SOP: Investigational Product Management -Version 12

PROTOCOL TITLE:

Convalescent Plasma to Limit Coronavirus Associated Complications: A Randomized, Double-Blinded, Controlled, Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 non-immune) Plasma Among Adult Outpatients with Symptomatic COVID-19.

PROTOCOL NO: CSSC-004.

CSSC-004: IRB00247590.

SPONSOR: Johns Hopkins University (BIOS)

INVESTIGATIONAL DRUG SERVICE PHARMACIST: Anusha Yarava, PharmD MPH.

LEAD PRINCIPAL INVESTIGATOR: David Sullivan, MD.

INTRODUCTION AND PURPOSE:

This standard operating procedure (SOP) describes the JHU (BIOS) processes at the investigator sites for the receipt, storage, dispensing, reconciliation and return or authorized destruction of the investigational drug (study drug).

SCOPE:

This SOP applies to all procedures related to handling of the investigation study product. It describes the steps monitored by JHU- BIOS from the time the investigational product is received on-site until it is either returned to the designated location in the protocol, dispensed, or destroyed on-site.

1. Objective:

To ensure that the Principal Investigator (PI) and all research team members assisting in the conduct of clinical research are informed about their obligations and responsibilities as they pertain to Good Clinical Practices (GCP), the investigational plan, applicable regulations, guidance's, and institutional policies. This Standard Operating Procedure (SOP) applies to the written procedures followed by all members of a clinical research team involved in the conduct of human subjects' research at investigational sites. These detailed instructions promote compliance in conducting clinical research.

2. Responsibility:

The Johns Hopkins University (BIOS) develops, implements, and maintains SOPs. The need to write a new or revise an existing SOP is based upon changes to federal regulations, guidelines, institutional policies, or procedures.

The PI is ultimately accountable for all clinical research activities and is responsible for the appropriate delegation of tasks to individuals with adequate training and education to perform such tasks. It is the responsibility of all members of the clinical research team involved in supervising, managing, or conducting study-related activities to follow the SOPs. The clinical research team may include but is not limited to the following members:

Research Team Members

Principal Investigator (PI).	Clinical Research Coordinator (CRC)
Sub-Investigator (Sub-I).	Clinical Research Assistant (CRA)
Clinical Research Manager (CRM).	Other Research Staff as appropriate
Clinical Research Specialist (CRS).	Administrative and Support Staff

3. Definitions:

The following definitions from the International Conference on Harmonization, Good Clinical Practice: Consolidated Guideline, apply to this SOP.

Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Source Documents: Original documents, data, and records (e.g. packing slips, documentation of receipts, site regulatory certificates, etc.)

4. Investigational Study Product:

Convalescent Plasma: The investigational product, HCIP, is anti-SARS-CoV-2 convalescent plasma. HCIP will be collected by apheresis from healthy adults identified as having recovered from COVID-19.

Healthy adult donors with SARS-CoV-2 antibody titers ≥ 1:320 dilution by an FDA approved test will donate plasma to be used in the trial. After **July 2021** the new March 9 **EUA for high titer** hospital plasma may be used to qualify plasma for study use including **Euroimmun ration >3.5; Ortho-Vitros >9.6; and Mt. Sinai titer greater than 1:2880.** The antibody testing will be performed in a CLIA certified laboratory. Potential donors who meet these qualification standards will be referred to an FDA-registered blood center where donors will be evaluated according to current blood donation requirements; plasma will then be collected as fresh frozen plasma (FFP) or plasma frozen within 24 hours of phlebotomy (PF24).

Control Plasma:

Control plasma will be provided to the participating site's hospital from FDA-registered blood centers as fresh frozen plasma (frozen within 8 hours) or plasma frozen within 24 hours (PF24) collected prior to 12/31/19, or confirmed as SARS-CoV-2 seronegative. Plasma will be transfused according to hospital standard operating procedures. Both the active Human Coronavirus Immune Plasma (HCIP) and control non-immune plasma arms will receive greater than 175 ml of plasma.

Source of Investigational Product:

Investigational Product	**Plasma Source**	**Storage Temperature (^{O}C)**
Active product: Human Coronavirus Immune Plasma (HCIP)/Convalescent Plasma	**<u>Central Suppliers:</u>** Blood Bank of Delmarva (NYBC) Evanston Hospital DOD Vitalant Impact Life (Mississippi Valley Blood Center). **<u>Local Suppliers:</u>** In-house manufactured units. Local blood bank centers	Frozen ≤ - 18°C Thawed 1-6°C
Control Product: SARS-CoV-2 Non-Immune Plasma collected prior to December 31, 2019 or confirmed as seronegative	**<u>Central Suppliers:</u>** Blood Bank of Delmarva (NYBC). American Red Cross. **<u>Local Suppliers:</u>** In-house manufactured units. Local blood bank centers	Frozen ≤ - 18°C Thawed 1-6°C

5. Process Overview:

A. Receipt and inventorying of the investigational product
B. Storage of the investigational product
C. Dispensing of the investigational product
D. Transfer of the investigational product
E. Return/destruction of the investigational product

6. Procedures:

A. Receipt and inventorying of investigational product

The Central IP team confirms that investigational product is shipped to a site only after the initiation visit training and applicable regulatory requirements, including IRB approval and contract, have been fulfilled by the site.

Upon receipt of study product, a delegated research team member has to inventory the shipment immediately into the blood bank freezers dedicated to store the study product. The staff will review the shipment to ensure the information on the packing slips matches exactly what has been received at the site blood bank. This includes verifying:

- Amount
- Quantity per carrier/container
- DIN numbers and ISBT codes
- ABO type & Expiration date
- Maintenance of temperature stability by visual inspection or measuring the temperature by using a monitoring device (temp tale).

The study staff determines if the site brought any discrepancies to the supplier's attention of the investigational product and also notify the **Sponsor Investigational Product** team.

The site staff verifies the investigational product to confirm it is packaged properly with the sufficient amount of dry ice and the labels and/or labeling provide the information that is required by the applicable regulations.

The information required on the investigational product label or in accompanying labeling may include but is not limited to the following:

- Investigational Product name (unless blinded).
- Plasma unit volume.
- DIN number
- Sponsor name
- FDA required statement: “Caution: New Drug – Limited by US law to investigational use.” (if applicable)
- Special instructions regarding storage.
- Expiration date
- Quantity in container
- Any other information required in the applicable investigational product labeling regulations.

The blood bank designee should enter the IP information in the study database (Locator) (Attachment A, SOP for the IP Locator Data Entry).

The blood bank staff verifies that if a form was included in the shipment to acknowledge receipt, that the network blood bank site staff obtained the appropriate signature and upload it to the appropriate location in the locator database. (Attachment A, SOP for the IP Locator Data Entry- Site level documentation).

For the local (in-house manufactured units or the units obtained from the local donors), the blood bank staff are required to upload documentation of receipt to the same location in the Locator database. (Attachment A, SOP for the IP Locator Data Entry- Site level documentation).

The Sponsor- IP team verifies that the site blood bank has enough supplies required for the blinding of the investigational product. (if applicable).

The blood bank research staff will need to maintain at least minimum inventory as follows.

ABO Group	Control Plasma (2019)	Convalescent Plasma (SARS-CoV-2)
O	2	2
A	2	2
B	1	1
AB	1	1

If the inventory falls below the minimum, the blood bank staff coordinates with the sponsor central IP team to place the IP orders from the central suppliers. (Attachment IP reorder forms.)

