID-19 convalescent plasma with high antibody titer may be effective in reducing mortality in hospitalized patients with COVID-19. Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by a test found acceptable for this purpose by FDA (see Product Description) are considered Low Titer COVID-19 Convalescent Plasma and are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of patient benefit-risk.

Risk-Benefit Assessment
Based on the totality of scientific evidence available at this time, the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks.

USE IN SPECIFIC POPULATIONS

Pediatric
Safety and effectiveness of COVID-19 convalescent plasma in the pediatric population has not been evaluated. The decision to treat patients <18 years of age with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

Geriatric
In the National Expanded Access Treatment Protocol sponsored by the Mayo Clinic, 69,811 patients were treated as of August 20, 2020. Preliminary analyses of the first 20,000 patients indicated that 5,423 (27.1%) were 60-69 years of age, 4,114 (20.6%) were 70-79 years of age, and 2,568 (12.8%) were 80 years of age or older. Although adverse event rates in the geriatric subgroup have not yet been provided, the rates in the overall population for the individual events of mortality within 4 hours, TACO, TRALI, severe allergic transfusion reaction, thrombotic/thromboembolic complication, sustained hypotension, and cardiac events were ≤ 0.37%.

Pregnancy
Safety and effectiveness of COVID-19 convalescent plasma in pregnancy has not been evaluated. It should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Nursing Mothers
It is not known whether or not transfused anti-SARS-CoV-2 antibodies are excreted in human milk. The safety and effectiveness of COVID-19 convalescent plasma in nursing mothers has not been evaluated. The decision to treat nursing mothers with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

REPORTING ADVERSE EVENTS
Health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required under 21 CFR 606.170.
As a health care provider, you must comply with the mandatory requirements of the EUA.

**FDA-APPROVED ALTERNATIVES**

There are no drugs or other therapeutics approved by the FDA to prevent or treat COVID-19 infection. There are EUAs for other COVID-19 treatments (visit [https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs](https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs)). The health care provider should visit [https://clinicaltrials.gov/](https://clinicaltrials.gov/) to determine whether the patient may be eligible for enrollment in a clinical trial.

**COUNTERMEASURES INJURY COMPENSATION PROGRAM**

The Countermeasures Injury Compensation Program (CICP) is a federal program created to help pay for related costs of medical care and other specific expenses for eligible people seriously injured by the administration or use of certain medical countermeasures. Medical countermeasures may include vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a current, or potential future, public health emergency or a security threat. For more information about CICP, visit [http://www.hrsa.gov/cicp/](http://www.hrsa.gov/cicp/) or call: 1-855-266-2427.

**AUTHORITY FOR ISSUANCE OF THE EUA**

The Secretary of the U.S. Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, the FDA has issued an EUA for the unapproved product, COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19. FDA issued this EUA requested by ASPR and based on their submitted data and other available data about COVID-19 convalescent plasma.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that COVID-19 convalescent plasma may be effective for the treatment of COVID-19 in hospitalized patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for COVID-19 convalescent plasma will end when the Secretary determines that the circumstances justifying the EUA no longer exist, if additional data were to become available to no longer support the product’s use under an EUA, or when there is a change in the approval status of the product such that an EUA is no longer needed.
FACT SHEET FOR PATIENTS AND PARENTS/CAREGIVERS

EMERGENCY USE AUTHORIZATION (EUA) OF COVID-19 CONVALESCENT PLASMA FOR TREATMENT OF COVID-19 IN HOSPITALIZED PATIENTS

You are being given COVID-19 convalescent plasma to treat COVID-19. This fact sheet contains information to help you understand the risks and benefits of taking the COVID-19 convalescent plasma you have received or may receive.

There is no U.S. Food and Drug Administration (FDA) approved product available to treat COVID-19. Transfusion of COVID-19 convalescent plasma may benefit patients hospitalized with COVID-19.

Read this Fact Sheet for information about COVID-19 convalescent plasma. Talk to your health care provider if you have questions. It is your choice to accept treatment with COVID-19 convalescent plasma or stop it at any time.

WHAT IS COVID-19?
You have been diagnosed with disease caused by the SARS-CoV-2 virus also known as coronavirus disease 2019 (COVID-19). This type of coronavirus has not been seen before. This new virus has caused a worldwide pandemic with many patients developing severe respiratory illness and other serious complications. You can get COVID-19 through contact with another person who has the virus.

WHAT ARE THE SYMPTOMS OF COVID-19?
Common symptoms are fever, cough, and shortness of breath, which may appear 2-14 days after exposure. COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can occur and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe chronic medical conditions like heart disease, lung disease, and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

WHAT IS COVID-19 CONVALESCENT PLASMA?
The blood from people who recover from COVID-19 contains substances called antibodies, which are capable of fighting the virus that causes the illness. For some other diseases caused by respiratory viruses, giving people the liquid portion of blood that contains these antibodies, called plasma, obtained from those who have recovered from the virus, may lead to more rapid improvement of the disease. Patients with COVID-19 may improve faster if they receive plasma from those who have recovered from COVID-19, because it may have the ability to fight the virus that causes COVID-19.

HOW IS COVID-19 CONVALESCENT PLASMA GIVEN?
You will be given plasma, the liquid portion of the blood, from a person who has recovered from COVID-19. It will be given into one of your veins, using a sterile single use needle, and will be given over the course of up to about one to two hours. Approximately 200 mL (a little less than 8 ounces) of plasma will be given in an initial infusion. Additional infusions of plasma may occur throughout your hospital stay if the treating physician determines that additional treatments are clinically justified.

WHAT ARE THE POSSIBLE BENEFITS OF GETTING COVID-19 CONVALESCENT PLASMA?
This treatment might be effective in improving the likelihood of you recovering from the disease.
WHAT ARE THE COMMON AND/OR POSSIBLE SIDE EFFECTS (RISKS) OF COVID-19 CONVALESCENT PLASMA?
Transfusion carries the risk of adverse reactions such as allergic reactions, transfusion-associated circulatory overload, or lung damage with profound breathing difficulty, cardiac (heart) rhythm irregularities, and blood clotting.

As with receipt of any blood product, there is a risk of transfusion-transmitted infection including HIV, hepatitis B, and hepatitis C. The risk of these infections is very low, because only screened blood is used for transfusion.

You may have other side effects that are not known at this time and may include serious injury or pain, disability, or death. There is also a chance that confidentiality of your private information could be lost; however, procedures are in place to minimize this risk.

WHO SHOULD NOT GET COVID-19 CONVALESCENT PLASMA?
Discuss with your health care provider if previously you had any reactions to plasma products or other blood products.

WHAT IF I AM PREGNANT OR BREASTFEEDING?
The safety and effectiveness of COVID-19 convalescent plasma in pregnancy and nursing mothers has not been evaluated. If you are pregnant or breastfeeding, please talk with your health care provider to decide if you should receive COVID-19 convalescent plasma.

HOW DO I REPORT SIDE EFFECTS?
After receiving COVID-19 convalescent plasma, if you are experiencing any side effects that are bothersome, serious, or that do not go away, please contact your health care provider. When you are reporting a side effect, you should identify that you received COVID-19 convalescent plasma.

ARE THERE OTHER ALTERNATIVES TO COVID-19 CONVALESCENT PLASMA?
There are no drugs or other therapeutics approved by the FDA to prevent or treat COVID-19 infection. Like convalescent plasma, FDA may allow for the emergency use of other medicines to treat people in the hospital with COVID-19.

In addition, your health care provider may talk to you about clinical trials you may be eligible for. It is your choice to be treated or not to be treated with COVID-19 convalescent plasma. You can decide not to get it or stop it at any time. Whether you decide to take COVID-19 convalescent plasma or not, it will not change your standard medical care. You may be given other available treatments that may include oxygen, fluids, and medications depending on your condition and determined by your doctor.

HOW CAN I LEARN MORE?
1. Ask your health care provider
2. Contact your local or state public health department

WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?
The United States FDA has made COVID-19 convalescent plasma available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Services (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

COVID-19 convalescent plasma has not undergone the same type of review as an FDA-approved or cleared product. FDA may issue an EUA when certain criteria are met, which includes that there are no adequate,
approved, and available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product. All of these criteria must be met to allow for the authorized product to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for COVID-19 convalescent plasma is in effect for the duration of the COVID-19 declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).
5. Protocol

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Note – The cumulative changes to the protocol are listed at the end of the document with the changes from one version to the next listed at the beginning of the document.
Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Unique Protocol Identification Number: 20-003312
National Clinical Trial (NCT) Identified Number:
Principal Investigator: Michael Joyner, MD
IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
Version 2.0
03 April 2020

The Mayo Clinic IRB will serve as the IRB of record for all sites participating in this protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the trial via sign up on www.uscovidplasma.org will serve as documentation of each participating institution’s reliance on Mayo’s IRB. A separate IRB reliance agreement is not required.

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The Sponsor may contact the treating physician as appropriate for completion of all data forms in a timely manner. You agree to respond to the sponsor in a timely manner with complete information. Failure to comply will be in violation with the protocol.
## 1.1 SYNOPSIS

**Title:** Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

**Study Description:** This expanded access program will provide access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with one unit of ABO compatible convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events judged to be related to the administration of convalescent plasma. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

**Objectives:**

- **Primary Objective:** Provide access to COVID-19 convalescent plasma
- **Secondary Objectives:** Safety

**Endpoints:**

- **Primary Endpoint:** Availability of convalescent plasma
- **Secondary Endpoints:** Serious adverse events

**Study Population:** Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

**Phase:** Expanded Access Program

**Description of Sites/Facilities Enrolling Participants:** Acute care facilities treating patients with COVID-19

**Description of Study Intervention:** Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

**Study Duration:** 12 months

**Participant Duration:** Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

☐ Eligibility Criteria met

Inclusion Criteria

1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe disease defined as any of the following:

- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease defined as any of the following:

- respiratory failure
- septic shock
- multiple organ dysfunction or failure

☐ Informed consent obtained from patient or healthcare proxy

☐ Blood type obtained at local laboratory per local institutional procedures and policies

☐ Patient Registered with Red Cross (for tracking purposes)

☐ Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol

Patients may be premedicated with acetaminophen and diphenhydramine, per local practice
Recommended administration rate for plasma administration is 100 to 250 mL/hr

☐ Serious adverse events judged related to plasma infusion to be reported by patient to provider

☐ Reporting of patient demographics and acute care resource utilization

Information entered on COVID-19 Plasma Expanded Access Program secure website

Information on plasma unit administered will be obtained directly from blood collector
2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

2.2 BACKGROUND

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.1,2

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Convalescent plasma represents a licensed blood product, for which the risks are well described. These are the risks associated with the administration of plasma, including allergic reaction and viral infections. There is also the risk that convalescent plasma may be ineffective.

2.3.2 KNOWN POTENTIAL BENEFITS

COVID-19 convalescent plasma has not yet been demonstrated to provide clinical benefit in patients affected by this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Thee safety profile of plasma administration is well established. Taking into account the preliminary data available on the possible benefit of COVID-19 plasma along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, providing patients access to ABO compatible COVID-19 plasma as part of this expanded access protocol appears to reasonably balance potential risks with possible benefit that may outweigh such risks.
### 3 OBJECTIVES AND ENDPOINTS

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Regulatory Documents for National EAP (IND 19832) Participating Sites – 9/2/2020
4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label expanded access program to make appropriately matched convalescent plasma available for the treatment of patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. COVID-19 convalescent plasma will be obtained from blood suppliers and will meet all regulatory requirements for conventional plasma and FDA’s additional considerations for COVID-19 convalescent plasma (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds). Information collected following plasma administration will include serious adverse events judged by the treating physician to be potentially related to the administration of the plasma, as well as patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered. Due to the nature of the COVID-19 outbreak, data on patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered may be collected retrospectively.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola and other pathogens. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19. At this time there are few therapeutic options for the treatment of COVID-19 and no prophylactic vaccine is currently available. Based on the preliminary evidence of possible efficacy, this protocol is making convalescent plasma available to individuals with documented SARS-CoV-2 disease at acute care facilities who have severe or life-threatening COVID-19, or who are judged by a provider to be at high risk of progression to severe or life-threatening disease.

4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused will be that of the full unit of COVID-19 convalescent plasma, or at least 200 mL.
4.4 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:
- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with the Red Cross. Since this involves the one-time administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION
This expanded program will make available ABO compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA’s regulations and the additional considerations for convalescent plasma on FDA’s webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-ind)[5]

6.1.1 STUDY INTERVENTION DESCRIPTION
ABO compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION
For practical purposes in the current outbreak, one unit of ABO compatible COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (volume of plasma to administer approximately 200-400 mL), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine. The duration of infusion will usually take 1 to 2 hours (rate of 100 to 250 mL/hr).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY
ABO compatible convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING
COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19 with either a label or tie tag on the bag indicating the presence of COVID-19 antibodies.

6.2.3 PRODUCT STORAGE AND STABILITY
Please see the AABB Circular of Information for product storage and stability.

6.2.4 PREPARATION
Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including ABO compatibility checks and thawing.
6.5 CONCOMITANT THERAPY

Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION
This study involves the one-time administration of ABO matched COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY
Patient are free to withdraw consent from participation in further data collection at any time during the study.

7.3 LOST TO FOLLOW-UP
Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex.

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting will only be required for serious adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma should be reported to the sponsor/principal investigator. Sponsor reports periodically to FDA.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner.
9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

9.2 SAMPLE SIZE DETERMINATION

This is an expanded access protocol that is intended to supply ABO compatible COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

9.3 POPULATIONS FOR ANALYSES

Serious adverse events will be collected on all treated individuals.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

9.4 STATISTICAL ANALYSES

Only exploratory statistical analyses will be performed as part of this expanded access program.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Below is a template of language that can be used for informed consent. The language has been deliberately streamlined for use in the setting of the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient’s health care proxy prior to treatment.

Example of a consent form for treatment with experimental convalescent plasma therapy follows.

IRB Reliance

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.

Safety Oversight

The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks of administered products and have sufficient research and trial experience to provide an independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate decision-making power to terminate the study evidence of early benefit or harm. The DSMB will generate monthly reports to the IRB and FDA, and the DSMB Chair, the PI, the appropriate FDA officials will review SAE aggregates weekly or less often as appropriate to ensure appropriate safety oversight.
DSMB Membership

The DSMB membership will include:

Allan S. Jaffe, MD, - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN

William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL
10.2 ABBREVIATIONS

AE  Adverse Event
CFR  Code of Federal Regulations
CRF  Case Report Form
EC  Ethics Committee
eCRF  Electronic Case Report Forms
FDA  Food and Drug Administration
IB  Investigator’s Brochure
IND  Investigational New Drug Application
IRB  Institutional Review Board
NIH  National Institutes of Health
SAE  Serious Adverse Event
SAP  Statistical Analysis Plan
SOP  Standard Operating Procedure
US  United States

10.3 PROTOCOL AMENDMENT HISTORY

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   Pmid:32219429


   Pmid:32219428


   Pmid:25030060


   Pmid:29923831

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IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
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- **Secondary Objectives:** Safety

Endpoints:
- **Primary Endpoint:** Availability of convalescent plasma
- **Secondary Endpoints:** Serious adverse events

Study Population: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

Phase: Expanded Access Program

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Description of Study Intervention: Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

Study Duration: 12 months

Participant Duration: Patients will complete the study when they are discharged from the acute care facility in which the received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

- Eligibility Criteria met

Inclusion Criteria
1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
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Life-threatening disease defined as any of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

- Informed consent obtained from patient or healthcare proxy
- Blood type obtained at local laboratory per local institutional procedures and policies
- Patient Registered with Red Cross (for tracking purposes)
- Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol
  - Patients may be premedicated with acetaminophen and diphenhydramine, per local practice
  - Recommended administration rate for plasma administration is 100 to 250 mL/hr
- Serious adverse events judged related to plasma infusion to be reported by patient to provider
- Reporting of patient demographics and acute care resource utilization
  - Information entered on COVID-19 Plasma Expanded Access Program secure website
  - Information on plasma unit administered will be obtained directly from blood collector
2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

2.2 BACKGROUND

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.1,2

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Convalescent plasma represents a licensed blood product, for which the risks are well described. These are the risks associated with the administration of plasma, including allergic reaction and viral infections. There is also the risk that convalescent plasma may be ineffective.

2.3.2 KNOWN POTENTIAL BENEFITS

COVID-19 convalescent plasma has not yet been demonstrated to provide clinical benefit in patients affected by this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The safety profile of plasma administration is well established. Taking into account the preliminary data available on the possible benefit of COVID-19 plasma along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, providing patients access to ABO compatible COVID-19 plasma as part of this expanded access protocol appears to reasonably balance potential risks with possible benefit that may outweigh such risks.
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This is an open-label expanded access program to make appropriately matched convalescent plasma available for the treatment of patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. COVID-19 convalescent plasma will be obtained from blood suppliers and will meet all regulatory requirements for conventional plasma and FDA’s additional considerations for COVID-19 convalescent plasma (https://www.fda.gov/vaccines-blood-biologics/ investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds). Information collected following plasma administration will include serious adverse events judged by the treating physician to be potentially related to the administration of the plasma, as well as patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered. Due to the nature of the COVID-19 outbreak, data on patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered may be collected retrospectively.

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Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola and other pathogens. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19. At this time there are few therapeutic options for the treatment of COVID-19 and no prophylactic vaccine is currently available. Based on the preliminary evidence of possible efficacy, this protocol is making convalescent plasma available to individuals with documented SARS-CoV-2 disease at acute care facilities who have severe or life-threatening COVID-19, or who are judged by a provider to be at high risk of progression to severe or life-threatening disease.

4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused will be that of the full unit of COVID-19 convalescent plasma, or at least 200 mL.
4.4 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:

• dyspnea
• respiratory frequency ≥ 30/min
• blood oxygen saturation ≤ 93%
• partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
• lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:

• respiratory failure
• septic shock
• multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with the Red Cross. Since this involves the one-time administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

This expanded program will make available ABO compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA’s regulations and the additional considerations for convalescent plasma on FDA’s webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).5

6.1.1 STUDY INTERVENTION DESCRIPTION
ABO compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION
For practical purposes in the current outbreak, one unit of ABO compatible COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (volume of plasma to administer approximately 200-400 mL), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine. The duration of infusion will usually take 1 to 2 hours (rate of 100 to 250 mL/hr).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY
ABO compatible convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING
COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19 with either a label or tie tag on the bag indicating the presence of COVID-19 antibodies.

6.2.3 PRODUCT STORAGE AND STABILITY
Please see the AABB Circular of Information for product storage and stability.

6.2.4 PREPARATION
Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including ABO compatibility checks and thawing.
6.5 CONCOMITANT THERAPY

Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION
This study involves the one-time administration of ABO matched COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY
Patient are free to withdraw consent from participation in further data collection at any time during the study.

7.3 LOST TO FOLLOW-UP
Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex.

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting will only be required for serious adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma should be reported to the sponsor/principal investigator. Sponsor reports periodically to FDA.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner.
9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES
This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

9.2 SAMPLE SIZE DETERMINATION
This is an expanded access protocol that is intended to supply ABO compatible COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

9.3 POPULATIONS FOR ANALYSES
Serious adverse events will be collected on all treated individuals.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

9.4 STATISTICAL ANALYSES
Only exploratory statistical analyses will be performed as part of this expanded access program.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Below is a template of language that can be used for informed consent. The language has been deliberately streamlined for use in the setting of the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient’s health care proxy prior to treatment.

We request permission to use the exception from informed consent similar to that described in 21 CFR 50.23 as an alternative when written informed consent from the subject or a legally authorized representative (LAR)/health care proxy/family member is unavailable. We will utilize the following alternative informed consent method only when 1) the patient is unable to give written informed consent due to their illness and 2) there is no LAR/proxy/family available and 3) time is not sufficient to delay treatment due to the imminent risk of deterioration and/or disease progression.

In the event this alternative informed consent process is utilized, the treating physician/PI will document that the use of the EAP is justified on the data form and that a second, unaffiliated physician concurs and documents such concurrence in the medical record before administration of the convalescent plasma.

Example of a consent form for treatment with experimental convalescent plasma therapy follows.

IRB Reliance

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.
Safety Oversight
The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks of administered products and have sufficient research and trial experience to provide an independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate decision-making power to terminate the study evidence of early benefit or harm. The DSMB will generate monthly reports to the IRB and FDA, and the DSMB Chair, the PI, the appropriate FDA officials will review SAE aggregates weekly or less often as appropriate to ensure appropriate safety oversight.

DSMB Membership

The DSMB membership will include:

Allan S. Jaffe, MD, - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN

William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL
10.2 ABBREVIATIONS

AE  Adverse Event
CFR  Code of Federal Regulations
CRF  Case Report Form
EC  Ethics Committee
eCRF  Electronic Case Report Forms
FDA  Food and Drug Administration
IB  Investigator’s Brochure
IND  Investigational New Drug Application
IRB  Institutional Review Board
NIH  National Institutes of Health
SAE  Serious Adverse Event
SAP  Statistical Analysis Plan
SOP  Standard Operating Procedure
US  United States

10.3 PROTOCOL AMENDMENT HISTORY

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<th>Brief Rationale</th>
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11 REFERENCES


   Pmid:32219429


   Pmid:32219428


   Pmid:25030060


   Pmid:29923831

Expanded Access to Convalescent Plasma for the
Treatment of Patients with COVID-19

Unique Protocol Identification Number: 20-003312
National Clinical Trial (NCT) Identified Number: 04338360
Principal Investigator: Michael Joyner, MD
IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
Version 4.0
15 April 2020

The Mayo Clinic IRB will serve as the IRB of record for all sites participating in this
protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the trial via
sign up on www.uscovidplasma.org will serve as documentation of each participating
institution’s reliance on Mayo’s IRB. A separate IRB reliance agreement is not required.

Summary of Changes from Previous Version:

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<th>Summary of Revisions Made</th>
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<td>Align with current procedures and consent</td>
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Statement of Compliance

The Expanded Access protocol will be carried out in accordance with applicable federal regulations:


Treating Physician Responsibilities

The Sponsor may contact the treating physician as appropriate for completion of all data forms in a timely manner. You agree to respond to the sponsor in a timely manner with complete information. Failure to comply will be in violation with the protocol.
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Study Description: This expanded access program will provide access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with one unit of ABO compatible convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events judged to be related to the administration of convalescent plasma. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

Objectives:
- Primary Objective: Provide access to COVID-19 convalescent plasma
- Secondary Objectives: Safety

Endpoints:
- Primary Endpoint: Availability of convalescent plasma
- Secondary Endpoints: Serious adverse events

Study Population: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

Phase: Expanded Access Program

Description of Sites/Facilities Enrolling Participants:
Acute care facilities treating patients with COVID-19

Description of Study Intervention:
Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

Study Duration: 12 months

Participant Duration: Patients will complete the study when they are discharged from the acute care facility in which the received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

☐ Eligibility Criteria Met

Inclusion Criteria

1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe disease defined as any of the following:
- dyspnea
- respiratory frequency > 30/min
- blood oxygen saturation < 93%
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- lung infiltrates > 50% within 24 to 48 hours

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☐ Informed consent obtained from patient or healthcare proxy

☐ Blood type obtained at local laboratory per local institutional procedures and policies

☐ Patient Registered with Red Cross (for tracking purposes)

☐ Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol

Patients may be premedicated with acetaminophen and diphenhydramine, per local practice

Recommended administration rate for plasma administration is 100 to 250 mL/hr

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4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused will be that of the full unit of COVID-19 convalescent plasma, or at least 200 mL.
4.4 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:
- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with the Red Cross. Since this involves the one-time administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

This expanded program will make available ABO compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA’s regulations and the additional considerations for convalescent plasma on FDA’s webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).5

6.1.1 STUDY INTERVENTION DESCRIPTION

ABO compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION

For practical purposes in the current outbreak, one – two units of ABO compatible COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (total volume of plasma to be administered approximately 200-500 mL), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL per unit). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine. The duration of infusion will usually take 1 to 2 hours (rate of 100 to 250 mL/hr).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

ABO compatible convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19 with either a label or tie tag on the bag indicating the presence of COVID-19 antibodies.

6.2.3 PRODUCT STORAGE AND STABILITY

Please see the AABB Circular of Information for product storage and stability.

6.2.4 PREPARATION

Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including ABO compatibility checks and thawing.
6.5 CONCOMITANT THERAPY

Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION
This study involves the one-time administration of ABO matched COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY
Patient are free to withdraw consent from participation in further data collection at any time during the study.

7.3 LOST TO FOLLOW-UP
Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex.

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting will only be required for serious adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma should be reported to the sponsor/principal investigator. Sponsor reports periodically to FDA.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner.
9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES
This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

9.2 SAMPLE SIZE DETERMINATION
This is an expanded access protocol that is intended to supply ABO compatible COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

9.3 POPULATIONS FOR ANALYSES
Serious adverse events will be collected on all treated individuals.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

9.4 STATISTICAL ANALYSES
Only exploratory statistical analyses will be performed as part of this expanded access program.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Below is a template of language that can be used for informed consent. The language has been deliberately streamlined for use in the setting of the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient’s health care proxy prior to treatment.

We request permission to use the exception from informed consent similar to that described in 21 CFR 50.23 as an alternative when written informed consent from the subject or a legally authorized representative (LAR)/health care proxy/family member is unavailable. We will utilize the following alternative informed consent method only when 1) the patient is unable to give written informed consent due to their illness and 2) there is no LAR/proxy/family available and 3) time is not sufficient to delay treatment due to the imminent risk of deterioration and/or disease progression.

In the event this alternative informed consent process is utilized, the treating physician/PI will document that the use of the EAP is justified on the data form and that a second, unaffiliated physician concurs and documents such concurrence in the medical record before administration of the convalescent plasma.

Example of a consent form for treatment with experimental convalescent plasma therapy follows.

IRB Reliance

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.
Safety Oversight
The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks of administered products and have sufficient research and trial experience to provide an independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate decision-making power to terminate the study evidence of early benefit or harm. The DSMB will generate monthly reports to the IRB and FDA, and the DSMB Chair, the PI, the appropriate FDA officials will review SAE aggregates weekly or less often as appropriate to ensure appropriate safety oversight.

DSMB Membership

The DSMB membership will include:

Allan S. Jaffe, MD, - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN

William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL
10.2 ABBREVIATIONS

AE  Adverse Event
CFR  Code of Federal Regulations
CRF  Case Report Form
EC  Ethics Committee
eCRF Electronic Case Report Forms
FDA  Food and Drug Administration
IB  Investigator’s Brochure
IND  Investigational New Drug Application
IRB  Institutional Review Board
NIH  National Institutes of Health
SAE  Serious Adverse Event
SAP  Statistical Analysis Plan
SOP Standard Operating Procedure
US  United States

10.3 PROTOCOL AMENDMENT HISTORY

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Description of Change</th>
<th>Brief Rationale</th>
</tr>
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<tr>
<td>1.0</td>
<td>4/1/2020</td>
<td>Initial Version</td>
<td>N/A</td>
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<tr>
<td>2.0</td>
<td>4/3/2020</td>
<td>Updated IND Number</td>
<td>Documentation</td>
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<tr>
<td></td>
<td></td>
<td>Added IRB Oversight</td>
<td>Clarification</td>
</tr>
<tr>
<td>3.0</td>
<td>4/9/2020</td>
<td>Updated Section 10.1.1.2 Consent Procedures and Documentation</td>
<td>Additional consenting procedures for patients unable to give consent and also no LAR available to give consent for patients qualifying for plasma infusion.</td>
</tr>
<tr>
<td>4.0</td>
<td>4/15/2020</td>
<td>Updated Section 6.1.2</td>
<td>Clarify 1-2 units of plasma and up to 500ml of volume delivered</td>
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</tbody>
</table>
REFERENCES


Pmid:32219429


Pmid:32219428


Pmid:25030060


Pmid:29923831

Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Unique Protocol Identification Number: 20-003312
National Clinical Trial (NCT) Identified Number: 04338360
Principal Investigator: Michael Joyner, MD
IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
Version 5.0
4 May 2020

The Mayo Clinic IRB will serve as the IRB of record for all sites participating in this protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the trial via sign up on www.uscovidplasma.org will serve as documentation of each participating institution’s reliance on Mayo’s IRB. A separate IRB reliance agreement is not required.

Summary of Changes from Previous Version:

<table>
<thead>
<tr>
<th>Affected Section(s)</th>
<th>Summary of Revisions Made</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Clarify 1 – 2 units of plasma</td>
<td>Consistency throughout protocol</td>
</tr>
<tr>
<td>1.2 and 5.2</td>
<td>Eligible patients will be registered with American Red Cross or other blood source by uscovidplasma.org</td>
<td>Clarification and consistency to coordinate patients and available plasma</td>
</tr>
<tr>
<td>1.2</td>
<td>Clarify infusion rate for plasma</td>
<td>Allow for flexibility to individual institutional and patient standards for care</td>
</tr>
<tr>
<td>4.3 and 6.1.2</td>
<td>Updated Sections 4.3 and 6.1.2 to define if 2 units are transfused the second unit must be transfused within 12 hours of first.</td>
<td>Reduce deviations and allow flexibility in scheduling if 2 units are administered.</td>
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<tr>
<td>6.2.2</td>
<td>Updated labeling of COVID-19 convalescent plasma</td>
<td>Align with current FDA guidance</td>
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<tr>
<td>8.2 &amp; 8.3</td>
<td>SAE reporting should be done using forms on website.</td>
<td>Clarify SAE reporting</td>
</tr>
<tr>
<td>9.3</td>
<td>Clarified collection of event information</td>
<td>Information should be collected from all consented and enrolled patients for whom plasma is ordered</td>
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<tr>
<td>9.5</td>
<td>Added Publication Plan</td>
<td>To clarify publication plans</td>
</tr>
<tr>
<td>10.1.1.1</td>
<td>Revised reference to informed consent document</td>
<td>IRB Approved Consent is available on the website not part of this document.</td>
</tr>
<tr>
<td>10.3</td>
<td>Clarified safety monitoring and updated DSMB Roster</td>
<td>Clarification and updates</td>
</tr>
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Statement of Compliance

The Expanded Access protocol will be carried out in accordance with applicable federal regulations:


Treating Physician Responsibilities

The Sponsor may contact the treating physician as appropriate for completion of all data forms in a timely manner. You agree to respond to the sponsor in a timely manner with complete information. Failure to comply will be in violation with the protocol.
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Study Description: This expanded access program will provide access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with one - two units of ABO compatible convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events judged to be related to the administration of convalescent plasma. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility.

Objectives:

Primary Objective: Provide access to COVID-19 convalescent plasma
Secondary Objectives: Safety

Endpoints:

Primary Endpoint: Availability of convalescent plasma
Secondary Endpoints: Serious adverse events

Study Population: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

Phase: Expanded Access Program

Description of Sites/Facilities
Enrolling Participants: Acute care facilities treating patients with COVID-19

Description of Study Intervention: Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

Study Duration: 12 months

Participant Duration: Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

☐ Eligibility Criteria Met

Inclusion Criteria

1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe disease defined as any of the following:
- dyspnea
- respiratory frequency > 30/min
- blood oxygen saturation < 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease defined as any of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

☐ Informed consent obtained from patient or healthcare proxy

☐ Blood type obtained at local laboratory per local institutional procedures and policies

Patient Registered with American Red Cross or other blood source by uscovidplasma.org.

☐ Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol

Patients may be premedicated with acetaminophen and diphenhydramine, per local practice

Recommended administration rate for plasma administration should follow best clinical practice procedures for the patient’s unique condition and your facility guidelines.

☐ Serious adverse events judged related to plasma infusion to be reported by patient to provider

☐ Reporting of patient demographics and acute care resource utilization

Information entered on COVID-19 Plasma Expanded Access Program secure website

(Information on plasma unit administered will be obtained directly from blood collector)
2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

2.2 BACKGROUND

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.1,2

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Plasma represents a licensed blood product, for which the risks are well described. These are the risks associated with the administration of plasma, including allergic reaction and viral infections. There is also the risk that convalescent plasma may be ineffective.

2.3.2 KNOWN POTENTIAL BENEFITS

COVID-19 convalescent plasma has not yet been demonstrated to provide clinical benefit in patients affected by this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The safety profile of plasma administration is well established. Taking into account the preliminary data available on the possible benefit of COVID-19 plasma along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, providing patients access to ABO compatible COVID-19 plasma as part of this expanded access protocol appears to reasonably balance potential risks with possible benefit that may outweigh such risks.
# 3 OBJECTIVES AND ENDPOINTS

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>ENDPOINTS</th>
<th>JUSTIFICATION FOR ENDPOINTS</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Availability of convalescent plasma</strong></td>
<td><strong>Expanded access protocol</strong></td>
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<tr>
<td>Provide access to COVID-19 convalescent plasma</td>
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<tr>
<td><strong>Secondary</strong></td>
<td><strong>Serious adverse events</strong></td>
<td><strong>Required as part of expanded access protocol under IND</strong></td>
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<tr>
<td>Safety</td>
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<tr>
<td><strong>Tertiary/Exploratory</strong></td>
<td><strong>Acute care facility length of stay</strong></td>
<td><strong>Evaluation of potential for efficacy</strong></td>
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<td>Health care utilization</td>
<td>1. Days spent in intensive care unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Survival to acute care facility discharge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Survival to acute care facility discharge</td>
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</tr>
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</table>
4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label expanded access program to make appropriately matched convalescent plasma available for the treatment of patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. COVID-19 convalescent plasma will be obtained from blood suppliers and will meet all regulatory requirements for conventional plasma and FDA's additional considerations for COVID-19 convalescent plasma (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds). Information collected following plasma administration will include serious adverse events judged by the treating physician to be potentially related to the administration of the plasma, as well as patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered. Due to the nature of the COVID-19 outbreak, data on patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered may be collected retrospectively.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola and other pathogens. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19. At this time there are few therapeutic options for the treatment of COVID-19 and no prophylactic vaccine is currently available. Based on the preliminary evidence of possible efficacy, this protocol is making convalescent plasma available to individuals with documented SARS-CoV-2 disease at acute care facilities who have severe or life-threatening COVID-19, or who are judged by a provider to be at high risk of progression to severe or life-threatening disease.

4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused will be that of 1-2 units of COVID-19 convalescent plasma, or approximately 200 mL per unit.
If a second unit of convalescent plasma is transfused, the treating physician will begin the transfusion of the second unit of convalescent plasma ≤ 12 hours following the completion of the transfusion of the first unit of convalescent plasma.

4.4 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:
- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with American Red Cross or other blood source by uscovidplasma.org. Since this involves the one-time administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

This expanded program will make available ABO compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA’s regulations and the additional considerations for convalescent plasma on FDA’s webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).5

6.1.1 STUDY INTERVENTION DESCRIPTION

ABO compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION

For practical purposes in the current outbreak, one – two units of ABO compatible COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (total volume of plasma to be administered approximately 200-500 mL), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL per unit). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine.

If a second unit of convalescent plasma is transfused, the treating physician will begin the transfusion of the second unit of convalescent plasma ≤ 12 hours following the completion of the transfusion of the first unit of convalescent plasma.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

ABO compatible convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19 The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.
6.2.3 PRODUCT STORAGE AND STABILITY
Please see the AABB Circular of Information for product storage and stability.

6.2.4 PREPARATION
Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including ABO compatibility checks and thawing.

6.5 CONCOMITANT THERAPY
Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION
This study involves the one-time administration of ABO matched COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY
Patients are free to withdraw consent from participation in further data collection at any time during the study.

7.3 LOST TO FOLLOW-UP
Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex.

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting is required for serious adverse events (SAEs); and we will ask the treating physician when reporting the event to determine if the event is potentially related to the administration of the COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events should be reported to the sponsor/principal investigator using the forms provided on the website (www.uscovidplasma.org). The sponsor/principal investigator is responsible to report to the FDA and IRB as required.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner by sending an email to uscovidplasma@mayo.edu
## 9 Statistical Considerations

### 9.1 Statistical Hypotheses
This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

### 9.2 Sample Size Determination
This is an expanded access protocol that is intended to supply ABO compatible COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

### 9.3 Populations for Analyses
Serious adverse event information will be collected on all consented and enrolled patients for whom convalescent plasma is ordered.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

### 9.4 Statistical Analyses
Exploratory statistical analyses will be performed as part of this expanded access program.

### 9.5 Publication Plan
The sponsor of this Expanded Access Program will limit the publication of any partial data collected by any participating treating physician or site without prior written authorization. With rare exceptions, such authorization will likely come after the sponsor has closed program enrollment, completed the data analysis and evaluated the final data set for the primary safety outcomes. The rationale for this approach is that the data being collected under the Convalescent Plasma EAP will be used to assess safety and help guide regulatory decision making. Thus, per FDA guidance, the data should not be subdivided until the sponsor has completed key safety (and to the extent possible) efficacy analyses.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The IRB approved informed consent form is available on the website www.uscovidplasma.org. The language has been deliberately streamlined for use in the setting of Expanded Access in the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient’s health care proxy prior to treatment.

We request permission to use the exception from informed consent similar to that described in 21 CFR 50.23 as an alternative when written informed consent from the subject or a legally authorized representative (LAR)/health care proxy/family member is unavailable. We will utilize the following alternative informed consent method only when

1) the patient is unable to give written informed consent due to their illness and
2) there is no LAR/proxy/family available and
3) time is not sufficient to delay treatment due to the imminent risk of deterioration and/or disease progression.

In the event this alternative informed consent process is utilized, the treating physician/PI will document that the use of the EAP is justified on the data form and that a second, unaffiliated physician concurs and documents such concurrence in the medical record before administration of the convalescent plasma.
10.2 IRB RELIANCE

IRB Reliance

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.

10.3 SAFETY OVERSIGHT

Safety Oversight

The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks of administered products and have sufficient research and trial experience to provide an independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate decision-making power to terminate the study evidence of early benefit or harm. The DSMB will generate regular reports to the IRB and FDA., The DSMB Chair, the regulatory sponsor, and additional team members will communicate with the appropriate FDA officials for review and guidance on study conduct. IND Safety Reports will be submitted to the FDA as required under the IND.

DSMB Membership

The DSMB membership will include:

Allan S. Jaffe, MD, - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN
William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Lawrence J. Appel, MD, MPH. David Molina, M.D., M.P.H. Professor of Medicine and International Health, and Nursing
Director, Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Medical Institution

Rickey E. Carter Ph.D.
Professor of Biostatistics
Mayo Clinic, Jacksonville Fl.

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL

Kristine Tree
Center for Individualized Medicine
Mayo Clinic, Rochester, MN
### 10.4 ABBREVIATIONS

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<th>Abbreviation</th>
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<td>AE</td>
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### 10.5 PROTOCOL AMENDMENT HISTORY

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<td>Section 8.2. and 8.3 SAE reporting should be done using forms on website.</td>
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<td>Information should be collected from all consented and enrolled patients for whom plasma is ordered</td>
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<td>Added Section 9.5 for Publication plans</td>
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<td>10.1.1.1 Revised reference to informed consent document</td>
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<td>Section 10.3 Clarified safety monitoring and updated DSMB Roster</td>
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11 REFERENCES


   Pmid:32219429


   Pmid:32219428


   Pmid:25030060


   Pmid:29923831

Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Unique Protocol Identification Number: 20-003312
National Clinical Trial (NCT) Identified Number: 04338360
Principal Investigator: Michael Joyner, MD
IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
Version 6.0
15 May 2020

The Mayo Clinic IRB will serve as the IRB of record for all sites participating in this protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the trial via sign up on www.uscovidplasma.org will serve as documentation of each participating institution’s reliance on Mayo’s IRB. A separate IRB reliance agreement is not required.

Summary of Changes from Previous Version:

<table>
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<tr>
<th>Affected Section(s)</th>
<th>Summary of Revisions Made</th>
<th>Rationale</th>
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<tr>
<td>Throughout Protocol</td>
<td>Removed reference to ABO</td>
<td>See New Section 4.4</td>
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<td>4.3</td>
<td>Dose justification of volume of convalescent plasma</td>
<td>The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities and allowance for multiple doses.</td>
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<td>4.4</td>
<td>Section Added to define preference for ABO compatible.</td>
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<td>Response to provide consistency between sections 4.3, 5.2, and 7.1</td>
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<td>Process for informing the IRB of the number of Emergency Use consent clarified.</td>
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Statement of Compliance

The Expanded Access protocol will be carried out in accordance with applicable federal regulations:


Treating Physician Responsibilities

The Sponsor may contact the treating physician as appropriate for completion of all data forms in a timely manner. You agree to respond to the sponsor in a timely manner with complete information. Failure to comply will be in violation with the protocol.
1.1 SYNOPSIS

Title: Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Study Description: This expanded access program will provide access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with one (or more) units of compatible convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

Objectives: Primary Objective: Provide access to COVID-19 convalescent plasma
Secondary Objectives: Safety

Endpoints: Primary Endpoint: Availability of convalescent plasma
Secondary Endpoints: Serious adverse events

Study Population: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

Phase: Expanded Access Program

Description of Sites/Facilities Enrolling Participants: Acute care facilities treating patients with COVID-19

Description of Study Intervention: Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

Study Duration: 12 months

Participant Duration: Patients will complete the study when they are discharged from the acute care facility in which the received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

☐ Eligibility Criteria Met

Inclusion Criteria

1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe disease defined as any of the following:
• dyspnea
• respiratory frequency > 30/min
• blood oxygen saturation ≤ 93%
• partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
• lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease defined as any of the following:
• respiratory failure
• septic shock
• multiple organ dysfunction or failure

☐ Informed consent obtained from patient or healthcare proxy

☐ Blood type obtained at local laboratory per local institutional procedures and policies

Patient Registered with American Red Cross or other blood source by uscovidplasma.org.

☐ Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol

Patients may be premedicated with acetaminophen and diphenhydramine, per local practice

Recommended administration rate for plasma administration should follow best clinical practice procedures for the patient’s unique condition and your facility guidelines.

☐ Serious adverse events observed by the treating physician or reported by patient to provider

☐ Reporting of patient demographics and acute care resource utilization

Information entered on COVID-19 Plasma Expanded Access Program secure website

(Information on plasma unit administered will be obtained directly from blood collector)
2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

2.2 BACKGROUND

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.1,2

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Plasma represents a licensed blood product, for which the risks are well described. These are the risks associated with the administration of plasma, including allergic reaction and viral infections. There is also the risk that convalescent plasma may be ineffective.

