Scope

This Standard Operating Procedure (SOP) describes investigative-site-specific steps to follow when conducting the COVID-19 convalescent plasma National Expanded Access Program multicenter clinical study entitled, "Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19" while following the protocol and complying with applicable guidelines, standards and United States (US) Code of Federal Regulations (CFR).

Flow Map

Plan→Start-up→Conduct→Close out→Report

Procedure

1. Plan

1.1. The Principal Investigator (PI) must read and understand the Investigator's Brochure, Protocol and Informed Consent documents and complete training to assure the safety of study participants, to comply with good clinical practices (GCPs) and to minimize risks to study participants and staff during the clinical study.

1.2. The PI (or designee) shall "Sign up to participate in this program" by completing the "Site Registration Form" online with the Lead Institution (Mayo Clinic) and the Study Sponsor (the US Government). *NOTE: The site blood bank supervisor who will receive the blood or "convalescent plasma" upon arrival at the investigational site must be listed in the form with an email address. If the investigational site is already listed, this form is not needed a second time.*

1.3. The PI (or designee) shall complete the "Physician/PI Registration Form" with their NPI or DEA number, email address and cell phone number. *NOTE: The PI must agree to adhere to the protocol and regulatory requirements including the completion of FORM FDA 1572 which is a legally binding agreement between the PI and the United States (US) Food and Drug Administration (FDA).*

1.4. Prior to study activation, the PI (or designee) shall ensure clinical study activities are ready to start in compliance with all legal, regulatory, site-specific and protocol-specific requirements.

1.4.1. The PI (or designee) shall secure Institutional Review Board (IRB) and regulatory approval to conduct the study prior to starting any clinical study activities.

1.4.2. The PI (or designee) shall establish and maintain the Study Master File (TMF) at the investigational site using the FDA good data integrity practices embodied in the ALCOA acronym for **Attributable, Legible, Contemporaneous, Original and Accurate** data. *NOTE: The TMF Index (**Table 1**) is provided here as a guide. Documents should be organized in each TMF section in reverse chronological order with most recent content in front. Do not remove outdated files. The TMF Index should be modified to meet study requirements.*

Table 1: TMF Index

Study Master File Category	Subsection Description
A. Study Protocol	1. Clinical Study Protocol and amendments (if applicable) 2. Investigator Protocol Agreement Signature Page

B. Investigator's Brochure	1. Clinical Investigator's Brochure and amendments
C. Master Informed Consent Forms	1. Blank copy of IRB-approved Informed Consent Forms (ICF) 2. All languages, standardized short forms and revisions, if any
D. Subject Files	1. Subject Screening Log 2. Subject Identification Code List 3. Signed Informed Consent Form for each subject (may include non-English versions or verbal translations documented in medical record as needed, questions can be directed to lead institution at uscovidplasma@mayo.edu) 4. Detailed Subject Case History 5. Complete Subject CRF/eCRFs including Serious Adverse Event (SAE) and protocol deviation forms 6. CRF Queries and Corrections 7. Other Source Documents
E. Study Site Personnel Records (PI and all key personnel)	1. Site Personnel Contact Information 2. Delegation of Responsibilities 3. Signature Log 4. Curriculum Vitaes 5. Medical Licenses 6. Financial Disclosures 7. Study-Specific (Protocol) Training Records 8. Good Clinical Practice (GCP) Training Records 9. Human Subjects Protection (HSP) Training Records 10. Health Insurance Portability and Accountability Act (HIPAA) Training Records
F. Institutional Review Board (IRB)	1. IRB/IEC Member Roster and/or IRB Registration Information 2. IRB/IEC FederalWide Assurance (FWA) Number 3. IRB/IEC Initial, Interim, Annual, Continuing Review Requirements 4. IRB/IEC Submission Materials (if required, outside of MAYO CLINIC IRB) 5. IRB/IEC Approval Letters or Waivers, if applicable 6. Other IRB/IEC Notifications and Acknowledgements
G. Financial Information	1. Study Agreements 2. Site Budgets 3. Insurance Agreements
H. Regulatory Authority Information	1. Signed and dated FORM FDA 1572 2. Regulatory Authority Inspection Reports, if any 3. Correspondence FDA/other regulatory authority, if any
I. Site/Sponsor Correspondence	1. Log of Study Sponsor Site Visits 2. Essential Correspondence between Lead Investigational Site (Mayo Clinic) and your institution (e.g. letters, e-mails, meeting minutes) 3. Safety Information/Notifications, e.g., to/from Lead Institution, Investigators 4. Communications about protocol deviations, if any 5. Notes to File (NTF) and other communications 6. Documentation of Study Termination
J. Blood Bank Information, Study Materials and Accountability	1. Process to receive, segregate/store, and release plasma 2. Investigational Product Accountability Log for Convalescent Plasma (Patient Code, Plasma Receipt, Storage, Use, Disposal Accounting) 3. Disposal/Destruction Documentation
K. Location and Authorized Access to Study Records	1. Study Records Location Form (e.g. location of Source Documents, CRFs) 2. Process for controlled access and data entry into the Mayo Clinic REDCap clinical study database 3. Written signature log, if using paper source documents or records for any part of this study