B. Storage of the investigational product

The study IP will be stored in a secure isolated section separate from the routine blood bank stock, with limited access for only delegated research team members. The site will ensure that the study plasma units are stored according to the storage requirements detailed as below.

Investigational Product (Convalescent or Control)	**Storage Temperature (^{O}C)**
Frozen Plasma Units	Frozen ≤ - 18°C
Thawed Plasma Units	Thawed 1-6°C

The storage requirements include ensuring the study plasma units are stored at the above appropriate temperature and a temperature log will be maintained and entered in the locator database by the blood bank study staff (Attachment – Locator data entry).

The blood bank site ensures that all refrigerators used for study IP storage will be plugged into outlets with backup power where available. The study IP is temperature-sensitive, the blood bank staff will take measures to capture the temperature continuously, and the logs are uploaded into the locator database once a week. (Attachment - Locator data entry).

In the event that a temperature deviation is identified, the sponsor will be notified automatically on completion of the Temperature Excursion Tab in the Locator database (Attachment – Locator data entry) and the affected IP will not be dispensed until further instruction is received from the sponsor.

No food, drink, or specimens will be stored in the same location as the study IP.

C. **Dispensing of the investigational product**

Prior to dispensing study IP, the delegated research team members will ensure that study IP supplies are adequate and within an appropriate expiration date.

If additional supplies are needed, the unblinded monitor or study sponsor will be contacted to request additional study IP. The locator database (Sites inventory page) should be updated on receipt of the study plasma units (Attachment – Locator database Entry Manual).

The PI is responsible for ensuring that study IP is appropriately dispensed and/or administered per protocol by delegated research team members.

The Site research staff ensures the subject is eligible for the study once the subject meets inclusion criteria, informed consent is obtained before enrolling the participant in the study.

Randomization

The site clinical research coordinator/VISION randomization system will assign a potential subject a subject number, which follows the format A-01-XXX-XXX for CSSC-001 and A-04-XXXX for CSSC-004.

Once the subject is randomized, an email notification from the VISION database system containing the unblinded treatment allocation (control vs active) is sent to the corresponding Site Blood Bank Responsible Staff to select the compatible plasma product from the blood bank freezer.

A confirmation email of randomization (without treatment allocation) is also sent to the site clinical research coordinators (who have VISION database) and the CCC/DCC.

After the compatible ABO unit is selected from the freezers, the Blood Bank Staff will dispense the IP for thawing and relabel the product as “thawed plasma,” as per hospital defined procedure.

Labeling:

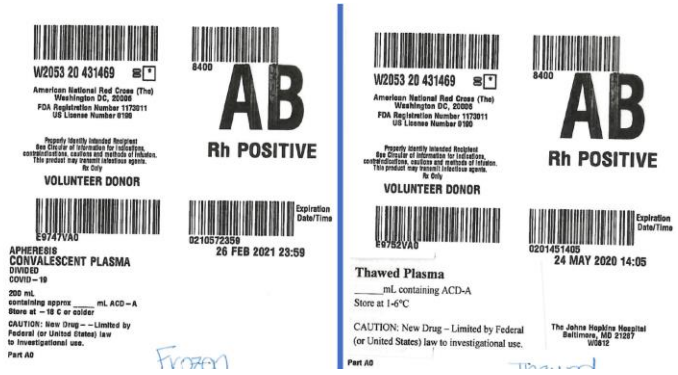
The Study Staff should ensure that the IP is relabeled in accordance with all cGMP, local and federal regulatory agencies.

The container label of COVID-19 convalescent plasma units must be labeled with the following statement: “Caution: New Drug--Limited by Federal (or United States) law to investigational use." (See 21 CFR 312.6 (a)).

The study plasma should be stored at <18º C when frozen and between 1-6°C when thawed. The FDA gave permission to label both control and convalescent plasma with the same label after thawing. The random difference is the anticoagulant which blinds the product.

The sample labels will be as follows:
Sample IP label for Human Coronavirus Immune Plasma (HCIP) (Frozen-left and Thawed-right):

Frozen label

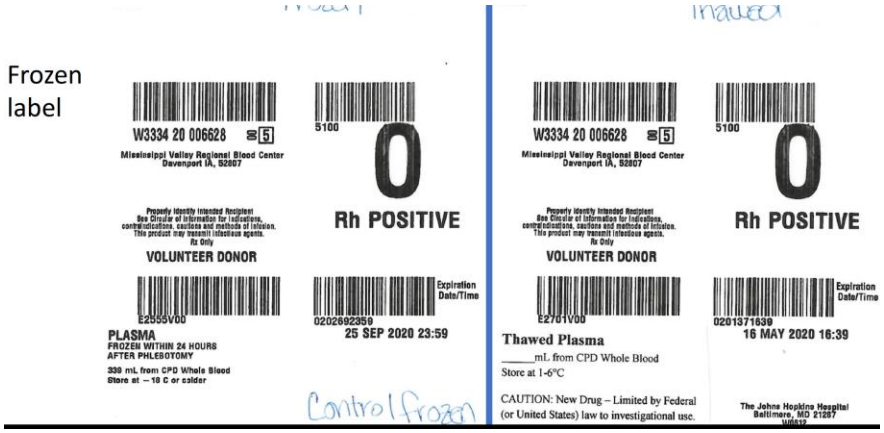


Frozen Label

Note that the form CPD or ACD-A are random and refer to anticoagulant Citrate-phos-dextrose (CPD)

Sample IP label for SARS-CoV-2 Non-Immune Plasma (Frozen and Thawed):

Frozen label



Thawed Label

Note that the form CPD or ACD-A are random and refer to anticoagulant ACD-A Anticoagulant Citrate Dextrose

Sample over-labels: Left, ACD-A Right, CPD whole blood

Thawed Plasma
_____mL containing ACD-A
Store at 1-6°C

CAUTION: New Drug – Limited by Federal
(or United States) law to investigational use.

Thawed Plasma
_____mL from CPD Whole Blood
Store at 1-6°C

CAUTION: New Drug – Limited by Federal
(or United States) law to investigational use.

The thawed blinded product plasma will be sent to the clinic location for the patient transfusion.

At the time of plasma dispensing, the blinded IP is cross verified by the unblinded staff with patient's subject name, date of birth & ABO plasma type as per the hospital defined policies and procedures. The blinded staff also checks the IP in a blinded process to match ABO type and Rh factor, and ensures right product is given to the right patient at the time of plasma administration (transfusion). In this way, the transfusion team, avoids any transfusion related errors to protect the patient safety.

D. Transfer of the investigational product

The transfer of investigational drug from one investigational site to another investigational site is permissible and may require authorization from the Sponsor.

The FDA regulations do not restrict interstate shipping of the Investigational Product when safety and precautions are taken to ship the product with the sponsor authorization. The JHU blood bank team verified with the FDA and agency gave permission to ship the investigational product across the state lines.

A request for the transfer of IP from one protocol to another protocol must be from a study protocol for which IPs are no longer needed to an active protocol.

Once the authorization for the transfer has been granted, shipment instruction with packaging **(proper box & packaging material),** and temperature monitoring devices such as **Temp Tale** \ will be sent to the site to which the IPs were originally shipped.

The process will be the same for all three different scenarios if permitted as per the Sponsor Pharmacist

- Different Protocol: IP Transfer within the Same Clinical Research Site
- Different Protocol: IP Transfer to a Different Clinical Research Site
- Same Protocol: IP Transfer to a Different Clinical Research Site.