2.3.2 KNOWN POTENTIAL BENEFITS

COVID-19 convalescent plasma has not yet been demonstrated to provide clinical benefit in patients affected by this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The safety profile of plasma administration is well established. Taking into account the preliminary data available on the possible benefit of COVID-19 plasma along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, providing patients access to compatible COVID-19 plasma as part of this expanded access protocol appears to reasonably balance potential risks with possible benefit that may outweigh such risks.
### 3 OBJECTIVES AND ENDPOINTS

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</table>
4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label expanded access program to make appropriately matched convalescent plasma available for the treatment of patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. COVID-19 convalescent plasma will be obtained from blood suppliers and will meet all regulatory requirements for conventional plasma and FDA’s additional considerations for COVID-19 convalescent plasma (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds). Information collected following plasma administration will include serious adverse events, as well as patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered. Due to the nature of the COVID-19 outbreak, data on patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered may be collected retrospectively.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola and other pathogens. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19. At this time there are few therapeutic options for the treatment of COVID-19 and no prophylactic vaccine is currently available. Based on the preliminary evidence of possible efficacy, this protocol is making convalescent plasma available to individuals with documented SARS-CoV-2 disease at acute care facilities who have severe or life-threatening COVID-19, or who are judged by a provider to be at high risk of progression to severe or life-threatening disease.
4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities (e.g. patients with impaired cardiac function and heart failure may require less volume or more prolonged transfusion times). The volume of plasma to be transfused should be at least one unit (approximately 200 mL) but may be greater if the treating clinician concludes a larger volume is appropriate. Transfusions may occur at any time throughout the hospitalization including multiple doses on non-sequential days. In general, it is expected that most patients will receive two units or less, but this language is not intended to restrict the use of convalescent plasma in larger quantities when the treating physician determines that such volumes and/or re-treatment are clinically justified.

4.4 CONVALESCENT PLASMA COMPATIBILITY

ABO compatible convalescent plasma will be transfused preferentially. In the absence of ABO compatible plasma, patients may receive as a second choice either Group A plasma or low anti-A titer Group O plasma, as available.

4.5 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:

- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:

- respiratory failure
- septic shock
- multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with American Red Cross or other blood source by uscovidplasma.org. Since this involves the administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

This expanded program will make available compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA’s regulations and the additional considerations for convalescent plasma on FDA’s webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).

6.1.1 STUDY INTERVENTION DESCRIPTION

Compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION

For practical purposes in the current outbreak, one – two units of compatible COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (total volume of plasma to be administered will be approximately 200 mL or more), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL per unit). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine.

If a subsequent unit of convalescent plasma is transfused, the treating physician will begin the transfusion at a time that is clinically compatible with the patient’s underlying condition.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Compatible convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19. The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug--Limited by Federal (or United States) law to investigational use.” (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.
6.2.3 PRODUCT STORAGE AND STABILITY
Please see the AABB Circular of Information for product storage and stability.

6.2.4 PREPARATION
Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including compatibility checks and thawing.

6.3 CONCOMITANT THERAPY
Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
## 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1 DISCONTINUATION OF STUDY INTERVENTION
This study involves the administration of compatible COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

### 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY
Patients are free to withdraw consent from participation in further data collection at any time during the study.
Study team encouragement of withdrawal from the EAP as a strategy to avoid completion of follow-up data requirements is not allowed.

### 7.3 LOST TO FOLLOW-UP
Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex.

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting is required for serious adverse events (SAEs); and we will ask the treating physician when reporting the event to determine if the event is potentially related to the administration of the COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events should be reported, by the treating physician to the sponsor/principal investigator using the forms provided on the website (www.uscovidplasma.org).

The sponsor/principal investigator is responsible for filing reports to the FDA and IRB as required.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner by sending an email to uscovidplasma@mayo.edu
9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES
This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

9.2 SAMPLE SIZE DETERMINATION
This is an expanded access protocol that is intended to supply compatible COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

9.3 POPULATIONS FOR ANALYSES
Serious adverse event information will be collected on all consented and enrolled patients for whom convalescent plasma is ordered.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

9.4 STATISTICAL ANALYSES
Exploratory statistical analyses will be performed as part of this expanded access program.

9.5 PUBLICATION PLAN
The sponsor of this Expanded Access Program will limit the publication of any partial data collected by any participating treating physician or site without prior written authorization. With rare exceptions, such authorization will likely come after the sponsor has closed program enrollment, completed the data analysis and evaluated the final data set for the primary safety outcomes.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The IRB approved informed consent form is available on the website www.uscovidplasma.org. The language has been deliberately streamlined for use in the setting of Expanded Access in the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient's health care proxy prior to treatment.

Expanded access to an investigational drug for treatment use, including emergency use, requires informed consent as described in 21 CFR part 50. Informed consent may be deemed infeasible if, in accordance with 21 CFR 50.23, the investigator and another physician who is not otherwise participating in the protocol certify in writing all of the following:

1. The patient is confronted by a life-threatening situation necessitating use of convalescent plasma

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

3. Time is not sufficient to obtain consent from the patient’s LAR

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

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 above, the determinations of the 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.
The investigator upon documentation of the use of emergency consent notifies the Mayo Clinic IRB via the web based patient entry portal. The study cannot proceed with an order for convalescent plasma until the documentation is complete. The IRB Senior Chair and medical director receives a daily update of study enrollment and key metrics. We will make sure this measure is also included in the daily report.

The computer system will generate a weekly report for the IRB office as a backup of the notification so that the IRB has the original and a backup notification. These will be submitted to the IRB office as notation items.

10.2 IRB RELIANCE

IRB Reliance

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.

10.3 SAFETY OVERSIGHT

Safety Oversight

The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks of administered products and have sufficient research and trial experience to provide an independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate decision-making power to terminate the study evidence of early benefit or harm. The DSMB will generate regular reports to the IRB and FDA., The DSMB Chair, the regulatory sponsor, and additional team members will communicate with the appropriate FDA officials for review and guidance on study conduct. IND Safety Reports will be submitted to the FDA as required under the IND.
DSMB Membership
The DSMB membership will include:

Allan S. Jaffe, MD, - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN

William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Lawrence J. Appel, MD, MPH. David Molina, M.D., M.P.H. Professor of Medicine and
International Health, and Nursing
Director, Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Medical Institution

Rickey E. Carter Ph.D.
Professor of Biostatistics
Mayo Clinic, Jacksonville Fl.

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL

Kristine Tree
Center for Individualized Medicine
Mayo Clinic, Rochester, MN
10.4 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Forms</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
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<td>US</td>
<td>United States</td>
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10.5 PROTOCOL AMENDMENT HISTORY

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Description of Change</th>
<th>Brief Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>4/1/2020</td>
<td>Initial Version</td>
<td>N/A</td>
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<tr>
<td>2.0</td>
<td>4/3/2020</td>
<td>Updated IND Number Added IRB Oversight</td>
<td>Documentation Clarification</td>
</tr>
<tr>
<td>3.0</td>
<td>4/9/2020</td>
<td>Updated Section 10.1.1.2 Consent Procedures and Documentation</td>
<td>Additional consenting procedures for patients unable to give consent and also no LAR available to give consent for patients qualifying for plasma infusion.</td>
</tr>
<tr>
<td>4.0</td>
<td>4/15/2020</td>
<td>Updated Section 6.1.2</td>
<td>Clarify 1-2 units of plasma and up to 500ml of volume delivered</td>
</tr>
<tr>
<td>5.0</td>
<td>4/23/2020</td>
<td>Study synopsis clarified to be consistent throughout 1-2 units</td>
<td>Consistency throughout protocol that 1-2 units of plasma may be administered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 1.2 and 5.2 Eligible patients will be registered with American Red Cross or other blood source by uscovidplasma.org</td>
<td>Clarification and consistency to coordinate patients and available plasma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 1.2 Clarify infusion rate for plasma deleted specific rate.</td>
<td>Allow for flexibility to individual institutional and patient standards for care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Updated Sections 4.3 and 6.1.2 to define if 2 units are transfused the second unit must be transfused within 12 hours of first.</td>
<td>Reduce deviations and allow flexibility in scheduling if 2 units are administered.</td>
</tr>
<tr>
<td>Updated Labeling in Section 6.2.2</td>
<td>Align with current FDA Guidance.</td>
<td></td>
<td></td>
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<tr>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td></td>
<td></td>
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<tr>
<td>Section 8.2. and 8.3 SAE reporting should be done using forms on website.</td>
<td>Clarify SAE reporting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Section 9.3 Clarified collection of event information</td>
<td>Information should be collected from all consented and enrolled patients for whom plasma is ordered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Added Section 9.5 for Publication plans</td>
<td>Clarify Publication Plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.1.1.1 Revised reference to informed consent document</td>
<td>IRB Approved Consent is available on the website not part of this document.</td>
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<td></td>
</tr>
<tr>
<td>Section 10.3 Clarified safety monitoring and updated DSMB Roster</td>
<td>Clarification and updates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 6.0 | 5/15/2020 | Throughout the protocol, removed reference to ABO |
|-----------------------------------|-----------------------------------|
| Section 4.3 - Dose justification of volume of convalescent plasma | The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities and allowance for multiple doses. |
| Section 4.4 - Added to define preference for ABO compatible | ABO compatible convalescent plasma will be transfused preferentially. In the absence of ABO compatible plasma, patients may receive as a second choice either Group A plasma or low anti-A titer Group O plasma, as available |
| Sections 5.2 & 7.1 - Clarifications for dosing and administration | To provide consistency between sections 4.3, 5.2, and 7.1. |
| Section 6.1.2 - Dosing and administration changed to subsequent units | To align with Section 4.3 |
| Section 10.1.1.2 - Process for informing the IRB of the number of Emergency Use consent clarified | To maintain communication with the IRB to provide the number of cases of Emergency Use consenting. |
11 REFERENCES

REFERENCES


Pmid:32219429


Pmid:32219428


Pmid:25030060


Pmid:29923831

Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Unique Protocol Identification Number: 20-003312
National Clinical Trial (NCT) Identified Number: 04338360
Principal Investigator: Michael Joyner, MD
IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
Version 7.0
23 May 2020

The Mayo Clinic IRB will serve as the IRB of record for all sites participating in this protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the trial via sign up on www.uscovidplasma.org will serve as documentation of each participating institution’s reliance on Mayo’s IRB. A separate IRB reliance agreement is not required.

Summary of Changes from Previous Version:

<table>
<thead>
<tr>
<th>Affected Section(s)</th>
<th>Summary of Revisions Made</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throughout Protocol</td>
<td>Changed the description of the investigational product to just be Convalescent Plasma.</td>
<td>The term “compatible” was removed since there is now the alternative to follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits</td>
</tr>
<tr>
<td>4.4</td>
<td>Changed the description for plasma compatibility, ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits</td>
<td>FDA Request for clarifications</td>
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Statement of Compliance

The Expanded Access protocol will be carried out in accordance with applicable federal regulations:


Treating Physician Responsibilities

The Sponsor may contact the treating physician as appropriate for completion of all data forms in a timely manner. You agree to respond to the sponsor in a timely manner with complete information. Failure to comply will be in violation with the protocol.
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Study Description: This expanded access program will provide access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with one (or more) units of convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility.

Objectives: Primary Objective: Provide access to COVID-19 convalescent plasma
Secondary Objectives: Safety

Endpoints: Primary Endpoint: Availability of convalescent plasma
Secondary Endpoints: Serious adverse events

Study Population: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

Phase: Expanded Access Program

Description of Sites/Facilities Enrolling Participants: Acute care facilities treating patients with COVID-19

Description of Study Intervention: Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

Study Duration: 12 months

Participant Duration: Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

☐ Eligibility Criteria Met

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)</td>
</tr>
<tr>
<td>2. Laboratory confirmed diagnosis of infection with SARS-CoV-2</td>
</tr>
<tr>
<td>3. Admitted to an acute care facility for the treatment of COVID-19 complications</td>
</tr>
<tr>
<td>4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease</td>
</tr>
<tr>
<td>5. Informed consent provided by the patient or healthcare proxy</td>
</tr>
</tbody>
</table>

Severe disease defined as any of the following:
- dyspnea
- respiratory frequency > 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease defined as any of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

☐ Informed consent obtained from patient or healthcare proxy

☐ Blood type obtained at local laboratory per local institutional procedures and policies

Patient Registered with American Red Cross or other blood source by uscovidplasma.org.

☐ Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol

Patients may be premedicated with acetaminophen and diphenhydramine, per local practice

Recommended administration rate for plasma administration should follow best clinical practice procedures for the patient’s unique condition and your facility guidelines.

☐ Serious adverse events observed by the treating physician or reported by patient to provider

☐ Reporting of patient demographics and acute care resource utilization

Information entered on COVID-19 Plasma Expanded Access Program secure website

(Information on plasma unit administered will be obtained directly from blood collector)
2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

2.2 BACKGROUND

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.1,2

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Plasma represents a licensed blood product, for which the risks are well described. These are the risks associated with the administration of plasma, including allergic reaction and viral infections. There is also the risk that convalescent plasma may be ineffective.

2.3.2 KNOWN POTENTIAL BENEFITS

COVID-19 convalescent plasma has not yet been demonstrated to provide clinical benefit in patients affected by this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The safety profile of plasma administration is well established. Taking into account the preliminary data available on the possible benefit of COVID-19 plasma along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, providing patients access to compatible COVID-19 plasma as part of this expanded access protocol appears to reasonably balance potential risks with possible benefit that may outweigh such risks.
### 3 OBJECTIVES AND ENDPOINTS

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>ENDPOINTS</th>
<th>JUSTIFICATION FOR ENDPOINTS</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide access to COVID-19</td>
<td>Availability of convalescent plasma</td>
<td>Expanded access protocol</td>
</tr>
<tr>
<td>convalescent plasma</td>
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<tr>
<td><strong>Secondary</strong></td>
<td></td>
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<tr>
<td>Safety</td>
<td>Serious adverse events</td>
<td>Required as part of expanded access protocol under IND</td>
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<tr>
<td><strong>Tertiary/Exploratory</strong></td>
<td></td>
<td></td>
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<tr>
<td>Health care utilization</td>
<td>1. Acute care facility length of stay</td>
<td>Evaluation of potential for efficacy</td>
</tr>
<tr>
<td></td>
<td>2. Days spent in intensive care unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Survival to acute care facility discharge</td>
<td></td>
</tr>
</tbody>
</table>
4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label expanded access program to make appropriately matched convalescent plasma available for the treatment of patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. COVID-19 convalescent plasma will be obtained from blood suppliers and will meet all regulatory requirements for conventional plasma and FDA’s additional considerations for COVID-19 convalescent plasma (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds). Information collected following plasma administration will include serious adverse events, as well as patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered. Due to the nature of the COVID-19 outbreak, data on patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered may be collected retrospectively.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola and other pathogens. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19. At this time there are few therapeutic options for the treatment of COVID-19 and no prophylactic vaccine is currently available. Based on the preliminary evidence of possible efficacy, this protocol is making convalescent plasma available to individuals with documented SARS-CoV-2 disease at acute care facilities who have severe or life-threatening COVID-19, or who are judged by a provider to be at high risk of progression to severe or life-threatening disease.
4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities (e.g. patients with impaired cardiac function and heart failure may require less volume or more prolonged transfusion times). The volume of plasma to be transfused should be at least one unit (approximately 200 mL) but may be greater if the treating clinician concludes a larger volume is appropriate. Transfusions may occur at any time throughout the hospitalization including multiple doses on non-sequential days. In general, it is expected that most patients will receive two units or less, but this language is not intended to restrict the use of convalescent plasma in larger quantities when the treating physician determines that such volumes and/or re-treatment are clinically justified.

4.4 CONVALESCENT PLASMA COMPATIBILITY

ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.

4.5 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:
- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with American Red Cross or other blood source by uscovidplasma.org. Since this involves the administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

This expanded program will make available compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA's regulations and the additional considerations for convalescent plasma on FDA's webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).5

6.1.1 STUDY INTERVENTION DESCRIPTION

Compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION

For practical purposes in the current outbreak, one – two units of COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (total volume of plasma to be administered will be approximately 200 mL or more), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL per unit). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine.

If a subsequent unit of convalescent plasma is transfused, the treating physician will begin the transfusion at a time that is clinically compatible with the patient’s underlying condition.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19. The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug--Limited by Federal (or United States) law to investigational use.” (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.
6.2.3 PRODUCT STORAGE AND STABILITY
Please see the AABB Circular of Information for product storage and stability.

6.2.4 PREPARATION
Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including compatibility checks and thawing.

6.3 CONCOMITANT THERAPY
Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION
This study involves the administration of COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY
Patients are free to withdraw consent from participation in further data collection at any time during the study.
Study team encouragement of withdrawal from the EAP as a strategy to avoid completion of follow-up data requirements is not allowed.

7.3 LOST TO FOLLOW-UP
Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex.

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting is required for serious adverse events (SAEs); and we will ask the treating physician when reporting the event to determine if the event is potentially related to the administration of the COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events should be reported, by the treating physician to the sponsor/principal investigator using the forms provided on the website (www.uscovidplasma.org).

The sponsor/principal investigator is responsible for filing reports to the FDA and IRB as required.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner by sending an email to uscovidplasma@mayo.edu
9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES
This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

9.2 SAMPLE SIZE DETERMINATION
This is an expanded access protocol that is intended to supply COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

9.3 POPULATIONS FOR ANALYSES
Serious adverse event information will be collected on all consented and enrolled patients for whom convalescent plasma is ordered.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

9.4 STATISTICAL ANALYSES
Exploratory statistical analyses will be performed as part of this expanded access program.

9.5 PUBLICATION PLAN
The sponsor of this Expanded Access Program will limit the publication of any partial data collected by any participating treating physician or site without prior written authorization. With rare exceptions, such authorization will likely come after the sponsor has closed program enrollment, completed the data analysis and evaluated the final data set for the primary safety outcomes.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The IRB approved informed consent form is available on the website www.uscovidplasma.org. The language has been deliberately streamlined for use in the setting of Expanded Access in the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient’s health care proxy prior to treatment.

Expanded access to an investigational drug for treatment use, including emergency use, requires informed consent as described in 21 CFR part 50. Informed consent may be deemed infeasible if, in accordance with 21 CFR 50.23, the investigator and another physician who is not otherwise participating in the protocol certify in writing all of the following:

1. The patient is confronted by a life-threatening situation necessitating use of convalescent plasma

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

3. Time is not sufficient to obtain consent from the patient’s LAR

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

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 above, the determinations of the 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.
The investigator upon documentation of the use of emergency consent notifies the Mayo Clinic IRB via the web based patient entry portal. The study cannot proceed with an order for convalescent plasma until the documentation is complete. The IRB Senior Chair and medical director receives a daily update of study enrollment and key metrics. We will make sure this measure is also included in the daily report.

The computer system will generate a weekly report for the IRB office as a backup of the notification so that the IRB has the original and a backup notification. These will be submitted to the IRB office as notation items.

10.2 IRB RELIANCE

IRB Reliance

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.

10.3 SAFETY OVERSIGHT

Safety Oversight

The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks of administered products and have sufficient research and trial experience to provide an independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate decision-making power to terminate the study evidence of early benefit or harm. The DSMB will generate regular reports to the IRB and FDA. The DSMB Chair, the regulatory sponsor, and additional team members will communicate with the appropriate FDA officials for review and guidance on study conduct. IND Safety Reports will be submitted to the FDA as required under the IND.
DSMB Membership
The DSMB membership will include:

Allan S. Jaffe, MD - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN

William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Lawrence J. Appel, MD, MPH, David Molina, M.D., M.P.H. Professor of Medicine and
International Health, and Nursing
Director, Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Medical Institution

Rickey E. Carter Ph.D.
Professor of Biostatistics
Mayo Clinic, Jacksonville Fl.

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL

Kristine Tree
Center for Individualized Medicine
Mayo Clinic, Rochester, MN
10.4 ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Forms</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>US</td>
<td>United States</td>
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## 10.5 PROTOCOL AMENDMENT HISTORY

<table>
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<tr>
<th>Version</th>
<th>Date</th>
<th>Description of Change</th>
<th>Brief Rationale</th>
</tr>
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<tbody>
<tr>
<td>1.0</td>
<td>4/1/2020</td>
<td>Initial Version</td>
<td>N/A</td>
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<tr>
<td>2.0</td>
<td>4/3/2020</td>
<td>Updated IND Number</td>
<td>Documentation</td>
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<td></td>
<td></td>
<td>Added IRB Oversight</td>
<td>Clarification</td>
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<tr>
<td>3.0</td>
<td>4/9/2020</td>
<td>Updated Section 10.1.1.2 Consent Procedures and Documentation</td>
<td>Additional consenting procedures for patients unable to give consent and also no LAR available to give consent for patients qualifying for plasma infusion.</td>
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<tr>
<td>4.0</td>
<td>4/15/2020</td>
<td>Updated Section 6.1.2</td>
<td>Clarify 1-2 units of plasma and up to 500ml of volume delivered</td>
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<tr>
<td>5.0</td>
<td>4/23/2020</td>
<td>Study synopsis clarified to be consistent throughout 1-2 units</td>
<td>Consistency throughout protocol that 1-2 units of plasma may be administered</td>
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<tr>
<td></td>
<td></td>
<td>Section 1.2 and 5.2 Eligible patients will be registered with American Red Cross or other blood source by uscovidplasma.org</td>
<td>Clarification and consistency to coordinate patients and available plasma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 1.2 Clarify infusion rate for plasma deleted specific rate.</td>
<td>Allow for flexibility to individual institutional and patient standards for care</td>
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<tr>
<td></td>
<td></td>
<td>Updated Sections 4.3 and 6.1.2 to define if 2 units are transfused the second unit must be transfused within 12 hours of first.</td>
<td>Reduce deviations and allow flexibility in scheduling if 2 units are administered.</td>
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<tr>
<td></td>
<td></td>
<td>Updated Labeling in Section 6.2.2</td>
<td>Align with current FDA Guidance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 8.2. and 8.3 SAE reporting should be done using forms on website.</td>
<td>Clarify SAE reporting</td>
</tr>
<tr>
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<td></td>
<td>Section 9.3 Clarified collection of event information</td>
<td>Information should be collected from all consented and enrolled patients for whom plasma is ordered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Added Section 9.5 for Publication plans</td>
<td>Clarify Publication Plan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.1.1.1 Revised reference to informed consent document</td>
<td>IRB Approved Consent is available on the website not part of this document.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 10.3 Clarified safety monitoring and updated DSMB Roster</td>
<td>Clarification and updates</td>
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<tr>
<td>6.0</td>
<td>5/15/2020</td>
<td>Throughout the protocol, removed reference to ABO</td>
<td>See New Section 4.4</td>
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<td></td>
<td>Section 4.3 - Dose justification of volume of convalescent plasma</td>
<td>The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities and allowance for multiple doses.</td>
</tr>
<tr>
<td>Version</td>
<td>Date</td>
<td>Description of Change</td>
<td>Brief Rationale</td>
</tr>
<tr>
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</tr>
<tr>
<td>7.0</td>
<td></td>
<td>Section 4.4 - Added to define preference for ABO compatible.</td>
<td>ABO compatible convalescent plasma will be transfused preferentially. In the absence of ABO compatible plasma, patients may receive as a second choice either Group A plasma or low anti-A titer Group O plasma, as available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sections 5.2 &amp; 7.1 - Clarifications for dosing and administration</td>
<td>To provide consistency between sections 4.3, 5.2, and 7.1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 6.1.2 - Dosing and administration changed to subsequent units</td>
<td>To align with Section 4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 10.1.1.2 - Process for informing the IRB of the number of Emergency Use consent clarified.</td>
<td>To maintain communication with the IRB to provide the number of cases of Emergency Use consenting.</td>
</tr>
<tr>
<td>7.0</td>
<td></td>
<td>Throughout the protocol, changed the description of the investigational product to just be Convalescent Plasma.</td>
<td>The term “compatible” was removed since there is now the alternative to follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 4.4 - Changed the description for plasma compatibility, ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits</td>
<td>FDA Request for clarifications</td>
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# REFERENCES


   Pmid:32219429


   Pmid:32219428


   Pmid:25030060


   Pmid:29923831

Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Unique Protocol Identification Number: 20-003312
National Clinical Trial (NCT) Identified Number: 04338360
Principal Investigator: Michael Joyner, MD
IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
Version 8.0
16 June 2020

The Mayo Clinic IRB will serve as the IRB of record for all sites participating in this protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the trial via sign up on www.uscovidplasma.org will serve as documentation of each participating institution’s reliance on Mayo’s IRB. A separate IRB reliance agreement is not required.

Summary of Changes from Previous Version:

<table>
<thead>
<tr>
<th>Affected Section(s)</th>
<th>Summary of Revisions Made</th>
<th>Rationale</th>
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</thead>
<tbody>
<tr>
<td>4.5</td>
<td>End of study definition is either discharge from acute care facility, or, 30 day after most recent COVID-19 convalescent plasma transfusion.</td>
<td>Clarification of end of study definition.</td>
</tr>
<tr>
<td>6.2.2</td>
<td>Labeling of COVID-19 convalescent plasma should include a label to indicate presence of COVID-19 antibodies, if testing is available.</td>
<td>Alignment with guidance from FDA.</td>
</tr>
<tr>
<td>8.4</td>
<td>Updated email address for reporting of other unanticipated issues, <a href="mailto:uscovidplasmaevents@mayo.edu">uscovidplasmaevents@mayo.edu</a></td>
<td>Specially designated email for reporting other unanticipated issues.</td>
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Statement of Compliance

The Expanded Access protocol will be carried out in accordance with applicable federal regulations:


Treating Physician Responsibilities

The Sponsor may contact the treating physician as appropriate for completion of all data forms in a timely manner. You agree to respond to the sponsor in a timely manner with complete information. Failure to comply will be in violation with the protocol.
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Study Description: This expanded access program will provide access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with one (or more) units of convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility.

Objectives: Primary Objective: Provide access to COVID-19 convalescent plasma
Secondary Objectives: Safety

Endpoints: Primary Endpoint: Availability of convalescent plasma
Secondary Endpoints: Serious adverse events

Study Population: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

Phase: Expanded Access Program

Description of Sites/Facilities Enrolling Participants: Acute care facilities treating patients with COVID-19

Description of Study Intervention: Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

Study Duration: 12 months

Participant Duration: Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

☐ Eligibility Criteria Met

Inclusion Criteria

1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe disease defined as any of the following:
• dyspnea
• respiratory frequency > 30/min
• blood oxygen saturation ≤ 93%
• partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
• lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease defined as any of the following:
• respiratory failure
• septic shock
• multiple organ dysfunction or failure

☐ Informed consent obtained from patient or healthcare proxy

☐ Blood type obtained at local laboratory per local institutional procedures and policies

Patient Registered with American Red Cross or other blood source by uscovidplasma.org.

☐ Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol

Patients may be premedicated with acetaminophen and diphenhydramine, per local practice

Recommended administration rate for plasma administration should follow best clinical practice procedures for the patient’s unique condition and your facility guidelines.

☐ Serious adverse events observed by the treating physician or reported by patient to provider

☐ Reporting of patient demographics and acute care resource utilization

Information entered on COVID-19 Plasma Expanded Access Program secure website

(Information on plasma unit administered will be obtained directly from blood collector)
2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

2.2 BACKGROUND

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.\(^1\)\(^2\)

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Plasma represents a licensed blood product, for which the risks are well described. These are the risks associated with the administration of plasma, including allergic reaction and viral infections. There is also the risk that convalescent plasma may be ineffective.

2.3.2 KNOWN POTENTIAL BENEFITS

COVID-19 convalescent plasma has not yet been demonstrated to provide clinical benefit in patients affected by this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The safety profile of plasma administration is well established. Taking into account the preliminary data available on the possible benefit of COVID-19 plasma along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, providing patients access to compatible COVID-19 plasma as part of this expanded access protocol appears to reasonably balance potential risks with possible benefit that may outweigh such risks.
## 3 OBJECTIVES AND ENDPOINTS

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>ENDPOINTS</th>
<th>JUSTIFICATION FOR ENDPOINTS</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
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<tr>
<td>Provide access to COVID-19</td>
<td>Availability of convalescent plasma</td>
<td>Expanded access protocol</td>
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<td>convalescent plasma</td>
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<td><strong>Secondary</strong></td>
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<tr>
<td>Safety</td>
<td>Serious adverse events</td>
<td>Required as part of expanded access protocol under IND</td>
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<td><strong>Tertiary/Exploratory</strong></td>
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<td>Health care utilization</td>
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<td></td>
<td>2. Days spent in intensive care unit</td>
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<td>3. Survival to acute care facility discharge</td>
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4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label expanded access program to make appropriately matched convalescent plasma available for the treatment of patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. COVID-19 convalescent plasma will be obtained from blood suppliers and will meet all regulatory requirements for conventional plasma and FDA’s additional considerations for COVID-19 convalescent plasma (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds). Information collected following plasma administration will include serious adverse events, as well as patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered. Due to the nature of the COVID-19 outbreak, data on patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered may be collected retrospectively.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola and other pathogens.\(^3\) Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course.\(^4,3\) Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19.\(^1,2\) At this time there are few therapeutic options for the treatment of COVID-19 and no prophylactic vaccine is currently available. Based on the preliminary evidence of possible efficacy, this protocol is making convalescent plasma available to individuals with documented SARS-CoV-2 disease at acute care facilities who have severe or life-threatening COVID-19, or who are judged by a provider to be at high risk of progression to severe or life-threatening disease.
4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities (e.g., patients with impaired cardiac function and heart failure may require less volume or more prolonged transfusion times). The volume of plasma to be transfused should be at least one unit (approximately 200 mL) but may be greater if the treating clinician concludes a larger volume is appropriate. Transfusions may occur at any time throughout the hospitalization including multiple doses on non-sequential days. In general, it is expected that most patients will receive two units or less, but this language is not intended to restrict the use of convalescent plasma in larger quantities when the treating physician determines that such volumes and/or re-treatment are clinically justified.

4.4 CONVALESCENT PLASMA COMPATIBILITY

ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.

4.5 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma or 30 days after most recent convalescent plasma transfusion whichever comes first.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:
- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with American Red Cross or other blood source by uscovidplasma.org. Since this involves the administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

This expanded program will make available compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA’s regulations and the additional considerations for convalescent plasma on FDA’s webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).5

6.1.1 STUDY INTERVENTION DESCRIPTION

Compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION

For practical purposes in the current outbreak, one – two units of COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (total volume of plasma to be administered will be approximately 200 mL or more), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL per unit). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine.

If a subsequent unit of convalescent plasma is transfused, the treating physician will begin the transfusion at a time that is clinically compatible with the patient’s underlying condition.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19. A label or tie tag on the bag should indicate the presence of COVID-19 antibodies, if testing is available.

The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug—Limited by Federal (or United States) law to investigational use." (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.
6.2.3 PRODUCT STORAGE AND STABILITY
Please see the AABB Circular of Information for product storage and stability.

6.2.4 PREPARATION
Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including compatibility checks and thawing.

6.3 CONCOMITANT THERAPY
Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION
This study involves the administration of COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY
Patients are free to withdraw consent from participation in further data collection at any time during the study.
Study team encouragement of withdrawal from the EAP as a strategy to avoid completion of follow-up data requirements is not allowed.

7.3 LOST TO FOLLOW-UP
Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex.

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting is required for serious adverse events (SAEs); and we will ask the treating physician when reporting the event to determine if the event is potentially related to the administration of the COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events should be reported, by the treating physician to the sponsor/principal investigator using the forms provided on the website (www.uscovidplasma.org).

The sponsor/principal investigator is responsible for filing reports to the FDA and IRB as required.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner by sending an email to uscovidplasmaevents@mayo.edu.
9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES
This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

9.2 SAMPLE SIZE DETERMINATION
This is an expanded access protocol that is intended to supply COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

9.3 POPULATIONS FOR ANALYSES
Serious adverse event information will be collected on all consented and enrolled patients for whom convalescent plasma is ordered.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

9.4 STATISTICAL ANALYSES
Exploratory statistical analyses will be performed as part of this expanded access program.

9.5 PUBLICATION PLAN
The sponsor of this Expanded Access Program will limit the publication of any partial data collected by any participating treating physician or site without prior written authorization. With rare exceptions, such authorization will likely come after the sponsor has closed program enrollment, completed the data analysis and evaluated the final data set for the primary safety outcomes.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The IRB approved informed consent form is available on the website www.uscovidplasma.org. The language has been deliberately streamlined for use in the setting of Expanded Access in the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient’s health care proxy prior to treatment.

Expanded access to an investigational drug for treatment use, including emergency use, requires informed consent as described in 21 CFR part 50. Informed consent may be deemed infeasible if, in accordance with 21 CFR 50.23, the investigator and another physician who is not otherwise participating in the protocol certify in writing all of the following:

1. The patient is confronted by a life-threatening situation necessitating use of convalescent plasma

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

3. Time is not sufficient to obtain consent from the patient’s LAR

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

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 above, the determinations of the 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.
The investigator upon documentation of the use of emergency consent notifies the Mayo Clinic IRB via the web based patient entry portal. The study cannot proceed with an order for convalescent plasma until the documentation is complete. The IRB Senior Chair and medical director receives a daily update of study enrollment and key metrics. We will make sure this measure is also included in the daily report.

The computer system will generate a weekly report for the IRB office as a backup of the notification so that the IRB has the original and a backup notification. These will be submitted to the IRB office as notation items.

### 10.2 IRB RELIANCE

**IRB Reliance**

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.

### 10.3 SAFETY OVERSIGHT

**Safety Oversight**

The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks of administered products and have sufficient research and trial experience to provide an independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate decision-making power to terminate the study evidence of early benefit or harm. The DSMB will generate regular reports to the IRB and FDA., The DSMB Chair, the regulatory sponsor, and additional team members will communicate with the appropriate FDA officials for review and guidance on study conduct. IND Safety Reports will be submitted to the FDA as required under the IND.
DSMB Membership
The DSMB membership will include:

Allan S. Jaffe, MD, - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN

William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Lawrence J. Appel, MD, MPHC. David Molina, M.D., M.P.H. Professor of Medicine and
International Health, and Nursing
Director, Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Medical Institution

Rickey E. Carter Ph.D.
Professor of Biostatistics
Mayo Clinic, Jacksonville Fl.

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL

Kristine Tree
Center for Individualized Medicine
Mayo Clinic, Rochester, MN
### 10.4 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>eCRF</td>
<td>Electronic Case Report Forms</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>United States</td>
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## 10.5 Protocol Amendment History

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<th>Description of Change</th>
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<tr>
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<td>Initial Version</td>
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<tr>
<td>2.0</td>
<td>4/3/2020</td>
<td>Updated IND Number</td>
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<td>Added IRB Oversight</td>
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<tr>
<td>3.0</td>
<td>4/9/2020</td>
<td>Updated Section 10.1.1.2</td>
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<td>Consent Procedures and Documentation</td>
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<tr>
<td>4.0</td>
<td>4/15/2020</td>
<td>Updated Section 6.1.2</td>
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<td>5.0</td>
<td>4/23/2020</td>
<td>Study synopsis clarified to be consistent throughout 1-2 units</td>
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<td>Consistency throughout protocol that 1-2 units of plasma may be administered</td>
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<td>Clarification and consistency to coordinate patients and available plasma</td>
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<td>Section 1.2 Clarify infusion rate for plasma deleted specific rate.</td>
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<td>Allow for flexibility to individual institutional and patient standards for care</td>
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<td>Updated Sections 4.3 and 6.1.2 to define if 2 units are transfused the second unit</td>
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<td>must be transfused within 12 hours of first.</td>
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<td>Reduce deviations and allow flexibility in scheduling if 2 units are administered.</td>
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<td>Updated Labeling in Section 6.2.2</td>
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<td>Align with current FDA Guidance.</td>
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<td>Section 8.2, and 8.3 SAE reporting should be done using forms on website.</td>
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<td>Clarify SAE reporting</td>
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<td>Section 9.3 Clarified collection of event information</td>
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<td>Information should be collected from all consented and enrolled patients for whom</td>
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<td>plasma is ordered</td>
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<td>Added Section 9.5 for Publication plans</td>
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<td>Clarify Publication Plan</td>
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<td>10.1.1.1 Revised reference to informed consent document</td>
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<td>Section 10.3 Clarified safety monitoring and updated DSMB Roster</td>
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<td>Clarification and updates</td>
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<td>6.0</td>
<td>5/15/2020</td>
<td>Throughout the protocol, removed reference to ABO</td>
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<td>See New Section 4.4</td>
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<td>Section 4.3 - Dose justification of volume of convalescent plasma</td>
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<td>The volume of plasma to be transfused should be based upon the patient’s weight and</td>
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<td>clinical comorbidities and allowance for multiple doses.</td>
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<td>Section 4.4 - Added to define preference for ABO compatible.</td>
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<td>Sections 5.2 &amp; 7.1 - Clarifications for dosing and administration</td>
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<td>Section 6.1.2 - Dosing and administration changed to subsequent units</td>
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<td>Section 10.1.1.2 - Process for informing the IRB of the number of Emergency Use consent clarified.</td>
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<td>7.0</td>
<td>5/23/2020</td>
<td>Throughout the protocol, changed the description of the investigational product to just be Convalescent Plasma.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 4.4 - Changed the description for plasma compatibility, ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits</td>
</tr>
<tr>
<td>8.0</td>
<td>6/16/2020</td>
<td>Section 4.5 - End of study definition is either discharge from acute care facility, or, 30 day after most recent COVID-19 convalescent plasma transfusion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 6.2.2 - Labeling of COVID-19 convalescent plasma should include a label to indicate presence of COVID-19 antibodies, if testing is available.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 8.4 – Added specific email address for reporting of other unanticipated issues. <a href="mailto:uscovidplasmaevents@mayo.edu">uscovidplasmaevents@mayo.edu</a></td>
</tr>
</tbody>
</table>
11 REFERENCES

REFERENCES


   Pmid:32219429


   Pmid:32219428


   Pmid:25030060


   Pmid:29923831

Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Unique Protocol Identification Number: 20-003312
National Clinical Trial (NCT) Identified Number: 04338360
Principal Investigator: Michael Joyner, MD
IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
Version 9.0
15 July 2020

The Mayo Clinic IRB will serve as the IRB of record for all sites participating in this protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the trial via sign up on www.uscovidplasma.org will serve as documentation of each participating institution’s reliance on Mayo’s IRB. A separate IRB reliance agreement is not required.

Summary of Changes from Previous Version:

<table>
<thead>
<tr>
<th>Affected Section(s)</th>
<th>Summary of Revisions Made</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>1.2 and 5.1</td>
<td>Eligibility criteria - added clinically suspected along with laboratory confirmed diagnosis.</td>
<td>Allow participation of patients with either laboratory confirmed or clinically suspected SARS-CoV-2 to be eligible.</td>
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<tr>
<td>6.2.2</td>
<td>Removed - Labeling of COVID-19 convalescent plasma should include a label to indicate presence of COVID-19 antibodies, if testing is available.</td>
<td>Alignment with more recent guidance from FDA.</td>
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Statement of Compliance

The Expanded Access protocol will be carried out in accordance with applicable federal regulations:


Treating Physician Responsibilities

The Sponsor may contact the treating physician as appropriate for completion of all data forms in a timely manner. You agree to respond to the sponsor in a timely manner with complete information. Failure to comply will be in violation with the protocol.
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Study Description: This expanded access program will provide access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with one (or more) units of convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility.

Objectives: Primary Objective: Provide access to COVID-19 convalescent plasma
Secondary Objectives: Safety

Endpoints: Primary Endpoint: Availability of convalescent plasma
Secondary Endpoints: Serious adverse events

Study Population: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

Phase: Expanded Access Program

Description of Sites/Facilities Enrolling Participants: Acute care facilities treating patients with COVID-19

Description of Study Intervention: Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

Study Duration: 12 months

Participant Duration: Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

☐ Eligibility Criteria Met

Inclusion Criteria

1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed or clinically suspected diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe disease defined as any of the following:
- dyspnea
- respiratory frequency > 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease defined as any of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

☐ Informed consent obtained from patient or healthcare proxy

☐ Blood type obtained at local laboratory per local institutional procedures and policies

Patient Registered with American Red Cross or other blood source by uscovidplasma.org.

☐ Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol

Patients may be premedicated with acetaminophen and diphenhydramine, per local practice

Recommended administration rate for plasma administration should follow best clinical practice procedures for the patient’s unique condition and your facility guidelines.

☐ Serious adverse events observed by the treating physician or reported by patient to provider

☐ Reporting of patient demographics and acute care resource utilization

Information entered on COVID-19 Plasma Expanded Access Program secure website

(Information on plasma unit administered will be obtained directly from blood collector)
2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

2.2 BACKGROUND

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.\(^1\,^2\)

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS
Plasma represents a licensed blood product, for which the risks are well described. These are the risks associated with the administration of plasma, including allergic reaction and viral infections. There is also the risk that convalescent plasma may be ineffective.