1.5. The PI (or designee) should ensure the site is prepared to allow the creation, storage and retention of appropriate case histories and documents with appropriate written data management, monitoring and training plans.

1.6. The PI (or designee) should identify and train the blood bank supervisor/s who will receive blood/convalescent plasma and any sub-investigators, coordinators or others who will support clinical study activities at the site. *NOTE: COVID-19 patient treatment requires appropriate training of all personnel and the site environment must be appropriate for this special population with allocation and use of necessary patient and clinician equipment and supplies including personal protective equipment (PPE).*

2. Start Up

2.1. The PI (or designee) should ensure all approvals, trainings and materials are ready for study subjects before activation of the study site to begin enrollment. *NOTE: the Department of Health & Human Services (DHHS) has empowered medical providers to use methods of communication which "may not fully comply with the requirements of the HIPAA rules" and they will exercise enforcement discretion during this emergency; so, the PI should use the most effective means of communication as required in each particular medical situation.*

2.2. The PI (or designee) should understand convalescent plasma transportation issues from "local supplier" to site blood bank. *NOTE: As stated online for this convalescent plasma study , suppliers will be "Red Cross, Vitalant, OneBlood, ABC, New York Blood Center or local source" and the "PI must work out this ordering process with their hospital blood bank, via the electronic health record, such as EPIC" as much as possible prior to needing the first dose of convalescent plasma for a patient with severe or life-threatening COVID-19. "The federal program will reimburse regardless of the convalescent plasma blood bank source."*

2.3. The blood bank shall designate a "segregated area" to securely and properly store investigational COVID-19 convalescent plasma products.

2.4. The PI (or designee) shall screen potential study subjects, document all screening and enrollment activities and prepare to enroll patients up to the maximum number allowed in the protocol.

2.5. The PI shall order appropriate testing for each patient as a part of their medical care (e.g., a confirmed diagnosis of COVID-19 and a specific ABO blood type is required for each potential convalescent plasma recipient to be enrolled into this study).

3. Conduct

3.1. Consent: The PI (or designee) shall secure voluntary, written, informed consent from the patient using the appropriate IRB-approved ICF. *NOTE: One original, signed and dated ICF will be given to the study subject and one original, signed and dated ICF will be stored in the TMF. Unless the individual patient emergency situation requires enrollment without informed consent, the PI (or designee) must secure written informed consent from the patient or legally authorized representative (LAR) before starting any clinical study activities. In situations where informed consent process is not appropriate "in the room" with the patient or LAR, the informed consent process may be discussed via a telemedicine or telephone device and a photograph of the consent form can be emailed to the PI. Also, in a life or death emergency situation for a patient unable to give informed consent at the time they need COVID-19 treatment, the PI can discuss the patient with a second physician who must document concurrence in the medical record so the patient can be treated in this protocol without informed consent. The PI must inform the patient or their LAR of their enrollment in the study in a timely fashion and the PI must answer their questions. The study subject is free to withdraw consent from participation in further*

data collection at any time; however, study subject data will remain in the databank and the PI must fill out the 4-hour infusion (whether or not the subject was treated with the convalescent plasma), 7-day and 30-day safety evaluation forms.