1. A request for the transfer of IP to a different research site or protocol must be from a protocol for which IPs are no longer needed by using the "IP Transfer" form. (Locator Data Entry Manual-IP transfer tab).
2. The Pharmacist evaluates the need for an IP transfer and contacts the site blood bank director.
3. The Site blood bank director determines if a CTA (Clinical Trial Agreement) has been executed for the IP and specific trial.
   i). If the IP is covered under terms of a CTA, the Pharmacist will:
   a) Contact the IP manufacturer for authorization. Authorization from the IP manufacturer must be obtained prior to any transfer.
   b) Amend the CTA or negotiate a new CTA, as applicable.
   ii). If the IP is not covered under terms of a CTA, the Pharmacist will attempt to communicate with the IP manufacturers for their opinion regarding such transfer.
4. The Pharmacist initiates an **IP Transfer Form,** and sends it to shipping blood bank for IP storage temperature record verification and signature.
5. The blood bank staff provides Pharmacist with the IP's storage temperature records. (Locator database – IP temp logs).
6. The Pharmacist reviews storage and chain of custody records and verifies the investigational product/material was stored in a controlled manner under the manufacturer-recommended temperature and that no temperature deviations occurred. (Locator Data Entry Manual – IP transfer tab).
7. The pharmacist sends shipping instructions and materials along with the original transfer form to site(s) for product transfer
8. The Pharmacist provides a training session to explain the procedures for preparing the shipping box, dry ice requirements and temp tale operation to the shipping & receiving blood bank staff.
9. Conditions of transfer (investigational drug will be transferred in a frozen condition)
   - Quantity and identity of the investigational drug to be transferred
   - Receiving site and site contact person's contact information.

Appropriate documentation to support the transportation activity will include:

- Transfer record that documents and confirms each step of the transfer is controlled and secured.
- Pick-up date
- Pick-up condition of the investigational drug
- Delivery date.
- individual's name and signature
- Delivery condition of the investigational drug
- Correspondence documentation that confirms the receiving site's knowledge and readiness to receive the investigational drug
- IP Accountability Record.

10. Once, the receiving blood bank receives the study plasma units, the blood bank staff measures the temperature on receipt and verifies with the IP transfer form regarding the quantity of units shipped. If there are any discrepancies, the blood bank staff notifies to Sponsor.
11. All the transfer information is entered in the Locator database (See Attachment – Locator data Entry IP transfer tab).

E. Return/destruction of the investigational product

The Blinded personnel will return the unused IP product, if the IP is not transfused for any reason. Notify the Site Blood Bank of the need to return

- IP(s) sent to <clinic> will be returned in the same delivery container. Study Nurse will arrange return of product via courier.
- IP(s) sent to <local satellite> Blood Bank will only be returned to <central site> Blood Bank if required.
- Returned IP(s) should be evaluated by the Sponsor for final disposition.
- The Blood bank will evaluate the returned IP(s) against hospital procedures to determine if product is acceptable to be returned to inventory or should be discarded.
- The blood bank staff enters the data in the locator data base at the IP return tab (Attachment – IP Locator Data Entry – IP return tab)
- The expired products, product broken on receipt, the products that went out of temperature range are all discarded as per the blood bank procedures.
- All blood products will be discarded in biohazard red bags in accordance with hospital policy.
- IP(s) that are damaged and unacceptable for use are documented in the LOCATOR database by the Responsible Blood Bank Site Staff.

At the conclusion of the study, the delegated research team member will ensure that all documentation regarding receipt, storage, dispensing, and return of used containers and unused study IP is complete and accurate.

The delegated research team members may appropriately destroy IP at the site with written authorization and approval from the sponsor to do so.

Destruction of IP must follow blood bank policies and procedures required by state and hospital policies. The delegated research team members will provide the sponsor with locator documentation of the destruction of the study IP drug and maintain a copy for the regulatory files. (Attachment - Locator Data Entry Manual– IP discard)

SEGMENT/TAIL COLLECTION

The blood bank staff should collect and save a tail or 1 ml segment for **Impact Life© (Mississippi Valley Blood Center) units**. The **Impact Life©** units begin with **DIN # W0383.**

1. Serum may be substituted for plasma.
2. The W-number (or DIN) must be maintained throughout collection for sample identification.
3. It may be optimal to batch samples and send them together in shipments of ~20.
4. When preparing to send a shipment, it is important to fill out the manifest in the Appendix. Make certain every sample tube has the appropriate labeling to easily match the manifest.
5. If samples are obtained at the time for donation, they must be packed with sufficient dry ice according to DOT/IATA requirements. If segments/tails are obtained at the time of transfusion, they must be shipped with frozen ice packs instead.
6. Send shipments via FedEx Priority Overnight, Monday – Thursday.

Shipping Address:
Tobian Lab/CCP Study
Attn: Yolanda Eby
Johns Hopkins University
855 N. Wolfe St, Rangos Rm 540
Baltimore, MD 21205
Phone: 443-525-2814

FedEx Account Number: 706936335.
Use the above number to charge directly to JHU for FedEx deliveries:
Place "JHU DOD" in the internal billing line.

7. Once a tracking number has been obtained, an email should be sent to **Yolanda Eby (yeby1@jh.edu)**. Copy the Sponsor IP team **Anusha Yarava (ayarava1@jh.edu)**, **Preeti Khanal (pkhanal2@jhmi.edu),** and **Sonya Griffin (sgriff48@jhu.edu)** to announce the delivery for the next day.
8. The mail should contain the following information: the name of the site shipping the samples, the electronic version of the manifest, the tracking number of the shipment, and the name plus contact information of the individual responsible for the shipment.
9. A confirmatory email will be sent back from the JHU lab to acknowledge receipt of the initial email.
10. The following day, upon receipt of the shipment, another email will be sent back to the site noting the shipment's arrival.
11. If there are issues with the shipment and/or manifest, an email will notify the responsible individual describing the discrepancies.

IP Reorder Forms.

Blood bank staff will be required to order replacement units weekly or twice a week in order to maintain the ideal minimum stock requirements. IP reorder Forms will be emailed to Central Investigational Product team.

Point of Contacts:

CSSC - IP Pharmacist, Anusha Yarava (ayarava1@jh.edu).
CSSC - IP Coordinator Preeti Khanal (pkhanal2@jhmi.edu).

Please note, blinded individuals must not be copied to prevent accidental unblinding.