2.3.2 KNOWN POTENTIAL BENEFITS
COVID-19 convalescent plasma has not yet been demonstrated to provide clinical benefit in patients affected by this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS
The safety profile of plasma administration is well established. Taking into account the preliminary data available on the possible benefit of COVID-19 plasma along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, providing patients access to compatible COVID-19 plasma as part of this expanded access protocol appears to reasonably balance potential risks with possible benefit that may outweigh such risks.
3 OBJECTIVES AND ENDPOINTS

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>ENDPOINTS</th>
<th>JUSTIFICATION FOR ENDPOINTS</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide access to COVID-19 convalescent plasma</td>
<td>Availability of convalescent plasma</td>
<td>Expanded access protocol</td>
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<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
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<tr>
<td>Safety</td>
<td>Serious adverse events</td>
<td>Required as part of expanded access protocol under IND</td>
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<tr>
<td><strong>Tertiary/Exploratory</strong></td>
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<td>Health care utilization</td>
<td>1. Acute care facility length of stay</td>
<td>Evaluation of potential for efficacy</td>
</tr>
<tr>
<td></td>
<td>2. Days spent in intensive care unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Survival to acute care facility discharge</td>
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</tbody>
</table>
4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label expanded access program to make appropriately matched convalescent plasma available for the treatment of patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. COVID-19 convalescent plasma will be obtained from blood suppliers and will meet all regulatory requirements for conventional plasma and FDA’s additional considerations for COVID-19 convalescent plasma ([https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds](https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds)). Information collected following plasma administration will include serious adverse events, as well as patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered. Due to the nature of the COVID-19 outbreak, data on patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered may be collected retrospectively.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola and other pathogens. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19. At this time there are few therapeutic options for the treatment of COVID-19 and no prophylactic vaccine is currently available. Based on the preliminary evidence of possible efficacy, this protocol is making convalescent plasma available to individuals with documented SARS-CoV-2 disease at acute care facilities who have severe or life-threatening COVID-19, or who are judged by a provider to be at high risk of progression to severe or life-threatening disease.
4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities (e.g. patients with impaired cardiac function and heart failure may require less volume or more prolonged transfusion times). The volume of plasma to be transfused should be at least one unit (approximately 200 mL) but may be greater if the treating clinician concludes a larger volume is appropriate. Transfusions may occur at any time throughout the hospitalization including multiple doses on non-sequential days. In general, it is expected that most patients will receive two units or less, but this language is not intended to restrict the use of convalescent plasma in larger quantities when the treating physician determines that such volumes and/or re-treatment are clinically justified.

4.4 CONVALESCENT PLASMA COMPATIBILITY

ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.

4.5 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma or 30 days after most recent convalescent plasma transfusion whichever comes first.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed or clinically suspected diagnosis of infection with SARS-CoV-2
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:
- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with American Red Cross or other blood source by uscovidplasma.org. Since this involves the administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION
This expanded program will make available compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA’s regulations and the additional considerations for convalescent plasma on FDA’s webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).5

6.1.1 STUDY INTERVENTION DESCRIPTION
Compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION
For practical purposes in the current outbreak, one – two units of COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (total volume of plasma to be administered will be approximately 200 mL or more), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL per unit). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine.

If a subsequent unit of convalescent plasma is transfused, the treating physician will begin the transfusion at a time that is clinically compatible with the patient’s underlying condition.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY
Convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING
COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19.

The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug--Limited by Federal (or United States) law to investigational use.” (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label applies, including the requirement to include a reference to the circular of information.
### 6.2.3 PRODUCT STORAGE AND STABILITY

Please see the AABB Circular of Information for product storage and stability.

### 6.2.4 PREPARATION

Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including compatibility checks and thawing.

### 6.3 CONCOMITANT THERAPY

Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
### 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

#### 7.1 DISCONTINUATION OF STUDY INTERVENTION

This study involves the administration of COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

#### 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients are free to withdraw consent from participation in further data collection at any time during the study.

Study team encouragement of withdrawal from the EAP as a strategy to avoid completion of follow-up data requirements is not allowed.

#### 7.3 LOST TO FOLLOW-UP

Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting is required for serious adverse events (SAEs); and we will ask the treating physician when reporting the event to determine if the event is potentially related to the administration of the COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events should be reported, by the treating physician to the sponsor/principal investigator using the forms provided on the website (www.uscovidplasma.org).

The sponsor/principal investigator is responsible for filing reports to the FDA and IRB as required.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner by sending an email to uscovidplasmaevents@mayo.edu.
9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES
This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

9.2 SAMPLE SIZE DETERMINATION
This is an expanded access protocol that is intended to supply COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

9.3 POPULATIONS FOR ANALYSES
Serious adverse event information will be collected on all consented and enrolled patients for whom convalescent plasma is ordered.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

9.4 STATISTICAL ANALYSES
Exploratory statistical analyses will be performed as part of this expanded access program.

9.5 PUBLICATION PLAN
The sponsor of this Expanded Access Program will limit the publication of any partial data collected by any participating treating physician or site without prior written authorization. With rare exceptions, such authorization will likely come after the sponsor has closed program enrollment, completed the data analysis and evaluated the final data set for the primary safety outcomes.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The IRB approved informed consent form is available on the website www.uscovidplasma.org. The language has been deliberately streamlined for use in the setting of Expanded Access in the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient's health care proxy prior to treatment.

Expanded access to an investigational drug for treatment use, including emergency use, requires informed consent as described in 21 CFR part 50. Informed consent may be deemed infeasible if, in accordance with 21 CFR 50.23, the investigator and another physician who is not otherwise participating in the protocol certify in writing all of the following:

1. The patient is confronted by a life-threatening situation necessitating use of convalescent plasma
2. Informed consent cannot be obtained from the patient because of an inability to communicate with or obtain legally effective consent
3. Time is not sufficient to obtain consent from the patient’s LAR
4. There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

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 above, the determinations of the 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.
The investigator upon documentation of the use of emergency consent notifies the Mayo Clinic IRB via
the web based patient entry portal. The study cannot proceed with an order for convalescent plasma
until the documentation is complete. The IRB Senior Chair and medical director receives a daily update
of study enrollment and key metrics. We will make sure this measure is also included in the daily report.

The computer system will generate a weekly report for the IRB office as a backup of the notification so
that the IRB has the original and a backup notification. These will be submitted to the IRB office as
notation items.

10.2 IRB RELIANCE

IRB Reliance

Your request to participate in the EAP, use of the product and the consent form indicates your
willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo
Clinic IRB and that you will follow all federal and state regulations regarding use and administration of
the investigational product and that you will conduct the EAP in accordance with the principles set forth
in the Belmont Report.

10.3 SAFETY OVERSIGHT

Safety Oversight

The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting
and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks
of administered products and have sufficient research and trial experience to provide an
independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate
decision-making power to terminate the study evidence of early benefit or harm. The DSMB will
generate regular reports to the IRB and FDA., The DSMB Chair, the regulatory sponsor, and
additional team members will communicate with the appropriate FDA officials for review and
guidance on study conduct. IND Safety Reports will be submitted to the FDA as required under
the IND.
DSMB Membership
The DSMB membership will include:

Allan S. Jaffe, MD - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN

William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Lawrence J. Appel, MD, MPH.C. David Molina, M.D., M.P.H. Professor of Medicine and
International Health, and Nursing
Director, Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Medical Institution

Rickey E. Carter Ph.D.
Professor of Biostatistics
Mayo Clinic, Jacksonville Fl.

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL

Kristine Tree
Center for Individualized Medicine
Mayo Clinic, Rochester, MN
### 10.4 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Forms</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>United States</td>
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## 10.5 Protocol Amendment History

<table>
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<tr>
<th>Version</th>
<th>Date</th>
<th>Description of Change</th>
<th>Brief Rationale</th>
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<tr>
<td>1.0</td>
<td>4/1/2020</td>
<td>Initial Version</td>
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<td>2.0</td>
<td>4/3/2020</td>
<td>Updated IND Number</td>
<td>Documentation</td>
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<td></td>
<td></td>
<td>Added IRB Oversight</td>
<td>Clarification</td>
</tr>
<tr>
<td>3.0</td>
<td>4/9/2020</td>
<td>Updated Section 10.1.1.2 Consent Procedures and Documentation</td>
<td>Additional consenting procedures for patients unable to give consent and also no LAR available to give consent for patients qualifying for plasma infusion.</td>
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<tr>
<td>4.0</td>
<td>4/15/2020</td>
<td>Updated Section 6.1.2</td>
<td>Clarify 1-2 units of plasma and up to 500ml of volume delivered</td>
</tr>
<tr>
<td>5.0</td>
<td>4/23/2020</td>
<td>Study synopsis clarified to be consistent throughout 1-2 units</td>
<td>Consistency throughout protocol that 1-2 units of plasma may be administered</td>
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<td></td>
<td></td>
<td>Section 1.2 and 5.2 Eligible patients will be registered with American Red Cross or other blood source by uscovidplasma.org</td>
<td>Clarification and consistency to coordinate patients and available plasma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 1.2 Clarify infusion rate for plasma deleted specific rate.</td>
<td>Allow for flexibility to individual institutional and patient standards for care</td>
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<td></td>
<td>Updated Sections 4.3 and 6.1.2 to define if 2 units are transfused the second unit must be transfused within 12 hours of first.</td>
<td>Reduce deviations and allow flexibility in scheduling if 2 units are administered.</td>
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<td></td>
<td></td>
<td>Updated Labeling in Section 6.2.2</td>
<td>Align with current FDA Guidance.</td>
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<td>Section 8.2, and 8.3 SAE reporting should be done using forms on website.</td>
<td>Clarify SAE reporting</td>
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<td></td>
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<td>Section 9.3 Clarified collection of event information</td>
<td>Information should be collected from all consented and enrolled patients for whom plasma is ordered</td>
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<td>Added Section 9.5 for Publication plans</td>
<td>Clarify Publication Plan</td>
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<td>10.1.1.1 Revised reference to informed consent document</td>
<td>IRB Approved Consent is available on the website not part of this document.</td>
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<td></td>
<td></td>
<td>Section 10.3 Clarified safety monitoring and updated DSMB Roster</td>
<td>Clarification and updates</td>
</tr>
<tr>
<td>6.0</td>
<td>5/15/2020</td>
<td>Throughout the protocol, removed reference to ABO</td>
<td>See New Section 4.4</td>
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<td>Section 4.3 - Dose justification of volume of convalescent plasma</td>
<td>The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities and allowance for multiple doses.</td>
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<td>Version</td>
<td>Date</td>
<td>Description of Change</td>
<td>Brief Rationale</td>
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<tr>
<td>7.0</td>
<td>5/23/2020</td>
<td>Throughout the protocol, changed the description of the investigational product to just be Convalescent Plasma.</td>
<td>The term “compatible” was removed since there is now the alternative to follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.</td>
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<td></td>
<td>Section 4.4 - Changed the description for plasma compatibility, ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits</td>
<td>FDA Request for clarifications</td>
</tr>
<tr>
<td></td>
<td>8/16/2020</td>
<td>Section 4.5 - End of study definition is either discharge from acute care facility, or, 30 day after most recent COVID-19 convalescent plasma transfusion.</td>
<td>Clarification of end of study definition.</td>
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<td>Section 6.2.2 - Labeling of COVID-19 convalescent plasma should include a label to indicate presence of COVID-19 antibodies, if testing is available.</td>
<td>Alignment with guidance from FDA.</td>
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<td></td>
<td>Section 8.4 – Added specific email address for reporting of other unanticipated issues. <a href="mailto:uscovidplasmaevents@mayo.edu">uscovidplasmaevents@mayo.edu</a></td>
<td>Specially designated email for reporting other unanticipated issues.</td>
</tr>
<tr>
<td>9.0</td>
<td>7/15/2020</td>
<td>Section 1.2 and 5.1 Eligibility criteria - added clinically suspected along with laboratory confirmed diagnosis.</td>
<td>Allow participation of patients with either laboratory confirmed or clinically suspected SARS-CoV-2 to be eligible.</td>
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<tr>
<td></td>
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<td>Section 6.2.2 – Removed Labeling of COVID-19 convalescent plasma should include a label to indicate presence of COVID-19 antibodies, if testing is available.</td>
<td>Alignment with more recent (5/1/2020) <a href="https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-convalescent-plasma">FDA Guidance</a> for Industry – Investigational COVID-19 Convalescent Plasma.</td>
</tr>
</tbody>
</table>
11 REFERENCES

REFERENCES


   Pmid:32219429


   Pmid:32219428


   Pmid:25030060


   Pmid:29923831

Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Unique Protocol Identification Number: 20-003312
National Clinical Trial (NCT) Identified Number: 04338360
Principal Investigator: Michael Joyner, MD
IND 19832 Sponsor: Michael Joyner, MD
Funded by: BARDA
Version 10.0
03 August 2020

The Mayo Clinic IRB will serve as the IRB of record for all sites participating in this protocol. In accordance with 45 CFR 46.103(e), agreeing to participate in the trial via sign up on www.uscovidplasma.org will serve as documentation of each participating institution's reliance on Mayo's IRB. A separate IRB reliance agreement is not required.

Summary of Changes from Previous Version:

<table>
<thead>
<tr>
<th>Affected Section(s)</th>
<th>Summary of Revisions Made</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 and 5.1</td>
<td>Eligibility criteria - Clinically suspected diagnosis should include a pending laboratory test result.</td>
<td>Patients enrolled based on clinically suspected infection with SARS-CoV-2 should have pending laboratory confirmation.</td>
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Statement of Compliance

The Expanded Access protocol will be carried out in accordance with applicable federal regulations:


Treating Physician Responsibilities

The Sponsor may contact the treating physician as appropriate for completion of all data forms in a timely manner. You agree to respond to the sponsor in a timely manner with complete information. Failure to comply will be in violation with the protocol.
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

Study Description: This expanded access program will provide access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with one (or more) units of convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

Objectives: Primary Objective: Provide access to COVID-19 convalescent plasma
Secondary Objectives: Safety

Endpoints: Primary Endpoint: Availability of convalescent plasma
Secondary Endpoints: Serious adverse events

Study Population: Patients with severe or life-threatening manifestations of COVID-19, or documented to be at high risk of developing such manifestations

Phase: Expanded Access Program

Description of Sites/Facilities Enrolling Participants: Acute care facilities treating patients with COVID-19

Description of Study Intervention: Administration of convalescent plasma obtained from donors with prior documented SARS-CoV-2 infection

Study Duration: 12 months

Participant Duration: Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma.
1.2 SCHEMA

Study Schema

☐ Eligibility Criteria Met

Inclusion Criteria

1. At least 18 years of age (if less than 18 years contact FDA for emergency IND authorization)
2. Laboratory confirmed or clinically suspected diagnosis of infection with SARS-CoV-2*
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

*Patients enrolled based on clinically suspected infection with SARS-CoV-2 should have pending laboratory confirmation.

Severe disease defined as any of the following:
- dyspnea
- respiratory frequency > 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease defined as any of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

☐ Informed consent obtained from patient or healthcare proxy

☐ Blood type obtained at local laboratory per local institutional procedures and policies

Patient Registered with American Red Cross or other blood source by uscovidplasma.org.

☐ Transfusion with appropriate COVID-19 convalescent plasma per institutional transfusion protocol

Patients may be premedicated with acetaminophen and diphenhydramine, per local practice

Recommended administration rate for plasma administration should follow best clinical practice procedures for the patient’s unique condition and your facility guidelines.

☐ Serious adverse events observed by the treating physician or reported by patient to provider

☑ Reporting of patient demographics and acute care resource utilization

Information entered on COVID-19 Plasma Expanded Access Program secure website

(Information on plasma unit administered will be obtained directly from blood collector)
2 INTRODUCTION

2.1 STUDY RATIONALE

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

2.2 BACKGROUND

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.1,2

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS
Plasma represents a licensed blood product, for which the risks are well described. These are the risks associated with the administration of plasma, including allergic reaction and viral infections. There is also the risk that convalescent plasma may be ineffective.

2.3.2 KNOWN POTENTIAL BENEFITS
COVID-19 convalescent plasma has not yet been demonstrated to provide clinical benefit in patients affected by this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS
The safety profile of plasma administration is well established. Taking into account the preliminary data available on the possible benefit of COVID-19 plasma along with the relative lack of other readily available therapeutic options for severe or life-threatening disease, providing patients access to compatible COVID-19 plasma as part of this expanded access protocol appears to reasonably balance potential risks with possible benefit that may outweigh such risks.
## 3 OBJECTIVES AND ENDPOINTS

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>ENDPOINTS</th>
<th>JUSTIFICATION FOR ENDPOINTS</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
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<tr>
<td>Provide access to COVID-19</td>
<td>Availability of convalescent plasma</td>
<td>Expanded access protocol</td>
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<td>convalescent plasma</td>
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<td><strong>Secondary</strong></td>
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<td>Safety</td>
<td>Serious adverse events</td>
<td>Required as part of expanded</td>
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<td>access protocol under IND</td>
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<td><strong>Tertiary/Exploratory</strong></td>
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<td>Health care utilization</td>
<td>1. Acute care facility length of stay</td>
<td>Evaluation of potential for efficacy</td>
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<td>2. Days spent in intensive care unit</td>
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<td></td>
<td>3. Survival to acute care facility discharge</td>
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4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label expanded access program to make appropriately matched convalescent plasma available for the treatment of patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. COVID-19 convalescent plasma will be obtained from blood suppliers and will meet all regulatory requirements for conventional plasma and FDA’s additional considerations for COVID-19 convalescent plasma (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds). Information collected following plasma administration will include serious adverse events, as well as patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered. Due to the nature of the COVID-19 outbreak, data on patient demographics, acute care resource utilization, and characteristics of the convalescent plasma administered may be collected retrospectively.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Convalescent plasma collected from individuals who have recovered from a prior viral infection for the passive transfer of antibodies has been used at various times over the past century. There has been some evidence for benefit against hepatitis B, polio, measles, influenza, Ebola and other pathogens. Results from small case series during the prior MERS and SARS coronavirus outbreaks documented safety and faster viral clearance following convalescent plasma administration, particularly when given early in the disease course. Additionally, there is preliminary clinical evidence that suggests that convalescent plasma might provide benefit to individuals with SARS-CoV-2 infection and manifestations of COVID-19. At this time there are few therapeutic options for the treatment of COVID-19 and no prophylactic vaccine is currently available. Based on the preliminary evidence of possible efficacy, this protocol is making convalescent plasma available to individuals with documented SARS-CoV-2 disease at acute care facilities who have severe or life-threatening COVID-19, or who are judged by a provider to be at high risk of progression to severe or life-threatening disease.
4.3 JUSTIFICATION FOR DOSE

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy. The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities (e.g. patients with impaired cardiac function and heart failure may require less volume or more prolonged transfusion times). The volume of plasma to be transfused should be at least one unit (approximately 200 mL) but may be greater if the treating clinician concludes a larger volume is appropriate. Transfusions may occur at any time throughout the hospitalization including multiple doses on non-sequential days. In general, it is expected that most patients will receive two units or less, but this language is not intended to restrict the use of convalescent plasma in larger quantities when the treating physician determines that such volumes and/or re-treatment are clinically justified.

4.4 CONVALESCENT PLASMA COMPATIBILITY

ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.

4.5 END OF STUDY DEFINITION

Patients will complete the study when they are discharged from the acute care facility in which they received the COVID-19 convalescent plasma or 30 days after most recent convalescent plasma transfusion whichever comes first.
5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Age at least 18 years
2. Laboratory confirmed or clinically suspected diagnosis of infection with SARS-CoV-2
   Note: Patients enrolled based on clinically suspected infection with SARS-CoV-2 should have pending laboratory confirmation.
3. Admitted to an acute care facility for the treatment of COVID-19 complications
4. Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
5. Informed consent provided by the patient or healthcare proxy

Severe COVID-19 is defined by one or more of the following:
- dyspnea
- respiratory frequency ≥ 30/min
- blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- lung infiltrates > 50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple organ dysfunction or failure

5.2 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients eligible for this Expanded Access Program will be identified by their treating providers and registered with American Red Cross or other blood source by uscovidplasma.org. Since this involves the administration of COVID-19 convalescent plasma to patients in acute care facilities, participant retention is not anticipated to be an issue.
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

This expanded program will make available compatible COVID-19 convalescent plasma collected by blood establishments in accordance with the AABB Circular of Information and FDA’s regulations and the additional considerations for convalescent plasma on FDA’s webpage (https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds).5

6.1.1 STUDY INTERVENTION DESCRIPTION

Compatible COVID-19 convalescent plasma will be administered according to standard hospital procedures.

6.1.2 DOSING AND ADMINISTRATION

For practical purposes in the current outbreak, one – two units of COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (total volume of plasma to be administered will be approximately 200 mL or more), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL per unit). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine.

If a subsequent unit of convalescent plasma is transfused, the treating physician will begin the transfusion at a time that is clinically compatible with the patient’s underlying condition.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Convalescent plasma units may be obtained from a registered or licensed blood collector following registration of the patient.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

COVID-19 convalescent plasma will be supplied as an investigational blood product for the treatment of COVID-19.

The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug—Limited by Federal (or United States) law to investigational use.” (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label applies, including the requirement to include a reference to the circular of information.
6.2.3 PRODUCT STORAGE AND STABILITY
Please see the AABB Circular of Information for product storage and stability.

6.2.4 PREPARATION
Please follow local institutional guidelines for conventional plasma administration for COVID-19 plasma preparation prior to administration, including compatibility checks and thawing.

6.3 CONCOMITANT THERAPY
Premedications may be administered prior to plasma administration according to individual acute care facility protocols.
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION
This study involves the administration of COVID-19 convalescent plasma. Patients are free to withdraw consent from participation at any time.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY
Patients are free to withdraw consent from participation in further data collection at any time during the study.
Study team encouragement of withdrawal from the EAP as a strategy to avoid completion of follow-up data requirements is not allowed.

7.3 LOST TO FOLLOW-UP
Since this protocol involves only the acute care of individuals with COVID-19, it is not anticipated that individuals will be lost to follow-up.
8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Patient demographic information will be obtained to include age and sex.

Assessments for potential efficacy are exploratory as part of this expanded access program but may include web-based collection of the following information:

1. Acute care facility length of stay
2. Number of days in an intensive care unit
3. Number of days on mechanical ventilation
4. Survival until discharge from an acute care facility

An exploratory analysis may be conducted correlating the level of neutralizing antibody titers with clinical outcomes observed.

8.2 SAFETY AND OTHER ASSESSMENTS

Reporting is required for serious adverse events (SAEs); and we will ask the treating physician when reporting the event to determine if the event is potentially related to the administration of the COVID-19 convalescent plasma.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Serious adverse events should be reported, by the treating physician to the sponsor/principal investigator using the forms provided on the website (www.uscovidplasma.org).

The sponsor/principal investigator is responsible for filing reports to the FDA and IRB as required.

8.4 UNANTICIPATED PROBLEMS

Any unanticipated issues should be reported to the principal investigator and to the IND Sponsor, Michael Joyner by sending an email to uscovidplasmaevents@mayo.edu.
## 9 Statistical Considerations

### 9.1 Statistical Hypotheses

This is an expanded access program and any statistical analyses for safety or efficacy will be exploratory.

### 9.2 Sample Size Determination

This is an expanded access protocol that is intended to supply COVID-19 convalescent plasma to individuals with severe or life-threatening disease or at high risk thereof. It is anticipated that up to several thousand COVID-19 patients might be enrolled, though this number is difficult to estimate, given the evolving nature of the current pandemic.

### 9.3 Populations for Analyses

Serious adverse event information will be collected on all consented and enrolled patients for whom convalescent plasma is ordered.

Exploratory analyses will be performed on data obtained from individuals providing informed consent.

### 9.4 Statistical Analyses

Exploratory statistical analyses will be performed as part of this expanded access program.

### 9.5 Publication Plan

The sponsor of this Expanded Access Program will limit the publication of any partial data collected by any participating treating physician or site without prior written authorization. With rare exceptions, such authorization will likely come after the sponsor has closed program enrollment, completed the data analysis and evaluated the final data set for the primary safety outcomes.
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Plasma represents a licensed blood product. However, the use of plasma for the treatment of COVID-19 is investigational.

10.1.1 INFORMED CONSENT PROCESS

Since the use of COVID-19 plasma is investigational at this time, a discussion of potential risks and benefits to its administration, as well as alternative options, should take place with patients or their healthcare proxies. This should be documented in the medical record.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The IRB approved informed consent form is available on the website www.uscovidplasma.org. The language has been deliberately streamlined for use in the setting of Expanded Access in the current COVID-19 pandemic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent must be obtained from the patient or the patient's health care proxy prior to treatment.

Expanded access to an investigational drug for treatment use, including emergency use, requires informed consent as described in 21 CFR part 50. Informed consent may be deemed infeasible if, in accordance with 21 CFR 50.23, the investigator and another physician who is not otherwise participating in the protocol certify in writing all of the following:

1. The patient is confronted by a life-threatening situation necessitating use of convalescent plasma

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

3. Time is not sufficient to obtain consent from the patient’s LAR

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

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 above, the determinations of the 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.
The investigator upon documentation of the use of emergency consent notifies the Mayo Clinic IRB via the web based patient entry portal. The study cannot proceed with an order for convalescent plasma until the documentation is complete. The IRB Senior Chair and medical director receives a daily update of study enrollment and key metrics. We will make sure this measure is also included in the daily report.

The computer system will generate a weekly report for the IRB office as a backup of the notification so that the IRB has the original and a backup notification. These will be submitted to the IRB office as notation items.

10.2 IRB RELIANCE

IRB Reliance

Your request to participate in the EAP, use of the product and the consent form indicates your willingness and that of your institution/hospital/practice/legal business entity to rely upon the Mayo Clinic IRB and that you will follow all federal and state regulations regarding use and administration of the investigational product and that you will conduct the EAP in accordance with the principles set forth in the Belmont Report.

10.3 SAFETY OVERSIGHT

Safety Oversight

The Mayo Clinic IRB, a DSMB and the US FDA will work collaboratively to follow SAE reporting and monitor the conduct of the EAP.

The DSMB will be composed of experienced physicians and scientists who understand the risks of administered products and have sufficient research and trial experience to provide an independent recommendation to the PI, the IRB and the FDA. The FDA will hold the ultimate decision-making power to terminate the study evidence of early benefit or harm. The DSMB will generate regular reports to the IRB and FDA. The DSMB Chair, the regulatory sponsor, and additional team members will communicate with the appropriate FDA officials for review and guidance on study conduct. IND Safety Reports will be submitted to the FDA as required under the IND.
DSMB Membership
The DSMB membership will include:

Allan S. Jaffe, MD, - Chair
Professor of Medicine and Laboratory Medicine
Consultant in the Division of Cardiac Critical Care and Ischemic Heart Disease
Mayo Clinic, Rochester, MN

David O. Warner, MD - Secretary
Professor of Anesthesiology
Mayo Clinic, Rochester, MN

William Morice, MD
Professor of Laboratory Medicine
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Paula Santrach, MD
Associate Professor of Laboratory Medicine and Pathology
Consultant in Transfusion Medicine
Mayo Clinic, Rochester, MN

Robert L. Frye, MD
Professor of Medicine, Mayo Clinic and Past Chair, Department of Medicine
Mayo Clinic, Rochester, MN

Lawrence J. Appel, MD, MPH.C. David Molina, M.D., M.P.H. Professor of Medicine and
International Health, and Nursing
Director, Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Medical Institution

Rickey E. Carter Ph.D.
Professor of Biostatistics
Mayo Clinic, Jacksonville Fl.

Ex Officio
Taimur Sher, MD, Associate Professor of Medicine,
Co-Chair Mayo Clinic Thursday IRB
Consultant in the Division of Hematology
Mayo Clinic, Jacksonville, FL

Kristine Tree
Center for Individualized Medicine
Mayo Clinic, Rochester, MN
### 10.4 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Forms</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug Application</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
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</table>
## 10.5 PROTOCOL AMENDMENT HISTORY

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Description of Change</th>
<th>Brief Rationale</th>
</tr>
</thead>
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<tr>
<td>1.0</td>
<td>4/1/2020</td>
<td>Initial Version</td>
<td>N/A</td>
</tr>
<tr>
<td>2.0</td>
<td>4/3/2020</td>
<td>Updated IND Number</td>
<td>Documentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Added IRB Oversight</td>
<td>Clarification</td>
</tr>
<tr>
<td>3.0</td>
<td>4/9/2020</td>
<td>Updated Section 10.1.1.2 Consent Procedures and Documentation</td>
<td>Additional consenting procedures for patients unable to give consent and also no LAR available to give consent for patients qualifying for plasma infusion.</td>
</tr>
<tr>
<td>4.0</td>
<td>4/15/2020</td>
<td>Updated Section 6.1.2</td>
<td>Clarify 1-2 units of plasma and up to 500ml of volume delivered</td>
</tr>
<tr>
<td>5.0</td>
<td>4/23/2020</td>
<td>Study synopsis clarified to be consistent throughout 1-2 units</td>
<td>Consistency throughout protocol that 1-2 units of plasma may be administered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 1.2 and 5.2 Eligible patients will be registered with American Red Cross or other blood source by uscovidplasma.org</td>
<td>Clarification and consistency to coordinate patients and available plasma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 1.2 Clarify infusion rate for plasma deleted specific rate.</td>
<td>Allow for flexibility to individual institutional and patient standards for care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Updated Sections 4.3 and 6.1.2 to define if 2 units are transfused the second unit must be transfused within 12 hours of first.</td>
<td>Reduce deviations and allow flexibility in scheduling if 2 units are administered.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Updated Labeling in Section 6.2.2</td>
<td>Align with current FDA Guidance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 8.2, and 8.3 SAE reporting should be done using forms on website.</td>
<td>Clarify SAE reporting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 9.3 Clarified collection of event information</td>
<td>Information should be collected from all consented and enrolled patients for whom plasma is ordered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Added Section 9.5 for Publication plans</td>
<td>Clarify Publication Plan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.1.1.1 Revised reference to informed consent document</td>
<td>IRB Approved Consent is available on the website not part of this document.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 10.3 Clarified safety monitoring and updated DSMB Roster</td>
<td>Clarification and updates</td>
</tr>
<tr>
<td>6.0</td>
<td>5/15/2020</td>
<td>Throughout the protocol, removed reference to ABO</td>
<td>See New Section 4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Section 4.3 - Dose justification of volume of convalescent plasma</td>
<td>The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities and allowance for multiple doses.</td>
</tr>
<tr>
<td>Version</td>
<td>Date</td>
<td>Description of Change</td>
<td>Brief Rationale</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>7.0</td>
<td>5/23/2020</td>
<td>Throughout the protocol, changed the description of the investigational product to just be Convalescent Plasma.</td>
<td>The term “compatible” was removed since there is now the alternative to follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits. FDA Request for clarifications.</td>
</tr>
<tr>
<td>8.0</td>
<td>6/16/2020</td>
<td>Section 4.5 - End of study definition is either discharge from acute care facility, or, 30 day after most recent COVID-19 convalescent plasma transfusion.</td>
<td>Clarification of end of study definition. Alignment with guidance from FDA. Specially designated email for reporting other unanticipated issues.</td>
</tr>
<tr>
<td>9.0</td>
<td>7/15/2020</td>
<td>Section 1.2 and 5.1 Eligibility criteria - added clinically suspected along with laboratory confirmed diagnosis. Section 6.2.2 – Removed Labeling of COVID-19 convalescent plasma should include a label to indicate presence of COVID-19 antibodies, if testing is available.</td>
<td>Allow participation of patients with either laboratory confirmed or clinically suspected SARS-CoV-2 to be eligible. Alignment with more recent (5/1/2020) FDA Guidance for Industry - Investigational COVID-19 Convalescent Plasma.</td>
</tr>
<tr>
<td>Version</td>
<td>Date</td>
<td>Description of Change</td>
<td>Brief Rationale</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10.0</td>
<td>8/3/2020</td>
<td>Section 1.2 and 5.1 Eligibility criteria suspected diagnosis should include a pending laboratory test result.</td>
<td>Any patient enrolled based on clinically suspected infection with SARS-CoV-2 should have pending laboratory confirmation. Recommendation from FDA 7/31/2020.</td>
</tr>
</tbody>
</table>
11 REFERENCES


   Pmid:32219429


   Pmid:32219428


   Pmid:25030060


   Pmid:29923831

6. Appendix 1

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<td>6/11/2020</td>
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<td>20-003312 Appendix 1 V2.0</td>
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<td>7/1/2020</td>
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<td>20-003312 Appendix 1 V3.0</td>
<td>8/3/2020</td>
<td>8/7/2020</td>
<td>Currently Posted</td>
</tr>
</tbody>
</table>

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Appendix 1: Modification to the US Convalescent Plasma Program to create a control group for Efficacy Analysis

Collaborating Investigators
Nigel Paneth, Michigan State University
Arturo Casadevall, Johns Hopkins University
Chenxi Li, Michigan State University
Mat Reeves, Michigan State University
Francis X. Campion, MITRE
Brian Anderson, MITRE
Rute Martins, MITRE
Peter Smart, Cerner Corporation
Rehan Waheed, Cerner Corporation
Andrea Noel, Epic
Janet Campbell, Epic

Goal
Create a control group for comparison of outcomes with hospitalization for COVID-19 by obtaining de-identified data on patients hospitalized with COVID-19 during the time of the US Convalescent Plasma study.

The aims of the comparison group are to better identify early signals of efficacy and harm by evaluating key outcomes including ventilator use, death rates, and discharge disposition for COVID-19 patients receiving convalescent plasma. The first phase will focus on the unadjusted outcomes. To fully validate those findings, a second phase of the study will require a second, more detailed data pull, with additional de-identified data elements such as co-morbidities and laboratory test results, enabling deeper covariate analysis.

Options for Hospital Participation
The master amendment protocol will allow for a variety of “sub-protocols” which vary only by specific data definitions in use by varying hospitals. In this manner, hospitals using different EHR system configurations can contribute to the research effort. Hospitals have a choice to perform their own data analysis, contribute data to a participating research consortium, or simply send their de-identified data to the Mayo Clinic data coordinating center. Research groups opting to perform their own analysis are encouraged to share the same data analysis plan.
Fundamental to all treatment-control protocols will be the creation of two cohorts – one cohort comprised of the treated population and a second of untreated controls, who will be as similar as possible in risk factors for the key outcomes using available data. All protocols will attempt to create the best approximation possible, from observational data, of a randomized controlled trial of CP.

The several sub-protocols may differ in:

1. The electronic record database used to select treated and untreated controls
2. The precise definition of each variable, which is subject to the nature of available data
3. The sample size
4. The outcomes of interest
5. The stage or stages of disease focused upon
6. The calendar time period of treatment

Design

This study is a historical observational design in which exposed patients (recipients of CP) are matched to an unexposed control population (non-recipients of CP) and followed from day of treatment in the exposed and a matched day in controls (referred to as day zero, see below) until the end of the period of observation which is designed to be at least 40 days in all subjects. This kind of design has been referred to as exposure-control study in the epidemiologic literature and differs from a traditional historical cohort design in the matching of unexposed to exposed, and from the usual case-control design by directionality, which here is from exposure to outcome and not from outcome to exposure.

1. Source population for the study.

The source population for the study will be all patients, 18 years and older, with COVID-19 admitted to hospitals in the Mayo registry study of COVID-19 treated with CP. The source population will be restricted to admissions occurring between the date of admission of the first recipient of CP in each hospital until the date extraction of data, with a follow up period up to discharge, death, or 40 days from hospital admission (if neither dead nor discharged).

2. Creation of a study variable set

All patients eligible to be included in the source population will have the data listed in the table below. Patients without data elements to be used in matching or to study outcomes will be excluded. Incompleteness in other variables will not be a reason to exclude the participant. Unless noted elsewhere, all variables will be extracted for the entire study population of COVID-19 patients from admission until death, discharge, or until the date the study is undertaken, if neither dead nor discharged. The source
population from whom data will be extracted are defined below under items 3 and 4 below.

Both Cerner and Epic are already working on detailed queries and data definitions in support of this study. For health systems who wish to leverage this work should contact:

- Cerner EHR: contact your account executive.
- Epic EHR: contact your Epic Best Friend Forever (BFF), inquire about the “Insights Project.”

3. Definition of COVID-19 patient and COVID-19 related hospitalization

The definition of COVID-19 case will be the diagnosis made in the hospital of care. It is recognized that there are several possible case definitions, but this study will not at this time attempt to impose a specific case definition unique to the study.

The COVID-19 Healthcare Coalition has worked to develop common data definitions that can be leveraged for the study. The current definitions are included in Appendix A.

4. Identification of the treated cohort.

An attempt will be made to identify all patients in the EPIC file with the diagnosis of COVID-19 disease who were admitted to the treating hospital until 28 days before the date of extraction of data, and who received, at some point during their hospitalization, one or more transfusions of convalescent plasma, regardless of the number of units or spike antibody titer. No exclusions will be made.

5. Identification of the untreated control cohort.

The pool of potential controls is all other COVID-19 patients not treated with convalescent plasma at any time during their hospitalization, admitted between the date of admission of the first COVID-19 patient treated with convalescent plasma at that hospital and a date 28 days or more before the date of extraction of data.

6. Omission of exact dates.

To maintain data confidentiality, a random number will be assigned, separately for each hospital, to the earliest date in the cohort, which is the date of admission of the first CP treated patient in each hospital. All dates subsequent to that date will be computed from that date. Thus if the first date is March 25th in hospital A, and the random number assigned to that date is 876, if a treated patient was intubated on March 29th, received CP on April 2nd, was extubated on April 5th, and discharged on April 10th, those dates would be recoded, respectively, as 880 (876 + 4), 884, 887 and 892.
Calculation of duration of events (see outcome variables below) will require subtraction of the random number from the disguised date number.

7. **Matching process and matching variables**

The six variables used in matching are listed in the table below. Hospital (to be identified only by a code), sex and ventilation status at onset of treatment are dichotomous; age will be matched in ten-year intervals (>80 is one interval); daily oxygenation requirement is defined as a proxy for severity of illness. Duration of stay prior to CP treatment will be used to determine date of cohort inception (referred to here as time zero) for the controls. If possible, that date will be the exact number of days between admission and treatment/time zero for the treated and control cohorts, but if that is not possible the match will be within 3 days duration (3 days pre or 3 days post day zero). Treatment/time zero will be the dates used to calculate all duration outcomes. Up to four controls for treated patients will be sought.

8. **Outcomes of interest**

a. **Primary outcome** – death at any time after admission recorded in the EMR. Deaths will be measured at 7 days, 14 days, 21 days and 28 days, and total deaths.

b. **Secondary outcomes** (all times measured from day of treatment in the treatment arm and from the corresponding day zero in controls).

   i. Number of days to first extubation (in mechanically ventilated patients)
   ii. Number of days to first intubation (in non-mechanically ventilated patients)
   iii. Number of days to death
   iv. Number of days to discharge

9. **Data analysis**

   a. **Initial analyses**

The initial analysis will examine death rates at the times specified above separately using mixed-effects logistic regression where the random effect account for the matched sampling. Mortality differences will be expressed as Odds Ratios for the treatment arm compared to the control arm.

For secondary outcomes, we will examine time from inception of treatment/time zero to each of the secondary outcomes specified above, including the appropriate sub-populations (mechanically ventilated at time zero/not mechanically ventilated at time zero) for analyses of time to intubation/extubation.
Time to death will be analyzed at first by the Kaplan-Meier curves and a shared-frailty (accounting for matching) model, treating discharged patients as being alive until the time of analysis. Then times to death and discharge will be analyzed jointly by a Cox-type, cause-specific hazard model with a bivariate log-normal frailty (accounting for matching), treating these two events as competing risks.

Times to extubation (intubation) and death will be analyzed jointly in the same way. In the analysis of times to extubation and death, treated patients will be further matched with untreated patients on duration of ventilation prior to CP to define time zero for the controls. In all the analyses, survival differences will be expressed as (cause-specific) hazard ratios. The Kaplan-Meier curves, the shared-frailty model and the cause-specific hazard frailty models all account for observation time of study subjects still in hospital at the time of data analysis.

b. Multivariate analysis of mortality

In the second phase of analysis, variables in Appendix B will be examined for their effects on mortality in the entire database. Any variable associated with mortality (change in OR of 20% or more, regardless of p value) will be entered into a separate mixed-effects logistic regression model for each of the four mortality time periods and into the regression models for survival analysis. These models will account for variable matching ratios of controls to cases.

10. Patient confidentiality

As this is study is restricted to the analysis of data, the only human subjects concern is confidentiality. The study does not abstract any identifying information on the participant, disguises all dates linked to individuals, and uses a large sample of participants with unidentified hospitals, thus minimizing the risk that non-identifying variables could be used to identify participants. Nonetheless, all Mayo procedures for protecting computerized data will be followed, including the use of password protection and the presence of firewalls separating the study data from other forms of data in storage.
### TABLE 1 – MATCHING VARIABLES

<table>
<thead>
<tr>
<th>Data Element Category</th>
<th>Data Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matching</td>
<td>Hospital (deidentified code for each facility)</td>
</tr>
<tr>
<td></td>
<td>Age[1]</td>
</tr>
<tr>
<td></td>
<td>Administrative gender[2]</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (see definition below) on day of admission (day 0)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 1)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 2)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 3)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 4)</td>
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<td>Severity of respiratory illness (day 5)</td>
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<td>Severity of respiratory illness (day 6)</td>
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<td></td>
<td>Severity of respiratory illness (day 8)</td>
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<tr>
<td></td>
<td>Severity of respiratory illness (day 9)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 10)</td>
</tr>
<tr>
<td>Outcome/time variable[3,4]</td>
<td>Admission date</td>
</tr>
<tr>
<td></td>
<td>Date of convalescent plasma administration</td>
</tr>
<tr>
<td></td>
<td>Date of first intubation (start of mechanical ventilation)</td>
</tr>
<tr>
<td></td>
<td>Date of first extubation (end of mechanical ventilation)</td>
</tr>
<tr>
<td></td>
<td>Date of death</td>
</tr>
<tr>
<td></td>
<td>Date of discharge</td>
</tr>
<tr>
<td>Other variables</td>
<td>Still in hospital on date of data extraction (Y/N)</td>
</tr>
</tbody>
</table>

---

[1] Should be “>90 years” instead of actual age for patients over 90 for deidentification purposes

[2] Male, female or unknown/other

[3] All that apply to each case

[4] Please reference disguising of dates section for details on how to deidentify the dates before submitting any data
Severity of illness refers to the severity of the patient’s respiratory symptoms. The goal is to measure severity on the day of treatment with CP infusion. It is recommended to calculate and store one daily value (midnight to midnight) of severity for the first 10 days of hospitalization. “Case matching” will require use of this value, therefore we need this value to be also calculated on “control” patients.

<table>
<thead>
<tr>
<th>Severity of Illness Allowable Value</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Not on supplemental oxygen</td>
<td>Not on supplemental oxygen, on high-flow supplemental oxygen or mechanically ventilated, per definitions below.</td>
</tr>
<tr>
<td>4</td>
<td>On conventional supplemental oxygen therapy</td>
<td>On nasal cannula or oxygen facial mask &lt; 30L/min</td>
</tr>
<tr>
<td>3</td>
<td>On high-flow supplemental oxygen</td>
<td>- On high-flow nasal cannula (HFNC) or oxygen facial mask &gt;= 30L/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Non-invasive positive pressure ventilation (NIPPV), including BiPAP, or CPAP between 8am and 9pm (8am to 9pm requirement on CPAP to rule-out regular home CPAP use)</td>
</tr>
<tr>
<td>2</td>
<td>Invasive mechanical ventilation</td>
<td>Mechanical ventilation (as evidenced by PEEP, vent mode change, FiO2 flowsheet documentation) or ECMO</td>
</tr>
</tbody>
</table>
Appendix A

These definitions were arrived upon through the work of the COVID-19 Healthcare Coalition partners, including a multidisciplinary group of clinical, informatics and EHR data experts. If you have any questions on these definitions, please contact Rute Martins (rute@mitre.org).

