

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

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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:

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

Table of Contents

1 Protocol Summary.....	4
1.1 Synopsis	4
1.2 Schema.....	5
2 Introduction	6
2.1 Study Rationale	6
2.2 Background	6
2.3 Risk/Benefit Assessment	6
2.3.1 Known Potential Risks	6
2.3.2 Known Potential Benefits	6
2.3.3 Assessment of Potential Risks and Benefits	6
3 Objectives and Endpoints.....	7
4 Study Design	8
4.1 Overall Design	8
4.2 Scientific Rationale for Study Design	8
4.3 Justification for Dose.....	8
4.4 End of Study Definition.....	9
5 Study Population.....	10
5.1 Inclusion Criteria	10
5.2 Strategies for Recruitment and Retention	10
6 Study Intervention	11
6.1 Study Intervention(s) Administration	11
6.1.1 Study Intervention Description.....	11
6.1.2 Dosing and Administration	11
6.2 Preparation/Handling/Storage/Accountability	11
6.2.1 Acquisition and accountability.....	11
6.2.2 Formulation, Appearance, Packaging, and Labeling.....	11
6.2.3 Product Storage and Stability	12
6.2.4 Preparation	12
6.5 Concomitant Therapy	12
7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal	13
7.1 Discontinuation of Study Intervention.....	13
7.2 Participant Discontinuation/Withdrawal from the Study.....	13
7.3 Lost to Follow-Up	13
8 Study Assessments and Procedures	14
8.1 Efficacy Assessments.....	14
8.2 Safety and Other Assessments	14
8.3 Adverse Events and Serious Adverse Events.....	14
8.4 Unanticipated Problems.....	14
9 Statistical Considerations	15
9.1 Statistical Hypotheses	15
9.2 Sample Size Determination	15
9.3 Populations for Analyses	15
9.4 Statistical Analyses	15
9.5 Publication Plan.....	15

10 Supporting Documentation and Operational Considerations 16

 10.1 Regulatory, Ethical, and Study Oversight Considerations..... 16

 10.1.1 Informed Consent Process..... 16

 10.2 IRB Reliance 17

 10.3 safety oversight..... 17

 10.4 Abbreviations 19

 10.5 Protocol Amendment History 19

11 References 21

 References 21

Statement of Compliance

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

- o United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312).

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. r

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 off 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

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Provide access to COVID-19 convalescent plasma	Availability of convalescent plasma	Expanded access protocol
Secondary		
Safety	Serious adverse events	Required as part of expanded access protocol under IND
Tertiary/Exploratory		
Health care utilization	<ol style="list-style-type: none"> 1. Acute care facility length of stay 2. Days spent in intensive care unit 3. Survival to acute care facility discharge 	Evaluation of potential for efficacy

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.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 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 \leq 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 $\leq 93\%$
- 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 \leq 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. w

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 a for 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

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

10.5 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	4/1/2020	Initial Version	N/A
2.0	4/3/2020	Updated IND Number Added IRB Oversight	Documentation Clarification
3.0	4/9/2020	Updated Section 10.1.1.2 Consent Procedures and Documentation	Additional consenting procedures for patients unable to give consent and also no LAR available to give consent for patients qualifying for plasma infusion.
4.0	4/15/2020	Updated Section 6.1.2	Clarify 1-2 units of plasma and up to 500ml of volume delivered
5.0	4/23/2020	Study synopsis clarified to be consistent throughout 1-2 units Section 1.2 and 5.2 Eligible patients will be registered with American Red Cross or other blood source by uscovidplasma.org Section 1.2 Clarify infusion rate for plasma deleted specific rate. 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.	Consistency throughout protocol that 1-2 units of plasma may be administered Clarification and consistency to coordinate patients and available plasma Allow for flexibility to individual institutional and patient standards for care Reduce deviations and allow flexibility in scheduling if 2 units are administered.

		Updated Labeling in Section 6.2.2	Align with current FDA Guidance.
		Section 8.2. and 8.3 SAE reporting should be done using forms on website.	Clarify SAE reporting
		Section 9.3 Clarified collection of event information	Information should be collected from all consented and enrolled patients for whom plasma is ordered
		Added Section 9.5 for Publication plans	Clarify Publication Plan
		10.1.1.1 Revised reference to informed consent document	IRB Approved Consent is available on the website not part of this document.
		Section 10.3 Clarified safety monitoring and updated DSMB Roster	Clarificaton and updates

11 REFERENCES

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