Applicable Regulations & Guidelines:

21 CFR 312.50 General responsibilities of sponsors
21 CFR 312.56 Review of ongoing investigations
21 CFR 312.57 Recordkeeping and record retention
21 CFR 312.59 Disposition of unused supply of investigational drug
21 CFR 312.60 General responsibilities of investigators
21 CFR312.61 Control of the investigational drug
21 CFR 312.62 Investigator recordkeeping and record retention
21 CFR 312.68 Inspection of investigator's records and reports
Pharmaceutical Management Branch (PMB): Investigational Drug Accountability Training Videos, and accountability record forms, transfer form and return forms/local destruction forms.
1988 Guidelines for the Monitoring of Clinical Investigations
October 2009 FDA Internal Compliance Program Guidance Manual
7348.811: Clinical Investigators Guidance for Industry Investigator Responsibilities-Protecting the Rights, Safety, and Welfare of Study Subjects
May 1997 International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline

Contacts List

Investigational Product Team	Title	Contact details	Responsibilities
Anusha Yarava, PharmD, MPH.	CSSC 001 and 004 IP Team Manager	ayarava1@jhu.edu 224-770-1035	IP Inventory Management. ICH -GCP regulatory compliance. Investigational Drug Services; IP SOP's & trainings. IP closeout activities. Locator Data Entry – Guidance to meet the regulatory requirements. Oversee; sites inventory & IP data entry regulatory compliance.
Aaron Ye, M.S.	CSSC - Data Manager / IP Coordinator.	aye4@jhu.edu O: 667-208-8351	IP Locator data entry assistance. Plasma Orders. Site weekly; Inventory reports. Ad hoc trainings.
Preeti Khanal	CSSC – IP Coordinator	pkhanal2@jhmi.edu 410-361-7999	IP Locator data entry assistance. Plasma Orders. Trainings
Craig Ou	CSSC- IP Data Manager	jou5@jhu.edu 667-208-8522	Data Reporting Data Integrity
Sonya Griffin	Unblinded Lead Monitor	sgriff48@jhu.edu 770-742-6619	Clinical Research Associate. Regulatory compliance Data entry & regulatory monitoring.
Melanie Morabito	Unblinded Monitor	mmorabi3@jhu.edu 267-742-7048	Clinical Research Associate. Regulatory compliance Data entry & regulatory monitoring.
Yolanda Eby	Sr. Research Program Coordinator	yeby1@jh.edu O: 410-614-1902 443-525-2814	Central Receipt of Plasma Specimen Manifest and Shipping Requests and Questions
Christi Marshall	Transfusion Medicine Division, Manager	cvoda@jhmi.edu 410-502-8169	Blood Bank Procedures Randomization Assistance
Evan Bloch, MD	Associate Professor, Transfusion Medicine, SOM	ebloch2@jhmi.edu 410-614-4246	FDA IND Liaison, Plasma Procurement Inventory procurement
Aaron Tobian, MD, PhD	Professor, Transfusion Medicine; Pathology, SOM	atobian1@jhmi.edu 443-287-0527	Tails/Segment Requirements Inventory procurement
Karen Lane	Assistant Professor, Neurology	klane@jhmi.edu 443-417-0184	Provides Clinical trial Coordination & Directions.

Manifest for Shipping Plasma Segments/Tails for CSSC Study to Repository at JHU

Name of Site Sending Samples: _____

Date of Shipment:
_____

Sample Number	Date of Collection	W-number (DIN)	Notes

Ship by FedEx, Priority Overnight, Mon-Thurs only, to:

Tobian Lab/CCP Study
Attn: Yolanda Eby
Johns Hopkins University
855 N. Wolfe St, Rangos Rm 540
Baltimore, MD 21205
Phone: 443-525-2814

FedEx Account Number: 706936335.
Use the above number to charge directly to JHU for FedEx deliveries:
Place “JHU DOD” in the internal billing line.

Point of Contacts:

CSSC - IP Pharmacist, Anusha Yarava (ayarava1@jh.edu).
CSSC- IP Coordinator, Preeti Khanal (pkhanal2@jhmi.edu).
CSSC- JHU Research Coordinator, Yolanda Eby (yeby1@jh.edu)

Date Requested:		
Receiving Facility:		
Address for Shipment		
Contact Information:	NAME:	EMAIL
	PHONE:	

* Please email IP order requests to ayarava1@jh.edu and pkhanal2@jhmi.edu

Convalescent Plasma

	O	A	B	AB	

FFP (Control Plasma)

	O	A	B	AB	

(We will make every attempt to accommodate ABO Type requests, but inventory may affect our ability to do so).

John Hopkins CSSC IP Management Contact Info

Name and Role	Email Address	Phone number
Preeti Khanal – Research Assistant / IP Coordinator	pkhanal2@jhmi.edu	(410) 361-7999
Sonya Griffin – IP Locator Monitor	sgriff48@jhu.edu	(770) 742-6619
Anusha Yarava – CSSC- Central Pharmacist Manager	ayarava1@jhu.edu	(410) 361-7999

COMMENTS OR SPECIAL REQUESTS:

COVID-19 PLASMA TRIALS
SPONSORED BY JOHNS HOPKINS UNIVERSITY

July 13, 2021

Dear Colleagues:

RE: TWO UPDATES ON CSSC-004 TRIAL CONVALESCENT PLASMA UNITS

Thanks for your hard work and allowing your blood bank to be utilized for our research studies. Thanks for your time to keep up with storage conditions and the LOCATOR database which have been the foundation for this trial.

Evan Bloch, Aaron Tobian and Tom Gniadek, along with the NYBC, have provided high titer plasma first qualified as positive after 1:320 dilution by the Euroimmun assay that probes the NTD and RBD region rather than entire spike as per IND 19725. Titers done in the research lab noted 98% over 1:1,000 and 90% over 1:4,000. Also, about 85% of the units qualified as high titer by the Euroimmun assay ratio equal to or greater than 3.5.

We have two very important updates for you.

UPDATE #1: Restriction to CSSC convalescent plasma qualified to be in line the new EUA with a EUROIMMUN ratio greater than 3.5

On March 26th, we asked the FDA if we should restrict future study transfusions of convalescent plasma qualified to be in line the new high titer hospital convalescent plasma EUA such as the EUROIMMUN ratio equal to or greater than 3.5. The FDA gave a positive response on April 19. We are pending sIRB approval in the next week or two to implement this EUA-aligned high titer plasma for the last month of the trial, that is, *after* July, 2021.

Evidence in the literature suggest that high titer convalescent plasma still neutralizes more than 80% of variants. We do not know if EUA qualified high titer plasma neutralizes in greater amounts. What happens in a test tube neutralization assay may not correlate to what happens in patients which is the purpose of the trial. We have attached the data utilized in the ask to the FDA for the high titer qualifications and for the extension of product for your records.

Our central blood bank staff will work with you individually over the next week isolating non-qualified plasma which will be removed from your inventory and documented in LOCATOR on July 31, 2021.

UPDATE #2: Extension on the expiry of our qualified study convalescent plasma units

On June 4, 2021, we requested a 3-month extension on the expiry of our qualified study convalescent plasma units. In early July, we provided data with no change in qualification

antibody levels at 1:320 dilution after 15 months, and the FDA, on July 12, 2021, approved extending the product expiration date, under use of IND 19725, of qualified convalescent plasma for this study only. This allows continued use of rare blood types which were set to expire before the study is closed to enrollment on August 31, 2021.

> *Our central blood bank staff is preparing LOCATOR directions for documenting your continued use of qualified convalescent plasma for three months after its expiration date. For LOCATOR, we are working on a central update to the expiration dates, so you do not have to change the dates in LOCATOR. You may have to update the expiration in your own systems. The relabeling of thawed plasma seen by study staff and patients will remain the same.*

Thanks again for your hard work.

David

David Sullivan, MD
CSSC-004 Study Chairman

Attachments:
March 26 request for high titer
April 19 FDA response
June request for 3-month extension
July response from FDA approving extension

Update regarding IND 19725

This update contains two questions to the Agency and sponsor response to FDA information request from our prior meeting. We were asked to provide a detailed description of the product that represents our intervention at our 12/21/2020 type B meeting (product descriptions are attached in this amendment). In this communication, we update our trial related data for several assays utilizing different commonly available methods which could allow for broader characterization of our intervention. We also describe the homogeneity of this product used in our trial. We present these current trial related results and seek agency's guidance on the EUROIMMUN assay threshold of the 3.5 OD ratio which could be used to qualify the investigational product. We pose the possibility of qualification of the remaining donors in the CSSC-004 trial with the EUROIMMUN Spike (S1 domain only) assay threshold of 3.5 as opposed to the IND19725 protocol current standard which is a positive test for the SARS-CoV-2 antibody with minimum titers of ≥1:320 as performed in CLIA laboratory. Most of our donors were qualified on Euroimmun Spike S1 domain testing at 1:320.