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Description</th>
<th>Logic</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 positive</td>
<td>A patient who has been clinically diagnosed with COVID-19 or who tested positive for COVID-19.</td>
<td>COVID-19 confirmed diagnosis OR COVID-19 confirmatory laboratory test</td>
</tr>
<tr>
<td>COVID-19-positive laboratory test</td>
<td>A laboratory test indicating that the patient has a COVID-19 infection</td>
<td>Laboratory test in COVID-19 Qualitative Laboratory Test value set AND (laboratory test result ~ detected OR ~positive)</td>
</tr>
<tr>
<td>COVID-19 confirmed diagnosis</td>
<td>A clinical diagnosis (any encounter diagnosis, billing diagnosis or problem list entry) of Confirmed COVID-19 infection</td>
<td>Condition in Confirmed COVID-19 Infection value set AND Condition.type ~ (encounter diagnosis, discharge diagnosis, final diagnosis, primary diagnosis, billing diagnosis, problem list entry) AND Condition.type NOT ~ admitting diagnosis</td>
</tr>
<tr>
<td>COVID-19-positive date</td>
<td>The earliest date associated with the confirmation of the COVID-19 infection.</td>
<td>Earliest of (COVID-19 confirmatory laboratory test specimen collection date, first COVID-19 confirmed diagnosis)</td>
</tr>
<tr>
<td>Age at COVID-19 positive date</td>
<td>The age (in years) of the patient on the date they were diagnosed with COVID-19.</td>
<td>COVID-19 positive date minus date of birth</td>
</tr>
</tbody>
</table>

---

5 The result date can be used when specimen collection date is not available
<table>
<thead>
<tr>
<th>Data Element</th>
<th>Description</th>
<th>Logic</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19-related hospitalization&lt;sup&gt;6&lt;/sup&gt;</td>
<td>An encounter for inpatient care that is associated with COVID-19.</td>
<td>Encounter class ~ INP OR ~ inpatient OR ~acute inpatient AND (COVID-19-positive date during hospitalization OR COVID-19-positive date &lt;= 14 days prior to hospitalization AND respiratory diagnosis associated with hospitalization&lt;sup&gt;7&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Respiratory diagnosis associated with hospitalization</td>
<td>Any diagnosis for a respiratory condition associated with a hospitalization</td>
<td>Condition code ICD-10-CM J00-J99 AND Condition.type ~ (encounter diagnosis, discharge diagnosis, final diagnosis, chief complaint, primary diagnosis, billing diagnosis, problem list entry)</td>
</tr>
<tr>
<td>Convalescent Plasma administration</td>
<td>Convalescent plasma administration regardless of the number of units or antibody titer.</td>
<td>Blood product order LIKE %COVID-19% OR Blood product order administration product code in ISBT 128 E codes for COVID-19 convalescent plasma</td>
</tr>
</tbody>
</table>

<sup>6</sup> It is recognized that this will include COVID-related hospitalizations but also hospitalizations of COVID-19 patients who may be asymptomatic and nosocomial COVID-19 infections.

<sup>7</sup> Proxy for symptomatic COVID-19 infection when patient is admitted for reasons unrelated to COVID-19
### Terminology

#### Confirmed COVID-19 Infection Value Set

<table>
<thead>
<tr>
<th>Includes</th>
<th>Conditions associated with confirmed COVID-19 infection, including laboratory-confirmed COVID-19 (symptomatic or asymptomatic).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICD-10-CM: U07.1 only available since 4/1/2020, will be used for lab-confirmed cases regardless of symptom presentation</td>
</tr>
<tr>
<td></td>
<td>B97.29 used largely before 4/1/2020.</td>
</tr>
<tr>
<td></td>
<td>SNOMED-CT: 840539006 Disease caused by severe acute respiratory syndrome coronavirus 2 (disorder)</td>
</tr>
<tr>
<td>Excludes</td>
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#### SARS-CoV-2 Laboratory Tests

| Includes | SARS-CoV-2-specific or SARS-like  
|          | PCR or NAAT  
|          | SARS-CoV-2 RNA in serum/plasma  
|          | SARS-CoV-2 panels (not recommended for results by Regenstrief but used in the field)  
|          | Qualitative results |
| Excludes | Human coronavirus tests (non-SARS/SARS-like tests) and MERS tests  
|          | Antibody and antigen tests  
|          | Quantitative results (e.g. cycle threshold #) |
Appendix B

The following table provides a list of data elements currently identified as potential covariates to support logistic regression and Cox models. These elements will be considered in a second phase of the study.

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Goal
Create a control group for comparison of outcomes with hospitalization for COVID-19 by obtaining de-identified data on patients hospitalized with COVID-19 during the time of the US Convalescent Plasma study.

The aims of the comparison group are to better identify early signals of efficacy and harm by evaluating key outcomes including ventilator use, death rates, and discharge disposition for COVID-19 patients receiving convalescent plasma. The first phase will focus on the unadjusted outcomes. To fully validate those findings, a second phase of the study will require a second, more detailed data pull, with additional de-identified data elements such as co-morbidities and laboratory test results, enabling deeper covariate analysis.

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Fundamental to all treatment-control protocols will be the creation of two cohorts – one cohort comprised of the treated population and a second of untreated controls, who will be as similar as possible in risk factors for the key outcomes using available data. All protocols will attempt to create the best approximation possible, from observational data, of a randomized controlled trial of CP.

The several sub-protocols may differ in:

1. The electronic record database used to select treated and untreated controls
2. The precise definition of each variable, which is subject to the nature of available data
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Design

This study is a historical observational design in which exposed patients (recipients of CP) are matched to an unexposed control population (non-recipients of CP) and followed from day of treatment in the exposed and a matched day in controls (referred to as day zero, see below) until the end of the period of observation which is designed to be at least 40 days in all subjects. This kind of design has been referred to as exposure-control study in the epidemiologic literature and differs from a traditional historical cohort design in the matching of unexposed to exposed, and from the usual case-control design by directionality, which here is from exposure to outcome and not from outcome to exposure.

1. **Source population for the study.**

   The source population for the study will be all patients, 18 years and older, with COVID-19 admitted to hospitals in the Mayo registry study of COVID-19 treated with CP. The source population will be restricted to admissions occurring between the date of admission of the first recipient of CP in each hospital until the date extraction of data, with a follow up period up to discharge, death, or 40 days from hospital admission (if neither dead nor discharged).

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population from whom data will be extracted are defined below under items 3 and 4 below.

Both Cerner and Epic are already working on detailed queries and data definitions in support of this study. For health systems who wish to leverage this work should contact:

- Cerner EHR: contact your account executive.
- Epic EHR: contact your Epic Best Friend Forever (BFF), inquire about the “Insights Project.”

3. Definition of COVID-19 patient and COVID-19 related hospitalization

The definition of COVID-19 case will be the diagnosis made in the hospital of care. It is recognized that there are several possible case definitions, but this study will not at this time attempt to impose a specific case definition unique to the study.

The COVID-19 Healthcare Coalition has worked to develop common data definitions that can be leveraged for the study. The current definitions are included in Appendix A.

4. Identification of the treated cohort.

An attempt will be made to identify all patients in the EPIC file with the diagnosis of COVID-19 disease who were admitted to the treating hospital until 28 days before the date of extraction of data, and who received, at some point during their hospitalization, one or more transfusions of convalescent plasma, regardless of the number of units or spike antibody titer. No exclusions will be made.

5. Identification of the untreated control cohort.

The pool of potential controls is all other COVID-19 patients not treated with convalescent plasma at any time during their hospitalization, admitted between the date of admission of the first COVID-19 patient treated with convalescent plasma at that hospital and a date 28 days or more before the date of extraction of data.

6. Omission of exact dates.

To maintain data confidentiality, a random number will be assigned, separately for each hospital, to the earliest date in the cohort, which is the date of admission of the first CP treated patient in each hospital. All dates subsequent to that date will be computed from that date. Thus if the first date is March 25th in hospital A, and the random number assigned to that date is 876, if a treated patient was intubated on March 29th, received CP on April 2nd, was extubated on April 5th, and discharged on April 10th, those dates would be recoded, respectively, as 880 (876 + 4), 884, 887 and 892.
Calculation of duration of events (see outcome variables below) will require subtraction of the random number from the disguised date number.

7. Matching process and matching variables

The six variables used in matching are listed in the table below. Hospital (to be identified only by a code), sex and ventilation status at onset of treatment are dichotomous; age will be matched in ten-year intervals (>80 is one interval); daily oxygenation requirement is defined as a proxy for severity of illness. Duration of stay prior to CP treatment will be used to determine date of cohort inception (referred to here as time zero) for the controls. If possible, that date will be the exact number of days between admission and treatment/time zero for the treated and control cohorts, but if that is not possible the match will be within 3 days duration (3 days pre or 3 days post day zero). Treatment/time zero will be the dates used to calculate all duration outcomes. Up to four controls for treated patients will be sought.

8. Outcomes of interest

a. Primary outcome – death at any time after admission recorded in the EMR. Deaths will be measured at 7 days, 14 days, 21 days and 28 days, and total deaths.

b. Secondary outcomes (all times measured from day of treatment in the treatment arm and from the corresponding day zero in controls).

i. Number of days to first extubation (in mechanically ventilated patients)
ii. Number of days to first intubation (in non-mechanically ventilated patients)
iii. Number of days to death
iv. Number of days to discharge

9. Data analysis

a. Initial analyses

The initial analysis will examine death rates at the times specified above separately using mixed-effects logistic regression where the random effect account for the matched sampling. Mortality differences will be expressed as Odds Ratios for the treatment arm compared to the control arm.

For secondary outcomes, we will examine time from inception of treatment/time zero to each of the secondary outcomes specified above, including the appropriate sub-populations (mechanically ventilated at time zero/not mechanically ventilated at time zero) for analyses of time to intubation/extubation.
Time to death will be analyzed at first by the Kaplan-Meier curves and a shared-frailty (accounting for matching) model, treating discharged patients as being alive until the time of analysis. Then times to death and discharge will be analyzed jointly by a Cox-type, cause-specific hazard model with a bivariate log-normal frailty (accounting for matching), treating these two events as competing risks.

Times to extubation (intubation) and death will be analyzed jointly in the same way. In the analysis of times to extubation and death, treated patients will be further matched with untreated patients on duration of ventilation prior to CP to define time zero for the controls. In all the analyses, survival differences will be expressed as (cause-specific) hazard ratios. The Kaplan-Meier curves, the shared-frailty model and the cause-specific hazard frailty models all account for observation time of study subjects still in hospital at the time of data analysis.

b. Multivariate analysis of mortality

In the second phase of analysis, variables in Appendix B will be examined for their effects on mortality in the entire database. Any variable associated with mortality (change in OR of 20% or more, regardless of p value) will be entered into a separate mixed-effects logistic regression model for each of the four mortality time periods and into the regression models for survival analysis. These models will account for variable matching ratios of controls to cases.

10. Patient confidentiality

As this study is restricted to the analysis of data, the only human subjects concern is confidentiality. The study does not abstract any identifying information on the participant, disguises all dates linked to individuals, and uses a large sample of participants with unidentified hospitals, thus minimizing the risk that non-identifying variables could be used to identify participants. Nonetheless, all Mayo procedures for protecting computerized data will be followed, including the use of password protection and the presence of firewalls separating the study data from other forms of data in storage.

11. Facility Remuneration

Sites providing data will be offered remuneration for the administrative and technical time at the rate of $100.00 per fully completed patient information.
<table>
<thead>
<tr>
<th>Data Element Category</th>
<th>Data Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matching</td>
<td>Hospital (deidentified code for each facility)</td>
</tr>
<tr>
<td></td>
<td>Age¹</td>
</tr>
<tr>
<td></td>
<td>Administrative gender²</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (see definition below) on day of admission (day 0)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 1)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 2)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 3)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 4)</td>
</tr>
<tr>
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<td>Severity of respiratory illness (day 5)</td>
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<td></td>
<td>Severity of respiratory illness (day 6)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 7)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 8)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 9)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 10)</td>
</tr>
<tr>
<td>Outcome/time variable³,⁴</td>
<td>Admission date</td>
</tr>
<tr>
<td></td>
<td>Date of convalescent plasma administration</td>
</tr>
<tr>
<td></td>
<td>Date of first intubation (start of mechanical ventilation)</td>
</tr>
<tr>
<td></td>
<td>Date of first extubation (end of mechanical ventilation)</td>
</tr>
<tr>
<td></td>
<td>Date of death</td>
</tr>
<tr>
<td></td>
<td>Date of discharge</td>
</tr>
<tr>
<td>Other variables</td>
<td>Still in hospital on date of data extraction (Y/N)</td>
</tr>
</tbody>
</table>

¹ Should be “>90 years” instead of actual age for patients over 90 for deidentification purposes
² Male, female or unknown/other
³ All that apply to each case
⁴ Please reference disguising of dates section for details on how to deidentify the dates before submitting any data
Severity of illness refers to the severity of the patient’s respiratory symptoms. The goal is to measure severity on the day of treatment with CP infusion. It is recommended to calculate and store one daily value (midnight to midnight) of severity for the first 10 days of hospitalization. “Case matching” will require use of this value, therefore we need this value to be also calculated on “control” patients.

<table>
<thead>
<tr>
<th>Severity of Illness Allowable Value</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Not on supplemental oxygen</td>
<td>Not on supplemental oxygen, on high-flow supplemental oxygen or mechanically ventilated, per definitions below.</td>
</tr>
<tr>
<td>4</td>
<td>On conventional supplemental oxygen therapy</td>
<td>On nasal cannula or oxygen facial mask &lt; 30L/min</td>
</tr>
</tbody>
</table>
| 3                                   | On high-flow supplemental oxygen | - On high-flow nasal cannula (HFNC) or oxygen facial mask >= 30L/min  
- Non-invasive positive pressure ventilation (NIPPV), including BiPAP, or CPAP between 8am and 9pm (8am to 9pm requirement on CPAP to rule-out regular home CPAP use) |
| 2                                   | Invasive mechanical ventilation | Mechanical ventilation (as evidenced by PEEP, vent mode change, FiO2 flowsheet documentation) or ECMO |
Appendix A

These definitions were arrived upon through the work of the COVID-19 Healthcare Coalition partners, including a multidisciplinary group of clinical, informatics and EHR data experts. If you have any questions on these definitions, please contact Rute Martins (rute@mitre.org).

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<thead>
<tr>
<th>Data Element</th>
<th>Description</th>
<th>Logic</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 positive</td>
<td>A patient who has been clinically diagnosed with COVID-19 or who tested positive for COVID-19.</td>
<td>COVID-19 confirmed diagnosis OR COVID-19 confirmatory laboratory test</td>
</tr>
<tr>
<td>COVID-19-positive laboratory test</td>
<td>A laboratory test indicating that the patient has a COVID-19 infection</td>
<td>Laboratory test in COVID-19 Qualitative Laboratory Test value set AND (laboratory test result ~ detected OR ~positive)</td>
</tr>
<tr>
<td>COVID-19 confirmed diagnosis</td>
<td>A clinical diagnosis (any encounter diagnosis, billing diagnosis or problem list entry) of Confirmed COVID-19 infection</td>
<td>Condition in Confirmed COVID-19 Infection value set AND Condition.type ~ (encounter diagnosis, discharge diagnosis, final diagnosis, primary diagnosis, billing diagnosis, problem list entry) AND Condition.type NOT ~ admitting diagnosis</td>
</tr>
<tr>
<td>COVID-19-positive date</td>
<td>The earliest date associated with the confirmation of the COVID-19 infection.</td>
<td>Earliest of (COVID-19 confirmatory laboratory test specimen collection date(^5), first COVID-19 confirmed diagnosis)</td>
</tr>
<tr>
<td>Age at COVID-19 positive date</td>
<td>The age (in years) of the patient on the date they were diagnosed with COVID-19.</td>
<td>COVID-19 positive date minus date of birth</td>
</tr>
</tbody>
</table>

---

\(^5\) The result date can be used when specimen collection date is not available
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<th>Data Element</th>
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<tr>
<td>COVID-19-related hospitalization(^6)</td>
<td>An encounter for inpatient care that is associated with COVID-19.</td>
<td>Encounter class ~ INP OR ~ inpatient OR ~acute inpatient AND (COVID-19-positive date during hospitalization OR COVID-19-positive date &lt;= 14 days prior to hospitalization AND respiratory diagnosis associated with hospitalization(^7))</td>
</tr>
<tr>
<td>Respiratory diagnosis associated with hospitalization</td>
<td>Any diagnosis for a respiratory condition associated with a hospitalization</td>
<td>Condition code ICD-10-CM J00-J99 AND Condition.type ~ (encounter diagnosis, discharge diagnosis, final diagnosis, chief complaint, primary diagnosis, billing diagnosis, problem list entry)</td>
</tr>
<tr>
<td>Convalescent Plasma administration</td>
<td>Convalescent plasma administration regardless of the number of units or antibody titer.</td>
<td>Blood product order LIKE %COVID-19% OR Blood product order administration product code in ISBT 128 E codes for COVID-19 convalescent plasma</td>
</tr>
</tbody>
</table>

\(^6\) It is recognized that this will include COVID-related hospitalizations but also hospitalizations of COVID-19 patients who may be asymptomatic and nosocomial COVID-19 infections.  
\(^7\) Proxy for symptomatic COVID-19 infection when patient is admitted for reasons unrelated to COVID-19
**Terminology**

**Confirmed COVID-19 Infection Value Set**

<table>
<thead>
<tr>
<th>Includes</th>
<th>Conditions associated with confirmed COVID-19 infection, including laboratory-confirmed COVID-19 (symptomatic or asymptomatic).</th>
</tr>
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<tbody>
<tr>
<td>ICD-10-CM:</td>
<td>U07.1 only available since 4/1/2020, will be used for lab-confirmed cases regardless of symptom presentation</td>
</tr>
<tr>
<td>SNOMED-CT:</td>
<td>840539006 Disease caused by severe acute respiratory syndrome coronavirus 2 (disorder)</td>
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2. Creation of a study variable set

All patients eligible to be included in the source population will have the data listed in the table below. Patients without data elements to be used in matching or to study outcomes will be excluded. Incompleteness in other variables will not be a reason to exclude the participant. Unless noted elsewhere, all variables will be extracted for the entire study population of COVID-19 patients from admission until death, discharge, or until the date the study is undertaken, if neither dead nor discharged. The source population from whom data will be extracted are defined below under items 3 and 4 below.
Both Cerner and Epic are already working on detailed queries and data definitions in support of this study. For health systems who wish to leverage this work should contact:

- Cerner EHR: contact your account executive.
- Epic EHR: contact your Epic Best Friend Forever (BFF), inquire about the “Insights Project.”

3. Definition of COVID-19 patient and COVID-19 related hospitalization

The definition of COVID-19 case will be the diagnosis made in the hospital of care. It is recognized that there are several possible case definitions, but this study will not at this time attempt to impose a specific case definition unique to the study.

The COVID-19 Healthcare Coalition has worked to develop common data definitions that can be leveraged for the study. The current definitions are included in Appendix A.

4. Identification of the treated cohort.

An attempt will be made to identify all patients in the EPIC file with the diagnosis of COVID-19 disease who were admitted to the treating hospital until 28 days before the date of extraction of data, and who received, at some point during their hospitalization, one or more transfusions of convalescent plasma, regardless of the number of units or spike antibody titer. No exclusions will be made.

5. Identification of the untreated control cohort.

The pool of potential controls is all other COVID-19 patients not treated with convalescent plasma at any time during their hospitalization, admitted between the date of admission of the first COVID-19 patient treated with convalescent plasma at that hospital and a date 28 days or more before the date of extraction of data.

6. Omission of exact dates.

To maintain data confidentiality, a random number will be assigned, separately for each hospital, to the earliest date in the cohort, which is the date of admission of the first CP treated patient in each hospital. All dates subsequent to that date will be computed from that date. Thus if the first date is March 25th in hospital A, and the random number assigned to that date is 876, if a treated patient was intubated on March 29th, received CP on April 2nd, was extubated on April 5th, and discharged on April 10th, those dates would be recoded, respectively, as 880 (876 + 4), 884, 887 and 892. Calculation of duration of events (see outcome variables below) will require subtraction of the random number from the disguised date number.
7. **Matching process and matching variables**

The six variables used in matching are listed in the table below. Hospital (to be identified only by a code), sex and ventilation status at onset of treatment are dichotomous; age will be matched in ten-year intervals (>80 is one interval); daily oxygenation requirement is defined as a proxy for severity of illness. Duration of stay prior to CP treatment will be used to determine date of cohort inception (referred to here as time zero) for the controls. If possible, that date will be the exact number of days between admission and treatment/time zero for the treated and control cohorts, but if that is not possible the match will be within 3 days duration (3 days pre or 3 days post day zero). Treatment/time zero will be the dates used to calculate all duration outcomes. Up to four controls for treated patients will be sought. Due to the rapidly changing treatment paradigms, the month of admission only will be used as a matching variable (hence the need for the submission of a limited data set).

8. **Outcomes of interest**

   a. **Primary outcome** – death at any time after admission recorded in the EMR. Deaths will be measured at 7 days, 14 days, 21 days and 28 days, and total deaths.

   b. **Secondary outcomes** (all times measured from day of treatment in the treatment arm and from the corresponding day zero in controls).

      i. Number of days to first extubation (in mechanically ventilated patients)
      ii. Number of days to first intubation (in non-mechanically ventilated patients)
      iii. Number of days to death
      iv. Number of days to discharge

9. **Data analysis**

   a. **Initial analyses**

   The initial analysis will examine death rates at the times specified above separately using mixed-effects logistic regression where the random effect account for the matched sampling. Mortality differences will be expressed as Odds Ratios for the treatment arm compared to the control arm.

   For secondary outcomes, we will examine time from inception of treatment/time zero to each of the secondary outcomes specified above, including the appropriate sub-populations (mechanically ventilated at time zero/not mechanically ventilated at time zero) for analyses of time to intubation/extubation.
Time to death will be analyzed at first by the Kaplan-Meier curves and a shared-frailty (accounting for matching) model, treating discharged patients as being alive until the time of analysis. Then times to death and discharge will be analyzed jointly by a Cox-type, cause-specific hazard model with a bivariate log-normal frailty (accounting for matching), treating these two events as competing risks.

Times to extubation (intubation) and death will be analyzed jointly in the same way. In the analysis of times to extubation and death, treated patients will be further matched with untreated patients on duration of ventilation prior to CP to define time zero for the controls. In all the analyses, survival differences will be expressed as (cause-specific) hazard ratios. The Kaplan-Meier curves, the shared-frailty model and the cause-specific hazard frailty models all account for observation time of study subjects still in hospital at the time of data analysis.

b. Multivariate analysis of mortality

In the second phase of analysis, variables in Appendix B will be examined for their effects on mortality in the entire database. Any variable associated with mortality (change in OR of 20% or more, regardless of p value) will be entered into a separate mixed-effects logistic regression model for each of the four mortality time periods and into the regression models for survival analysis. These models will account for variable matching ratios of controls to cases.

10. Patient confidentiality

As this is study is restricted to the analysis of data, the only human subjects concern is confidentiality. The study does not abstract any identifying information on the participant, disguises all dates linked to individuals, and uses a large sample of participants with unidentified hospitals, thus minimizing the risk that non-identifying variables could be used to identify participants. Nonetheless, all Mayo procedures for protecting computerized data will be followed, including the use of password protection and the presence of firewalls separating the study data from other forms of data in storage.

11. Facility Remuneration

Sites providing data will be offered remuneration for the administrative and technical time at the rate of $100.00 per fully completed patient information.
<table>
<thead>
<tr>
<th>Data Element Category</th>
<th>Data Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matching</td>
<td>Hospital (deidentified code for each facility)</td>
</tr>
<tr>
<td></td>
<td>Age¹</td>
</tr>
<tr>
<td></td>
<td>Administrative gender²</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (see definition below) on day of admission (day 0)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 1)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 2)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 3)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 4)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 5)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 6)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 7)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 8)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 9)</td>
</tr>
<tr>
<td></td>
<td>Severity of respiratory illness (day 10)</td>
</tr>
<tr>
<td>Outcome/time variable³⁴</td>
<td>Admission date (month only)</td>
</tr>
<tr>
<td></td>
<td>Date of convalescent plasma administration</td>
</tr>
<tr>
<td></td>
<td>Date of first intubation (start of mechanical ventilation)</td>
</tr>
<tr>
<td></td>
<td>Date of first extubation (end of mechanical ventilation)</td>
</tr>
<tr>
<td></td>
<td>Date of death</td>
</tr>
<tr>
<td></td>
<td>Date of discharge</td>
</tr>
<tr>
<td>Other variables</td>
<td>Still in hospital on date of data extraction (Y/N)</td>
</tr>
</tbody>
</table>

¹ Should be “>90 years” instead of actual age for patients over 90 for deidentification purposes
² Male, female or unknown/other
³ All that apply to each case
⁴ Please reference disguising of dates section for details on how to deidentify the dates before submitting any data
Severity of illness refers to the severity of the patient’s respiratory symptoms. The goal is to measure severity on the day of treatment with CP infusion. It is recommended to calculate and store one daily value (midnight to midnight) of severity for the first 10 days of hospitalization. “Case matching” will require use of this value, therefore we need this value to be also calculated on “control” patients.

<table>
<thead>
<tr>
<th>Severity of Illness Allowable Value</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Not on supplemental oxygen</td>
<td>Not on supplemental oxygen, on high-flow supplemental oxygen or mechanically ventilated, per definitions below.</td>
</tr>
<tr>
<td>4</td>
<td>On conventional supplemental oxygen therapy</td>
<td>On nasal cannula or oxygen facial mask &lt; 30L/min</td>
</tr>
<tr>
<td>3</td>
<td>On high-flow supplemental oxygen</td>
<td>- On high-flow nasal cannula (HFNC) or oxygen facial mask &gt;= 30L/min - Non-invasive positive pressure ventilation (NIPPV), including BiPAP, or CPAP between 8am and 9pm (8am to 9pm requirement on CPAP to rule-out regular home CPAP use)</td>
</tr>
<tr>
<td>2</td>
<td>Invasive mechanical ventilation</td>
<td>Mechanical ventilation (as evidenced by PEEP, vent mode change, FiO2 flowsheet documentation) or ECMO</td>
</tr>
</tbody>
</table>
Appendix A

These definitions were arrived upon through the work of the COVID-19 Healthcare Coalition partners, including a multidisciplinary group of clinical, informatics and EHR data experts. If you have any questions on these definitions, please contact Rute Martins (rute@mitre.org).

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Description</th>
<th>Logic</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 positive</td>
<td>A patient who has been clinically diagnosed with COVID-19 or who tested positive for COVID-19.</td>
<td>COVID-19 confirmed diagnosis OR COVID-19 confirmatory laboratory test</td>
</tr>
<tr>
<td>COVID-19-positive laboratory test</td>
<td>A laboratory test indicating that the patient has a COVID-19 infection.</td>
<td>Laboratory test in COVID-19 Qualitative Laboratory Test value set AND (laboratory test result ~ detected OR ~positive)</td>
</tr>
<tr>
<td>COVID-19 confirmed diagnosis</td>
<td>A clinical diagnosis (any encounter diagnosis, billing diagnosis or problem list entry) of Confirmed COVID-19 infection</td>
<td>Condition in Confirmed COVID-19 Infection value set AND Condition.type ~ (encounter diagnosis, discharge diagnosis, final diagnosis, primary diagnosis, billing diagnosis, problem list entry) AND Condition.type NOT ~ admitting diagnosis</td>
</tr>
<tr>
<td>COVID-19-positive date</td>
<td>The earliest date associated with the confirmation of the COVID-19 infection.</td>
<td>Earliest of (COVID-19 confirmatory laboratory test specimen collection date(^5), first COVID-19 confirmed diagnosis)</td>
</tr>
<tr>
<td>Age at COVID-19 positive date</td>
<td>The age (in years) of the patient on the date they were diagnosed with COVID-19.</td>
<td>COVID-19 positive date minus date of birth</td>
</tr>
</tbody>
</table>

\(^5\) The result date can be used when specimen collection date is not available
<table>
<thead>
<tr>
<th>Data Element</th>
<th>Description</th>
<th>Logic</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19-related hospitalization(^6)</td>
<td>An encounter for inpatient care that is associated with COVID-19.</td>
<td>Encounter class ~ INP OR ~ inpatient OR ~acute inpatient AND () COVID-19-positive date during hospitalization OR COVID-19-positive date &lt;= 14 days prior to hospitalization AND respiratory diagnosis associated with hospitalization(^7)</td>
</tr>
<tr>
<td>Respiratory diagnosis associated with hospitalization</td>
<td>Any diagnosis for a respiratory condition associated with a hospitalization</td>
<td>Condition code ICD-10-CM J00-J99 AND Condition.type ~ (encounter diagnosis, discharge diagnosis, final diagnosis, chief complaint, primary diagnosis, billing diagnosis, problem list entry)</td>
</tr>
<tr>
<td>Convalescent Plasma administration</td>
<td>Convalescent plasma administration regardless of the number of units or antibody titer.</td>
<td>Blood product order LIKE %COVID-19% OR Blood product order administration product code in ISBT 128 E codes for COVID-19 convalescent plasma</td>
</tr>
</tbody>
</table>

\(^6\) It is recognized that this will include COVID-related hospitalizations but also hospitalizations of COVID-19 patients who may be asymptomatic and nosocomial COVID-19 infections.

\(^7\) Proxy for symptomatic COVID-19 infection when patient is admitted for reasons unrelated to COVID-19
**Terminology**

**Confirmed COVID-19 Infection Value Set**

<table>
<thead>
<tr>
<th>Includes</th>
<th>Conditions associated with confirmed COVID-19 infection, including laboratory-confirmed COVID-19 (symptomatic or asymptomatic).</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-10-CM:</td>
<td>U07.1 only available since 4/1/2020, will be used for lab-confirmed cases regardless of symptom presentation</td>
</tr>
<tr>
<td>B97.29 used largely before 4/1/2020.</td>
<td></td>
</tr>
<tr>
<td>SNOMED-CT:</td>
<td>840539006 Disease caused by severe acute respiratory syndrome coronavirus 2 (disorder)</td>
</tr>
</tbody>
</table>

| Excludes | ICD-10-CM and SNOMED-CT codes indicative of suspicion or exposure only |

**SARS-CoV-2 Laboratory Tests**

| Includes | SARS-CoV-2-specific or SARS-like  
PCR or NAAT  
SARS-CoV-2 RNA in serum/plasma  
SARS-CoV-2 panels (not recommended for results by Regenstrief but used in the field)  
Qualitative results |
|----------|-----------------------------------------------------------------------------------------------------------------------------------|

| Excludes | Human coronavirus tests (non-SARS/SARS-like tests) and MERS tests  
Antibody and antigen tests  
Quantitative results (e.g. cycle threshold #) |
Appendix B

The following table provides a list of data elements currently identified as potential covariates to support logistic regression and Cox models. These elements will be considered in a second phase of the study.

<table>
<thead>
<tr>
<th>Data Element Category</th>
<th>Data Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>Race</td>
</tr>
<tr>
<td></td>
<td>Ethnicity</td>
</tr>
<tr>
<td></td>
<td>Body Mass Index</td>
</tr>
<tr>
<td></td>
<td>Smoking status</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Pre-hospital diabetes</td>
</tr>
<tr>
<td></td>
<td>Pre-hospital chronic lung disease</td>
</tr>
<tr>
<td></td>
<td>Pre-hospital asthma</td>
</tr>
<tr>
<td></td>
<td>Pre-hospital hypertension</td>
</tr>
<tr>
<td></td>
<td>Pre-hospital cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Pre-hospital cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Pre-hospital End Stage Renal Disease (ESRD)</td>
</tr>
<tr>
<td></td>
<td>Pre-hospital chronic kidney disease (CKD) other than ESRD</td>
</tr>
<tr>
<td></td>
<td>Pre-hospital malignancy</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>ICU admission</td>
</tr>
<tr>
<td></td>
<td>In-hospital renal impairment</td>
</tr>
<tr>
<td></td>
<td>In-hospital sepsis</td>
</tr>
<tr>
<td></td>
<td>In-hospital multi-organ failure</td>
</tr>
<tr>
<td>Laboratory test results(^8)</td>
<td>D-dimer</td>
</tr>
<tr>
<td></td>
<td>Full WBC</td>
</tr>
<tr>
<td></td>
<td>pO2/FIO2 and SpO2/FIO2 ratios</td>
</tr>
<tr>
<td></td>
<td>SPO2</td>
</tr>
<tr>
<td></td>
<td>CRP</td>
</tr>
<tr>
<td></td>
<td>LDH</td>
</tr>
<tr>
<td></td>
<td>Cardiac troponin</td>
</tr>
<tr>
<td>Other therapies administered during hospitalization</td>
<td>Antivirals (Remdesivir)</td>
</tr>
<tr>
<td></td>
<td>Interleukin-6 agents (tocilizumab, sarilumab)</td>
</tr>
<tr>
<td></td>
<td>H2-blockers (famotidine)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids (prednisone, methylprednisolone, dexamethasone)</td>
</tr>
</tbody>
</table>

\(^8\) For laboratory values, we will have to determine whether we want all values downloaded or select highs or lows or other fractions of the distributions, since there are likely to be multiple tests, especially with oxygenation.
7. Clinical Investigator’s Brochure

<table>
<thead>
<tr>
<th>Filename and Version</th>
<th>Version Date</th>
<th>Date Posted on Website</th>
<th>Date Removed from Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB 20-003312 COVID-19 Plasma V4.0</td>
<td>7/15/2020</td>
<td>7/17/2020</td>
<td>Currently Posted</td>
</tr>
</tbody>
</table>

Note – Version 3.0 was never posted on the website so it is not included.

The most up to date information about the product can be obtained from the FDA emergency use authorization (EUA). This includes risks along with the potential benefits contained within the decision memorandum, and fact sheets.

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Clinical Investigator’s Brochure for Use of Convalescent Plasma to Treat Coronavirus-19 (COVID-19) Disease

Regulatory Sponsor and Principal Investigator: Michael J. Joyner, MD
Mayo Clinic
200 First Street SW
Rochester, MN 55905

Study Product: ABO Compatible COVID-19 Convalescent Plasma

Protocol Number: (IRBe) 20-003312
IND Number: 19832

Initial version: [4/9/2020] Version (1.0)
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AABB</td>
<td>American Association of Blood Banks</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Hepatitis B core antibodies</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>BMT</td>
<td>Bone marrow transplant</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Infectious Disease -19 (novel coronavirus) disease caused by SARS-CoV-2 virus</td>
</tr>
<tr>
<td>CCP</td>
<td>COVID-19 Convalescent Plasma</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FFP</td>
<td>Fresh Frozen Plasma</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Surface antigen of the hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HTLV</td>
<td>Human T-cell lymphotropic virus</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IVIG</td>
<td>Intravenous immune globulin</td>
</tr>
<tr>
<td>NAT</td>
<td>Nucleic acid testing</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe Acute Respiratory Syndrome</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19</td>
</tr>
<tr>
<td>TACO</td>
<td>Transfusion-associated circulatory overload</td>
</tr>
<tr>
<td>TRALI</td>
<td>Transfusion related acute lung injury</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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2 Summary

This information brochure has been developed specifically for use with the Expanded Access Program (EAP) under IND 19832. The information contained within the document is being provided to participating treating physicians along with the protocol and consent form to assist in protecting the patients being treated as part of this EAP.

This expanded access program will provide access to investigational COVID-19 convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with ABO compatible convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events judged to be related to the administration of convalescent plasma. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

Plasma has been and is being collected by registered or licensed blood banks, including the American Red Cross. Collection of plasma will be done using the guidelines from AABB, the FDA, and the American Red Cross or as contained in the COVID-19 Convalescent Plasma Collection Protocol, and using otherwise standard operating procedures at the blood establishments.

Plasma from patients who have recovered from a documented SARS-CoV-2 infection may contain high titer anti-SARS CoV-2 antibodies which may be able to modify the course of the infection and decrease morbidity and mortality associated with SARS-CoV-2 infection when transfused into hospitalized patients in a serious or life-threatening situation or at high risk for progression of severe disease.
3 Introduction

Severe morbidity and mortality is occurring during this COVID-19 Pandemic. Since there is no currently recognized effective standard of care treatment for patients infected with SARS-CoV-2, multiple investigational agents are being tested. These include antivirals marketed or approved for other indications or being developed specifically for SARS-CoV-2 and other immunotherapies.

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

The collection and transfusion of convalescent plasma as a treatment was first used in the 1890s and helped reduce the severity of a number of infectious disease outbreaks prior to the development of antimicrobial therapy in the 1940s.

In the early 20th century, convalescent plasma treatment was used during outbreaks of various infectious diseases, including measles, mumps and influenza. More recently, it was used during the H1N1 influenza pandemic in 2009, and again in 2013 during the Ebola outbreak in West Africa.

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19. [1, 2]

The FDA is permitting the use of convalescent plasma as an investigational treatment for patients with moderate or severe COVID-19 infection. It is considered an investigational treatment because clinical studies have started but have not yet been completed. We know there is evidence that convalescent plasma has helped patients with other illnesses, but doctors and researchers will not know how effective convalescent plasma will be in treating COVID-19 patients until more studies are completed.

While additional treatment options are evolving, convalescent plasma can be considered and may help some moderately or severely ill patients. The idea to use this treatment for the new coronavirus was suggested by Arturo Casadevall, MD, PhD, from Johns Hopkins University; and Liise-anne Pirofski, MD, from the Albert Einstein College of Medicine.[3]
4 Physical, Chemical and Pharmaceutical Properties and Formulation.

The product to be administered is COVID-19 Convalescent Plasma. This is human plasma, collected from patients who have recovered from a documented infection with the novel coronavirus, SARS-CoV-2 who have been screened for blood borne pathogens, according to standard FDA criteria to be qualified as plasma/blood donors.

4.1 Donor Qualifications

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Plasma Donations from Recovered COVID-19 Patients[^1][^2]

The American Red Cross is seeking people who are fully recovered from COVID-19 and may be able to donate plasma to help current patients with serious or immediately life-threatening COVID-19 infections, or those judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Donor qualifications will be assessed based on the current guidelines at the time of donation.

4. American Red Cross – Plasma Donations from Recovered COVID-19 Patients


People who have fully recovered from COVID-19 have antibodies in their plasma that can attack the virus. This convalescent plasma is being evaluated as treatment for patients seriously ill with COVID-19. Historically, convalescent plasma has been used as a potentially lifesaving treatment when new diseases or infections develop quickly, and no treatments or vaccines were available yet. The American Red Cross has been asked by the U.S. Food and Drug Administration (FDA) to help identify prospective donors and manage the distribution of these products to hospitals treating patients in need.

The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug–Limited by Federal (or United States) law to investigational use.” (21 CFR 312.6 (a))

All units of plasma have been collected at registered or licensed blood banks and in accordance with the blood bank SOPs for a plasma product. Units of plasma will have been stored at the collection site or a central repository prior to shipping to the sites participating in the Expanded Access Program.
All plasma collected for use under this Expanded Access Program will have the following characteristics:

- Negative Anti-HIV-1/2
- Negative Anti-HTLV-I/II
- Negative Anti-HCV
- Negative HBsAg
- Negative for anti-HBe
- Negative serologic test for syphilis
- Negative anti- *T. cruzi* or history of a negative test if a previous blood donor
- Negative testing for Babesia or a history of a negative test for Babesia, depending upon geographic residency of the donor. (Note: This testing is required in beginning May 4, 2020. Residents of endemic areas are tested with each donation.)
- Negative West Nile Virus (WNV) NAT
- Negative HCV NAT
- Negative HIV NAT
- Negative HBV NAT
- Negative Zika NAT

In the event of new infectious diseases that are potentially transmitted by blood products, all plasma collected under this Expanded Access Program will follow FDA guidance regarding the screening of donors and/or additional serologic or nucleic acid testing (NAT). All plasma products will be labeled in a manner to allow traceability for the purpose of infectious disease testing, identification and if necessary recipient notification.

### 4.2 Convalescent Plasma Preparation

This Expanded Access Program will make available ABO compatible COVID-19 Convalescent Plasma collected by registered or licensed blood establishments in accordance with the AABB Circular of Information[28] the American Red Cross – Plasma Donations from Recovered COVID-19 Patients[4] and FDA’s regulations and the additional Investigational COVID-19 Convalescent Plasma – Guidance for Industry[5]
4.3 Convalescent Plasma Administration

Before administration of the COVID-19 convalescent plasma the treating clinician must have registered as a site, as a physician and have registered the patient in the EAP. The treating clinician or designee must document properly obtained informed consent, read through the protocol and appropriately direct the use of the convalescent plasma. The physician or designee must check the label to verify that the information on the label as it relates to the transfusion to the intended patient is correct.

ABO compatible COVID-19 Convalescent Plasma will be administered according to standard hospital procedures.

The infusion can occur through a peripheral or central venous catheter and will be given according to standard institutional medical and nursing practices for the administration of plasma.

For practical purposes in the current outbreak, one unit of ABO compatible COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (volume of plasma to administer approximately 200-400 mL), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedication, such as acetaminophen and diphenhydramine. The duration of infusion will usually take 1 to 2 hours (rate of 100 to 250 mL/hr).

COVID-19 Convalescent Plasma will be supplied as an investigational blood product for the treatment of COVID-19 with either a label or tie tag on the bag indicating the presence of COVID-19 antibodies.

Premedication may be administered prior to plasma administration according to individual acute care facility protocols.
5 Preclinical Development

COVID-19 Convalescent Plasma has not undergone any preclinical evaluation.

6 Previous Human Experience

6.1 Use in COVID-19


In a limited case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment, PAO2/ FIO2 < 300 and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. The study was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020; final date of follow-up was March 25, 2020. Clinical outcomes were compared before and after convalescent plasma transfusion.