3.2. Enroll: The PI (or designee) shall enroll the subject into the study by following the "physician workflow section" online to "Access plasma through your local supplier" and completing the "Patient Enrollment Form." *NOTE: the patient code must be properly documented in the medical record, case history records and enrollment log and the patient code must match the plasma product given to the patient.*

3.3. Order and Treat: The PI shall follow online steps to "Order Convalescent Plasma" based on the identified patient ABO type. The hospital blood bank will receive and enter "named patient" units into inventory and will store the "named patient" units in a segregated area per the blood bank's own SOPs. The blood bank will inform the PI of the available units and the PI will place the transfusion order for the designated patient. Once ordered, the blood bank will thaw and issue the plasma to be transfused at the patient bedside following local hospital procedures. The PI shall complete the 4-hour infusion. *NOTE: The PI shall maintain traceability records including the order, shipment, receipt, storage, use, disposal of each and every unit of convalescent plasma received at the site (e.g., in the Investigational Product Accountability Log. medical record, study subject case history file and required electronic CRFs). The 4-hour infusion CRF must be completed to include the unit number, (i.e., "code") and patient medical record number even if the transfusion is not given. The PI (or designee) should dispose of any unused study materials as specified in the study protocol or in communication with the FDA, Mayo Clinic as the Lead Investigational Site or IRB.*

3.4. Follow Up: The PI (or designee) must follow the study subject and must document information in the 7-day (transfusion outcomes) and 30-day CRFs (if the patient remains hospitalized). In addition, the PI must complete the SAE form to report any COVID-19 convalescent-plasma-specific SAE data between 4 hours and 7 days post-infusion. *NOTE: Data collection (e.g., in the Investigational Product Accountability Log. medical record, study subject case history file and required electronic CRFs) includes patient demographics, acute care facility resource utilization (e.g., length of stay, days in ICU, days intubated and survival to discharge from acute care facility). In addition, when documenting SAE, refer to the online study protocol FAQs for a list of anticipated Serious Adverse Events*.

3.5. Correspond with Appropriate Parties when Required: The PI (or designee) should report any SAEs, unanticipated problems or protocol deviations in a timely fashion to appropriate parties (e.g., IRB, Mayo Clinic as the lead investigational site, other investigators, sites, regulatory authorities) as required in the protocol, relevant regulations and guidelines. *NOTE: The PI shall report promptly to the IRB/sponsor/lead investigational site any AE reasonably regarded as caused by, or probably caused by, the drug and, if the AE is alarming, the PI shall report the AE immediately. The PI is also required to promptly report any unanticipated problems, AEs or protocol deviations involving risks to human subjects or others. The PI must maintain a copy of all correspondence regarding these SAEs, unanticipated problems, AEs or protocol deviations in the TMF. Retraining may be needed for protocol deviations and documentation should include the nature of the protocol deviation as well as the retraining and study process changes completed to correct and prevent recurrence of the protocol deviations. The study sponsor may monitor or audit the study using remote monitoring techniques, so records should be completed in real time and kept in an accessible location.*

3.6. Respond to Queries: The PI (or designee) should respond in a timely fashion to queries from the study sponsor/lead investigational site, IRB or the FDA including, but not

limited to, any data corrections for any subject or data point. *NOTE: Maintain query correspondence in the appropriate TMF section and document key oral communications (e.g., phone calls) in writing as soon as possible (e.g., follow-up with a brief summary document in the form of an email or other appropriate media to document the oral communication).*

3.7. Suspend/Terminate: The PI (or designee) should prematurely suspend/terminate the study at the site if safety of participants is in question and report to the FDA, IRB, Sponsor/Lead Investigational Site with appropriate documentation in the TMF. *NOTE: The FDA, Mayo Clinic, or the IRB may also prematurely suspend/terminate the study at the site (e.g., if safety of participants is in question).*

4. Close Out

4.1. The PI (or designee) should inform all appropriate parties (e.g., sponsor/Lead Investigational Site, IRB, FDA) of planned site close out with documentation in writing maintained in the TMF.