Background: In February 2021, FDA made revisions to the EUA to limit the authorization to the use of high titer COVID-19 convalescent plasma for the treatment of hospitalized patients early in the disease course. Our current data describes the standardization of the IND 19725 "test article" with the results of our assessment of the investigational product used in the 424 convalescent plasma treated participants taken from the first 848 randomized participants (1:1 test article to control).

In IND 19725 CSSC-004 our plan required we qualified the donor plasma for this outpatient study at positive test for the SARS-CoV-2 antibody with minimum titers of ≥1:320 as performed in CLIA laboratory. The hospital EUA uses threshold at EUROIMMUN Anti-SARS-CoV-2 ELISA (IgG) above a 3.5 ratio at the single 1:101 dilution on the same assay. The EUROIMMUN test is not robustly linear such that a positive SARS-CoV02 signal at 1:320 dilution does not always equal an optical density of 3.2 at the 1:101 dilution.

We have compared 195 unique qualified donor units by EUROIMMUN 1:101 OD and by our core laboratory full length spike endpoint titer and AUC. These donors have supplied plasma transfused into 400+ recipients (donor volume allowed multiple units from single donor at 200 to 250 mL). According to our trial core lab testing, only two of the donated convalescent plasmas would have been considered medium titer at 1:540 as they were below 1:1000 and only 11 at below 1:1620. These data suggest that 98% of the convalescent plasma used in IND 19725 CSSC-004 study are with titer above 1:1000 and would be considered reasonable titer by our current separate endpoint titer assay. Conversely, 49 units of 195 units (25%) were below the EUROIMMUN 3.5 ratio threshold even after qualification at the 1:320 dilution.

Please find graphical relationships between the anti-spike protein antibody titer from our lab and the EUROIMMUN 1:101 OD results.

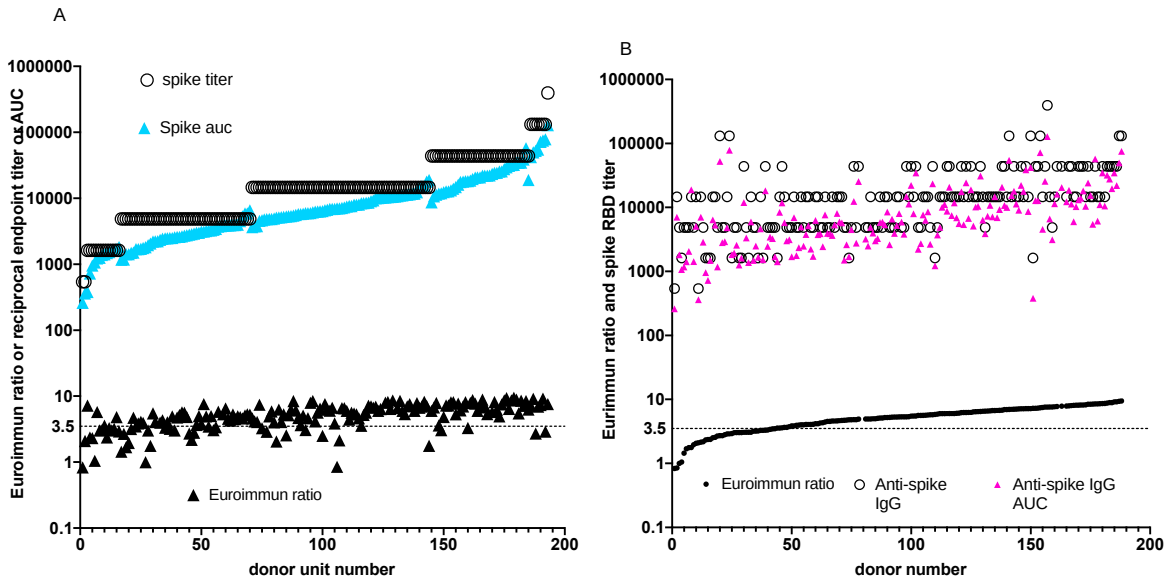


Figure 1A Relationship of Euroimmun S1 ratio at 1:101 to ascending endpoint titers ranked by full length spike (S1 and S2) protein IgG and AUC. The spike protein IgG and AUC were determined as in **Klein … Tobian JCI 2020 (**10.1172/JCI142004**).** The reciprocal endpoint titers were 540, 1620, 4860, 14580, 43740, 131,220 and 393,660. **Figure 1B** shows the first 49 units with EUROIMMUN ratio below 3.5 with corresponding EPT and AUC to full length spike protein. The EPT are similar for those below or above the 3.5 ratio.

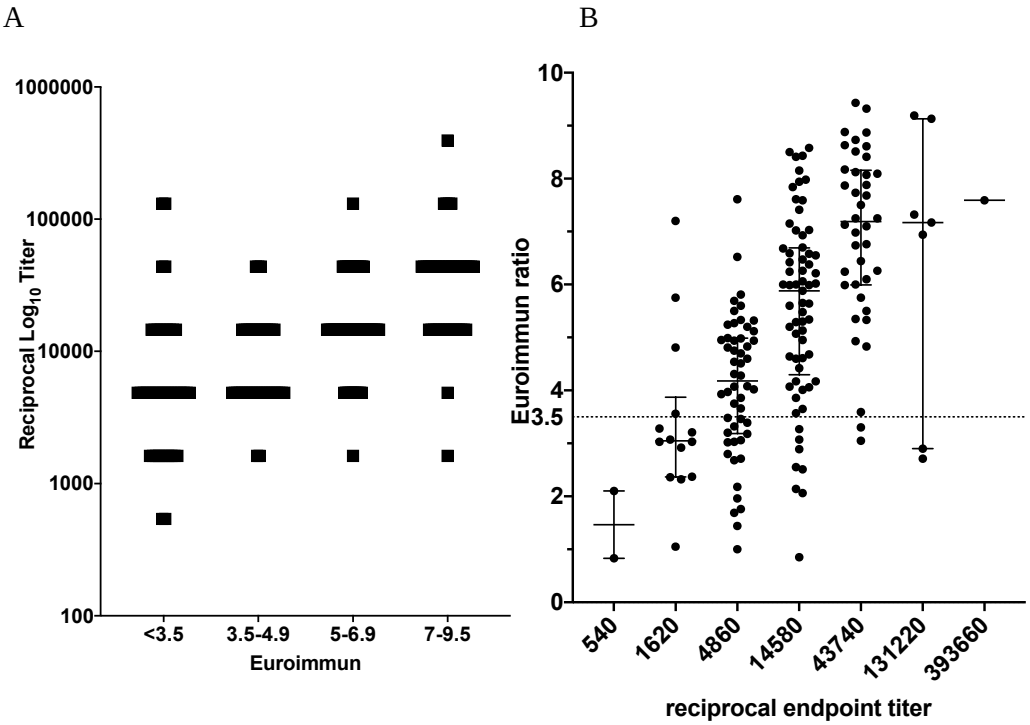


Figure 2A shows that for the EUROIMMUN ratios below 3.5 and also positive above 1:320 dilution that would not qualify for hospital high titer use, that the range of EPT from 540 to 131,220 exists in the 49 units below this ratio number. **Figure 2B** depicts the range of EUROIMMUN ratio for each reciprocal EPT with the median and lower and higher quartiles.