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. Convalescent plasma was administered between 10 and 22 days after admission.

All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/ FIO2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.

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. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials. [2]
6.2 Use in SARS (Severe Acute Respiratory Syndrome)


This study involved the treatment of 80 patients with SARS in Hong Kong. Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis.

SARS was diagnosed according to CDC criteria. Starting in mid-March 2003, patients admitted with suspected SARS were given cefotaxime and levofloxacin (or clarithromycin) on the day of admission to cover community-acquired pneumonia. If fever persisted, ribavirin (administered as 1200 mg p.o. t.i.d. or i.v. 400 mg q8h) and prednisolone (0.5–1 mg/kg) were started on day 3. Patients with radiographic progression and hypoxemia were given pulsed methylprednisolone (500 mg i.v. daily for 2–3 doses).

Patients whose condition continued to deteriorate, as defined by SaO₂<90% on 0.5 FiO₂, were then given 200–400 ml (4–5 ml/kg) of ABO-compatible convalescent plasma at the discretion of the attending clinicians and according to convalescent plasma availability. The potential benefits and risks of convalescent plasma were carefully explained to the patients and their families.

Convalescent plasma was obtained from patients who had recovered from SARS patients. Recovery was defined as an afebrile status for at least 7 days, radiographic improvement of 25%, no further need of an oxygen supplement, and at least 14 days following symptom onset. Informed consent was obtained from the donors who needed to be seronegative for hepatitis B and C, HIV and syphilis and seropositive for coronavirus (titer range, 160–2,560).

Good outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death before day 22 or hospitalization beyond 22 days. The discharge criteria of the Hospital Authority were as follows: (i) afebrile status for 4 consecutive days; (ii) improvement in previously abnormal leukocyte counts, platelet counts, creatinine phosphatase kinase, lactate dehydrogenase, liver function tests and C-reactive protein; (iii) radiographic improvement; and (iv) at least 21 days following the onset of illness. This last factor led us to define good outcome as discharge by day 22. Using this definition, we were able to divide the patients into two distinct non-overlapping outcome groups.

The eighty patients (43 females and 37 males) were given convalescent plasma around day 14 (range, 7–30 days) following the onset of symptoms. The median age of the patients receiving convalescent plasma was 45 years (range, 21–82 years). The mean volume of plasma infused was 279.3±127.1ml (range, 160–640ml). Thirty-three patients had a good clinical outcome; they were given convalescent plasma earlier than the
patients with a poor outcome. Patients given convalescent plasma before day 14 had a better outcome than those given plasma after day 14. The mortality rates in the two groups were 6.3% and 21.9%, respectively. One major factor affecting the timing of convalescent plasma administration was plasma availability. Overall, the mortality rate was 12.5% among the 80 patients given convalescent plasma. The overall SARS-related mortality rate in Hong Kong was 17% (299/1755) during the SARS epidemic from 6 March to 24 May 2003.

Sixty-one percent of the patients with a good outcome were PCR positive and seronegative for coronavirus at the time of plasma infusion as compared with 21% in the group with a poor outcome. The 30 patients who were PCR positive and seronegative for coronavirus at the time of convalescent plasma therapy had a better outcome than those who were already seropositive (66.7% vs 20%). Age was a poor prognostic factor. In the multivariate analysis, only the time of convalescent plasma therapy and coronavirus PCR positivity were significant factors.

No immediate adverse effects were observed with convalescent plasma infusion. There was no correlation between clinical outcome and either the volume of plasma infused or the coronavirus antibody titers of the donors.

6.3 Use in H1N1 Influenza
A cohort study was conducted in Hong Kong by recruiting 93 patients aged >18 years with severe H1N1 2009 infection requiring intensive care.[7] All subjects were offered treatment with 500 mL convalescent plasma with a neutralizing H1N1 2009 antibody titer of >1:160, collected from patients recovering from H1N1 2009 infection. Twenty subjects (21.5%) agreed to receive the plasma treatment, and 73 subjects declined. All subjects received standard antiviral treatment and other supportive medical care. Clinical outcome was compared in the subjects treated with plasma with those who declined plasma treatment as the “untreated” controls. Mortality in the treatment group was significantly lower than in the control group (20.0% vs. 54.8%; P = .01). There were no adverse events (AEs) attributed to the convalescent plasma.

A multi-center, prospective, double-blind, randomized controlled trial of a hyperimmune intravenous immunoglobulin was also conducted in Hong Kong. [8] Convalescent plasma from patients who recovered from the 2009 pandemic influenza infection was made into an immunoglobulin (H-IVIG). Patients with severe A (H1N1) infection on standard antiviral treatment requiring intensive care and ventilatory support were randomized to receive H-IVIG or normal IVIG. Thirty-five patients were randomized to receive H-IVIG (17 patients) or IVIG (18 patients). H-IVIG treatment was associated with significantly lower day 5 and 7 post-treatment viral load when compared to the control (p=0.04 and p=0.02 respectively). Subgroup multivariate analysis of the 22 patients who received treatment within 5 days of symptom onset demonstrated that H-IVIG treatment was the only factor that independently reduced mortality [OR: 0.14, 95% CI, 0.02-0.92; p=0.04].
6.4 Use of Convalescent Plasma Therapy in Other Diseases

Multiple clinical trials conducted in the Soviet Union reported that convalescent plasma, serum and IVIG were efficacious in the treatment of influenza pneumonia and the prevention of influenza. \[9-14\]

Luke et al. conducted a meta-analysis of studies using convalescent blood products during the Spanish Influenza pandemic of 1918 and concluded that the approach may have been beneficial in the treatment of influenza pneumonia and Acute Respiratory Distress Syndrome (ARDS). \[15\]

A number of other viral diseases are treated with antibody preparations with variable results. These antibody preparations are generally given as IVIG but curative treatment with IVIG is rare. Red blood cell aplasia caused by parvovirus B19 infection is the only recognized viral infection in which treatment with IVIG may eradicate the infection. \[16, 17\] However, there is considerable evidence that immune globulin preparations may modify the natural history of viral diseases. These are summarized below.

**Cytomegalovirus (CMV):** CMV enriched immune globulin preparations have shown benefit when used in combination with ganciclovir in the treatment of CMV pneumonia. \[18\] This immune globulin preparation is also utilized in the treatment of ganciclovir-resistant CMV infections.

**Respiratory Syncytial Virus (RSV):** In adult bone marrow transplant (BMT) patients with RSV pneumonia, combination therapy using aerosolized ribavirin and standard IVIG (500 mg/kg every other day for 12 days) for the treatment had a 22% mortality rate, compared to a historical mortality rate of 70%. \[19\] In pediatric BMT patients with RSV pneumonia, patients treated with combination aerosolized ribavirin and RSV antibody enriched IVIG (RespiGam®) had a 9.1% mortality, compared with a historical 50-70% mortality rate of such patients given ribavirin alone. \[20\]

**Vaccinia Virus:** Certain complications of vaccination with the vaccinia virus (smallpox vaccine) are treated with vaccinia immune globulin (VIG). These included generalized vaccinia, eczema vaccinatum, and progressive vaccinia. There have been no controlled trials of the efficacy of VIG. However, anecdotal experience suggests that treatment with VIG for these conditions is beneficial, and is now considered the standard of care. \[21\]
**Hepatitis A:** IVIG has also been shown useful in hepatitis A. Persons who have been recently exposed to hepatitis A and who have not been previously vaccinated with hepatitis A are recommended to receive standard IVIG as post-exposure prophylaxis. This is based on data that showed IVIG, when administered within 2 weeks following an exposure to hepatitis A, is greater than 85% effective in preventing hepatitis A. [22]

IVIG can also attenuate the clinical expression of hepatitis A infection when given later in the incubation period. [23] Standard IVIG is used because it does contain sufficient anti-hepatitis A antibodies.

**Hepatitis B:** For patients with hepatitis B and cirrhosis undergoing orthotopic liver transplant, hepatitis B hyperimmune IgG is given pre-operatively and post-operatively to prevent reinfection with hepatitis B. This has been shown to be 50-85% effective in preventing recurrence of hepatitis B in the transplanted liver. [24, 25] This efficacy may be improved with the concurrent use of the antiviral lamivudine. [25]

**Rabies:** Rabies hyperimmune IgG is the standard recommended therapy after exposure to the rabies virus/rabid animal. [26]

**Argentine Hemorrhagic Fever:** Convalescent plasma from survivors is the standard of care and has been shown to reduce mortality from 50% to 4% if therapy is initiated within eight days of disease onset. [27]

### 7 Biohazard Information

This material should be handled as if capable of transmitting infectious agents. Please use universal precautions. No test method can provide total assurance that Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus, or Other Infectious Agents are absent. Thus, all biological products that we provide should be handled at the Bio-Safety Level 2 as recommended by the CDC/NHI Manual “Biosafety In Microbiological And Biomedical Laboratories, From Potentially Infectious Human Serum Or Blood Specimens”.

8  Risk / Benefit Analysis

8.1 Benefits

The benefits of COVID-19 Convalescent Plasma therapy in patients actively infected with SARS-CoV-2 are unknown. However, it is possible that CCP in addition to other standard of care treatments or investigational antiviral therapy will more rapidly decrease viral replication, reduce the duration and severity of illness, reduce complications, and improve outcomes after infection with SARS-CoV-2.

8.2 Risks

8.2.1 Side Effects and Hazards for Plasma

Side effects from plasma and plasma components are listed in the Circular of Information for Human Blood and Blood Components (2017) [28]

Hazards that pertain to transfusion of FFP can be classified as:

- Immunologic Complications, Immediate
  - Hemolytic transfusion reaction
  - Febrile nonhemolytic reaction
  - Allergic reactions
  - Anaphylactoid/anaphylactic reactions
  - Transfusion-related acute lung injury (TRALI)
- Immunologic Complications, Delayed
  - Posttransfusion purpura
- Nonimmunologic Complications
  - Transmission of infectious diseases
  - Bacterial sepsis
  - Transfusion-associated circulatory overload (TACO)
  - Hypothermia
  - Metabolic complications

Plasma must be ABO compatible with the recipient’s red cells. The volume transfused depends on the clinical situation and patient size and may be guided by laboratory assays of coagulation and function.

Do not use FFP if there is evidence of container breakage or of thawing during storage. FFP must be thawed in a waterbath at 30-37°C or in an FDA-cleared device. If a waterbath is used, thaw the component in a protective plastic overwrap using gentle agitation.
Common risks of plasma transfusions may include one or more of the following: fever, rash, hives, or headache. Other more serious risks are rare and may include the following: serious allergic reactions including anaphylaxis, bacterial infections, or viral infections like Hepatitis B, Hepatitis C and human immunodeficiency virus (HIV).

Transfusion-related acute lung injury (TRALI) may occur, but this risk will be minimized by using male donated plasma or female donors who have not been pregnant or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies. TRALI is characterized by a clinical constellation of symptoms including dyspnea, hypotension and fever. Although the precise pathogenesis of TRALI remains unknown, it has been shown to be most often related to the transfusion of anti-HLA and anti-neutrophil antibodies from plasma from multiparous women (antibodies presumably generated during pregnancy) or donors who have received multiple blood transfusions. The risk of TRALI is reported as 1 out of 5000 transfusions.  

Each unit of plasma contains 200-400 mL of volume. Depending on the total volume infused, there is the risk of volume overload in the recipient that could cause pulmonary edema. Transfusion-associated circulatory overload (TACO) has been associated with plasma infusion and may be clinically indistinguishable from TRALI even though the physiologic mechanisms differ. TACO is hydrostatic not permeability edema and more responsive to diuresis when it occurs. Subjects with preexisting conditions who may not tolerate this volume of plasma will be excluded from this study, but this condition could still occur in recipients.

There are case reports of pulmonary emboli occurring after administration of IVIG and plasma therapy, though definitive studies assessing risk are lacking. Pulmonary emboli have been shown to develop in approximately 10-15% of critically ill adults. However, the potential risk of pulmonary embolism exists.

There is the risk of other infections that can be transmitted by blood products. In all cases, the study plasma will follow FDA guidance for donor screening and testing of plasma products. Zika virus is one such possible infection. As of November 2017, there has been no documented transmission associated Zika virus infection in the United States. Universal testing for Zika virus was implemented at the end of November 2016. The risk of transfusion associated Zika virus infection is considered low.
9 Summary of Data and Guidance for the Treating Physicians

There is no known benefit to administering the COVID-19 Convalescent Plasma to infected patients. The plasma will be stored, prepared and administered by standard hospital practices associated with the administration of plasma.

Until there is an approved indication for COVID-19 Convalescent Plasma as a treatment, this product must only be administered to patients properly consented and registered in this Expanded Access Program being executed in accordance with applicable Federal regulations and in accordance with the inclusion and exclusion criteria specified in the study protocol.
10 References


Clinical Investigator’s Brochure for Use of Convalescent Plasma to Treat Coronavirus-19 (COVID-19) Disease

Regulatory Sponsor and Principal Investigator
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Study Product:
COVID-19 Convalescent Plasma

Protocol Number: (IRBe) 20-003312
IND Number: 19832

Initial version: [4/9/2020] Version (1.0)
Revised: [6/16/2020] Version (1.1)
Revised: [6/16/2020] Version (2.0) [Clean]
## List of Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>AABB</td>
<td>American Association of Blood Banks</td>
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<tr>
<td>Anti-HBc</td>
<td>Hepatitis B core antibodies</td>
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<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
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<td>BMT</td>
<td>Bone marrow transplant</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
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| COVID-19     | Coronavirus Infectious Disease -19 (novel coronavirus)  
|              | disease caused by SARS-CoV-2 virus                                       |
| CCP          | COVID-19 Convalescent Plasma                                              |
| FDA          | Food and Drug Administration                                              |
| FFP          | Fresh Frozen Plasma                                                      |
| HBsAg        | Surface antigen of the hepatitis B virus                                  |
| HCV          | Hepatitis C virus                                                         |
| HIV          | Human Immunodeficiency Virus                                              |
| HTLV         | Human T-cell lymphotropic virus                                            |
| ICU          | Intensive Care Unit                                                       |
| IVIG         | Intravenous immune globulin                                               |
| MERS         | Middle East Respiratory Syndrome                                          |
| NAT          | Nucleic acid testing                                                      |
| RSV          | Respiratory syncytial virus                                               |
| SARS         | Severe Acute Respiratory Syndrome                                         |
| SARS-CoV-2   | Severe Acute Respiratory Syndrome Coronavirus 2 
|              | (SARS-CoV-2), the virus that causes COVID-19                              |
| TACO         | Transfusion-associated circulatory overload                               |
| TRALI        | Transfusion related acute lung injury                                      |
| WHO          | World Health Organization                                                 |
1 Table of Contents

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2 Summary

This information brochure has been developed specifically for use with the Expanded Access Program (EAP) under IND 19832. The information contained within the document is being provided to participating treating physicians along with the protocol and consent form to assist in protecting the patients being treated as part of this EAP.

This expanded access program will provide access to investigational COVID-19 convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

Plasma has been and is being collected by registered or licensed blood banks, including the American Red Cross. Collection of plasma will be done using the guidelines from AABB, the FDA, and the American Red Cross or as contained in the COVID-19 Convalescent Plasma Collection Protocol, and using otherwise standard operating procedures at the blood establishments.

Plasma from patients who have recovered from a documented SARS-CoV-2 infection may contain high titer anti-SARS CoV-2 antibodies which may be able to modify the course of the infection and decrease morbidity and mortality associated with SARS-CoV-2 infection when transfused into hospitalized patients in a serious or life-threatening situation or at high risk for progression of severe disease.
3 Introduction

Background [6]

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.1 In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.

One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19. Convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic.

Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials. This guidance provides recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. This guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

Severe morbidity and mortality is occurring during this COVID-19 Pandemic. Since there is no currently recognized effective standard of care treatment for patients infected with SARS-CoV-2, multiple investigational agents are being tested. These include antivirals marketed or approved for other indications or being developed specifically for SARS-CoV-2 and other immunotherapies.

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

The collection and transfusion of convalescent plasma as a treatment was first used in the 1890s and helped reduce the severity of a number of infectious disease outbreaks prior to the development of antimicrobial therapy in the 1940s.
In the early 20th century, convalescent plasma treatment was used during outbreaks of various infectious diseases, including measles, mumps and influenza. More recently, it was used during the H1N1 influenza pandemic in 2009, and again in 2013 during the Ebola outbreak in West Africa.

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.\footnote{1-3}

The FDA is permitting the use of convalescent plasma as an investigational treatment for patients with moderate or severe COVID-19 infection. It is considered an investigational treatment because clinical studies have started but have not yet been completed. We know there is evidence that convalescent plasma has helped patients with other illnesses, but doctors and researchers will not know how effective convalescent plasma will be in treating COVID-19 patients until more studies are completed.

While additional treatment options are evolving, convalescent plasma can be considered and may help some moderately or severely ill patients. The idea to use this treatment for the new coronavirus was suggested by Arturo Casadevall, MD, PhD, from Johns Hopkins University; and Liise-anne Pirofski, MD, from the Albert Einstein College of Medicine.\footnote{4}
4 Physical, Chemical and Pharmaceutical Properties and Formulation.

The product to be administered is COVID-19 Convalescent Plasma. This is human plasma, collected from patients who have recovered from a documented infection with the novel coronavirus, SARS-CoV-2 who have been screened for blood borne pathogens, according to standard FDA criteria to be qualified as plasma/blood donors.

4.1 Donor Qualifications

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Plasma Donations from Recovered COVID-19 Patients

The American Red Cross and other organizations are seeking people who are fully recovered from COVID-19 and may be able to donate plasma to help current patients with serious or immediately life-threatening COVID-19 infections, or those judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Donor qualifications will be assessed based on the current guidelines at the time of donation.

5. American Red Cross – Plasma Donations from Recovered COVID-19 Patients


People who have fully recovered from COVID-19 have antibodies in their plasma that can attack the virus. This convalescent plasma is being evaluated as treatment for patients seriously ill with COVID-19. Historically, convalescent plasma has been used as a potentially lifesaving treatment when new diseases or infections develop quickly, and no treatments or vaccines were available yet. The American Red Cross and other organizations have been asked by the U.S. Food and Drug Administration (FDA) to help identify prospective donors and manage the distribution of these products to hospitals treating patients in need.

The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a)

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All plasma collected for use under this Expanded Access Program will have the following characteristics:

- Negative Anti-HIV-1/2
- Negative Anti-HTLV-I/II
- Negative Anti-HCV
- Negative HBsAg
- Negative for anti-HBc
- Negative serologic test for syphilis
- Negative anti-\textit{T. cruzi} or history of a negative test if a previous blood donor
- Negative testing for Babesia or a history of a negative test for Babesia, depending upon geographic residency of the donor. (Note: This testing is required in beginning May 4, 2020. Residents of endemic areas are tested with each donation.)
- Negative West Nile Virus (WNV) NAT
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In the event of new infectious diseases that are potentially transmitted by blood products, all plasma collected under this Expanded Access Program will follow FDA guidance regarding the screening of donors and/or additional serologic or nucleic acid testing (NAT). All plasma products will be labeled in a manner to allow traceability for the purpose of infectious disease testing, identification and if necessary recipient notification.

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This Expanded Access Program will make available COVID-19 Convalescent Plasma collected by registered or licensed blood establishments in accordance with the AABB Circular of Information\textsuperscript{29} the American Red Cross – Plasma Donations from Recovered COVID-19 Patients\textsuperscript{5} and FDA's regulations and the additional Investigational COVID-19 Convalescent Plasma – Guidance for Industry\textsuperscript{6}
4.3 Convalescent Plasma Administration

Before administration of the COVID-19 convalescent plasma the treating clinician must have registered as a site, as a physician and have registered the patient in the EAP. The treating clinician or designee must document properly obtained informed consent, read through the protocol and appropriately direct the use of the convalescent plasma. The physician or designee must check the label to verify that the information on the label as it relates to the transfusion to the intended patient is correct.

ABO compatible convalescent plasma will be transfused preferentially. In the absence of ABO compatible plasma, patients may receive as a second choice either Group A plasma or low anti-A titer Group O plasma, as available.

COVID-19 Convalescent Plasma will be administered according to standard hospital procedures.

The infusion can occur through a peripheral or central venous catheter and will be given according to standard institutional medical and nursing practices for the administration of plasma.

For practical purposes in the current outbreak, a dose of one – two units of COVID-19 convalescent plasma will be administered. This will be provided by a registered or licensed blood collector and will be collected preferably by apheresis (total volume of plasma to be administered will be approximately 200 mL or more), or if necessary, by conventional methods (volume of plasma to administer approximately 200-250 mL per unit). Individual institutional guidelines for the administration of plasma should be followed, including the use of any premedications, such as acetaminophen and diphenhydramine.

If a subsequent dose of convalescent plasma is administered, the treating physician will begin the transfusion at a time that is clinically compatible with the patient’s underlying condition.

COVID-19 Convalescent Plasma will be supplied as an investigational blood product for the treatment of COVID-19. A label or tie tag on the bag should indicate the presence of COVID-19 antibodies, if testing is available.
5 Preclinical Development
COVID-19 Convalescent Plasma has not undergone any preclinical evaluation.

6 Previous Human Experience

6.1 Use in COVID-19

Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients
Joyner MJ et al., May 2020, doi: https://doi.org/10.1101/2020.05.12.20099879

- Mayo Clinic and collaborators reported safety data on the first 5,000 hospitalized patients transfused with investigational convalescent plasma as part of the U.S. Food and Drug Administration’s national Expanded Access Program (EAP) for COVID-19.
- The early indicators suggest experimental convalescent plasma is safe in treating severely ill patients.
- At this time, convalescent plasma is the only antibody-based therapy available for COVID-19.
- Patients received plasma between April 3 and May 3. The seven-day incidence of mortality was 14.9%. Sixty-six percent of the patients were in the ICU, and nearly 20% carried the diagnosis of multi-organ dysfunction or failure. Importantly, the reports of serious adverse events related to transfusion of the plasma was small (<1%).
- The researchers note that while the study was not designed to evaluate the efficacy of convalescent plasma, a seven day incidence of mortality of 14.9% in this number of patients indicates “no signal of toxicity beyond what is expected from plasma use in severely ill patients.”
- It is important to note that this is a first safety report and does not provide any findings on the effectiveness of convalescent plasma in the treatment of COVID-19. Also, the EAP is ongoing and data are still being gathered. This is not a clinical trial; there is no control arm.
Treatment of COVID-19 Patients with Convalescent Plasma [41],

COVID-19 disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally, and no proven treatments are available. Convalescent plasma therapy has been used with varying degrees of success to treat severe microbial infections for more than 100 years. Patients (n = 25) with severe and/or life-threatening COVID-19 disease were enrolled at the Houston Methodist hospitals from March 28 – April 14, 2020. Patients were transfused with convalescent plasma obtained from donors with confirmed SARS-CoV-2 infection and had recovered. The primary study outcome was safety, and the secondary outcome was clinical status at day 14 post-transfusion. Clinical improvement was assessed based on a modified World Health Organization 6-point ordinal scale and laboratory parameters. Viral genome sequencing was performed on donor and recipient strains. At day 7 post-transfusion with convalescent plasma, nine patients had at least a 1-point improvement in clinical scale, and seven of those were discharged. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged. No adverse events as a result of plasma transfusion were observed. Whole genome sequencing data did not identify a strain genotype-disease severity correlation. The data indicate that administration of convalescent plasma is a safe treatment option for those with severe COVID-19 disease.


In a limited case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment, PAO2/ FIO2 < 300 and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. The study was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020; final date of follow-up was March 25, 2020. Clinical outcomes were compared before and after convalescent plasma transfusion.

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. Convalescent plasma was administered between 10 and 22 days after admission.

All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5
patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.

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. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials. [3]

6.2 Use in SARS (Severe Acute Respiratory Syndrome)


This study involved the treatment of 80 patients with SARS in Hong Kong. Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis.

SARS was diagnosed according to CDC criteria. Starting in mid-March 2003, patients admitted with suspected SARS were given cefotaxime and levofloxacin (or clarithromycin) on the day of admission to cover community-acquired pneumonia. If fever persisted, ribavirin (administered as 1200 mg p.o. t.i.d. or i.v. 400 mg q8h) and prednisolone (0.5–1 mg/kg) were started on day 3. Patients with radiographic progression and hypoxemia were given pulsed methylprednisolone (500 mg i.v. daily for 2–3 doses).

Patients whose condition continued to deteriorate, as defined by SaO2<90% on 0.5 FiO2, were then given 200–400 ml (4–5 ml/kg) of ABO-compatible convalescent plasma at the discretion of the attending clinicians and according to convalescent plasma availability. The potential benefits and risks of convalescent plasma were carefully explained to the patients and their families.

Convalescent plasma was obtained from patients who had recovered from SARS patients. Recovery was defined as an afebrile status for at least 7 days, radiographic improvement of 25%, no further need of an oxygen supplement, and at least 14 days following symptom onset. Informed consent was obtained from the donors who needed to be seronegative for hepatitis B and C, HIV and syphilis and seropositive for coronavirus (titer range, 160–2,560).
Good outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death before day 22 or hospitalization beyond 22 days. The discharge criteria of the Hospital Authority were as follows: (i) afebrile status for 4 consecutive days; (ii) improvement in previously abnormal leukocyte counts, platelet counts, creatinine phosphatase kinase, lactate dehydrogenase, liver function tests and C-reactive protein; (iii) radiographic improvement; and (iv) at least 21 days following the onset of illness. This last factor led us to define good outcome as discharge by day 22. Using this definition, we were able to divide the patients into two distinct non-overlapping outcome groups.

The eighty patients (43 females and 37 males) were given convalescent plasma around day 14 (range, 7–30 days) following the onset of symptoms. The median age of the patients receiving convalescent plasma was 45 years (range, 21–82 years). The mean volume of plasma infused was 279.3±127.1ml (range, 160–640ml). Thirty-three patients had a good clinical outcome; they were given convalescent plasma earlier than the patients with a poor outcome. Patients given convalescent plasma before day 14 had a better outcome than those given plasma after day 14. The mortality rates in the two groups were 6.3% and 21.9%, respectively. One major factor affecting the timing of convalescent plasma administration was plasma availability. Overall, the mortality rate was 12.5% among the 80 patients given convalescent plasma. The overall SARS-related mortality rate in Hong Kong was 17% (299/1755) during the SARS epidemic from 6 March to 24 May 2003.

Sixty-one percent of the patients with a good outcome were PCR positive and seronegative for coronavirus at the time of plasma infusion as compared with 21% in the group with a poor outcome. The 30 patients who were PCR positive and seronegative for coronavirus at the time of convalescent plasma therapy had a better outcome than those who were already seropositive (66.7% vs 20%). Age was a poor prognostic factor. In the multivariate analysis, only the time of convalescent plasma therapy and coronavirus PCR positivity were significant factors.

No immediate adverse effects were observed with convalescent plasma infusion. There was no correlation between clinical outcome and either the volume of plasma infused or the coronavirus antibody titers of the donors.
6.3 Use in H1N1 Influenza

A cohort study was conducted in Hong Kong by recruiting 93 patients aged >18 years with severe H1N1 2009 infection requiring intensive care. All subjects were offered treatment with 500 mL convalescent plasma with a neutralizing H1N1 2009 antibody titer of >1:160, collected from patients recovering from H1N1 2009 infection. Twenty subjects (21.5%) agreed to receive the plasma treatment, and 73 subjects declined. All subjects received standard antiviral treatment and other supportive medical care. Clinical outcome was compared in the subjects treated with plasma with those who declined plasma treatment as the “untreated” controls. Mortality in the treatment group was significantly lower than in the control group (20.0% vs. 54.8%; P = .01). There were no adverse events (AEs) attributed to the convalescent plasma.

A multi-center, prospective, double-blind, randomized controlled trial of a hyperimmune intravenous immunoglobulin was also conducted in Hong Kong. Convalescent plasma from patients who recovered from the 2009 pandemic influenza infection was made into an immunoglobulin (H-IVIG). Patients with severe A (H1N1) infection on standard antiviral treatment requiring intensive care and ventilatory support were randomized to receive H-IVIG or normal IVIG. Thirty-five patients were randomized to receive H-IVIG (17 patients) or IVIG (18 patients). H-IVIG treatment was associated with significantly lower day 5 and 7 post-treatment viral load when compared to the control (p=0.04 and p=0.02 respectively). Subgroup multivariate analysis of the 22 patients who received treatment within 5 days of symptom onset demonstrated that H-IVIG treatment was the only factor that independently reduced mortality [OR: 0.14, 95% CI, 0.02-0.92; p=0.04].

6.4 Use of Convalescent Plasma Therapy in Other Diseases

Multiple clinical trials conducted in the Soviet Union reported that convalescent plasma, serum and IVIG were efficacious in the treatment of influenza pneumonia and the prevention of influenza. Luke et al. conducted a meta-analysis of studies using convalescent blood products during the Spanish Influenza pandemic of 1918 and concluded that the approach may have been beneficial in the treatment of influenza pneumonia and Acute Respiratory Distress Syndrome (ARDS).

A number of other viral diseases are treated with antibody preparations with variable results. These antibody preparations are generally given as IVIG but curative treatment with IVIG is rare. Red blood cell aplasia caused by parvovirus B19 infection is the only recognized viral infection in which treatment with IVIG may eradicate the infection. However, there is considerable evidence that immune globulin preparations may modify the natural history of viral diseases. These are summarized below.
Cytomegalovirus (CMV): CMV enriched immune globulin preparations have shown benefit when used in combination with ganciclovir in the treatment of CMV pneumonia. [19] This immune globulin preparation is also utilized in the treatment of ganciclovir-resistant CMV infections.

Respiratory Syncytial Virus (RSV): In adult bone marrow transplant (BMT) patients with RSV pneumonia, combination therapy using aerosolized ribavirin and standard IVIG (500 mg/kg every other day for 12 days) for the treatment had a 22% mortality rate, compared to a historical mortality rate of 70%. [20] In pediatric BMT patients with RSV pneumonia, patients treated with combination aerosolized ribavirin and RSV antibody enriched IVIG (RespiGam®) had a 9.1% mortality, compared with a historical 50-70% mortality rate of such patients given ribavirin alone. [21]

Vaccinia Virus: Certain complications of vaccination with the vaccinia virus (smallpox vaccine) are treated with vaccinia immune globulin (VIG). These included generalized vaccinia, eczema vaccinatum, and progressive vaccinia. There have been no controlled trials of the efficacy of VIG. However, anecdotal experience suggests that treatment with VIG for these conditions is beneficial, and is now considered the standard of care. [22]

Hepatitis A: IVIG has also been shown useful in hepatitis A. Persons who have been recently exposed to hepatitis A and who have not been previously vaccinated with hepatitis A are recommended to receive standard IVIG as post-exposure prophylaxis. This is based on data that showed IVIG, when administered within 2 weeks following an exposure to hepatitis A, is greater than 85% effective in preventing hepatitis A. [23] IVIG can also attenuate the clinical expression of hepatitis A infection when given later in the incubation period. [24] Standard IVIG is used because it does contain sufficient anti-hepatitis A antibodies.

Hepatitis B: For patients with hepatitis B and cirrhosis undergoing orthotopic liver transplant, hepatitis B hyperimmune IgG is given pre-operatively and post-operatively to prevent reinfection with hepatitis B. This has been shown to be 50-85% effective in preventing recurrence of hepatitis B in the transplanted liver. [25,26] This efficacy may be improved with the concurrent use of the antiviral lamivudine. [26]

Rabies: Rabies hyperimmune IgG is the standard recommended therapy after exposure to the rabies virus/rabid animal. [27]

Argentine Hemorrhagic Fever: Convalescent plasma from survivors is the standard of care and has been shown to reduce mortality from 50% to 4% if therapy is initiated within eight days of disease onset. [28]
7 Biohazard Information

This material should be handled as if capable of transmitting infectious agents. Please use universal precautions. No test method can provide total assurance that Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus, or Other Infectious Agents are absent. Thus, all biological products that we provide should be handled at the Bio-Safety Level 2 as recommended by the CDC/NHI Manual “Biosafety In Microbiological And Biomedical Laboratories, From Potentially Infectious Human Serum Or Blood Specimens”.
8 Risk / Benefit Analysis

8.1 Benefits

The benefits of COVID-19 Convalescent Plasma therapy in patients actively infected with SARS-CoV-2 are unknown. However, it is possible that CCP in addition to other standard of care treatments or investigational antiviral therapy will more rapidly decrease viral replication, reduce the duration and severity of illness, reduce complications, and improve outcomes after infection with SARS-CoV-2.

8.2 Risks

8.2.1 Side Effects and Hazards for Plasma

Side effects from plasma and plasma components are listed in the Circular of Information for Human Blood and Blood Components (2017) [29]

Hazards that pertain to transfusion of FFP can be classified as:

- Immunologic Complications, Immediate
  - Hemolytic transfusion reaction
  - Febrile nonhemolytic reaction
  - Allergic reactions
  - Anaphylactoid/anaphylactic reactions
  - Transfusion-related acute lung injury (TRALI)

- Immunologic Complications, Delayed
  - Posttransfusion purpura

- Nonimmunologic Complications
  - Transmission of infectious diseases
  - Bacterial sepsis
  - Transfusion-associated circulatory overload (TACO)
  - Hypothermia
  - Metabolic complications

ABO compatible convalescent plasma will be transfused preferentially. In the absence of ABO compatible plasma, patients may receive as a second choice either Group A plasma or low anti-A titer Group O plasma, as available. The volume transfused depends on the clinical situation and patient size and may be guided by laboratory assays of coagulation and function.
Do not use FFP if there is evidence of container breakage or of thawing during storage. FFP must be thawed in a waterbath at 30-37C or in an FDA-cleared device. If a waterbath is used, thaw the component in a protective plastic overwrap using gentle agitation.

Common risks of plasma transfusions may include one or more of the following: fever, rash, hives, or headache. Other more serious risks are rare and may include the following: serious allergic reactions including anaphylaxis, bacterial infections, or viral infections like Hepatitis B, Hepatitis C and human immunodeficiency virus (HIV).

Transfusion-related acute lung injury (TRALI) may occur, but this risk will be minimized by using male donated plasma or female donors who have not been pregnant or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies. TRALI is characterized by a clinical constellation of symptoms including dyspnea, hypotension and fever. Although the precise pathogenesis of TRALI remains unknown, it has been shown to be most often related to the transfusion of anti-HLA and anti-neutrophil antibodies from plasma from multiparous women (antibodies presumably generated during pregnancy) or donors who have received multiple blood transfusions. The risk of TRALI is reported as 1 out of 5000 transfusions.\(^{[30]}\)

Each unit of plasma contains 200-400 mL of volume. Depending on the total volume infused, there is the risk of volume overload in the recipient that could cause pulmonary edema. Transfusion-associated circulatory overload (TACO) has been associated with plasma infusion and may be clinically indistinguishable from TRALI even though the physiologic mechanisms differ.\(^{[31]}\) TACO is hydrostatic not permeability edema and more responsive to diuresis when it occurs. Subjects with preexisting conditions who may not tolerate this volume of plasma will be excluded from this study, but this condition could still occur in recipients.

There are case reports of pulmonary emboli occurring after administration of IVIG and plasma therapy, though definitive studies assessing risk are lacking.\(^{[32]}\) Pulmonary emboli have been shown to develop in approximately 10-15% of critically ill adults.\(^{[33]}\) However, the potential risk of pulmonary embolism exists.

There is the risk of other infections that can be transmitted by blood products. In all cases, the study plasma will follow FDA guidance for donor screening and testing of plasma products. Zika virus is one such possible infection. As of November 2017, there has been no documented transmission associated Zika virus infection in the United States. Universal testing for Zika virus was implemented at the end of November 2016. The risk of transfusion associated Zika virus infection is considered low.

There is a theoretical risk of antibody-dependent enhancement of disease and suppressed long-term immune response.\(^{[34-36]}\)
8.2.2 Side Effects and Risks Associated with COVID-19 Disease

There is initial emerging evidence in disease progression of patients with COVID-19 disease that there is a potential for increased risk of cardiac arrhythmias.

Various cardiac arrhythmias associated with COVID-19 infection and treatment that may not correlate with severity of lung injury on CXR. In patients presenting with symptoms of COVID-19 infection, clinicians need to be wary of the potential for significant, often life-threatening arrhythmias, particularly if fulminant myocarditis is also suspected, and perform appropriate rhythm monitoring. Likewise, when making decisions regarding choice of antiarrhythmics, ionotropes and vasopressors, clinicians need to keep in mind potential proarrhythmic effects of antimalarial and antibiotic therapies currently being investigated as therapeutic agents against COVID-19 disease. [37-38]

Along with the previously mentioned risk of plasma therapy associated with pulmonary embolism, there is potential for increase of overall thrombotic or thromboembolic events.

COVID-19 disease causes not only hypercoagulability but also fibrinolysis shutdown which is associated with VTE, stroke, and renal failure. [39]
9 Summary of Data and Guidance for the Treating Physicians

There is no known benefit to administering the COVID-19 Convalescent Plasma to infected patients. The plasma will be stored, prepared and administered by standard hospital practices associated with the administration of plasma.

Until there is an approved indication for COVID-19 Convalescent Plasma as a treatment, this product must only be administered to patients properly consented and registered in this Expanded Access Program being executed in accordance with applicable Federal regulations and in accordance with the inclusion and exclusion criteria specified in the study protocol.

Along with the Circular of Information for the Use of Blood and Blood Components (2017)\(^{29}\), the NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol v2.5.2 \(^{40}\) can be used to assess transfusion-associated adverse reactions. This document can assist in classification of the reaction-specific case definition, severity, and imputability criteria.
10 References


Clinical Investigator’s Brochure for Use of Convalescent Plasma to Treat Coronavirus-19 (COVID-19) Disease

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Study Product: COVID-19 Convalescent Plasma

Protocol Number: (IRBe) 20-003312
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Revised: [6/30/2020] Version (3.0) [Clean]
Revised: [7/15/2020] Version (3.1) [Tracked Changes]
Revised: [7/15/2020] Version (4.0) [Clean]
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<tr>
<td>AABB</td>
<td>American Association of Blood Banks</td>
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<tr>
<td>Anti-HBc</td>
<td>Hepatitis B core antibodies</td>
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<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
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<tr>
<td>BMT</td>
<td>Bone marrow transplant</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
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<tr>
<td>COVID-19</td>
<td>Coronavirus Infectious Disease -19 (novel coronavirus) disease caused by SARS-CoV-2 virus</td>
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<td>CCP</td>
<td>COVID-19 Convalescent Plasma</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FFP</td>
<td>Fresh Frozen Plasma</td>
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<tr>
<td>HBsAg</td>
<td>Surface antigen of the hepatitis B virus</td>
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<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HTLV</td>
<td>Human T-cell lymphotropic virus</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<tr>
<td>IVIG</td>
<td>Intravenous immune globulin</td>
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<tr>
<td>MERS</td>
<td>Middle East Respiratory Syndrome</td>
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<td>NAT</td>
<td>Nucleic acid testing</td>
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<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
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<tr>
<td>SARS</td>
<td>Severe Acute Respiratory Syndrome</td>
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<tr>
<td>SARS-CoV-2</td>
<td>Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19</td>
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<tr>
<td>TACO</td>
<td>Transfusion-associated circulatory overload</td>
</tr>
<tr>
<td>TRALI</td>
<td>Transfusion related acute lung injury</td>
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2 Summary

This information brochure has been developed specifically for use with the Expanded Access Program (EAP) under IND 19832. The information contained within the document is being provided to participating treating physicians along with the protocol and consent form to assist in protecting the patients being treated as part of this EAP.

This expanded access program will provide access to investigational COVID-19 convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

Plasma has been and is being collected by registered or licensed blood banks, including the American Red Cross. Collection of plasma will be done using the guidelines from AABB, the FDA, and the American Red Cross or as contained in the COVID-19 Convalescent Plasma Collection Protocol, and using otherwise standard operating procedures at the blood establishments.

Plasma from patients who have recovered from a documented SARS-CoV-2 infection may contain high titer anti-SARS CoV-2 antibodies which may be able to modify the course of the infection and decrease morbidity and mortality associated with SARS-CoV-2 infection when transfused into hospitalized patients in a serious or life-threatening situation or at high risk for progression of severe disease.
3 Introduction

Background [6]

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.1 In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.

One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19. Convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic.

Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials.

FDA guidance (https://www.fda.gov/media/136798/download) provides recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. FDA guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

Severe morbidity and mortality is occurring during this COVID-19 Pandemic. Since there is no currently recognized effective standard of care treatment for patients infected with SARS-CoV-2, multiple investigational agents are being tested. These include antivirals marketed or approved for other indications or being developed specifically for SARS-CoV-2 and other immunotherapies.

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

The collection and transfusion of convalescent plasma as a treatment was first used in the 1890s and helped reduce the severity of a number of infectious disease outbreaks prior to the development of antimicrobial therapy in the 1940s.
In the early 20th century, convalescent plasma treatment was used during outbreaks of various infectious diseases, including measles, mumps and influenza. More recently, it was used during the H1N1 influenza pandemic in 2009, and again in 2013 during the Ebola outbreak in West Africa.

One of the ways that people fight of infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.[1-3]

The FDA is permitting the use of convalescent plasma as an investigational treatment for patients with moderate or severe COVID-19 infection. It is considered an investigational treatment because clinical studies have started but have not yet been completed. We know there is evidence that convalescent plasma has helped patients with other illnesses, but doctors and researchers will not know how effective convalescent plasma will be in treating COVID-19 patients until more studies are completed.

While additional treatment options are evolving, convalescent plasma can be considered and may help some moderately or severely ill patients. The idea to use this treatment for the new coronavirus was suggested by Arturo Casadevall, MD, PhD, from Johns Hopkins University; and Liise-anne Pirofski, MD, from the Albert Einstein College of Medicine.[4]
4 Physical, Chemical and Pharmaceutical Properties and Formulation.

The product to be administered is COVID-19 Convalescent Plasma. This is human plasma, collected from patients who have recovered from a documented infection with the novel coronavirus, SARS-CoV-2 who have been screened for blood borne pathogens, according to standard FDA criteria to be qualified as plasma/blood donors.

4.1 Donor Qualifications

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

Plasma Donations from Recovered COVID-19 Patients[5,6]

The American Red Cross and other organizations are seeking people who are fully recovered from COVID-19 and may be able to donate plasma to help current patients with serious or immediately life-threatening COVID-19 infections, or those judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Donor qualifications will be assessed based on the current guidelines at the time of donation.