4.2. The PI (or designee) shall account for all study materials including all units of convalescent plasma requested, received, dispensed, returned or destroyed as detailed in the study protocol. *NOTE: The PI (or designee) should use the Investigational Product Accountability Log and store this record in the appropriate section of the TMF. The PI (or designee) should ensure the site environmental considerations are met for disposal, clean up, reuse and all study records must be retained and not destroyed*

4.3. The PI (or designee) shall cooperate with the sponsor/Lead Investigational Site and FDA to complete close out activities including data clean-up activities and study record dispositioning to ensure all TMF documents are ALCOA.

5. Report and Archive

5.1. The PI (or designee) should cooperate with the study sponsor and FDA during data verifications, inspections and statistical analyses needed for report writing and publication activities. These activities should be documented in the TMF.

5.2. The PI (or designee) should prepare appropriate reports as needed (e.g., interim, annual and final study reports may be required). The PI should sign and date the reports and ensure appropriate distribution to the FDA, study sponsor/lead investigational site, IRB and other investigators as appropriate. Maintain a copy of any interim and final study reports in the TMF.

5.3. The TMF and trial records should be archived in a location where these records will be maintained for future retrieval as required.

6. References

Title (Link)
Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 (20-003312; NCT04338360) (https://www.uscovidplasma.org/pdf/COVID-19%20Plasma%20EAP.pdf)
Expanded access program patient consent and privacy authorization form (https://www.uscovidplasma.org/pdf/EAP%20CP%20English%20Consent%2020.00331200.pdf)
Clinical Investigator's Brochure for Use of Convalescent Plasma to Treat Coronavirus-19 (COVID-19) Disease (https://www.uscovidplasma.org/pdf/IB%20COVID-19%20Plasma.pdf)
Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19 (https://www.uscovidplasma.org/)

Investigational COVID-19 Convalescent Plasma Guidance for Industry (April 2020) (https://www.fda.gov/media/136798/download)
FDA Guidance on Conduct of Clinical Studys of Medical Products during COVID-19 Public Health Emergency (https://www.fda.gov/media/136238/download)
Notification of Enforcement Discretion for Telehealth Remote Communications During the COVID-19 Nationwide Public Health Emergency (https://www.hhs.gov/hipaa/for-professionals/special-topics/emergency-preparedness/notification-enforcement-discretion-telehealth/index.html)
45 CFR Part 46 Protection of Human Subjects (https://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title45/45cfr46_main_02.tpl)
21 CFR Part 50 Informed Consent of Human Subjects (https://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title21/21cfr50_main_02.tpl)
21 CFR Part 56 Institutional Review Boards (https://www.ecfr.gov/cgi-bin/text-idx?SID=f822314ea94b03ef0d32ee6c4a233869&mc=true&node=pt21.1.56&rgn=div5)
21 CFR Part 312 Investigational New Drug Application (https://www.ecfr.gov/cgi-bin/text-idx?SID=f822314ea94b03ef0d32ee6c4a233869&mc=true&node=pt21.5.312&rgn=div5)
FORM FDA 1572: Statement of Investigator and FAQ https://www.fda.gov/media/71816/download *and* https://www.fda.gov/media/78830/download
Electronic Source Data in Clinical Investigations (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-source-data-clinical-investigations)
ICH E6 (R2) Good Clinical Practice (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1))

Document Revision History

Version	Date	Description
1	4-22-20	Initial Release

Signature

Principal Investigator Signature/Date	Print or Type Name, Department, Institution