Specific Questions for the FDA

1. We propose, for the IND 19725 protocol (CSSC-004) in the early outpatient COVID-19 treatment in RCT, to restrict future study transfusions of convalescent plasma qualified in accord with a EUROIMMUN ratio greater than 3.5. Does the Agency concur?
2. Will adoption of this threshold pose any concerns for our trial CSSC-004 predicated regulatory approval of convalescent plasma product in the outpatient setting?

Desired Method of Feedback

We seek written feedback to our questions about the EUROIMMUN threshold. Please send feedback via email to Evan Bloch (ebloch2@jhmi.edu) and copy Daniel Amirault (damirault@jhmi.edu).

U.S. FOOD & DRUG ADMINISTRATION

Written Responses

Our Reference: IND 19725
CRMTS 13251

DATE: April 19, 2021 **PAGES:** 3

TO: Evan M. Bloch, MD, MS
Johns Hopkins University School of Medicine
1830 Monument Street, Suite 453
Baltimore, MD 21205
Email address: ebloch2@jhmi.edu

FROM: Sonday L. Kelly, MS, RAC, PMP
Chief, Regulatory Project Management Staff
Office of Blood Research and Review

SUBJECT: Guidance on the EUROIMMUN assay threshold of 3.5 OD ratio to qualify the investigational product

PRODUCT: Convalescent COVID-19 Plasma

PROPOSED INDICATION: Outpatient early treatment of COVID-19

FDA Participants:
Salim Haddad, MD, CRS/DBCD/OBRR
Orieji Illoh, MD, DBCD/OBRR
Carlos Villa, MD, PhD, CRS/DBCD/OBRR

We completed our review of your meeting package for Convalescent COVID-19 Plasma and are providing the following Written Responses to the questions you posed in the package.

Please be aware that your submission should include all components for a complete submission and should be in compliance with all appropriate statutes and regulations.

If you have any questions, please contact LCDR Kimberly Bissohong, at Kimberly.Bissohong@fda.hhs.gov or (301) 796-5350.

Please include a reference to IND 19725, CRMTS 13251 in your future submissions related to the subject product.

Written Responses

Johns Hopkins Question 1:
We propose, for the IND 19725 protocol (CSSC-004) in the early outpatient COVID-19 treatment in RCT, to restrict future study transfusions of convalescent plasma qualified in accord with a EUROIMMUN ratio greater than 3.5. Does the Agency concur?

FDA Response to Question 1:
Yes, we concur that a EUROIMMUN ratio of 3.5 (based on the Anti-SARS-CoV-2 ELISA (IgG) test) or greater may be used to qualify the study COVID-19 convalescent plasma (CCP).

Johns Hopkins Question 2:
Will adoption of this threshold pose any concerns for our trial CSSC-004 predicated regulatory approval of convalescent plasma product in the outpatient setting?

FDA Response to Question 2:
No, we do not have concerns with adoption of the proposed EUROIMMUN threshold with respect to the ability of data from CSSC-004 to support future regulatory submissions.

Additional FDA Questions/Comments:

1. Please clarify if the EUROIMMUN test will also be used to qualify the study CCP for CSSC-001.

2. Please submit an amendment describing the manufacturing change to use the EUROIMMUN assay.

END

Department of Pathology
600 North Wolfe Street
Baltimore, Maryland 21287-6417

JOHNS HOPKINS
MEDICINE
JOHNS HOPKINS
MEDICAL INSTITUTIONS

Attention: LCDR Bissohong
U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20993-0002

June 4, 2021

Re: IND 19725; "Convalescent Plasma to Stem Coronavirus: A Randomized, blinded Phase 2 Study Comparing the Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. control (SARS-CoV-2 non-immune plasma) among Adults Exposed to COVID-19," (CSSC-001) & "Convalescent Plasma to Limit Coronavirus Associated Complications: A Randomized, Double-Blind, Controlled, Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 nonimmune) Plasma Among Outpatients with Symptomatic COVID-19" (CSSC-004)

Dear LCDR Bissohong,

In this communication we are formally requesting a two month extension on the expiry of our qualified study convalescent plasma units, changing the expiration period from 12 months to 14 months.

We anticipate continuing enrollment through August 2021 with recruitment of up to 400 additional participants, half of which will receive convalescent plasma. We have about 100 qualified convalescent plasma units expiring at our active clinical trial sites during June, July and August. We foresee that the extension will have minimal impact on product safety and antibody levels in regards to our study. The extension will support use of the current supply through the end of enrollment. We seek urgent written yes/no feedback and the agency's approval of this IND 19725 plasma product expiration extension to 14 months.

Thank you once again for your continued responsiveness. Please feel free to contact me if any questions.

Sincerely

Evan M Bloch, MD, MS
Associate Professor of Pathology | Associate Director, Transfusion Medicine
Johns Hopkins University School of Medicine
Department of Pathology
600 N. Wolfe Street/Carnegie 446 D1, Baltimore, MD 21287
Ebloch2@jhmi.edu | Telephone: 410-614-4246

Our Reference: IND 19725

Johns Hopkins University School of Medicine
Attention: Evan M. Bloch, MD, MS
July 12, 2021
Sent by secure email: ebloch2@jhmi.edu

Dear Dr. Bloch:

Please refer to your investigational New Drug Application (IND) submitted March 19, 2020, received March 20, 2020, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Convalescent COVID-19 Plasma.”

Please also refer to your amendment dated and received July 6, 2021.

- Your request to extend the expiry of the study convalescent plasma from 12 to 15 months is acceptable.

If you have any questions, please contact me.

Thank you,

Kim Bissohong, MPH
LCDR, U.S. Public Health Service
Regulatory Health Project Manager

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Blood Research and Review
Tel: 301-796-5350
Kimberly.Bissohong@fda.hhs.gov

Our Reference: IND 19725

Johns Hopkins University School of Medicine
Attention: Evan M. Bloch, MD, MS
July 12, 2021
Sent by secure email: ebloch2@jhmi.edu

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If you have any questions, please contact me.

Thank you,

Kim Bissohong, MPH
LCDR, U.S. Public Health Service
Regulatory Health Project Manager

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Blood Research and Review
Tel: 301-796-5350
Kimberly.Bissohong@fda.hhs.gov

Instructions – LOCATOR Data Entry

Table of Contents

Introduction

The LOCATOR database is the primary EDC used to capture data regarding the Investigational Product (IP). LOCATOR acts as the unblinded side of the CSSC studies, and works with the 001 and 004 databases to assign units to enrolled patients. As a result, keeping LOCATOR clean and up-to-date is important to maintaining data integrity and patient safety.