5. American Red Cross – Plasma Donations from Recovered COVID-19 Patients


People who have fully recovered from COVID-19 have antibodies in their plasma that can attack the virus. This convalescent plasma is being evaluated as treatment for patients seriously ill with COVID-19. Historically, convalescent plasma has been used as a potentially lifesaving treatment when new diseases or infections develop quickly, and no treatments or vaccines were available yet. The American Red Cross and other organizations have been asked by the U.S. Food and Drug Administration (FDA) to help identify prospective donors and manage the distribution of these products to hospitals treating patients in need.

The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug--Limited by Federal (or United States) law to investigational use.” (21 CFR 312.6 (a))

All units of plasma have been collected at registered or licensed blood banks and in accordance with the blood bank SOPs for a plasma product. Units of plasma will have been stored at the collection site or a central repository prior to shipping to the sites participating in the Expanded Access Program.
All plasma collected for use under this Expanded Access Program will have the following characteristics:

- Negative Anti-HIV-1/2
- Negative Anti-HTLV-I/II
- Negative Anti-HCV
- Negative HBsAg
- Negative for anti-HBc
- Negative serologic test for syphilis
- Negative anti-*T. cruzi* or history of a negative test if a previous blood donor
- Negative testing for Babesia or a history of a negative test for Babesia, depending upon geographic residency of the donor. (Note: This testing is required in beginning May 4, 2020. Residents of endemic areas are tested with each donation.)
- Negative West Nile Virus (WNV) NAT
- Negative HCV NAT
- Negative HIV NAT
- Negative HBV NAT
- Negative Zika NAT

In the event of new infectious diseases that are potentially transmitted by blood products, all plasma collected under this Expanded Access Program will follow FDA guidance regarding the screening of donors and/or additional serologic or nucleic acid testing (NAT). All plasma products will be labeled in a manner to allow traceability for the purpose of infectious disease testing, identification and if necessary recipient notification.

### 4.2 Convalescent Plasma Preparation

This Expanded Access Program will make available COVID-19 Convalescent Plasma collected by registered or licensed blood establishments in accordance with the AABB Circular of Information[^29] the American Red Cross – Plasma Donations from Recovered COVID-19 Patients[^5] and FDA’s regulations and the additional Investigational COVID-19 Convalescent Plasma – Guidance for Industry[^6]
4.3 Convalescent Plasma Administration

Before administration of the COVID-19 convalescent plasma the treating clinician must have registered as a site, as a physician and have registered the patient in the EAP. The treating clinician or designee must document properly obtained informed consent, read through the protocol and appropriately direct the use of the convalescent plasma. The physician or designee must check the label to verify that the information on the label as it relates to the transfusion to the intended patient is correct.

ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.

COVID-19 Convalescent Plasma will be administered according to standard hospital procedures.

The infusion can occur through a peripheral or central venous catheter and will be given according to standard institutional medical and nursing practices for the administration of plasma.

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy.

The volume of plasma to be transfused should be based upon the patient’s weight and clinical comorbidities (e.g. patients with impaired cardiac function and heart failure may require less volume or more prolonged transfusion times). The volume of plasma to be transfused should be at least one unit (approximately 200 mL) but may be greater if the treating clinician concludes a larger volume is appropriate. Transfusions may occur at any time throughout the hospitalization including multiple doses on non-sequential days. In general, it is expected that most patients will receive two units or less, but this language is not intended to restrict the use of convalescent plasma in larger quantities when the treating physician determines that such volumes and/or re-treatment are clinically justified.

COVID-19 Convalescent Plasma will be supplied as an investigational blood product for the treatment of COVID-19.
5 Preclinical Development
COVID-19 Convalescent Plasma has not undergone any preclinical evaluation.

6 Previous Human Experience

6.1 Use in COVID-19

Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients[42]
Joyner MJ et al., Mayo Clinic Proceedings Pre-print June 2020

Objective: To provide an update on key safety metrics after transfusion of convalescent plasma in hospitalized COVID-19 patients, having previously demonstrated safety in 5,000 hospitalized patients.

Patients and Methods: From April 3 to June 2, 2020, the US FDA Expanded Access Program for COVID-19 convalescent plasma transfused a convenience sample of 20,000 hospitalized patients with COVID-19 convalescent plasma.

Results: The incidence of all serious adverse events was low; these included transfusion reactions (n=89; <1%), thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were judged to be unrelated to the plasma transfusion per se. The seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).

Conclusion: These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.
Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients \[2]\nJoyner MJ et al., May 2020, doi: https://doi.org/10.1101/2020.05.12.20099879

- Mayo Clinic and collaborators reported safety data on the first 5,000 hospitalized patients transfused with investigational convalescent plasma as part of the U.S. Food and Drug Administration’s national Expanded Access Program (EAP) for COVID-19.
- The early indicators suggest experimental convalescent plasma is safe in treating severely ill patients.
- At this time, convalescent plasma is the only antibody-based therapy available for COVID-19.
- Patients received plasma between April 3 and May 3. The seven-day incidence of mortality was 14.9%. Sixty-six percent of the patients were in the ICU, and nearly 20% carried the diagnosis of multi-organ dysfunction or failure. Importantly, the reports of serious adverse events related to transfusion of the plasma was small (<1%).
- The researchers note that while the study was not designed to evaluate the efficacy of convalescent plasma, a seven day incidence of mortality of 14.9% in this number of patients indicates “no signal of toxicity beyond what is expected from plasma use in severely ill patients.”
- It is important to note that this is a first safety report and does not provide any findings on the effectiveness of convalescent plasma in the treatment of COVID-19. Also, the EAP is ongoing and data are still being gathered. This is not a clinical trial; there is no control arm.
Treatment of COVID-19 Patients with Convalescent Plasma \cite{41},

COVID-19 disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally, and no proven treatments are available. Convalescent plasma therapy has been used with varying degrees of success to treat severe microbial infections for more than 100 years. Patients \((n = 25)\) with severe and/or life-threatening COVID-19 disease were enrolled at the Houston Methodist hospitals from March 28 – April 14, 2020. Patients were transfused with convalescent plasma obtained from donors with confirmed SARS-CoV-2 infection and had recovered. The primary study outcome was safety, and the secondary outcome was clinical status at day 14 post-transfusion. Clinical improvement was assessed based on a modified World Health Organization 6-point ordinal scale and laboratory parameters. Viral genome sequencing was performed on donor and recipient strains. At day 7 post-transfusion with convalescent plasma, nine patients had at least a 1-point improvement in clinical scale, and seven of those were discharged. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged. No adverse events as a result of plasma transfusion were observed. Whole genome sequencing data did not identify a strain genotype-disease severity correlation. The data indicate that administration of convalescent plasma is a safe treatment option for those with severe COVID-19 disease.

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma, JAMA. 2020 Mar 27, Shen C et al.; Pmid:32219428.\cite{3}

In a limited case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment, \(\text{PAO}_2/\text{FIO}_2 < 300\) and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. The study was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020; final date of follow-up was March 25, 2020. Clinical outcomes were compared before and after convalescent plasma transfusion.

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 immnosorbent 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. Convalescent plasma was administered between 10 and 22 days after admission.

All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5
patients, the SOFA score decreased, and PAO2/ FIO2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.

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. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials. [3]

6.2 Use in SARS (Severe Acute Respiratory Syndrome)

Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005, 24(1):44-46. Cheng, Y C et al.; [7] This study involved the treatment of 80 patients with SARS in Hong Kong. Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis.

SARS was diagnosed according to CDC criteria. Starting in mid-March 2003, patients admitted with suspected SARS were given cefotaxime and levofloxacin (or clarithromycin) on the day of admission to cover community-acquired pneumonia. If fever persisted, ribavirin (administered as 1200 mg p.o. t.i.d. or i.v. 400 mg q8h) and prednisolone (0.5–1 mg/kg) were started on day 3. Patients with radiographic progression and hypoxemia were given pulsed methylprednisolone (500 mg i.v. daily for 2–3 doses).

Patients whose condition continued to deteriorate, as defined by SaO2<90% on 0.5 FiO2, were then given 200–400 ml (4–5 ml/kg) of ABO-compatible convalescent plasma at the discretion of the attending clinicians and according to convalescent plasma availability. The potential benefits and risks of convalescent plasma were carefully explained to the patients and their families.

Convalescent plasma was obtained from patients who had recovered from SARS patients. Recovery was defined as an afebrile status for at least 7 days, radiographic improvement of 25%, no further need of an oxygen supplement, and at least 14 days following symptom onset. Informed consent was obtained from the donors who needed to be seronegative for hepatitis B and C, HIV and syphilis and seropositive for coronavirus (titer range, 160–2,560).
Good outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death before day 22 or hospitalization beyond 22 days. The discharge criteria of the Hospital Authority were as follows: (i) afebrile status for 4 consecutive days; (ii) improvement in previously abnormal leukocyte counts, platelet counts, creatinine phosphatase kinase, lactate dehydrogenase, liver function tests and C-reactive protein; (iii) radiographic improvement; and (iv) at least 21 days following the onset of illness. This last factor led us to define good outcome as discharge by day 22. Using this definition, we were able to divide the patients into two distinct non-overlapping outcome groups.

The eighty patients (43 females and 37 males) were given convalescent plasma around day 14 (range, 7–30 days) following the onset of symptoms. The median age of the patients receiving convalescent plasma was 45 years (range, 21–82 years). The mean volume of plasma infused was 279.3±127.1ml (range, 160–640ml). Thirty-three patients had a good clinical outcome; they were given convalescent plasma earlier than the patients with a poor outcome. Patients given convalescent plasma before day 14 had a better outcome than those given plasma after day 14. The mortality rates in the two groups were 6.3% and 21.9%, respectively. One major factor affecting the timing of convalescent plasma administration was plasma availability. Overall, the mortality rate was 12.5% among the 80 patients given convalescent plasma. The overall SARS-related mortality rate in Hong Kong was 17% (299/1755) during the SARS epidemic from 6 March to 24 May 2003.

Sixty-one percent of the patients with a good outcome were PCR positive and seronegative for coronavirus at the time of plasma infusion as compared with 21% in the group with a poor outcome. The 30 patients who were PCR positive and seronegative for coronavirus at the time of convalescent plasma therapy had a better outcome than those who were already seropositive (66.7% vs 20%). Age was a poor prognostic factor. In the multivariate analysis, only the time of convalescent plasma therapy and coronavirus PCR positivity were significant factors.

No immediate adverse effects were observed with convalescent plasma infusion. There was no correlation between clinical outcome and either the volume of plasma infused or the coronavirus antibody titers of the donors.
6.3 Use in H1N1 Influenza

A cohort study was conducted in Hong Kong by recruiting 93 patients aged >18 years with severe H1N1 2009 infection requiring intensive care. All subjects were offered treatment with 500 mL convalescent plasma with a neutralizing H1N1 2009 antibody titer of >1:160, collected from patients recovering from H1N1 2009 infection. Twenty subjects (21.5%) agreed to receive the plasma treatment, and 73 subjects declined. All subjects received standard antiviral treatment and other supportive medical care. Clinical outcome was compared in the subjects treated with plasma with those who declined plasma treatment as the “untreated” controls. Mortality in the treatment group was significantly lower than in the control group (20.0% vs. 54.8%; P = .01). There were no adverse events (AEs) attributed to the convalescent plasma.

A multi-center, prospective, double-blind, randomized controlled trial of a hyperimmune intravenous immunoglobulin was also conducted in Hong Kong. Convalescent plasma from patients who recovered from the 2009 pandemic influenza infection was made into an immunoglobulin (H-IVIG). Patients with severe A (H1N1) infection on standard antiviral treatment requiring intensive care and ventilatory support were randomized to receive H-IVIG or normal IVIG. Thirty-five patients were randomized to receive H-IVIG (17 patients) or IVIG (18 patients). H-IVIG treatment was associated with significantly lower day 5 and 7 post-treatment viral load when compared to the control (p=0.04 and p=0.02 respectively). Subgroup multivariate analysis of the 22 patients who received treatment within 5 days of symptom onset demonstrated that H-IVIG treatment was the only factor that independently reduced mortality [OR: 0.14, 95% CI, 0.02-0.92; p=0.04].

6.4 Use of Convalescent Plasma Therapy in Other Diseases

Multiple clinical trials conducted in the Soviet Union reported that convalescent plasma, serum and IVIG were efficacious in the treatment of influenza pneumonia and the prevention of influenza. Luke et al. conducted a meta-analysis of studies using convalescent blood products during the Spanish Influenza pandemic of 1918 and concluded that the approach may have been beneficial in the treatment of influenza pneumonia and Acute Respiratory Distress Syndrome (ARDS).

A number of other viral diseases are treated with antibody preparations with variable results. These antibody preparations are generally given as IVIG but curative treatment with IVIG is rare. Red blood cell aplasia caused by parvovirus B19 infection is the only recognized viral infection in which treatment with IVIG may eradicate the infection. However, there is considerable evidence that immune globulin preparations may modify the natural history of viral diseases. These are summarized below.
Cytomegalovirus (CMV): CMV enriched immune globulin preparations have shown benefit when used in combination with ganciclovir in the treatment of CMV pneumonia. [19] This immune globulin preparation is also utilized in the treatment of ganciclovir-resistant CMV infections.

Respiratory Syncytial Virus (RSV): In adult bone marrow transplant (BMT) patients with RSV pneumonia, combination therapy using aerosolized ribavirin and standard IVIG (500 mg/kg every other day for 12 days) for the treatment had a 22% mortality rate, compared to a historical mortality rate of 70%. [20] In pediatric BMT patients with RSV pneumonia, patients treated with combination aerosolized ribavirin and RSV antibody enriched IVIG (RespiGam®) had a 9.1% mortality, compared with a historical 50-70% mortality rate of such patients given ribavirin alone. [21]

Vaccinia Virus: Certain complications of vaccination with the vaccinia virus (smallpox vaccine) are treated with vaccinia immune globulin (VIG). These included generalized vaccinia, eczema vaccinatum, and progressive vaccinia. There have been no controlled trials of the efficacy of VIG. However, anecdotal experience suggests that treatment with VIG for these conditions is beneficial, and is now considered the standard of care. [22]

Hepatitis A: IVIG has also been shown useful in hepatitis A. Persons who have been recently exposed to hepatitis A and who have not been previously vaccinated with hepatitis A are recommended to receive standard IVIG as post-exposure prophylaxis. This is based on data that showed IVIG, when administered within 2 weeks following an exposure to hepatitis A, is greater than 85% effective in preventing hepatitis A. [23] IVIG can also attenuate the clinical expression of hepatitis A infection when given later in the incubation period. [24] Standard IVIG is used because it does contain sufficient anti-hepatitis A antibodies.

Hepatitis B: For patients with hepatitis B and cirrhosis undergoing orthotopic liver transplant, hepatitis B hyperimmune IgG is given pre-operatively and post-operatively to prevent reinfection with hepatitis B. This has been shown to be 50-85% effective in preventing recurrence of hepatitis B in the transplanted liver. [25,26] This efficacy may be improved with the concurrent use of the antiviral lamivudine. [26]

Rabies: Rabies hyperimmune IgG is the standard recommended therapy after exposure to the rabies virus/rabid animal. [27]

Argentine Hemorrhagic Fever: Convalescent plasma from survivors is the standard of care and has been shown to reduce mortality from 50% to 4% if therapy is initiated within eight days of disease onset. [28]
7 Biohazard Information

This material should be handled as if capable of transmitting infectious agents. Please use universal precautions. No test method can provide total assurance that Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus, or Other Infectious Agents are absent. Thus, all biological products that we provide should be handled at the Bio-Safety Level 2 as recommended by the CDC/NHI Manual “Biosafety In Microbiological And Biomedical Laboratories, From Potentially Infectious Human Serum Or Blood Specimens”.
8 Risk / Benefit Analysis

8.1 Benefits

The benefits of COVID-19 Convalescent Plasma therapy in patients actively infected with SARS-CoV-2 are unknown. However, it is possible that CCP in addition to other standard of care treatments or investigational antiviral therapy will more rapidly decrease viral replication, reduce the duration and severity of illness, reduce complications, and improve outcomes after infection with SARS-CoV-2.

8.2 Risks

8.2.1 Side Effects and Hazards for Plasma

Side effects from plasma and plasma components are listed in the Circular of Information for Human Blood and Blood Components (2017) [29]

Hazards that pertain to transfusion of FFP can be classified as:

- Immunologic Complications, Immediate
  - Hemolytic transfusion reaction
  - Febrile nonhemolytic reaction
  - Allergic reactions
  - Anaphylactoid/anaphylactic reactions
  - Transfusion-related acute lung injury (TRALI)
- Immunologic Complications, Delayed
  - Posttransfusion purpura
- Nonimmunologic Complications
  - Transmission of infectious diseases
  - Bacterial sepsis
  - Transfusion-associated circulatory overload (TACO)
  - Hypothermia
  - Metabolic complications

ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution’s guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.
Do not use FFP if there is evidence of container breakage or of thawing during storage. FFP must be thawed in a waterbath at 30-37°C or in an FDA-cleared device. If a waterbath is used, thaw the component in a protective plastic overwrap using gentle agitation.

Common risks of plasma transfusions may include one or more of the following: fever, rash, hives, or headache. Other more serious risks are rare and may include the following: serious allergic reactions including anaphylaxis, bacterial infections, or viral infections like Hepatitis B, Hepatitis C and human immunodeficiency virus (HIV).

Transfusion-related acute lung injury (TRALI) may occur, but this risk will be minimized by using male donated plasma or female donors who have not been pregnant or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies. TRALI is characterized by a clinical constellation of symptoms including dyspnea, hypotension and fever. Although the precise pathogenesis of TRALI remains unknown, it has been shown to be most often related to the transfusion of anti-HLA and anti-neutrophil antibodies from plasma from multiparous women (antibodies presumably generated during pregnancy) or donors who have received multiple blood transfusions. The risk of TRALI is reported as 1 out of 5000 transfusions. [30]

Each unit of plasma contains 200-400 mL of volume. Depending on the total volume infused, there is the risk of volume overload in the recipient that could cause pulmonary edema. Transfusion-associated circulatory overload (TACO) has been associated with plasma infusion and may be clinically indistinguishable from TRALI even though the physiologic mechanisms differ. [31] TACO is hydrostatic not permeability edema and more responsive to diuresis when it occurs. Subjects with preexisting conditions who may not tolerate this volume of plasma will be excluded from this study, but this condition could still occur in recipients.

There are case reports of pulmonary emboli occurring after administration of IVIG and plasma therapy, though definitive studies assessing risk are lacking. [32] Pulmonary emboli have been shown to develop in approximately 10-15% of critically ill adults. [33] However, the potential risk of pulmonary embolism exists.

There is the risk of other infections that can be transmitted by blood products. In all cases, the study plasma will follow FDA guidance for donor screening and testing of plasma products. Zika virus is one such possible infection. As of November 2017, there has been no documented transmission associated Zika virus infection in the United States. Universal testing for Zika virus was implemented at the end of November 2016. The risk of transfusion associated Zika virus infection is considered low.

There is a theoretical risk of antibody-dependent enhancement of disease and suppressed long-term immune response. [34-36]
8.2.2 Side Effects and Risks Associated with COVID-19 Disease

There is initial emerging evidence in disease progression of patients with COVID-19 disease that there is a potential for increased risk of cardiac arrhythmias.

Various cardiac arrhythmias associated with COVID-19 infection and treatment that may not correlate with severity of lung injury on CXR. In patients presenting with symptoms of COVID-19 infection, clinicians need to be wary of the potential for significant, often life-threatening arrhythmias, particularly if fulminant myocarditis is also suspected, and perform appropriate rhythm monitoring. Likewise, when making decisions regarding choice of antiarrhythmics, ionotropes and vasopressors, clinicians need to keep in mind potential proarrhythmic effects of antimalarial and antibiotic therapies currently being investigated as therapeutic agents against COVID-19 disease. [37-38]

Along with the previously mentioned risk of plasma therapy associated with pulmonary embolism, there is potential for increase of overall thrombotic or thromboembolic events.

COVID-19 disease causes not only hypercoagulability but also fibrinolysis shutdown which is associated with VTE, stroke, and renal failure. [39]
9 Summary of Data and Guidance for the Treating Physicians

There is no known benefit to administering the COVID-19 Convalescent Plasma to infected patients. The plasma will be stored, prepared and administered by standard hospital practices associated with the administration of plasma.

Until there is an approved indication for COVID-19 Convalescent Plasma as a treatment, this product must only be administered to patients properly consented and registered in this Expanded Access Program being executed in accordance with applicable Federal regulations and in accordance with the inclusion and exclusion criteria specified in the study protocol.

Along with the Circular of Information for the Use of Blood and Blood Components (2017)[29], the NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol v2.5.2 [40] can be used to assess transfusion-associated adverse reactions. This document can assist in classification of the reaction-specific case definition, severity, and imputability criteria.
10 References


8. Consents

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Note – English Consent first posted on website was Version 03. Versions 01 and 02 were not posted on website and not used to consent any patients.

Note – Consent Version Date is equivalent to the IRB Approval date.

Note – The non-English version consents which were approved by the IRB were accompanied by a certificate to verify the accuracy of the non-English translated consent.

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EXPANDED ACCESS PROGRAM
PATIENT CONSENT AND PRIVACY AUTHORIZATION FORM

Title: Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19
IRB#: 20-003312
Clinical Staff: Michael Joyner, M.D.

Please read this information carefully. It tells you important things about this program for use of the investigational product, Convalescent Plasma, for patients with COVID-19. A member of the clinical staff will talk to you about taking part in this program. If you have questions at any time, please ask us. Feel free to discuss the program with your family, friends, and healthcare provider before you make your decision. NOTE: If you are a family member or legally authorized representative (LAR) signing this consent form for someone else, “you” in the consent form refers to the patient with COVID-19.

If you decide to take part in this program, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

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<th>At …</th>
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<tr>
<td><strong>Principal Clinician/Physician:</strong> Michael Joyner, M.D.</td>
<td><strong>Phone:</strong> (507) 255-7197</td>
<td>▪ Tests and procedures</td>
</tr>
<tr>
<td><strong>Institution Name and Address:</strong> Mayo Clinic Hospital, Saint Marys Campus 4-184 Joseph 1216 Second Street SW Rochester, Minnesota 55905</td>
<td><strong>Institutional Review Board (IRB)</strong></td>
<td><strong>Phone:</strong> (507) 266-4000</td>
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Clinical Staff: Michael Joyner, M.D.

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People who recover from COVID-19 do so, at least in part, because their blood contains substances called antibodies, which are capable of fighting the virus that causes the illness. It turns out that for some other diseases caused by respiratory viruses, giving people the liquid portion of blood, called plasma, obtained from those who have recovered from the virus, leads to more rapid improvement of the disease. We think that patients with COVID-19 may improve faster if they receive plasma from those who have recovered from COVID-19, because it may have the ability to fight the virus that causes COVID-19.

We are asking you to consider receiving plasma from someone who has recovered from COVID-19. Their plasma will have substances that could improve your chances of recovery.
We do not know if this treatment will or will not help you, and we don't know if it will have any harmful effects either. This is one of the only treatments that we have at present, but you need to know that it has not yet been proven to work. Because we do not have other better treatment options at present, if you are willing, we would like to try this treatment out, and learn from the testing.

**What will happen to you while you are in this program?** You will be given plasma, the liquid portion of the blood, from a person who has recovered from COVID-19 that is compatible with your blood type. It will be given into one of your veins, using a sterile single use needle, and will be given over the course of about one to two hours. Approximately 200 mL of plasma will be given in an initial infusion. Additional infusions of plasma may occur throughout your hospital stay if the treating physician determines that additional treatments are clinically justified.

Because this therapy has not yet been tested, and you want to try this new therapy, we would like to learn as much as possible about its effects. We will therefore record some information about your response to the treatment, such as how long you needed to stay in the hospital or needed help with breathing.

**What are the possible risks or discomforts from being in this program?** Blood and plasma have been used for many other conditions, and in general are very safe. Although the risk of contracting COVID-19 infection from receiving the treatment has not been formally tested yet, we believe that it would be very low because the donor has fully recovered from the infection. Transfusion also carries the risk of adverse reactions such as allergic reactions, transfusion-associated circulatory overload or lung damage with profound breathing difficulty, cardiac (heart) rhythm irregularities, blood clotting, and transmission of infections including HIV and Hepatitis B and C; although the risk of these infections is very low, as only screened and compatible blood is used for transfusion. The risks to pregnancy are unknown. You may have other side effects that are not known at this time and may include serious injury or pain, disability or death. There is also a chance that confidentiality of your private information could be lost; however, procedures are in place to minimize this risk.

**Can I change my mind after I say “Yes”?** Taking part in this program is voluntary. You can change your mind at any time. If you wish to stop the treatment, just tell your doctor. Your decision will not stop you from getting the usual care that all patients receive at this center.

**What are the possible benefits from being in this program?** We do not know if convalescent plasma will be an effective treatment for COVID-19, and you might not experience any benefit. However, we believe that this treatment might be effective in improving the likelihood of you recovering from the disease.

**Do you have other choices?** You can choose to get this treatment or not. Your choice will not affect the care that you are receiving at this center. We will always do our best to take care of you. If you agree to this treatment, you will also be helping us learn whether the treatment works and how it works to help other patients, though you can withdraw at any time.

**What tests or procedures will you need to pay for if you take part in this program?** You will not need to pay for the convalescent plasma. However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care, including co-payments and deductibles. You will have to pay for any costs not covered by your insurance.

**How will your privacy and the confidentiality of your information be protected?** The Mayo Clinic and Dr. Joyner will use medical information collected or created as part of your medical care, such as medical records and test results that identify you by name or in another way that they request from your physicians and other health care providers. Your medical information will also be shared with appropriate regulatory authorities, including the U.S. Food and Drug Administration (FDA). Additionally, all the information or data collected about you to help understand if the therapy is effective will be kept confidential and only be used by
the recipients listed here to better understand COVID-19 and its potential treatment(s) and for regulatory oversight of this program.

By signing this form, you give permission to your medical provider to disclose your medical information as described in this form. This permission lasts until the end of the program. Recipients of your medical information may not be subject to federal privacy laws, and your medical information may no longer be protected by federal privacy laws after disclosure. You may take back this permission at any time by telling your doctor. No new medical information will be collected from you after you take back your permission, but any medical information that was already collected will continue to be used and shared as needed for the scientific integrity of the program.

Your signature documents permission for you (or the patient) to take part in this program.

________________________________________
Printed Name of Patient

/ / : AM/PM

Signature (Patient or Authorized Representative) Date Time

Person Obtaining Consent
I have explained the program to the patient/authorized representative and have answered all questions about this program to the best of my ability.

/ / : AM/PM

Printed Name Date Time

_____________________________
Signature
PROGRAMA DE ACCESO AMPLIADO
CONSENTIMIENTO DEL PACIENTE Y AUTORIZACIÓN PARA PRIVACIDAD

Título: Acceso ampliado al plasma de una persona convaleciente para el tratamiento de pacientes con COVID-19

IRB Nº: 20-003312 Personal clínico: Dr. Michael Joyner

Por favor lea atentamente esta información. Le notifica asuntos importantes acerca de este programa para el uso de un producto experimental, el plasma de una persona convaleciente, en pacientes con COVID-19. Un miembro del personal clínico hablará con usted acerca de su participación en este programa. Si en algún momento tiene alguna pregunta, por favor consúltenos.

Converse libremente sobre el programa con familiares, amigos y el proveedor de atención médica, antes de tomar su decisión. NOTA: Si usted es un familiar del paciente o el representante legalmente autorizado (LAR, por sus siglas en inglés) que firma este consentimiento a nombre de otra persona, tome nota que la palabra “usted” en este documento se refiere al paciente con COVID-19.

Si decide participar en el programa, firmará este consentimiento para demostrar que desea hacerlo. Recibirá una copia de este documento para guardarla. Se pondrá una copia de este documento en su expediente médico.

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<td>Dr. Michael Joyner</td>
<td>Nombre y dirección de la institución: Mayo Clinic Hospital, campus de Saint Marys 4-184 edificio Joseph 1216 Second Street SW Rochester, Minnesota 55905</td>
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Las personas que se recuperan de la COVID-19 logran hacerlo, al menos en parte, porque su sangre contiene unas sustancias llamadas anticuerpos que son capaces de combatir al virus que provoca la enfermedad. Dado que en algunas otras enfermedades provocadas por virus respiratorios, la administración de la porción líquida de la sangre (llamada plasma) obtenida de quienes se recuperaron del virus lleva a una mejoría más rápida de la enfermedad, creemos que los pacientes con COVID-19 pueden mejorar con mayor rapidez si se le administra el plasma de quienes ya se recuperaron de la COVID-19 porque ese plasma posiblemente tiene la capacidad de combatir el virus que causa la enfermedad de la COVID-19.

Le pedimos que considere recibir el plasma de alguien que se recuperó de la COVID-19. Ese plasma contiene sustancias que pueden mejorar la probabilidad de recuperación.

No se sabe si este tratamiento le ayudará o no y tampoco se sabe si tendrá algún efecto nocivo, pero es uno de los pocos tratamientos que hay por el momento; sin embargo, usted debe saber que no se ha comprobado que funcione. Debido a que no existe ninguna otra alternativa de tratamiento por el momento, si desea, nos gustaría probar el tratamiento en usted y aprender de dicha prueba.

¿Qué ocurrirá durante su participación en el programa? Se le administrará el plasma, o parte líquida de la sangre, de una persona que se recuperó de la COVID-19 y cuyo tipo sanguíneo es compatible con el suyo. La administración será en una vena, mediante una aguja estéril y de uso único durante el transcurso de una o dos horas. Recibirá alrededor de 200 a 500 ml de plasma con esta infusión.

Dado que aún no se han hecho pruebas con esta terapia y usted desea probar este nuevo tratamiento, nos gustaría estudiar sus efectos al máximo posible. Por ello, registremos cierta información sobre su respuesta al tratamiento, como cuánto tiempo necesitó permanecer en el hospital o si requirió ayuda para respirar.

¿Cuáles son los posibles riesgos o molestias de su participación en el programa? En muchas otras afecciones, ya se ha usado tanto sangre como plasma y, en general, ha sido muy seguro. Aunque todavía no se ha probado formalmente el riesgo de contraer la infección por COVID-19 con la administración de este tratamiento, creemos que será muy bajo porque el donante ya se
Fecha de aprobación: 3 de abril de 2020   Vigencia hasta: 31 de marzo de 2021

recuperó completamente de la infección. La transfusión también conlleva el riesgo de presentar reacciones adversas, como reacciones alérgicas, sobrecarga circulatoria por la transfusión o daño pulmonar con dificultad de respirar profundamente y transmisión de infecciones, incluido VIH y hepatitis B o C; no obstante, el riesgo de estas infecciones es muy bajo, porque en la transfusión solamente se usa sangre escrutada y compatible.

¿Puede cambiar de opinión después de haber dicho “sí”? Participar en este programa es un acto voluntario. Usted puede cambiar de opinión en cualquier momento. Si desea suspender el tratamiento, tan solo digáselo al médico. Su decisión no impedirá que usted reciba los cuidados habituales que se brindan a todos los pacientes en este centro.

¿Cuáles son los posibles beneficios de participar en este programa? No se sabe si el plasma de una persona convaleciente será un tratamiento eficaz contra la COVID-19 y existe la posibilidad de que usted no obtenga ningún beneficio. Sin embargo, creemos que este tratamiento podría servir para mejorar la probabilidad de que usted se recupere de la enfermedad.

¿Hay alguna otra alternativa para usted? Usted decide si recibe este tratamiento o no lo hace. Su decisión no alterará los cuidados que usted recibe en este centro. Siempre haremos todo lo posible por cuidar de usted. Si está de acuerdo con recibir este tratamiento, usted también nos ayudará a entender si el tratamiento funciona y cómo lo hace a fin de asistir a otros pacientes, pero usted puede retirarse en cualquier momento.

¿Por cuáles análisis o procedimientos deberá usted pagar si participa en este programa? Usted no tendrá que pagar nada por el plasma de una persona convaleciente. Sin embargo, usted y su seguro de salud deberán pagar por todos los demás exámenes y procedimientos que se le harían como parte de su atención clínica, lo cual incluye copagos y deducibles. Usted tendrá que pagar todo costo no cubierto por su seguro de salud.

¿Cómo se protegerá su privacidad y la confidencialidad de sus expedientes? Mayo Clinic y el Dr. Joyner usarán la información médica recolectada o creada como parte del cuidado de su salud, como expedientes médicos y resultados de análisis que lo identifican por su nombre o de alguna otra manera y solicitados a sus médicos u otros proveedores de atención de la salud. Se compartirá también su información médica con las autoridades reguladoras correspondientes, entre ellas, la Administración de Alimentos y Medicamentos de EE. UU. (FDA, por sus siglas en inglés). Además, toda la información o los datos recolectados sobre usted para entender si la terapia surte efecto se mantendrán confidenciales y solamente los usarán los receptores aquí mencionados para entender mejor la COVID-19 y los posibles tratamientos contra ella, así como para la supervisión reguladora de este programa.

Al firmar este documento, usted autoriza a su proveedor de atención médica a revelar su información de salud, según lo descrito en este documento. Dicha autorización estará vigente
Fecha de aprobación: 3 de abril de 2020    Vigencia hasta: 31 de marzo de 2021

hasta el fin del programa. Los receptores de su información médica pueden no estar sujetos a las leyes federales sobre privacidad y su información médica una vez revelada puede tampoco estar protegida por las leyes federales de privacidad. Usted puede retirar esta autorización en cualquier momento con solo informarlo a su médico. Una vez que retire su autorización, ya no se obtendrá ninguna información médica nueva sobre usted, pero se continuará usando y compartiendo cualquier información médica ya obtenida, según sea necesario para la integridad científica del programa.

Su firma demuestra que usted autoriza su participación (o la del paciente) en este programa.

Nombre del paciente en letra de imprenta

/ / : AM/PM
Firma (Paciente o representante autorizado) Fecha Hora

Persona que obtiene el consentimiento
Expliqué el programa al paciente o a su representante autorizado y en la medida de mis capacidades, respondí todas las preguntas acerca del programa.

/ / : AM/PM
Nombre en letra de imprenta Fecha Hora

_______________________________
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PROGRAMA DE ACCESO AMPLIADO
CONSENTIMIENTO DEL PACIENTE Y AUTORIZACIÓN PARA PRIVACIDAD

Título: Acceso ampliado al plasma de una persona convaleciente para el tratamiento de pacientes con COVID-19
IRB N°: 20-003312  Personal clínico: Dr. Michael Joyner

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No sabemos si este tratamiento lo ayudará o no lo ayudará y tampoco sabemos si tendrá algún efecto nocivo. Este es uno de los pocos tratamientos que existen al momento, pero usted debe saber que aún no se ha comprobado que funcione. Debido a que no existe ninguna otra alternativa mejor de tratamiento por el momento, si desea, nos gustaría probar el tratamiento en usted y aprender de dicha prueba.

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¿Cuáles son los posibles riesgos o molestias de su participación en el programa? En muchas otras afecciones, ya se ha usado tanto sangre como plasma y, en general, ha sido muy seguro. Aunque todavía no se ha probado formalmente el riesgo de contraer la infección por COVID-19 con la administración de este tratamiento, creemos que será muy bajo porque el donante ya se recuperó completamente de la infección. La transfusión también conlleva el riesgo de presentar reacciones adversas, como reacciones alérgicas, sobrecarga circulatoria por la transfusión o daño pulmonar con dificultad de respirar profundamente y transmisión de infecciones, incluido VIH y hepatitis B o C; no obstante, el riesgo de estas infecciones es muy bajo, porque en la transfusión solamente se usa sangre escrutada y compatible. Se desconocen los riesgos para el embarazo. Usted puede presentar otros efectos secundarios que se desconocen por el momento y
Fecha de aprobación: 15 de abril de 2020  Válido hasta: 31 de marzo de 2021

que tal vez incluyan lesiones graves o dolor fuerte, discapacidad o muerte. Si usted está embarazada o se embaraza, este programa podría dañar al feto o al embarazo de maneras aún desconocidas. Esos riesgos desconocidos podrían ser menores o importantes (incluida la muerte). Usted no debe embarazarse ni embarazar a una mujer mientras esté en este programa.

Puede presentar otros efectos secundarios que son desconocidos por ahora. Los efectos secundarios desconocidos pueden ser de lesiones graves o dolor fuerte, discapacidad o muerte.

Existe también la posibilidad de que se pierda la confidencialidad de su información privada, aunque se han implementado procedimientos para reducir al mínimo este riesgo.

¿Puede cambiar de opinión después de haber dicho “sí”? Participar en este programa es un acto voluntario. Usted puede cambiar de opinión en cualquier momento. Si desea suspender el tratamiento, tan solo dígaselo al médico. Su decisión no impedirá que usted reciba los cuidados habituales que se brindan a todos los pacientes en este centro.

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Su firma demuestra que usted autoriza su participación (o la del paciente) en este programa.

Nombre del paciente en letra de imprenta

/ / :

AM/PM

Firma (Paciente o representante autorizado) Fecha Hora

Persona que obtiene el consentimiento

Expliqué el programa al paciente o a su representante autorizado y en la medida de mis capacidades, respondí todas las preguntas acerca del programa.

/ / :

AM/PM

Nombre en letra de imprenta Fecha Hora

_____________________________
Firma
PROGRAMA DE ACCESO AMPLIADO
CONSENTIMIENTO DEL PACIENTE Y AUTORIZACIÓN PARA PRIVACIDAD

Título: Acceso ampliado al plasma de convalecientes para el tratamiento de pacientes con COVID-19
IRB N.°: 20-003312 Personal clínico: Dr. Michael Joyner

Por favor, lea atentamente esta información. Le notifica asuntos importantes acerca de este programa para el uso de un producto experimental, el plasma de convalecientes, en pacientes con COVID-19. Un miembro del personal clínico hablará con usted acerca de su participación en este programa. Si en algún momento tiene alguna pregunta, por favor consúltenos.

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Si decide participar en el programa, firmará este consentimiento para demostrar que desea hacerlo. Recibirá una copia de este documento para guardarla. Se pondrá también una copia de este documento en su expediente médico.

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</tbody>
</table>
¿Por qué se le solicita participar en este programa? Se solicita su participación porque se le diagnosticó la enfermedad causada por el SARS-CoV-2, también conocida como enfermedad del coronavirus 2019 o COVID-19. El SARS-CoV-2 se transmite de manera similar a la gripe o influenza y otros virus respiratorios, y se lo ha relacionado con tos, fiebre y falta de aire, además de incapacidad de respirar e incluso muerte en algunos casos graves. Actualmente, no existe ningún medicamento ni vacuna autorizados para el tratamiento o la prevención de la COVID-19.

Las personas que se recuperan de la COVID-19 logran hacerlo, al menos en parte, porque su sangre contiene unas sustancias llamadas anticuerpos que son capaces de combatir al virus que provoca la enfermedad. Dado que en algunas otras enfermedades provocadas por virus respiratorios, la administración de la porción líquida de la sangre (llamada plasma) obtenida de quienes se recuperaron del virus lleva a una mejoría más rápida de la enfermedad, creemos que los pacientes con COVID-19 pueden mejorar con mayor rapidez si se les administra el plasma de quienes ya se recuperaron de la COVID-19 porque ese plasma posiblemente tiene la capacidad de combatir el virus que causa la enfermedad de la COVID-19.

Le pedimos que considere recibir el plasma de alguien que se recuperó de la COVID-19. Ese plasma contiene sustancias que pueden mejorar la probabilidad de recuperación.

No se sabe si este tratamiento le ayudará o no y tampoco se sabe si tendrá algún efecto nocivo, pero es uno de los pocos tratamientos que hay por el momento; sin embargo, usted debe saber que no se ha comprobado que funcione. Debido a que no existe ninguna otra alternativa de tratamiento por el momento, si desea, nos gustaría probar el tratamiento en usted y aprender de dicha prueba.

¿Qué ocurrirá durante su participación en el programa? Se le administrará el plasma, o parte líquida de la sangre, de una persona que se recuperó de la COVID-19 y cuyo grupo sanguíneo es compatible con el suyo. La administración será en una vena, mediante una aguja estéril y de uso único durante el transcurso de una o dos horas. Recibirá alrededor de 200 ml de plasma con esta infusión. Durante el tiempo de su permanencia en el hospital, puede haber más infusiones de plasma si el médico tratante determina que existe justificación clínica para más tratamientos.

Dado que aún no se han hecho pruebas con esta terapia y usted desea probar este nuevo tratamiento, nos gustaría estudiar sus efectos al máximo posible. Por ello, registraremos cierta información sobre su respuesta al tratamiento, como cuánto tiempo necesitó permanecer en el hospital o si requirió ayuda para respirar.
¿Cuáles son los posibles riesgos o molestias de su participación en el programa? En muchas otras afecciones, ya se ha usado tanto sangre como plasma y, en general, ha sido muy seguro. Aunque todavía no se ha probado formalmente el riesgo de contraer la infección por COVID-19 con la administración de este tratamiento, creemos que será muy bajo porque el donante ya se recuperó completamente de la infección. La transfusión también conlleva el riesgo de presentar reacciones adversas, como reacciones alérgicas, sobrecarga circulatoria por la transfusión o daño pulmonar con dificultad de respirar profundamente, irregularidades en el ritmo cardíaco (corazón), coagulación de la sangre y transmisión de infecciones, incluido VIH y hepatitis B o C; no obstante, el riesgo de estas infecciones es muy bajo, porque en la transfusión solamente se usa sangre escrutada y compatible. Se desconocen los riesgos de esto para un embarazo. Usted puede presentar otros efectos secundarios aún desconocidos por el momento, pero que pueden incluir lesiones graves o dolor fuerte, discapacidad o muerte. Existe también la probabilidad de que se pierda la confidencialidad de su información privada, aunque existen procedimientos para reducir al mínimo este riesgo.

¿Puede cambiar de opinión después de haber dicho “sí”? Participar en este programa es un acto voluntario. Usted puede cambiar de opinión en cualquier momento. Si desea suspender el tratamiento, tan solo dígaselo al médico. Su decisión no impedirá que usted reciba los cuidados habituales que se brindan a todos los pacientes en este centro.