Inventory Management

While the central IP operations team will be monitoring your plasma inventories, we also require blood bank personnel to also keep track of their own inventory levels, and to order more in anticipation of upcoming enrollments. At a minimum, we require blood banks to have at all times, for each plasma type (control and convalescent):

A	**B**	**AB**	**O**
2	1	1	2

However, during high enrollment times, we require:

A	**B**	**AB**	**O**
4	2	2	4

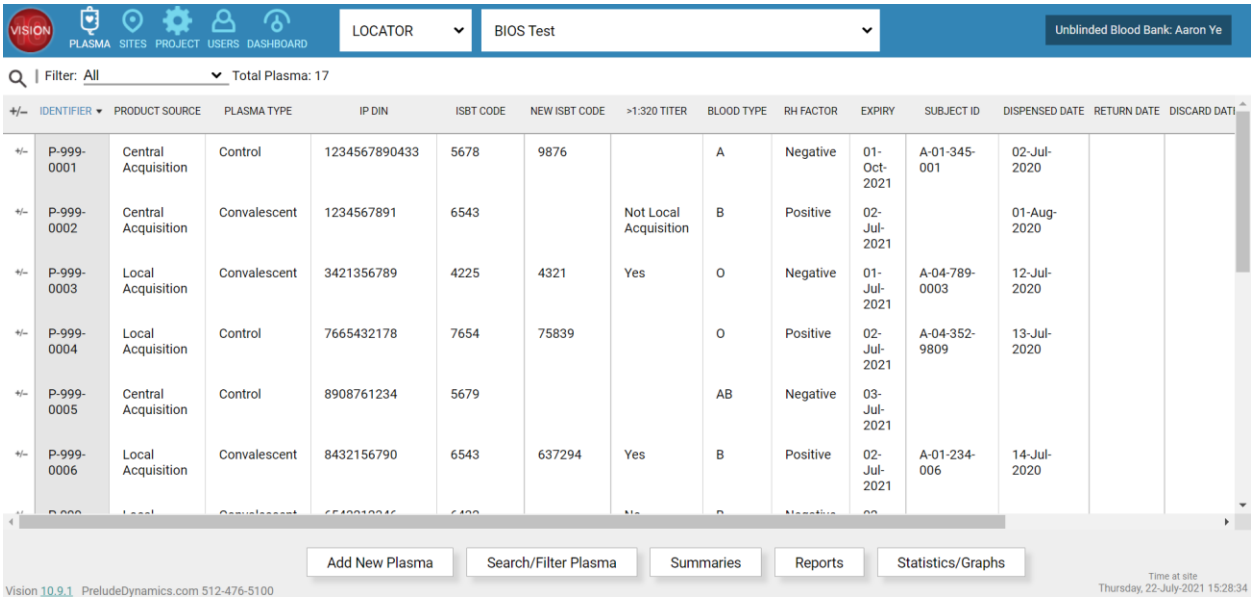
This allows us to ensure that your blood bank has enough plasma units in case more patients are randomized. When inventory drops below the indicated minimum, we will supply more units to your blood bank at your request.

To request more plasma from our central suppliers, fill out the Plasma Reorder form and send it to our central IP team. With the exception of weekends, your order should be delivered to you overnight, or the day after.

Purpose

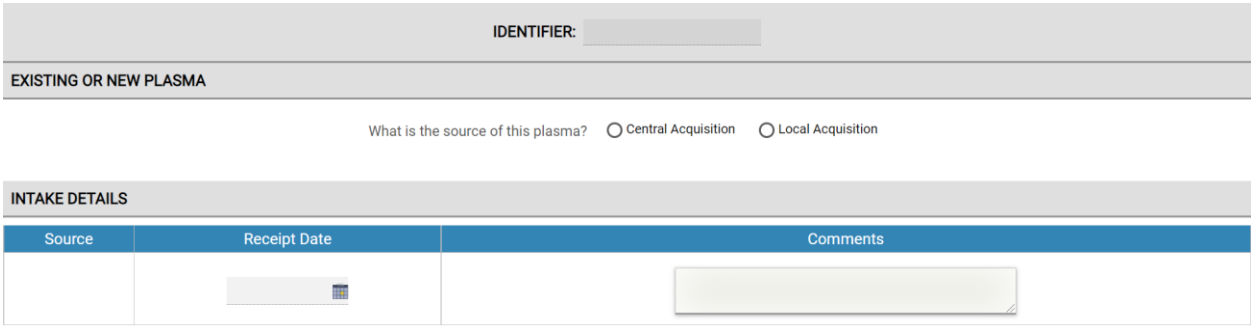
The primary purpose of this document is to detail the steps and procedures regarding data entry in LOCATOR. Each section of LOCATOR will be listed separately. Please follow the instructions provided in this document regarding when and where data should be entered.

Plasma Level: Main Plasma Page



Upon logging into LOCATOR, the main plasma page lists out all units that have been entered into the database for your site thus far. This page is an overview that allows the blood bank personnel to quickly find available units for dispense. Each unit that is created and documented in the database will appear on this overview page.

Screening – Plasma Intake



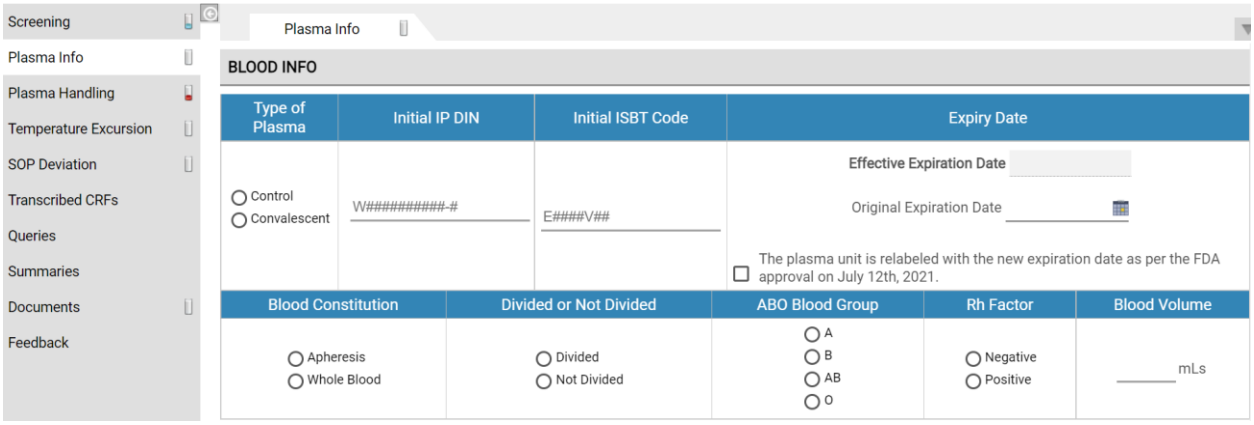
Upon the creation of a plasma unit, the first form to be filled out is the Plasma Intake form, in the Screening tab. Once this form is completed and saved by the blood bank, the unit will be listed in the site's LOCATOR page.

The fields to fill out in this form are:

- **Source of Plasma - Central or Local Acquisition**: If this unit was provided by a central supplier, including but not limited to Delmarva, Northshore, American Red Cross, Vitalent, DoD, and Impact Life, then "Central Acquisition" is the radio button that needs to be selected. Otherwise, if the blood bank obtained plasma through other local means, such as through a local hospital collection center, then the unit is considered "Local Acquisition".
- **Source**: If "Central Acquisition" is selected, indicate the supplier. This can be found on the packing slip of the received plasma shipment. Ensure that the name entered into this field matches the name on the packing slip *exactly*.
- **Receipt Date**: The date of receipt of the plasma units, not the date of data entry.
- **Comments**:
- **Enter the following shipping conditions upon receipt.**
    - Whether or not the IP is in acceptable frozen condition on Visual Inspection
    - Whether or not there is a sufficient amount of dry ice is present in the shipment box
    - If sites measure temperature on receipt, then the temperature is entered in the comments box.

Once this form is saved, the rest of the tabs will become available. Fill out the Plasma Info form at this time as well (next page).