¿Cuáles son los posibles beneficios de participar en este programa? No se sabe si el plasma de convalecientes será un tratamiento eficaz contra la COVID-19, por lo que existe la posibilidad de que usted no obtenga ningún beneficio. Sin embargo, creemos que este tratamiento podría servir para mejorar la probabilidad de que usted se recupere de la enfermedad.

¿Hay alguna otra alternativa para usted? Usted decide si recibe este tratamiento o no lo hace. Su decisión no alterará los cuidados que usted recibe en este centro. Siempre haremos todo lo posible por cuidar de usted. Si está de acuerdo con recibir este tratamiento, usted también nos ayudará a entender si el tratamiento funciona y cómo lo hace a fin de asistir a otros pacientes, pero usted puede retirarse en cualquier momento.

¿Por cuáles análisis o procedimientos deberá usted pagar si participa en este programa? Usted no tendrá que pagar nada por el plasma de convalecientes. Sin embargo, usted o su seguro de salud deberán pagar por todos los demás exámenes y procedimientos que se le harán como parte de su atención clínica, lo cual incluye copagos y deducibles. Usted tendrá que pagar todo costo no cubierto por su seguro de salud.

¿Cómo se protegerá su privacidad y la confidencialidad de sus expedientes? Mayo Clinic y el Dr. Joyner usarán la información médica recolectada o creada como parte del cuidado de su salud, como son expedientes médicos y resultados de análisis que lo identifican...
por su nombre o de alguna otra manera y solicitados a sus médicos u otros proveedores de atención de la salud. Se compartirá también su información médica con las autoridades reguladoras correspondientes, entre ellas, la Administración de Alimentos y Medicamentos de EE. UU. (FDA, por sus siglas en inglés). Además, toda la información o los datos recolectados sobre usted para entender si la terapia surte efecto se mantendrán confidenciales y solamente los usarán los receptores aquí mencionados para entender mejor la COVID-19 y los posibles tratamientos contra ella, así como para la supervisión reguladora de este programa.

Al firmar este documento, usted autoriza a su proveedor de atención médica a revelar su información de salud, según lo descrito en este documento. Dicha autorización estará vigente hasta el fin del programa. Los receptores de su información médica pueden no estar sujetos a las leyes federales sobre privacidad y su información médica una vez revelada puede tampoco estar protegida por las leyes federales de privacidad. Usted puede retirar esta autorización en cualquier momento con solo informarlo a su médico. Una vez que retire su autorización, ya no se obtendrá ninguna información médica nueva sobre usted, pero se continuará usando y compartiendo cualquier información médica ya obtenida, según sea necesario para la integridad científica del programa.

**Su firma demuestra que usted autoriza su participación (o la del paciente) en este programa.**

Nombre del paciente en letra de imprenta

/ / : AM/PM  
Firma (Paciente o representante autorizado)  Fecha  Hora

**Persona que obtiene el consentimiento**  
Expliqué el programa al paciente o a su representante autorizado y en la medida de mis capacidades, respondí todas las preguntas acerca del programa.

/ / : AM/PM  
Nombre en letra de imprenta  Fecha  Hora

_______________________________  
Firma
ملاحظة: إن كنت تستوطن السهم "أنت" في هذا الإقرار يعود على المريض هذا الإقرار نيابة عن شخص آخر، أو ممثله قانوناً يعلم أن الضمير "أنت" في هذا الإقرار يعود على المريض المصاب بـKoVid-19.

إذا قررت المشاركة في هذا البرنامج، فهناك إقرار تفصيل عن رغباتك في المشاركة. سوف نعطيك نسخة من هذا الإقرار للاحتفاظ بها. ستستوطن نسخة من هذا الإقرار في ملفك الطبي.

إذا كان عندك سؤال يتعلق به...

الأياه: 971-719/14000
اسم المؤسسة وعائده: Mayo Clinic السبتمبر مايكل كلينج
المبيب سانت ماري,
جوزيف 4-184
سانت ماري,
روتشستر, مينيسوتا 55905

يمكنك أن تتصل به...

هاتف: (507) 266-4000
رقم الهاتف المجاني: (866) 273-4681

حقوق المشاركين في البرنامج
• أي شكايات أو انشغالات
• استعمال معلوماتي الصحية المحمية

على الرقم...

الياه: 971-719/14000
اسم المؤسسة وعائده: Mayo Clinic السبتمبر مايكل كلينج
المبيب سانت ماري,
جوزيف 4-184
سانت ماري,
روتشستر, مينيسوتا 55905

لم أطلب ملك ملك المشاركة في هذا البرنامج؟ تم تحشيل بالمرض الذي يسببك فيروس كورونا-2 المتلازمة التنفسية الحادة الرخيمة (سارس) ينقل هذا الفيروس بطريقة مشابهة للإنسان، ويقبس الفيروسات التنفسية، وقد تم ربطه بالسعال، والحمى، وضيق التنفس، وفي الحالات الأشد تم إبطاء في التلف أو حتى الموت. ليس عددنا حالياً أي دواء معتمد لعلاج KoVid-19، أو للاحتراف منه.

الأشخاص الذين تعاونوا من KoVid-19، تعانون -على الأقل جزئياً، بسب أنهم يحتوي على مواد تسمى الأيضاد، وهي قائدة على ممارسة الفيروس الذي يسبك المرض. نحن باعتبار الأيضاد الذي أضعف أول أصبغيها الفيروسات تنفسية الجزء السائل من الدم، والتي يسمى مصل الدم. من أن يصحة تعاونوا من المرض، أدى إلى تحسين حالة المرضي بشكل أسرع. نعتقد أن المريض المصابين بـKoVid-19 قد يتسمى حالياً بشكل أسرع إذا تحسنوا على مصل الدم من أشخاص تعاونوا من KoVid-19، لأن مصل الدم هذا قد يكون عند الفيروس الذي يسبك مرض KoVid-19.

إذا نطلب ملك أن أتأخد بعين الاعتبار تلقى مصل الدم من مريض تعافى من مرض KoVid-19. قد يحتوي مصل الدم من هؤلاء موارد تحسن من فرصة تعافيك.
لا يجب استعماله بعد 31 مارس 2020

لا نعلم إن كان هذا العلاج قد يساعد أم لا، كما أننا لا نعلم إن كانت له أي أضرار. ولكن بعض هذه العلاج واحدًا من العلاجات القليلة التي لدينا الآن، والذي ينبغي عليك أن تدرك أن فاعليته لم تثبت بعد. بالنظر إلى عدم وجود خيار آخر للعلاج حالياً فإنه وفي حال رغبتك بذلك فإننا نود أن نحزم هذا العلاج وأن نعرف المزيد من خلال الفحص.

ما الذي سيحدث لك أثناء اشتراكك في هذا البرنامج؟

ستتملص مصل الدم وهو الجزء السائل من الدم والمستخلص من دم مريض تعافي من مرض كوفيد-19، ومتواقيق مع فصيلة دمك. سيتم تسريب مصل الدم عبر الوريد باستخدام إبرة معقمة، وخلال فترة زمنية في حدود ساعة إلى ساعتين. سيتم تسريب حوالي 200-500 ملليتر من المصل.

وبالنظر إلى أن هذا العلاج لم تسبق تجربته وإلى رغبتك في تجربته، فإننا نسعى لتعلم كل ما يمكن عن هذا العلاج وأثره. سنقوم تسجيل بعض المعلومات عن استجابتك للعلاج على سبيل المثال المدة التي قضيتها في المستشفى أو تلك التي احتجت فيها دعما للتنفس.

ما هي المخاطر أو المشاكل المحتملة من المشاركة في هذا البرنامج؟

بشكل عام فقد تم استخدام مصل الدم وصلبه بآمان لأمراض عديدة أخرى. بالرغم من أن احتمالية نقل العدوى بمرض كوفيد-19 من جزء ثلثي هذا العلاج لم تفسى بعد لكننا نعتقد أن هذه الاحتمالات ضئيلة جدا وذلك لأن المبتكر تعافي بالكامل من تلك العدوى. نقل الدم ومنتجاته يؤدي مخاطر مثل حدوث تفاعلات تحسسية أو زيادة الإصابة على الدورة الدموية المرتبط بنقل الدم أو تلف الرئة مع صعوبة كبيرة في التنفس أو نقل العدوى مثل فيروس نقص المناعة البشرية أو التهاب الكبد الوبائي من النوع ب أو ج، ولكن نقل العدوى بشيء احتمال ضئيلي لأن الدم المستخدم يكون محفوظًا ومتوافقًا.

هل يمكنني تغيير رأيي بعد الإفصاح "بنعم"؟

تخليق الرعاية المتاعة التي تقدم لكل المرضى في هذا المركز. 

ماهي الفوائد المحتملة المشاركة في هذا البرنامج؟

لا نعلم مدى فعالية مصل الأشخاص المتعافين كعلاج لمرض كوفيد-19، وقد لا تحصل على فائدة ولكننا نعتقد أن هذا العلاج قد يكون فعالًا في تحسين فرصك للتعافي من المرض.

هل لديك خيارات أخرى؟

لك الخيار في تلقى هذا العلاج من عندنا. خارك لن يؤثر على الرعاية التي تلقاها في هذا المركز. سنقوم ببذل أقصى ما يمكن لرعايك. في حال موافقتك على تلقى هذا العلاج سنداعينا على معرفة ما إذا كان هذا العلاج فعالًا وكيف يعمل وذلك لمساعدة مرضى آخرين. وسيكون بإمكانك الانسحاب في أي وقت.

ماهي الفحوصات أو الإجراءات التي ستتوجه عليك دفع تكاليفها في حال شاركتك في هذا البرنامج؟

لن يكون من الواجب عليك دفع تكاليف مصل الأشخاص المتعافين. ولكن على كل حال سيتوجه عليك و/أو مقدم التأمين الصحي دفع تكاليف كافة الفحوصات والإجراءات التي تجري أو تقدم لك كجزء من رعايك السريري والمتضمنة لمساهمتك في المدفوعات الخاصة بالتأمين.

ويستجيب عليك دفع أي تكاليف لا يغطيها التأمين.

كيف نحمي خصوصيتك وسرية المعلومات المتعلقة بك؟

نحن نحن خاصي الصحة والتعليم المعلومات الصحية التي يتكونون عليها أو يصنعونها كجزء من رعايك الطبي، مثل Mayo Clinic مستخدمون بوابة Mayo Clinic ونتيجة للفحوصات التي قد نطلبونها من أطباءك، أو أي مقدم آخر للخدمة الصحية، والتي يمكن من خلالها التعرف على هو بك عن طريق اسمك أو أي طرق أخرى. المعلومات الطبية الخاصة بك سنستخدمها أيضًا مع الجهات التنظيمية المختصة مثل هيئة الأطعمة والدواء الأمريكية. بالإضافة لذلك فإن أي معلومات جمعت عنك للمساعدة في معرفة ما إذا كان العلاج فعالًا ستحافظ بسرية وسنتخدم فقط بواسطة المستفيدين المذكورين هنا لزيادة معرفتهم حول كوفيد-19 وعلاجات المتملئة، وكذلك مع الجهات المنظمة والنشرة على ماستر البرنامج.
Date: March 31, 2021

The agreement must be signed before 31 March 2021. It will not be valid after this date.

The patient (or their legally authorized representative) will not need to provide additional permissions after this date. Permission may be revoked by the patient at any time. However, Continued use and participation in any new information will need to be renewed in accordance with the governing regulations.

If the patient or their legally authorized representative agrees to participate in this program, they have signed this agreement.

_______________________________

Name: [Signature]

Date: [Date]

Time: [Time]

The patient or their legally authorized representative has been informed and answered all questions related to the program and has participated in the program accordingly.

At [Date] [Time]

_______________________________

Name: [Signature]

Date: [Date]

Time: [Time]

[Signature of person obtaining the authorization]
برنامج الوصول الموسع

استمرار إقرار موافقة المريض وتفويض الخصوصية

العنوان:
برنامج الوصول الموسع على مصل الدم الاسمي المتعدد من أجل علاج مرضي كوفيد-19
الطرفاء الطبي: الدكتور مايكل جوينر
الرقم: IRB#20-003312 02

لا يجب استعماله بعد 31 مارس 2021

تاريخ الموافقة: 15 أبريل 2020

لا يجب استعماله بعد 31 مارس 2021

إذا قررت المشاركة في هذا البرنامج، فيجب أن توقع هذا الإقرار لتفصيح عن رغبتك في المشاركة. سوف نعطيك نسخة من هذا الإقرار للاحتفاظ بها. ستوضع نسخة من هذا الإقرار في ملفك الطبي.

إذا كان عندك سؤال يتعلق ب… على الرقم … يمكن أن أتصل ب…

الاختبارات والإجراءات
الروائح والحالات الطارية
أي شكاوى أو اتشغالات
الإلغاء من البرنامج
الموارد التي تستلمها
المواعد

الهاتف: 977-719 (507)
اسم المؤسسة وعنوانها:
Mayo Clinic
Saint Marys
Joseph 4-184
Second Street SW 1216
Rochester, Minnesota 55905

إذا كان عندك سؤال يتعلق ب… على الرقم … يمكن أن أتصل ب…

حقوق المشاركين في البرنامج
أي شكاوى أو اتشغالات
استعمل معلومات الصحية المحمية

الهاتف: (507) 266-4000

رقم الهاتف المحمي:
(866) 273-4681

إذا قررت المشاركة في هذا البرنامج، فيجب أن توقع هذا الإقرار لتفصيح عن رغبتك في المشاركة. سوف نعطيك نسخة من هذا الإقرار للاحتفاظ بها. ستوضع نسخة من هذا الإقرار في ملفك الطبي.

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المراجعات والإجراءات
الروائح والحالات الطارية
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حقوق المشاركين في البرنامج
أي شكاوى أو اتشغالات
استعمل معلومات الصحية المحمية

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حقوق المشاركين في البرنامج
أي شكاوى أو اتشغالات
استعمل معلومات الصحية المحمية

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أي شكاوى أو اتشغالات
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حقوق المشاركين في البرنامج
أي شكاوى أو اتشغالات
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رقم الهاتف المحمي:
(866) 273-4681

إذا قررت المشاركة في هذا البرنامج، فيجب أن توقع هذا الإقرار لتفصيح عن رغبتك في المشاركة. سوف نعطيك نسخة من هذا الإقرار للاحتفاظ بها. ستوضع نسخة من هذا الإقرار في ملفك الطبي.

إذا كان عندك سؤال يتعلق ب… على الرقم … يمكن أن أتصل ب…

المراجعات والإجراءات
الروائح والحالات الطارية
أي شكاوى أو اتشغالات
الإلغاء من البرنامج
الموارد التي تستلمها
المواعد

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حقوق المشاركين في البرنامج
أي شكاوى أو اتشغالات
استعمل معلومات الصحية المحمية

الهاتف: (507) 266-4000

رقم الهاتف المحمي:
(866) 273-4681

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الروائح والحالات الطارية
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حقوق المشاركين في البرنامج
أي شكاوى أو اتشغالات
استعمل معلومات الصحية المحمية

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لا يجب استعماله بعد 31 مارس 2021

تاريخ الموافقة: 15 أبريل 2020

لا تعلم إن كان هذا العلاج قد يساعد أم لا، كما أننا لا نعلم إن كانت له أي أضرار. يبقى هذا العلاج واحداً من العلاجات القليلة التي لدينا الآن، والذي ينبغي عليك أن تدرك أن فاعليةه لم تثبت بعد. بالنظر إلى عدم وجود خيار أفضل منه للعلاج حالياً فإنه وفي حال رغبتك بذلك فإننا نود أن نحبز هذا лечения وأن نعرّف المزيد من خلال الفحص.

ما الذي سيحدث لك أثناء الاشتراك في هذا البرنامج؟

ستتم توقف الدم، وعلى الجزء السابق من الدم المستقل من الدم يجري علاج كوفيد-19، وتوقف مع فصيلة دمك. سيتم تسريع ممارسة الدم، بما في ذلك النزاعات المحتفظة أو زيادة الدورة الدموية الممتدة بين الدم أو تلف الرئة مع صعوبة كبيرة في التنفس أو نقل الدم عن طريق قلب مشترك أو النزاعات المحتفظة.

ونتقل إلى أن هذا العلاج لا يتسبب في أضرار، وإننا نسعى لنعلم كل ما يمكن عن هذا العلاج وأثره. سنقوم بتسجيل بعض المعلومات عن استجابة للعلاج على سبيل المثال المدة التي قضيتها في المستشفى أو تلك التي احتت فيها دعماً للتنفيذ.

ماهي المخاطر أو المشاكل المحتملة من المشاركة في هذا البرنامج؟

هناك عدة مخاطر قد تم استخدام الدم والصورة بأن الأمراض عديدة أخرى. بالرغم من أن احتمالية نقل العدوى بمرض كوفيد-19 من جزء تلقى هذا العلاج لم تفحص بعد لكننا نعتقد إن هذه الاحتمال ضئيلة جداً وذلك لأن المتبرع تعاني بالأكمل من تلك العدوى. نقل الدم من مصدر إلى مستقبل من صعوبة كبيرة في التنفس أو نقل الدم عن طريق قلب مشترك أو النزاعات المحتفظة.

وتكون فصول ومتوافقة، وأننا نعتقد أن هذه العلاجات تتكون من قبل الدم غير المكثف. قد تتحول إلى جائحة أخرى غير معرفحة حتى الآن، تتضمن هذه الأعراض الجانبية غير المعروفة للإصابات الباردة أو الألم أو الإعاقة، أو الموت. هناك أيضاً احتمال أن تفقد معلومات الشخصية خصوصيتها، ولكن قد يتم وضع تدابير للتفق من هذا الاحتمال.

هل يمكنني تغيير رأيي بعد الحاجة "نعم"?

تعتبر المشاركة في هذا البرنامج طوعية. يمكن تغيير رأيك في أي وقت. أبلغ طبيبك في حال رغبتك في التوقف عن العلاج. لن يتم قرارك.

ماهي الفوائد المحتملة للمشاركة في هذا البرنامج؟

لا تعلم مدى فعالية مصل الأشخاص المتعاقدين كعلاج لمرض كوفيد-19، وقد لا تحصل على فائدة، ولكننا نعتقد أن هذا العلاج قد يكون فعالاً في تحسين فرصتك للتعافي من المرض.

هل لديك خيارات أخرى؟

لك الخيار في تقييم هذا العلاج من عدمه. خيارك لن يؤثر على الرعاية التي تتلقاها في هذا المركز. سنقوم ببذل أقصى ما يمكن لرعايتك في حال مواقفك على قلقك. لا يمكن أن يكون هذا العلاج فعالاً وكيف يعمل ذلك لمساعدة مرضى أخرين. وسيكون بإمكانك الانسحاب في أي وقت.

ماهي الفحوصات أو الإجراءات التي سيتوجب عليك دفع تكاليفها في حال مشاركتك في هذا البرنامج؟

لن يكون من الواجب عليك دفع تكاليف الأشخاص المتعاقدين. ولكن على كل حال سيتوجب عليك أو ومقدم التأمين الصحي دفع تكاليف كافة الفحوصات والإجراءات التي تجري أو تقدم لك كجزء من رعايتك السريرية والمتضمنة لمساهمتك في المدفوعات الخاصة بالتأمين. وسيتوجب عليك دفع أي تكاليف لا يغطيها التأمين.

كيف تحصل على خصوصية وسرية المعلومات الموثقة؟

يرجى ملاحظة Mayo Clinic والدكتور جوينر المعلومات الطبية التي يتلقاها عنا أو يصنعونها كجزء من رعايتك الطبية، مثل المعلومات الأدوية، ونتائج الفحوصات التي قد يطرحها في المراض.��ة الذي يمكن من خلالها الفحص على أجهزة التشفير أن تكون من خيارات التشفير على نظام يوين هيت في طريق 스스로 أو أي آخر لخدمة الصحة، والتي يمكن من خلالها التعرف على أي معلومات الطبية الخاصة بك، سيتم مشاركتها أيضاً مع الجهات التنظيمية المختصة مثل هيئة الأطعمة والدواء الأمريكية. بالإضافة لذلك فإن أي معلومات جمعت عنها للمساعدة في معرفة ما إذا كان العلاج فعالاً ستجتذب بسرية وستستخدم فقط بواسطة المستفيدين المذكورين هنا لزيادة معرفتهم حول كوفيد-19 وعلاجات المحتفظة، وكذلك مع الجهات المنظمة والمشرفة على هذا البرنامج.

IRB#:20-003312 02
لا يجب استعماله بعد 31 مارس 2021

لا توقعتك على هذا الإقرار فإنك تمنح الإذن لمقدمي الخدمة الصحية بإفساء معلوماتك الطبية الموضحة بهذا الإقرار. يعتبر هذا الإذن سريا حتى نهاية البرنامج. قد لا تشمل قواعد القوانين الفيدرالية المتعلقة بالخصوصية المستقبلية المعلومات الطبية الخاصة بك وقد تصبح معلوماتك الطبية غير مجمعة بالقوانين الفيدرالية بعد اشانتها. يمكن سحب هذا الإذن في أي وقت بإبلاغ طبيبك. لن يتم جمع معلومات طبية جديدة بعد سحبك للإذن ولكن سيستمر استخدام ومشاركة أي معلومات تم جمعها قبل سحبك للإذن حسب الحاجة للحفاظ على التماسك العلمي للبرنامج.

إن توقعتك سيوثق موافقتك (أو موافقة المريض) على المشاركة في هذا البرنامج.

<table>
<thead>
<tr>
<th>الاسم المريض كتابة</th>
</tr>
</thead>
<tbody>
<tr>
<td>صباحاً/مساءً</td>
</tr>
<tr>
<td>الوقت</td>
</tr>
<tr>
<td>التاريخ</td>
</tr>
<tr>
<td>توقيع (المريض أو ممثله المخول)</td>
</tr>
</tbody>
</table>

اسم الشخص الذي حصل على التوقيع

لقد شرحت البرنامج للمريض أو ممثله المخول وأجبت عن كل الأسئلة المتعلقة بالبرنامج وبدلت في ذلك قصارى جهدي.

<table>
<thead>
<tr>
<th>الاسم كتابة</th>
</tr>
</thead>
<tbody>
<tr>
<td>صباحاً/مساءً</td>
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<tr>
<td>الوقت</td>
</tr>
<tr>
<td>التاريخ</td>
</tr>
<tr>
<td>التوقيع</td>
</tr>
</tbody>
</table>
Not to be used after: March 31, 2021

Approval Date: July 10, 2020

Program: Accessing the Music

Approval of the Accessing the Music Program

The program accessing the music on behalf of the patient from the laboratory from March 31, 2019 is among those who have been released from the program. The program is to be used after: March 31, 2021.

IRB#:20-003312 02

The doctor: 20-003312

The musician: 20-003312

If you have any questions about this program, feel free to contact us at any time.

Mayo Clinic Institutional Review Board (IRB):

Phone: (507) 255-7197

Mayo Clinic

St. Mary's

Joseph 4-184

Second Street SW 1216

Rochester, Minnesota 55905

If you have any questions about this program, feel free to contact us at any time.

Mayo Clinic Institutional Review Board (IRB):

Phone: (507) 266-4000

Mayo Clinic

St. Mary's

Joseph 4-184

Second Street SW 1216

Rochester, Minnesota 55905

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Phone: (866) 273-4681

Mayo Clinic Institutional Review Board (IRB):

Phone: (507) 266-4000

Regulatory Documents for National EAP (IND 19832) Participating Sites – 9/2/2020

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Page 410 of 435
لا نعلم إن هذا العلاج قد يساعد أم لا، كما أنا لا نعلم إن كانت له أي أضرار. ولكن يبقى هذا العلاج واحدا من العلاجات القليلة التي لدينا الآن، والذي ينبغي عليك أن تدرك أن فعاليته لم تثبت بعد. بالنظر إلى عدم وجود خيار أفضل منه للعلاج حاليا فإنه في حال رغبتك بذلك فإننا نود أن ننجب هذا العلاج وأن نعرف المزيد من خلال الفحص.

ما الذي سيحدث لك أثناء شراكتك في هذا البرنامج؟

ستتلقى مصل الدم وهو الجزء السائد من الدم والمستخلص من دم مريض تعافي من مرض كوفيد-19، ومتوافق مع فصيلة دمك. سيتسبّب مصل الدم عبر الوريد باستخدام إبرة متحركة، وتتخلص في حدود ساعتين. سيتم تسريب جرعة إضافية من مصل الدم خلال مدة تفاوت في المستشفى، إذا قرر الطبيب المعالج أن جرعات إضافية مفيدة. سيتم تسجيل ن_cycleي عند الحالة.

ماثى المخاطر أو الإجراءات المحتومة في هذا البرنامج؟

شكلا عام قد يتم استخدام الدم وصقله لأغراض عديدة أخرى. بالرغم من أن احتمالية نقل العدوى بمرض كوفيد-19 من جزاء تلقّي هذا العلاج لم تفحص بعد لكننا نعتقد بأن هذه الاحتمالات ضئيلة جدا وذلك لأن المبتراق يتعافى بالكامل من تلك العدوى. تلق الدم من منتجات يحتوي مخاطر مثل حدوث تفاعلات خسيسة، أو زيادة العبء على الدورة الدموية المرتبط بنقل الدم، أو تلف الرئة ومعصبة كبيرة في التنفس، أو اضطرابات في النظام التغذوي، أو تجفف الدم، أو نقل العدوى مثل فيروس نقص المناعة البشرية، أو التهاب الكبد الهائي من النوع B أو G، ولكن نقل الدم يمكن احتمالي احتمالي أن النتيجة ستكون مفيدة ومتوافقة. إذا حتمي فإن مشاركتك في هذا البرنامج قد تؤدي جينيك أو حملن بشكل غير معروف. قد تكون هذه المخاطر غير المعروفة إما صغيرة وإما كبيرة (بما في ذلك الموت). يجب أن تتحلى عند مشاركتك في هذا البرنامج، ويجيب على الرجال أن يبحثوا عند مشاركتهم فيه.

قد تصاب بأعراض جانبية أخرى غير معروفة حتى الآن. تتضمن هذه الأعراض الجانبية غير المعروفة إصابات بالغة، أو الألم، أو الإعاقة، أو الموت.

هناك أيضا احتمال أن تفقد معلوماتك الشخصية خصوصيتها، ولكن قد توضع تدابير لتكمل من هذا الاحتمال.

هل يمكنني تغيير رأيي بعد الإجابة "نعم"؟

تعتبر المشاركة في هذا البرنامج طوعية. يمكنك تغيير رأيك في أي وقت. أبلغ طبيبك في حال رغبت في التوقف عن العلاج. لن يمنع قرارك تلقّي الدعم المعتاد الذي تحصل على فائدة. ولكننا نعتقد أن هذا العلاج قد يكون فعالا في تحسين فرصتك للتعافي من المرض.

هل لديك خيارات أخرى؟

لك الخيار في تلقى هذا العلاج من عدمه. خيارك لن يؤثر على الرعاية التي تتلقاها في هذا المركز. سنقوم بنقل أقصى ميكن لرعايةك. في حال مismatch들이 على نقل هذا العلاج مستعدا على معرفة ما إذا كان هذا العلاج فعالا وكيف يعمل وذلك لمساعدة مرضى أخرين. وسيكون بإمكانك الانسحاب في أي وقت.

ما هي الخصومات أو الإجراءات التي سيتوجب عليك دفع تكاليفها في حال مشاركتك في هذا البرنامج؟

لن يكون من الواجب عليك دفع تكاليف مصل الأشخاص المعالجين. ولكن على كل حالة سيتوجب عليك وأو مقدم التأمين الصحي دفع تكاليف كافة الفحوصات والإجراءات التي تجري أو تقدم لك كجزء من رعايتك السريرية والمتضمنة لمساعديك في المفروقات الخاصة بالتامين.

سيتوجب عليك دفع أي تكاليف لا يغطيها التامين.
Approval Date: July 10, 2020

How do I keep my Mayo Clinic doctor informed about the health information I share with others? Do Mayo Clinic

The health information you share with others may be used for research purposes, including the development of new treatments or therapies. This information may be used anonymously, so that you cannot be identified. This may include information about your health status, health care provider, or related conditions.

By participating in this program, you are agreeing to share your health information for research purposes. You may withdraw your consent at any time by contacting the program administrator.

Date of withdrawal:

Signature:

Your signature is required to confirm your consent. You may withdraw your consent at any time by contacting the program administrator.

Date of withdrawal:

Signature:

Your signature is required to confirm your consent. You may withdraw your consent at any time by contacting the program administrator.

Date of withdrawal:

Signature:
Chương trình tiếp cận mở rộng

Đơn đồng ý và mẫu giấy phép bộ mặt cho bệnh nhân

Tiêu đề: mở rộng cấp sử dụng huyết tương để điều trị bệnh nhân với COVID-19

IRB #: 20-003312

Nhân viên y tế: Michael Joyner, MD


Nếu bạn quyết định tham gia chương trình này, bạn sẽ ký vào mẫu đồng ý này để cho thấy rằng bạn muốn tham gia. Chúng tôi sẽ cung cấp cho bạn một bản sao của mẫu đơn này để giữ. Một bản sao của mẫu đơn này sẽ được đưa vào hồ sơ y tế của bạn.

<table>
<thead>
<tr>
<th>Bạn có thể liên hệ...</th>
<th>Tại...</th>
<th>Nếu bạn có thắc mắc về...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bác sĩ/Y sĩ trưởng:</td>
<td>Điền thoai: (507) 255-7197 Ten cờ quan và địa chỉ: Bệnh viện Mayo Clinic, Saint Marys 4-184 Joseph 1216 Second Street SW Rochester, Minnesota 55905 • • Kiểm tra và thủ tục • Chấn thương hoặc khó khăn • Thắc mắc hoặc khiếu nại • Rút khỏi chương trình • Vật liệu ban nhân được • Cuộc hẹn</td>
<td></td>
</tr>
<tr>
<td>Michael Joyner, MD</td>
<td>Điện thoại: (507) 266-4000 Miễn phí: (866) 273-4681</td>
<td>• Quyền của người tham gia chương trình • Mô적 thắc mắc hoặc khiếu nại liên quan đến chương trình • Sử dụng thông tin sức khỏe bảo mật</td>
</tr>
</tbody>
</table>


Chúng tôi không biết cuộc điều trị này sẽ giúp được bạn hay không, và chúng tôi không biết nó sẽ có bất kỳ tác dụng có hại nào hay không. Đây là một trong những phương pháp điều trị duy nhất mà chúng tôi có hiện nay, nhưng bạn cần phải biết rằng nó vẫn chưa được chứng minh là có thành công hay không. Bởi vì hiện nay chúng tôi không có phương pháp điều trị nào tốt hơn, nếu bạn sẵn sàng, chúng tôi muốn thử điều trị này, và họ có từ các thư nghiên cứu.

Điều gì sẽ xảy ra với bạn trong khi bạn đang ở trong chương trình này? Bạn sẽ được cung cấp huyết tương, phần lớn của máu, từ một người đã hồi phục từ COVID-19 và có cùng loại máu với bạn. Nó sẽ được đưa vào một trong các tinh mạch của bạn, bằng cách sử dụng một kim vô trùng sử dụng một lần duy nhất, và trong quá trình khoảng một đến hai giờ. Khoảng 200 ml huyết tương sẽ được chuyển vào cho bạn để hiểu. Bơ sung huyết tương có thể xảy ra trong thời gian bạn nằm bệnh viện nếu bác sĩ điều trị xác định điều trị hỗ trợ nguồn huyết tương là hợp lý.

Bởi vì liệu pháp này chưa được thử nghiệm, và bạn muốn thử điều trị mới này, chúng tôi muốn tìm hiểu càng tốt về hiểu ứng của nó. Do đó chúng tôi sẽ ghi lại một số thông tin về phản ứng của bạn khi điều trị, chẳng hạn như bao lâu bạn cảm ở trong bệnh viện hoặc cảm giác đỡ với hồi thở.

Những rủi ro có thể có hoặc sự khó chịu khi tham gia trong chương trình này là gì? Máu và huyết tương đã được sử dụng cho nhiều điều kiện khác, và nói chung là rất an toàn. Mặc dù Nguy cơ nhiễm trùng COVID-19 từ việc nhận được điều trị chưa được biết trước nhưng chúng tôi tin rằng nó sẽ rất thấp bởi vì các nhà công nghiệp đã hoàn toàn hồi phục từ nhiễm trùng. Chuyển dịch cũng mang phần ứng bất lợi như phản ứng dị ứng, quá tải hệ tuần hoàn hoặc tổn thương phối gây khó thở nặng, rối loạn nhịp
tim, tử máu cục và truyền nhiễm trùng bao gồm cả HIV và viêm gan B và C; mặc dù nguy cơ nhiễm trùng là rất thấp, vì chỉ sử dụng máu đã được kiểm tra và thích hợp để truyền. Những rủi ro cho thai kỳ chưa được biết. Bạn có thể có tác dụng phụ khác mà chưa được biết đến vào thời gian này và có thể bao gồm thường tích nhiễm trùng hoặc đau đơn, Khuyết tật hoặc tử vong. Cúng có thể báo mạt thông tin cá nhân của bạn bị mất; Tuy nhiên, các thù tục được sử dụng để giảm thiểu rủi ro này.

Tôi có thể thay đổi ý của tôi sau khi tôi nói “Đồng ý”? Tham gia chương trình này là tự nguyện. Bạn có thể thay đổi ý kiến của bạn bất cứ lúc nào. Nếu bạn muốn dừng cuộc tham gia, chỉ cần nói với bác sĩ của bạn. Quyết định của bạn sẽ không ảnh hưởng đến bất kỳ lợi ích nào. Tuy nhiên, chúng tôi tin rằng điều này có thể có hiệu quả trong việc cải thiện khả năng phục hồi bệnh của bạn.

Bạn có lựa chọn khác? Bạn có thể chọn hay không chọn để có được điều trị này. Sự lựa chọn của bạn sẽ không ảnh hưởng đến sự chăm sóc bạn đang nhận được tại Trung tâm này. Chúng tôi sẽ luôn làm tốt nhất để chăm sóc bạn. Nếu bạn dừng ý với điều trị này, bạn cũng sẽ giúp chúng tôi tìm hiểu xem việc điều trị này có kết quả tốt không và làm thế nào để giúp bệnh nhân khác, mắc đủ bạn có thể rủi ro bất cố lúc nào.

Những xét nghiệm hoặc thủ tục nào bạn sẽ cần phải trải tiện nếu bạn tham gia chương trình này? Bạn sẽ không cần phải trải tiện cho huyết tương. Tuy nhiên, bạn và/hoặc bảo hiểm của bạn sẽ cần phải trải tiện cho tất cả các xét nghiệm và thủ tục khác mà bạn cần có theo chăm sóc y tế cho bạn, bao gồm cả tiêm đong thanh toán và tiền khám ưu. Bạn sẽ phải trải tiện cho những chi phí không được bảo hiểm của bạn thanh toán.

Sự riêng tư và tính bảo mật của thông tin bạn sẽ được bảo vệ như thế nào? Bệnh viện Mayo Clinic và bác sĩ Joyner sẽ sử dụng thông tin y tế thu thập được hoặc tạo ra như là một phần của sự chăm sóc y tế của bạn, chẳng hạn như hồ sơ bệnh lý và kết quả thử nghiệm với tên bạn dinh kèm, hoặc theo cách khác mà họ yêu cầu từ bác sĩ của bạn và các nhà cung cấp chăm sóc y tế khác. Thông tin y tế của bạn cũng sẽ được chia sẻ với các cơ quan quản lý y tế, bao gồm Cơ quan Quản lý Thực phẩm và dược phẩm của U.S. (FDA). Ngoài ra, tất cả thông tin hoặc dữ liệu thu thập được về bạn để giúp tìm hiểu xem thị liệu có hiệu quả không sẽ được giữ bí mật và chỉ được sử dụng bởi những người liên kết ở đây để hiểu rõ hơn về COVID-19 và những tiềm năng thị liệu cho nó và giảm sát quy định của chương trình này.
Khi ký tên vào mẫu đơn này bạn cho phép nhà cung cấp dịch vụ y tế tiết lộ thông tin y tế của bạn như được mô tả trong mẫu này. Quyền này kéo dài đến cuối chương trình. Người nhận thông tin y tế của bạn có thể không tuân theo các luật về quyền riêng tư của Liên bang và thông tin y tế của bạn có thể không còn được bảo vệ bởi luật bảo mật liên bang sau khi tiết lộ. Bạn có thể lấy lại quyền này bất cứ lúc nào bằng việc nói cho bác sĩ của bạn. Không có thông tin y tế mới nào được thu thập từ bạn sau khi bạn lấy lại sự cho phép của bạn, nhưng bất kỳ thông tin y tế đã được thu thập sẽ tiếp tục được sử dụng và chia sẻ khi cần thiết cho sự toàn vẹn khoa học của chương trình.

Chữ ký của bạn cho phép bạn (hoặc bệnh nhân) tham gia vào chương trình này.

________________________
Tên in của Bệnh nhân

________________________________________________________________________________

Chữ ký (Bệnh nhân hay người đại diện)  Ngày  Giờ

Người chứng nhận sự đồng ý

Tôi đã giải thích chương trình cho bệnh nhân/đại diện được ủy quyền và đã trả lời tất cả các câu hỏi về chương trình này với khả năng tốt nhất của tôi.

________________________________________________________________________________

Tên in  Ngày  Giờ

________________________
Chữ ký
标题： 扩大取得康复者血浆作为感染新型冠状病毒（COVID-19）患者的治疗用途
IRB#： 20-003312
临床医护人员： Michael Joyner, 执业医生 (M.D.)

请详阅本文内容。本文件告知您在此项目中对 COVID-19 患者所使用的试验型药物也就是康复者的血浆的重要信息。一名临床医护人员代表将会与您沟通参与本项目的事宜。如果您有任何疑问，请随时向我们咨询。在您做出决定前，您可以尽可以地与您的家人、朋友和医疗保健提供者讨论本项目。 注明：如果您是代表他人签署本同意书之家属或法定授权代表 (LAR)，则在本同意书中的“您”系指感染 COVID-19 患者本人。

若您决定参与本项目，则您需签署本同意书，以表明您的意愿。我们将提供本同意书的副本，供您自己留存。该副本将存档于您的病历资料中。

我们可以联系... | 联系方式... | 如果您对下列内容有问题...
--- | --- | ---
首席 临床诊治医生/医生： Michael Joyner, M.D. | 电话：(507) 255-7197 机构名称和地址：妙佑医疗国际医院, 圣玛丽院区 4-184 Joseph 1216 Second Street SW Rochester, Minnesota 55905 | ▪ 检测及医疗服务 ▪ 受伤或紧急情况 ▪ 任何疑问或投诉 ▪ 退出本项目 ▪ 您所收到的材料 ▪ 预约
妙佑医疗国际机构审查委员会 (IRB) | 电话：(507) 266-4000 免付费电话：(866) 273-4681 | ▪ 项目参与者的权利 ▪ 任何与项目相关的疑问或投诉 ▪ 对您受保护的健康信息的使用

我们为何邀请您参与本项目？您经诊断患有严重急性呼吸综合征冠状病毒（SARS-CoV-2）所引起的疾病，也就是所谓的 2019 新型冠状病毒（COVID-19）。SARS-CoV-2 的传播方式与流感及其他呼吸道病毒类似，并伴有咳嗽、发烧和呼吸急促;在更严重的病况下，会导致呼吸功能衰竭甚至死亡。目前，我们尚无任何获批准有效的药物或疫苗可用来治疗或预防 COVID-19。

COVID-19 康复患者之所以能够康复，至少部分契机归因于其血液中含有一种叫做抗体的物质，该物质可对抗导致此一疾病的病毒。研究结果发现，对于其他一些由呼吸道病毒所引起的疾病，为患者输注从该病毒的康复患者血液中采集的清夜成分（即血浆），可以使疾病更加快速的好转。我们认为，如果 COVID-19 的患者能够接受已经从 COVID-19 中康复者的血浆，可能因此具有抵抗造成 COVID-19 之病毒的能力而更快康复。

我们希望您考虑接受已经从 COVID-19 康复患者的的血浆。康复患者血浆中所含的物质将提高您的治愈几率。
我们不清楚此一治疗是否对您有所助益，也并不清楚该治疗本身是否具有任何不良影响。这是我们目前仅有的治疗方法之一，但是您必须知悉，本治疗尚未经过证实具有疗效。鉴于我们目前并没有其他更好的治疗方案，如果您愿意，我们希望能够验证此治疗方案之疗效，并从研究检试过程中吸取经验。

在您参与本项目过程中之进行流程为何？您将接受已经从 COVID-19 中康复，且血型与您相匹配的康复患者血浆，即为血液中的清液成份。血浆会通过无菌的单次使用式针头输注到您的静脉血管中，全程所需时间大概为一至两个小时。首次输注的血浆量估计约近 200 毫升 (mL)。于您住院期间若您的治疗主治医师判定进一步治疗具临床合理性的情况下将会进行额外血浆的输注。

鉴于此疗法尚未经验证，并且在您愿意尝试这项新疗法的情况下，我们希望可以竭尽所能的探究治疗本身的疗效。因此，我们会记录一些您在治疗后的反应情况，比如您所需要住院的时间长短，或是您需要呼吸辅助所持续的时间有多久。

参与本项目过程中会面临的潜在风险或不适有哪些？血液和血浆均有应用在很多其他病症的治疗，通常来说是非常安全的。尽管因接受此治疗而感染 COVID-19 的风险尚无正式验证，但我们相信感染的几率是极低的，因为捐献者已经完全从感染中彻底康复了。输血也会存在不良反应的风险，比如过敏反应、与输血相关的循环负荷过重或是造成肺部损伤所伴随的严重呼吸困难、心律不整、凝血块形成，以及包括艾滋病 (HIV) 和乙型及丙型肝炎在内的感染性疾病的传播；当然，会发生此类感染的风险极低，因为只有经过筛查和配型的血液才能做为输血使用。针对妊娠期所造成的风险目前尚不清楚。您可能还会有其他目前未知的副作用包括严重的受伤或疼痛、残疾甚至死亡。您个人信息的保密性也有泄露的风险，但是，我们已配套好程序性措施以将此风险减到最低。

我在“同意”后，可以改变心意吗？参与本项目纯属自愿。您可以随时改变心意。如果您希望停止治疗，只需告知您的医生。您所做的决定并不会导致您因此而无法获得本中心提供给所有患者的常规医疗护理。

参加本项目的潜在益处有哪些？我们不知道康复者的血浆是否能有效治疗 COVID-19，因此您可能无法体验到任何益处。但是，我们相信此一治疗很可能会有效提高您从此疾病中康复的几率。

您还有其他选择吗？您可以选择是否接受本治疗。您的选择将不会影响您在本中心所获得的常规护理。我们会一如既往的尽力为您提供医疗照护。如果您同意接受该疗法，您同时也帮助了我们了解此一治疗是否有效以及该治疗本身的有效运作原理从而受益其他患者，当然，您仍可于中途随时退出。

如果您参加本项目，有哪些检测或医疗程序是需要您付费的？您无需支付康复者血浆。但是，您及/或您的保险公司应支付所有您在临床治疗中所接受的其他检测和医疗程序的费用，包括挂号/共付定额费用和保险自付扣除额。您需要支付您保险承保范围以外的所有费用。

您的隐私权和机密性的个人信息会如何受到保护？妙佑医疗国际与 Joyner 执业医生会于您医疗护理过程中所收集到或是创建的医疗信息进行使用，在此所指称的医疗信息例如具有您的姓名做为身份辨认的病历资料及检测结果，或者是他们用其它方式向您的医生以及您的其他医疗保健提供者所要求的信息。您的医疗信息将会与相关的监管机构进行共享，其中包括美国食品药物管理局 (FDA)。此外，为帮助了解治疗是否有效而收集的关于您自身的所有信息或数据均将严格保密，并且只能提供给本文件所列名的接受者使用，以便能够更确切了解 COVID-19 以及该治疗方法的潜在可行性，并籍此对本项目进行规范性监管。
签署本同意书，即表示您允许您的医疗保健提供者得以披露按本文所陈述与您切身相关的医疗信息。此一授权将持续至本项目结束为止。您的医疗信息的接收者可能不受限于联邦隐私权法规的约束，在此情况下您的医疗信息于披露后可能不再受到联邦隐私权法规的保护。在告知您的医生后，您可以随时撤回本授权。在您撤回授权后，我们不会再收集关于您的任何新医疗信息，但是我们会继续使用已经收集到的既有医疗信息，并在保有本项目的科学完整性需要下进行信息共享。

您在此之签署即表明您本人（或患者）的授权同意参加本项目。

患者正楷姓名

/ / ： 上午/下午

签名（患者或授权代表） 日期 时间

取得同意书之相关人员
我已经向患者/授权代表进行了本项目的解释，并尽我所能回答了有关本项目的所有问题。

/ / ： 上午/下午

正楷姓名 日期 时间

签名

Fasax ayaad u tahay inaad kala tashato barnaamijaanka hoyskaaga, asxaabtaada iyo dhaqankaaga inta aadan go’aan gaar in. **OGSOONOW:** Haddii aad tahay qof ka mid ah hoyska bukaanka ama aad tahay qof bukaanka si sharciyaysan mas’uul ah uga ah oo aad waraaqdaada adiga wakil ah na ahaan u saxiixayso, marka “adiga” la yiraahdo waxay u dhigan tahay iyadoo lala hadlaayo bukaanka qaba COVID-19.

Haddii aad go’aan ku gaarto inaad ka qayb qaada barnaamijaanka, waxaad sixiixi doontaa waraaqdaan oggolaanshaha oo aad ku tusayso inaad rabto inaad ka qayb qaada barnaamijaanka. Waxaan ku siinaynaa waraaqdaan oggolaanshaha oo aad ku tusayso inaad rabto inaad ka qayb qaada barnaamijaanka. 

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**Waxaad la xiriiri kartaa ...**

<table>
<thead>
<tr>
<th>Dhaqtarka ugu sareeyo:</th>
<th>Taleefoon: (507) 255-7197</th>
<th>Magaca iyo Cinwaanka Isbitaalka:</th>
<th>Mayo Clinic Hospital, Saint Marys Campus 4-184 Joseph 1216 Second Street SW Rochester, Minnesota 55905</th>
</tr>
</thead>
</table>

**Waxaad Kala xiriiri Kartaa ...**

- **Guddiga Mayo Clinic U Qaabblisan Xaqdhowrka Ka Qayb Galayaasha Cilmi Baarista [Institutional Review Board (IRB)]**
- **Taleefoon:** (507) 266-4000
- **Taleefoon bilaash lagu soo woco:** (866) 273-4681

**Haddii aad su’aalo ka qabto waxyaabahan ...**

- Baaritaanada iyo Qalliinada
- Dhaawaca iyo gargaarka degdegga
- Su’aalo ama cabasho
- Ka bixidda barnaamijaanka
- Alaabaha lagu siiyo
- Balamada

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**Maxaad laagu waydinaayaa inaad barnaamijaanka uga qayb qaadaato?** Waxaad lagaa helay cudurka uu keeno SARS-CoV-2 oo loo yaqaan cudurka koroonofayraska 2019 (COVID-19). SARS-CoV-2 waxaas lays kugu gudbiyaa si la mid sida hargabka infuluweensada iyo fayrasyada ku dhaca marinka hawada oo wata qunfaac, qandho, dhibaato neefsasho, iyo jirooyin aad halis u ah sida awood beelidda neefsiga, iyo xitaa

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dhimasho. Waqtigan xaadirka ah, ma hayno daawo ama talaal la oggolaaday inay daawayn karaan ama ka hortagi karaan COVID-19.


Maaddaama daawayntan hore aan weli loo tijaabin, oo adigana aad rabto inaad tijaabiso, waxaan jeclaan lahayn inaan ka baranno intiiba aan wax ka baran karno waxтаркееда. Sidii darteeda, waxaan diyaar waxa uu xidhiistooyinka ku noqdo, sida muddada ay qaado isbitaalo ku jiriddaada ama inta mar aad u baahatay in neefsashada lagaa caawiyiyo.

Maxay yihiin qatarta iyo xanuunada aana kala kulmi karo intaan barnaamijkaan ku jirto? Dhiigga iyo balaasmadabaa hore ayaa loo isticmaalay sidii jirrooyinka qaar looq luqduu daaweyo, guud ahaana, waa kuwa aan halis lahayn. Inkastoo aan weli loo isticmaalay qatarta ka imaan karta inaad infekshanka (caabubqaa) COVID-19 aad ka qaadda maaddaama lagu siiyay daawadaan, waxaana aaminsanahay inay qatartaas tahay mid aad u hooxsaysa sababtoo ah qofkii deeqda bixiyay si kaamil ah ayuu uga bogsooday infekshanka. Dhiig iyo dheecaanka isku duridda waxay leeyihiin inuu jirka isbadallooyin xun uku uu kaqado sidii inuu alerji ku dhoco, ama inuu ka qaado jirrooyinka ka yimaado dhiig iyo dheecaanka isku duridda, dhigga oo xinjirooba, wandahaaga oo si toos ah u garacamin, ama sambabada uu daawac gaar oo kaasoo keeno dhibaato neefsasho oo aad u daran, iyo isku gudbinta infekshanada ay ka mid yihiin HIV, cagaarshoogga beerka qaybahaada B iyo C; inkastoo infekshanadaa fursadda ay kuugno dhaacaan ay aad u hooxsaynaa maaddaama dhiig iyo dheecaanka la soo baaray kaliya la isticmaalo, oona waafaqka dhigga bukaanka. Lamana oga halisyada kaga imaan kara dumarro uurka leh. Waxaa suurto gal ah in waxyeelooyin kale oo aan la aqoon waqtigan xaadirka ah ay ugu dhaacaan kuwaas oo ka mid ahaan kara, dhaawac xooggan ama xanuun, curyaanimo ama dhimasho. Waxaa xitaa dhici karta in
qarsoonida macluumaadkaaga kuu gaarka ah uu dhumo; hase ahaatee, waxaa jira nidaam la raaco sidii qatartaan lagu yarayn lahaa.

Ra’yigayga ma baddalan karaa kadib markii aan iraahdo “Haa”? Ka qayb qaadaashada barnaamijkaan waa mid ikhtiyaari ah. Markasta ayaad go’aankaaga ka noqon kartaa. Haddii aad damacdo in aad joojiso daawayntaan, waxaa kugu fiican lahaa dhaqtarkaaga u sheegto oo kaliya. Go’aankaas aad gaartay wax kama baddalaayo daryeelka aad halayso sida daryeelka bukaanada xaruntaan lagu siiyo oo idil.

Maxay yiihiin faa’idooyinka suurto galka ah inta aan barnaamijkaan ku jiro? Ma naqaano haddii balaasmade qof fiyoobaaday laga soo qaaday ay wax u tari doonto daawaynta COVID-19 iyo in kale, waxaana suurto gal ah inaadan wax faa’iido ah kala kulmin. Hase ahaatee, waxaan aaminsannahay in daawayntaan ay tahay mid wuxtar u lahaan karta inaad ka raysato cutoon.

Ma leeyahay doorashooyin kale? Waxaad go’aan ku gaari kartaa inaad qaadato daawayntaan ama aad iska dhaafta. Go’aankaaga ma saamaynayno daryeelka aad ka helayso xaruntaan. Markasta waxaan samaynaynado in sida ugu wanaagsan aan ku daryeeno. Haddii aad oggolaato daawayntaan, waxaad kaloo nagu caawin lahayd inaan wax ka baranno haddii dadaawntaan ay shaqaynayso, qaabka ay u shaqaynayso sidii aad u caawino bukaanada kale, inkastoo aad waqtigaad rabto aad ka bixi karto.

Baaritaanadee iyo qaliimadee ayaad lacag ka bixin doontaa haddii aad barnaamijkaan ka qayb qaadato? Ma u baahnid inaad wax lacag ah aad bixiso sidii aad ku hesho balaasmade laga soo qaaday qof kale. Laakiin, adiga iyo/ama caymiskaaga ayaa waxaad bixin doontaan wixii baaritaano kale ama qaliinada aad marayso oo ka mid daryeelka isbitaalka laguugu qabanaayo, taas oo ay ka mid tahay qaybta lacagta kugu soo aadayso ka dib markuu caaymiskaaga lacagta bixiyo iyo wixii caymiska kaa jarto. Waxaad kaloo bixinaysaa qarash kasta oo aan caymiskaaga bixinaynin.

Sidee arintaada kuu qaska ah kuuna qarsoon loo ilaaliin doonaa? Mayo Clinic iyo Dr. Joyner ayaa waxay isticmaali doonaan macluumaadka ku saabsan caafimaadkaaga ee sababtaan darteeda loo qaaday ama ay dhaqaalintirtaada ka cobsan doonaan macluumaadkaaga caafimaadka ee diiwaanka ku jira, sida wixii ku saabsan caafimaadkaaga iyo natiiyooyinka baaritaanadaada oo magac ahaan kuu aqoonsanaa. Macluumaadkaaga caafimaadka caafimaadka waxaa lala wadaagaayaa maamulada dawladda, kuwaas oo ka mid ah U.S. Food and Drug Administration (FDA), (oo ah maamulka qaabbilsan ansaxinta cuntooyinka iyo daawooyinka ee Maraykanka). Waxaa dheerad ah, in wixii macluumaad laaga qaaday oo dhax siduu u caawiyaha fahanka inay daawayntaan wax tarayso iyo in kale ay sir ahaan doonaan, oo ay dadka halkaan ku qoran iyo maamulka qaabbilsan shaqada barnaamijkaan kala ay isticmaali karaan sidii si fiican loogu fahmo COVID-19 iyo daawayntiisa.
Sixiixidda warqaddaan waxay fasax siinaysaa oo dhaqtarkaaga u oggolaanaysaa isla wadaagidda macluumaadkaaga caafimaadka sida warqaddaan hore laguugu soo sharaxay. Fasaxaan wuxuu soconaayaan ilaa barnaamijkaan ka dhamaado. Dadka heli doona macluumaadkaaga caafimaadka ma hoos yimaadaan sharciyada federaalka ee ilaaliya arimaha qofka qaaska u ah, macluumaadkaaga caafimaadkana ma ilaalin karaan sharciyada federaalka ee ilaaliya arimaha qofka qaaska u ah haddii uu shaaca ka qaadmo. Waqtigaad rabto ayaad ka noqon kartaa fasaxaan adigoo la socodsinaayo dhaqtarkaaga. Macluumaad caafimaad oo cusub oo lagaa qaadi doono malaha ka dib markii aad fasaxaan ka noqoto, laakiin waa lasii isticmaali doonaa ama lala wadaagi doonaa (maamul) kale wixii macluumaad ahaa ee horay loo qaaday iyadoo la dhowraayo daacadnimada sayniseed ee barnaamijkaan.

Saxiixaaga wuxuu caddaynaayaa inaad u fasaxan tahay (ama bukaanka) ka qayb qaadashada barnaamijkaan.

Qoraalka Bukaanka Magaciisa oo Buuxa

/ / : AM/PM

Saxiixa (Bukaanka ama Wakiil sharciyaysan) Taariikhda Saacadda

Qofka Oggolaanshaha La Siinaayo
Waana u sharxay barnaamijkaan bukaanka ama qofka ka mas’uul ah waana uga jawaabay su’aalaha barnaamijkaan ku saabsan oo dhan sida uga fiican oo ay awooddayda ahayd.

/ / : AM/PM

Qoraalka Magaca oo Buuxa Taariikhda Saacadda

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Saxiixa
Утверждено: 26 июня 2020 г. Не использовать после: 31 марта 2021 г

РАСШИРЕННАЯ ПРОГРАММА ДОСТУПА
ФОРМА СОГЛАСИЯ ПАЦИЕНТА И ФОРМА РАЗРЕШЕНИЯ НА ПРЕДОСТАВЛЕНИЕ КОНФИДЕНЦИАЛЬНОЙ МЕДИЦИНСКОЙ ИНФОРМАЦИИ

Заголовок: Расширенный доступ к реконвалесцентной плазме для лечения пациентов с COVID-19
ЭСО №: 20-003312

Представитель медицинского персонала: доктор Майкл Джойнер (Michael Joyner, M.D.)

Внимательно прочтите информацию, приведенную в этом документе. Он содержит важные сведения о программе по применению исследуемого препарата, реконвалесцентной плазмы, для лечения пациентов с COVID-19. Сотрудник клиники проведет с Вами беседу об участии в этой программе. Если у Вас есть вопросы, Вы можете задать их нам в любой момент. Прежде чем принять решение, обсудите эту программу со своей семьей, друзьями и поставщиком медицинских услуг. ПРИМЕЧАНИЕ. Если Вы подписываете эту форму согласия от имени другого лица (как член семьи или законный уполномоченный представитель (legally authorized representative, LAR)), «Вы» в этом согласии относится к пациенту с COVID-19.

Если Вы решили принять участие в этой программе, подпишите данную форму информированного согласия для подтверждения своего желания принять участие в программе. Мы предоставим Вам копию этой формы, которую Вы сможете сохранить у себя. Другая копия будет приложена к Вашей медицинской документации.

<table>
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<tr>
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| Основной лечащий врач: доктор Майкл Джойнер (Michael Joyner, M.D.) | Телефон: (507) 255-7197  
Название организации и адрес: Mayo Clinic Hospital, Saint Marys Campus  
4-184 Joseph  
1216 Second Street SW  
Rochester, Minnesota 55905 | ▪ Тесты и процедуры  
▪ Травмы или необходимость срочной медицинской помощи  
▪ Любые нежелательные проявления или жалобы  
▪ Выход из программы  
▪ Полученные Вами материалы  
▪ Назначение встреч |
| Экспертный совет (Institutional Review Board (IRB)) клиники Mayo Clinic | Телефон: (507) 266-4000  
Бесплатная линия: (866) 273-4681 | ▪ Права участника программы  
▪ Все вопросы и жалобы, связанные с участием в программе  
▪ Использование закрытой медицинской информации о Вас |
Почему Вас просят принять участие в этой программе? У Вас диагностировали заболевание, вызванное вирусом SARS-CoV-2, которое известно также как коронавирусное заболевание 2019 г. (COVID-19). SARS-CoV-2 передается аналогично вирусу гриппа и других респираторных заболеваний. Его симптомами являются кашель, повышенная температура и одышка, а в более тяжелых случаях оно может привести к неспособности дышать или даже к смерти. В настоящее время у нас нет специализированных одобренных лекарств или вакцин для лечения или предотвращения COVID-19.


Мы просим Вас рассмотреть возможность получения плазмы от людей, выздоровевших после COVID-19. Их плазма будет содержать вещества, которые могут повысить Ваши шансы на выздоровление.

Мы не знаем, поможет ли Вам это лечение, и также не знаем, может ли оно оказать какое-либо вредное воздействие. Это единственное средство лечения, которое у нас есть на данный момент, но Вы должны знать, что его действенность пока не доказана. Так как сейчас у нас нет других, лучших средств лечения, мы хотели бы, с Вашего согласия, испытать это средство и исследовать результаты его применения.

Что произойдет с Вами во время участия в этой программе? Вам будут вливать плазму (жидкий компонент крови) от человека, который выздоровел после COVID-19 и имеет совместимую с Вашей группу крови. Плазма будет вливаться внутривенно при помощи стерильной одноразовой иглы, процесс займет около одного-двух часов. Во время первого вливания Вам будет введено 200 мл плазмы. Если Ваш лечащий врач сочтет продолжение лечения клинически оправданным, во время Вашего пребывания в больнице Вам могут провести дополнительные вливания плазмы.

Так как этот способ лечения пока не прошел испытания, а вы желаете попробовать его, мы хотели бы как можно больше узнать о его действии. Мы будем фиксировать определенную информацию о Вашей ответной реакции на лечение, например, как долго Вам придется оставаться в больнице или потребуется ли Вам искусственная вентиляция легких.

Каковы возможные риски или неудобства, связанные с участием в этой программе? Кровь и плазма использовались от лечения многих других заболеваний, и в основном этот метод показал высокую безопасность. Хотя пока риск переноса инфекции COVID-19 при получении лечения формально не исследовался, мы считаем, что он крайне низок, так как донор полностью выздоровел после болезни. Вливание также связано с риском возникновения нежелательных реакций, например, аллергических реакций, перегрузки кровеносной системы в связи с вливанием или повреждения легких с серьезным затруднением дыхания, нарушения сердечного ритма, тромбоаза, а также переноса инфекций, включая ВИЧ и гепатит В и С, хотя такой риск инфицирования очень низок, так как для переливания используется только проверенная и совместимая кровь. Риски для беременности неизвестны. У Вас могут возникнуть другие побочные эффекты, неизвестные на настоящий момент, в том числе...
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серьезные травмы, боль, инвалидность или смерть. Существует также шанс нарушения конфиденциальности Вашей личной информации, однако мы применяем процедуры для минимизации этого риска.

Могу ли я изменить решение после того, как дам согласие? Участие в этой программе является добровольным. Вы можете в любое время изменить свое решение. Если Вы захотите прекратить лечение, просто сообщите об этом своему врачу. Такое решение не приведет к прекращению получения обычной медицинской помощи, которая оказывается всем пациентам в этом центре.

Каковы возможные преимущества участия в этой программе? Мы не знаем, будет ли реконвалесцентная плазма эффективной для лечения COVID-19, и может оказаться, что ее применение не принесет Вам никакой пользы. Однако мы считаем, что это лечение может быть эффективным и может повышить вероятность Вашего выздоровления.

Предлагаются ли какие-либо другие варианты? Вы выбираете, получать такое лечение или нет. Ваш выбор не повлияет на медицинское обслуживание, которое Вы уже получаете в этом центре. Мы всегда прилагаем все усилия для Вашего лечения. Если Вы дадите согласие на участие, Вы поможете нам узнать, действует ли оно, и как оно помогает другим пациентам, но при этом Вы можете в любой момент выйти из программы.

Какие анализы или процедуры Вам нужно будет оплатить, если Вы примете участие в этой программе? Вам не нужно будет платить за реконвалесцентную плазму. Однако Вы и (или) Ваша страховая компания должны будете оплатить остальные анализы и процедуры, которые Вам делали бы в ходе обычного клинического лечения, включая долевые выплаты и франшизы. Вам нужно будет оплатить все затраты, которые не покроет Ваша страховка.

Как будет осуществляться защита Вашей частной жизни и конфиденциальной информации? Клиника Mayo Clinic и доктор Joyner будут использовать медицинскую информацию, собранную или созданную в ходе предоставления Вам медицинского обслуживания, например, медицинские документы и результаты анализов, которые идентифицируют Вас по имени или другим способом и которые будут запрашиваться у Вашего врача и у других поставщиков медицинских услуг. Ваша медицинская информация будет также направляться в соответствующие государственные регулирующие органы, в том числе в Управление США по контролю пищевых продуктов и лекарственных препаратов (Food and Drug Administration, FDA). Кроме того, будет сохраняться конфиденциальность всей собранной о Вас информации и данных, которые могут помочь в понимании того, является ли это лечение эффективным. Данные будут использоваться только указанными в данном документе получателями для лучшего понимания COVID-19 и потенциальных возможностей его лечения, а также для контроля данной программы со стороны регулирующих органов.

Подписывая данную форму, Вы даете своему поставщику медицинских услуг разрешение раскрывать Вашу медицинскую информацию в соответствии с описанием, приведенным в данной форме. Это разрешение действует до момента окончания программы. Получатели Вашей медицинской информации могут не подчиняться федеральным законам о неприкосновенности частной жизни, и может случиться, что Ваша медицинская информация более не будет защищена федеральными законами о неприкосновенности частной жизни после ее раскрытия. Вы можете отозвать свое разрешение в любой момент, сообщив об этом своему врачу. После отзыва Вашего согласия медицинская информация о Вас больше не будет собираться, но вся медицинская информация, которая уже была собрана, будет

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использоваться дальше и при необходимости передаваться для обеспечения научной целостности программы.

Ваша подпись подтверждает Ваше согласие (или согласие Вашего пациента) на участие в данной программе.

________________________________________________________________________

Имя пациента печатными буквами

________________________________________________________________________ /  /  :

Подпись (Пациента или уполномоченного представителя)       Дата                 Время

Лицо, получающее согласие

Я предоставил исчерпывающую информацию о программе пациенту (уполномоченному представителю) и ответил на все вопросы, касающиеся данной программы, в рамках своей компетентности.

________________________________________________________________________ /  /  :

Имя печатными буквами       Дата                 Время

________________________________________________________________________

Подпись
বর্ণিত অ্যাক্সেস প্রোগ্রাম

রোগীর সম্মতি ও গোপনীয়তা সম্পর্কিত অনুমোদন ফর্ম

শিরোনাম: COVID-19 আক্রান্ত রোগীদের চিকিৎসার জন্য কলাম্যানেসেট প্লাজমায় বর্ণিত অ্যাক্সেস

IRB#: 20-003312

কমিটির কমমন্টার Michael Joyner, M.D.

অনুমান অনুযায়ী এই তথ্যগুলো ব্যবহার করে এই ফর্মটিকে সম্পর্কিত একটি আপনাকে গোপনীয় ছাড়াই জানাবে। কমিটির কমমন্টারের একজন সম্মত যোগাযোগের মোডেল এই ফর্মটিকে ব্যবহার করে আপনাকে এই ফর্মের সম্মতি ফর্মের সাথে যোগাযোগ করার জন্য নিকটতম প্রতিফলিত (LAR) হিসেবে আপনাকে প্রাথমিক যোগাযোগের মাধ্যমে অনুমান করে।

আপনি যদি এই ফর্মটিকে অনুমান করেন না, তাহলে আপনি অনুমান করার জন্য এই ফর্মটি নিজে প্রেক্ষাপট করেন।

আপনি যদি এই ফর্মটি অনুমান করেন না, তাহলে আপনি অনুমান করার জন্য এই ফর্মটি নিজে প্রেক্ষাপট করেন।

<table>
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<tr>
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<th>এই ঠিকানায়...</th>
<th>আপনার যদি নিচের বিষয়গুলোর সম্পর্কে কোনো প্রশ্ন থাকে...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal কমিটির চেয়ারম্যান:</td>
<td>নাম: Mayo Clinic Hospital, Saint Marys Campus 4-184 Joseph 1216 Second Street SW Rochester, Minnesota 55905</td>
<td>পরীক্ষা ও পদ্ধতি প্রতিষ্ঠানের নাম ও ঠিকানা:</td>
</tr>
<tr>
<td>Michael Joyner, M.D.</td>
<td>ফোন: (507) 255-7197</td>
<td>আয়তন ও জরুরি অবস্থাসমূহ</td>
</tr>
<tr>
<td></td>
<td>প্রতিষ্ঠালীর নাম ও ঠিকানা:</td>
<td>কোনো উদ্দেশ্য বা আসুস্থা ফর্মাচারের নাম ও ঠিকানা:</td>
</tr>
<tr>
<td></td>
<td>Mayo Clinic</td>
<td>আসুস্থা ও জরুরি অবস্থাসমূহ</td>
</tr>
<tr>
<td></td>
<td>Hospital,</td>
<td>কোনো উদ্দেশ্য বা আসুস্থা ফর্মাচারের নাম ও ঠিকানা:</td>
</tr>
<tr>
<td></td>
<td>Saint Marys Campus</td>
<td>কোনো উদ্দেশ্য বা আসুস্থা ফর্মাচারের নাম ও ঠিকানা:</td>
</tr>
<tr>
<td></td>
<td>4-184 Joseph</td>
<td>আপনি কী কী উপকরণ পাবেন</td>
</tr>
<tr>
<td></td>
<td>1216 Second Street SW</td>
<td>আ্যাপারেন্টন্সসমূহ</td>
</tr>
<tr>
<td></td>
<td>Rochester, Minnesota 55905</td>
<td>আপনি সুরুবাচ্চ বিষয়ের ভাষায় ব্যবহার</td>
</tr>
<tr>
<td>Mayo Clinic চিকিৎসার্থক পর্যালোচনা সমিতি বোর্ড (IRB)</td>
<td>ফোন: (507) 266-4000</td>
<td>কর্মসূচিতে অসংগঠনকারীদের অবৈধ সমূহ</td>
</tr>
<tr>
<td></td>
<td>সংক্রান্ত মুক্তি: (866) 273-4681</td>
<td>কর্মসূচিতে সম্পর্কিত যেকোনো উদ্দেশ্য বা আসুস্থা</td>
</tr>
<tr>
<td></td>
<td></td>
<td>আপনার সূরুবাচ্চ বিষয়ের ভাষায় ব্যবহার</td>
</tr>
</tbody>
</table>

আপনার যদি এই কর্মসূচিকে অনুমান করতে বলা হবে তাহলে SARS-CoV-2 এর জন্য সম্মতিটি রোগ ধরা পড়া যা করোনাভাইরাস রোগ 2019 (COVID-19) নামেও পরিচিত। ইন্টারেন্টে এবং সামগ্রিক অনুসন্ধান ভাইরাস দ্বারা SARS-CoV-2 ছড়ান এবং কাশি, ব্যথা এবং ব্যক্তির মত উপসর্গসমূহের প্যাভাপনি
আরও তীর মাঝে স্বাস নেওয়ার অক্ষত্তা বা এমনকি মৃত্যুও হতে পারে। বর্তমানে কোভিড-19 এর চিকিৎসা বা তা প্রতিবাদ করার জন্য আমাদের কোনো অসুস্থতার উদ্ধৃতি বা ডিকা নেই।

যারা কোভিড-19 থেকে আরোগ্যলাভ করেন, তারা অভিজ্ঞ এই কারণে সরে যায় যে তাদের হয়ে আরেকটির ব্যাপারে সেনানিয় কর্মকর্তা। যদেহ যখন স্বাস্থ্যং ভাইরাসগুলির কারণে যাবার বাহায় রোগগুলির ক্ষেত্রে, যারা তাইরিতে থেকে আরোগ্যলাভ করতেন তাদের থেকে নেওয়া প্লাজমা নামে পরিচিত রকের তরল অংশটি মনুষকে হলে রোগের আরও চক্তি উন্মুক্ত হয়। আমারা স্পষ্ট করি যে কোভিড-19 এর অর্জন রোগীদের আরও চক্তি উন্মুক্ত হতে পারে যদি তারা কোভিড-19 থেকে আরোগ্যলাভ করা মানুষদের থেকে প্লাজমা পান, কারণ এটে কোভিড-19 এর জন্য দায়ী ভাইরাসের সদৃশ সমত্তর থাকতে পারে।

আমরা আপনাকে কোভিড-19 থেকে আরোগ্যলাভ করেন এমন কারণ কাছ থেকে প্লাজমা নেওয়ার কথা বিবেচনা করার অনুমতি নেই। তাদের প্লাজমায় এমন উদ্ধৃতি থাকতে যা আপনার আরোগ্যলাভের সমাপ্ত বৃদ্ধি করতে পারে।

এই চিকিৎসাটি আপনাকে সাহায্য করার জন্য সেনানায় আমরা জানি নিশ্চিত নেই এবং এর কোনো অক্ষত্তার প্রভাব থাকায় কিনা সেটিকে আমরা অবতে নেই। বর্তমানে আমাদের কাছে যে চিকিৎসাসাগর আপনি তাকে মধ্যে এটি অনজান, যদি আমাদের এটা জানা প্রয়োজন যে এটি এক্ষেত্রে কাজকর্ত্র বলে প্রমাণিত হয়নি। যেহেতু আমাদের কাছে বর্তমানে আমাদের উপস্থিত চিকিৎসা বিকল্প নেই, তাই আমি আরেক হলে আমরা এই চিকিৎসাটি প্রতিবাদ করে দেখতে চাই এবং পরিকল্পনা থেকে স্থিতিতে চাই।

আমিনি এই কর্মসূচিতে থাকার সময় আমার কী হবে? কোভিড-19 থেকে আরোগ্যলাভ করেন এমন একজন মানুষের থেকে প্লাজমা অথবা রকের তরল অংশটি আপনাকে দেওয়া হবে, যা আপনার রকের ধরনের সাথে সামান্য হবে। একটি জীবাণুপূর্ণ এককাল ব্যবহারযোগ্য সুচ ব্যবহার করে আপনাকে কোনো একটি নিরীক্ষা এটি দেওয়া হবে এবং প্রায় এক থেকে দুই ঘণ্টা সময় ধরে এটা দেওয়া হবে। সর্বনাম্ন ইনফিকশন গ্রাম ২০০ মিলিয়ন প্লাজমা দেওয়া হবে। যদি চিকিৎসাটি প্রদানকারী চিকিৎসক মোট করে নে যে অতিরিক্ত চিকিৎসা প্রয়োজন রয়েছে তাহলে আপনি হাসপাতাল থাকাকালীন অতিরিক্ত প্লাজমা উন্মুক্ত প্রয়োজন হতে পারে।

যেহেতু এই চিকিৎসাটি গ্রামের পরিচিতি হয়নি এবং আপনি এই নতুন চিকিৎসাটি পরিভাষা করে দেখতে চান, সেনানায় আমারা এর প্রতিক্ষে ভেবে দেখা যায় যে এই প্রক্রিয়া সম্পন্ন হবে এবং প্রায়ং সর্বনাম্ন প্রতি আমার প্রতিক্ষিয়।

এই কর্মসূচিতে অংশগ্রহণ করার থেকে কী করার সম্ভাব্য বুকি বা অসম্ভাব্য আছে? এর অনেক বাধ্য বাড়ার জন্য রক ও প্লাজমা ব্যবহার করা হচ্ছে এবং সাধারণভাবে এটা খুবই নিরাপদ। যদিও চিকিৎসাটি পাওয়া থেকে কোভিড-19 সংক্রমণের শিকার হওয়ার বুকি, এটা প্রথাগতভাবে পরিচিত নয়। এবং আমারা বিশ্বাস করি যে এটা খুবই কম হবে। কারণ দাতা সংক্রমণ থেকে সংক্রমণটি কথা প্রোগ্রামীয় আরোগ্যলাভ করেন।

রক সংক্রমণের ফলস্বরূপ অ্যালকটিমিটেড প্রতিক্ষিয়, সংক্রমণের সাথে সাম্যের সাথে সংক্রমণের ক্ষতি, হৃৎপিণ্যটি (হৃৎপিণ্য)- খণ্ডের অন্তর্ভুক্তি, এই রক ও হৃৎপিণ্যের বা রক ক্লিনিকো এবং HIV ও হেমোফিলিয় বি ও সি সামী সংক্রমণগুলি ছড়ানোর মত প্রতিকৌশল প্রতিক্ষিয়গুলির বুকি আছে; যদিও এই সংক্রমণগুলির বুকি খুবই কম, যেহেতু শুধুমাত্র পরিচিক করা ও সামাজিক সংক্রমণ সম্পর্কে জন্য ব্যবহার করা হয়। গোষ্ঠীবর্গের বুকিরগুলো
IRB#: 20-003312 00

MAYO CLINIC

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যে কানো চিকিৎসা সংক্রান্ত তথ্য কর্মসূচির বিজ্ঞাপন বিশেষত জন্য প্রয়োজন মত ব্যবহার ও বিনিময় করার জন্য অনুমোদন হবে না:

IRB#: 20-003312 00

আপনার যাচ্ছে এই কর্মসূচিতে আপনার (বা রোগীর) অংশগ্রহণকে লক্ষ্য করে।

_______________________________

স্পষ্ট অঙ্কের রোগীর নাম

/ / : AM/PM

স্বাস্ত (রোগী বা অনুমোদিত প্রতিনিধি) তারিখ সময়

সম্প্রতি গ্রহণকারী ব্যক্তি

আমি রোগী/অনুমোদিত ব্যক্তির কাছে কর্মসূচি ব্যাখ্যা করেছি এবং আমার সর্বোচ্চ সাধ্য অনুযায়ী এই কর্মসূচি সম্পর্কে সকল প্রশ্নের উত্তর দিয়েছি।

/ / : AM/PM

স্পষ্ট অঙ্কের নাম তারিখ সময়

_______________________________

স্বাস্ত
Tit: Aksè Elaji nan Plasma Konvalesan pou Tretman Pasyan ki gen COVID-19
IRB#: 20-003312
Pèsonèl Klinik: Michael Joyner, M.D.


**REMAK:** Si ou se yon manm fanmi oswa yon reprezantan legal otorize (Legally Authorized Representative, LAR) k ap siyen fòm konsantman sa a pou yon lòt moun, “ou, w, oumenm” nan fòm konsantman an vle pale de pasyan ki gen COVID-19 la.

Si ou deside patisipe nan pwogram sa a, ou pral siyen fòm konsantman sa a pou montre ou vle patisipe. Nou pral ba w yon kòpie nan yon moun ki te refè nan COVID-19 la. Y ap mete yon kòpie nan yon moun ki te refè nan COVID-19 la.

<table>
<thead>
<tr>
<th>Ou kapab kontakte ...</th>
<th>Nan ...</th>
<th>Si ou gen kesyon sou ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinisyen/Doktè Prensipal: Michael Joyner, M.D.</td>
<td><strong>Telefòn:</strong> (507) 255-7197 <strong>Non ak Adrès Enstitisyon an:</strong> Mayo Clinic Hospital, Saint Marys Campus 4-184 Joseph 1216 Second Street SW Rochester, Minnesota 55905</td>
<td>▪ Tès ak pwosedi yo ▪ Chòk oswa ijans ▪ Nenpòt enkyetid oswa plent ▪ Sòti nan pwogram lan ▪ Materyèl ou resevwa yo ▪ Randevou yo</td>
</tr>
<tr>
<td>Komite Revizyon Enstitisyonèl (IRB) Mayo Clinic</td>
<td><strong>Telefòn:</strong> (507) 266-4000 <strong>Apèl Gratis:</strong> (866) 273-4681</td>
<td>▪ Dwa yon patisipan nan pwogram lan ▪ Nenpòt pwoblèm oswa plent anrapò ak pwogram lan ▪ Itilizasyon Enfòmasyon Medikal Pwoteje ou</td>
</tr>
</tbody>
</table>


Nou pa konnen si tretman sa a pral ede ou oswa si li pa pral ede ou, epi nou pa konnen nonplis si li pral gen nenpòt efè danjere. Sa se youn sèlman nan tretman ke nou gen aktyèlman yo, men ou dwe konnen li poko bay prèv ke li mache. Piske nou pa gen lòt meyè opsyon pou tretman aktyèlman, nou ta renmen eseye tretman sa a, si ou vle, epi aprann apati tès la.

**Kisa ki pral rive ou pandan ou nan pwogram sa a?** Yo pral ba ou plasma, pòsyon likid san an, ki sòti sou yon moun ki refè nan COVID-19, ki konpatib avèk goup sangen ou. Yo pral bay li nan yon nan venn ou yo, avèk itilizasyon yon zegwi esteril ki itilize yon sèl fwa, epi yo pral bay li pandan aperè yon a dezèdyan. Y ap bay aperè 200 mL Plasma nan yon premye pèfizyoon. Lòt pèfizyoon plasma yo ka fêt pandan tout sejou ou nan lopital la si doktè ki responsab tretman an detèmine ke tretman anplis yo jistifye sou plan klinik.

Paske yo pokoko teste terapi sa a, epi ou vle eseye nouvo terapi sa a, nou ta renmen aprann tout sa ki posib pou nou aprann sou efè li genyen yo. Se pòtèt sa, nou pral anprejistre kòk enfòmasyon sou reyaksyon ou ak tretman an, pa egzanz pandan konbyen tan ou te oblije rete nan lopital la osa ou te bezwen èd pou respire.

**Ki risk oswa malèz ki posib nan patisipasyon nan pwogram sa a?** Yo te itilize san ak plasma pou anpil lòt pwoblèm medikal, epi yo gen anpli sekirite anjeneral. Malgre yo pokoko te teste ofisyèlman risk ki genyen pou trape enfeksyon COVID-19 lè moun resevwa tretman an, nou kwè risk la ta trè fèb paske donatè a te refè konplètman nan enfeksyon an. Transfizyoon an tou gen ladan risk pou reyaksyon negatif tankou reyaksyon aléjik, sijach sikilatwa anrapò ak transfizyoon oswa domaj nan poumon avèk gwo difikilte pou respire, ritm kadyak (kè) iregilye, kowagilasyon san, ak transfizyoon enfeksyon, sa gen ladan VIH ak Epatit B ak C; men risk pou enfeksyon sa yo se trè fèb, paske yo itilize pou transfizyoon an sèlman ki te evalye epi ki konpatib. Yo pa konnen risk ki genyen pou gwosès. Ou ka gen lòt efè segondè ke yo pa konnen pou lemonman, epi yo ka gen ladan chòk oswa doulé grav, andikap oswa lamò. Genyen tou yon risk pou ta gen pèt konfidsyalite enfòmasyo prin ou; men, gen pwosedi an plas pou diminye risk sa a nèt.


**Ki avantaj ki posib nan patisipasyon nan pwogram sa a?** Nou pa konnen si plasma konvalesan an pral yon tretman efikas pou COVID-19, epi ou ta ka pa jwenn okenn avantaj. Men, nou kwè tretman sa a ta ka efikas pou amelyore chans pou ou refè nan maladi a.

Èske ou gen lòt chwa? Ou kapab chwazi pou pran tretman sa a oswa pou pa pran li. Chwa ou fè a pa pral afekte swen ke w ap resevwa nan sant sa a. N ap toujou fè tout sa nou kapab pou pran li. Si ou aksepte tretman sa a, ou pral ede nou aprann tou si tretman an mache ak kijan li fonksyone pou ede lòt pasyan yo, menm si ou ka sòti ladan nenpòt lè.

**Ki tès oswa pwosedi ou pral gen pou peye pou yo si ou patisipe nan pwogram sa a?** Ou p ap gen pou peye pou plasma konvalesan an. Men, oumenm ak/oswa asirans ou ap gen pou peye pou tout lòt tès ak pwosedi ki ta fè pati swen klinik ou, sa gen ladan ko-peman ak dediktib yo. Ou pral responsab nenpòt frè ke asirans ou pa kouviri.

**Kijan yo pral pwoteje entimite ak konfidsyalite enfòmasyon ou yo?** Mayo Clinic ak Doktè Joyner pral itilize enfòmasyon medikal yo kolekte oswa kreye nan kad swen medikal ou, tankou dosye medikal ak rezilta tès ki idantifye ou avèk non ou oswa nan yon lòt fason yo mande doktè ou yo ak lòt founisé swen sante ou yo. Yo pral kominke enfòmasyon medikal ou yo tou bay otorite kontwòl apnopriye yo, sa gen ladan Ajans Etazini pou Kontwòl Manje ak Medikaman (Food and Drug Administration, FDA). Anplis, tout enfòmasyon oswa done yo pran ki konsènse ou pou ede konprann si terapi a efikas pral rete konfidsyél epi se sèlman moun ki resevwa.
Dat Apwobasyon: 26 Jen 2020          Pa dwe itilize apre: 31 Mas 2021

yo ki endike la a ki pral itilize yo pou konprann COVID-19 pi byen ak tretman ki ka genyen pou li, ak pou sipèvizyon reglemantè pwogram sa a.

Lè ou siyen fòm sa a, ou bay founisè swen medikal ou otorizasyon pou komininke enfômasyon medikal ou jan li dekri nan fòm sa a. Otorizasyon sa a dire jiskaske pwogram lan fini. Moun ki resevwa enfômasyon medikal ou yo gendwa pa anba liwa sou federal sou konfidansyalite yo, epi enfômasyon medikal ou gendwa pa pwoteje ankò anba liwa federal sou konfidansyalite apre komunikasyon enfômasyon yo. Ou ka di dioktè ou sa pou repran otorizasyon sa a nenpòt lè. Yo p ap pran okenn nouvo enfômasyon medikal sou ou apre ou repran otorizasyon ou, men y ap kontinye itilize ak pataje nenpòt enfômasyon medikal ki te deja kolekte, jan sa nesesè pou entegrite syantifik pwogram lan.

Your signature documents permission for you (or the patient) to take part in this program.
Siyati ou fè konnen ou bay otorizasyon pou ou (oswa pasyan an) patisipe nan pwogram sa a.

Printed Name of Patient
Non Pasyan an ak lèt detache

Signature (Patient or Authorized Representative)    Date    Time
Siyati (Pasyan an / Reprezantan Otorize a)          Dat    Lè

Person Obtaining Consent
I have explained the program to the patient/authorized representative and have answered all questions about this program to the best of my ability.

Moun ki Resevwa Konsantman an
Mwen te eksplike pwogram lan pou pasyan an/reprezantan otorize a epi mwen te reppon tout kesyon konsènan pwogram sa a nan meyè fason mwen kapab.

Printed Name
Non an ak Lèt Detache

Signature
Siyati
9. References