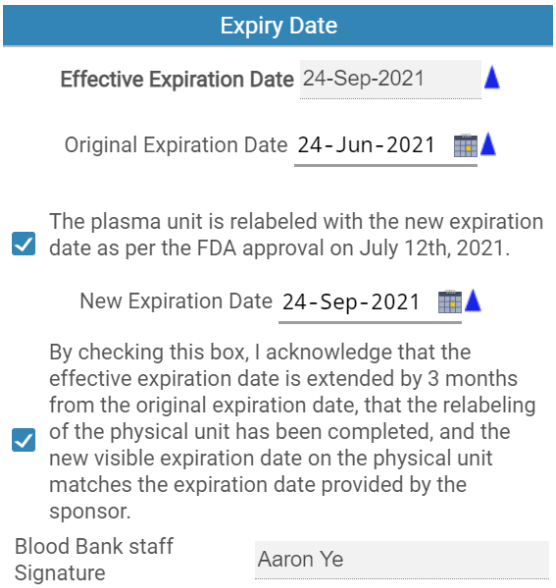
Plasma Info – Plasma Info



The Plasma Info form primarily holds information regarding the plasma unit itself. After a unit is created, it is important to fill out this form so that the sponsor IP team can keep track of inventory at your site. The information on this page is essential for IP Accountability and reporting. This form, along with the screening tab, must be completed upon receipt of the unit.

The Plasma Info form has 9 separate fields, as listed below.

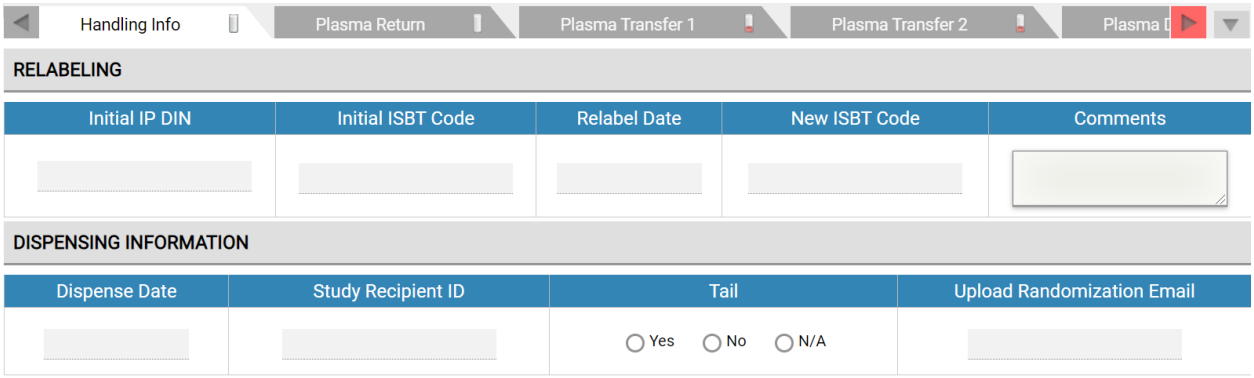
- **Type of Plasma**: Specify if this unit is a control plasma unit, or a convalescent plasma unit. Exact definitions of each can be found in the main CSSC-004 protocol version 9 and in the IP SOP version 12.
- **Initial IP DIN**: This is the DIN identifier of the plasma unit. It starts with "W" followed by 12-digit numbers. Some DIN numbers may have extensions where a hyphen and letter follow after the initial 13 characters, but for the purposes of this study, omit these extensions and enter only the "W" followed by 12 digits.
- **Initial ISBT Code**: The ISBT code of the unit is an identifier essential for differentiating between units from the same donor. It begins with an "E", followed by 4 digits, followed by "V", followed by a letter and a digit. Example: E9747VA0.
- **Expiry Date**: The expiry date field contains multiple types of expiration dates.
    - Original Expiration Date: The original expiration date of the plasma unit, which is 12 months from the donation date.
    - New Expiration Date: For convalescent units in the CSSC-004 study expiring in May, June, July, or August, an expiration date extension of 3 calendar months was approved by the FDA on July 12, 2021. Blood bank staff is required to check the box indicating that 3 months have been added to the unit, then enter in the new expiration date in the prompted field before checking the second box to sign.
    - Effective Expiration Date: The effective expiration date refers to the expiration date that should be used for the unit. This date is the original expiration date for most units, but becomes the new expiration date if a signature is detected for the expiration date extension.



- **Blood Constitution**: Whether the plasma unit is apheresis or whole blood.
- **Divided or Not Divided**: Was this plasma donation divided to multiple units?
- **ABO Blood Group**: The blood type (A, B, AB, O) of the plasma unit.
- **Rh Factor**: The Rh factor (positive or negative) of the plasma unit.
- **Blood Volume**: The volume of the plasma unit. Per protocol regulations, only units at or above 180ml are acceptable for dispense for CSSC patients.

Plasma Handling – Handling Info

The Handling Info is used for when plasma has been dispensed to a patient in the CSSC study. It is divided into two sections: relabeling and dispense. This form should be filled out whenever a plasma unit has been dispensed for CSSC patient transfusion and holds data regarding which patient received the product.



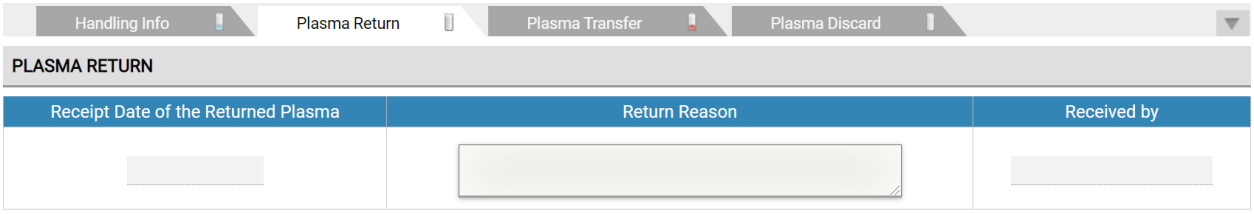
The following fields in this form are as follows:

- **Initial IP DIN**: this field automatically imports the DIN number filled in the Plasma Info form.
- **Initial ISBT Code**: This field automatically imports the ISBT code filled in the Plasma Info form.
- **Relabel Date**: The date in which relabeling of the plasma unit occurred.
- **New ISBT Code**: The new ISBT code that is relabeled.
- **Comments**: Optional comments you would like the monitor to know, or for note-keeping.
- **Dispense Date**: The date in which dispense of the plasma unit occurred.
- **Study Recipient ID**: The identifier of the patient receiving this plasma unit. You can find it on the randomization email or in the 001/004 EDC. It starts with an A, followed by the site number, followed by the patient number. This number is automatically assigned by VISION.
- **Tail**: A question reminding you about tail/segment collection. For all CCP units that are locally collected and not sent to JHU for titer testing, reserve a 1ml tail/segment and send to Yolanda Eby at the JHU laboratory. More instructions are found in the blood bank SOP.
- **Upload Randomization Email**: Upload the randomization email you received for the patient in which this unit is being assigned to. Randomization emails are sent out automatically by the VISION database once a patient is randomized.

There may be situations in which a plasma is dispensed but was not transfused, in which case this form should be filled out regardless, along with any other necessary forms (return/discard). If a second dispense occurs after the return of the first, a new dispense form should be created for that purpose by clicking the “Add New Form” button on the bottom. All forms in the Plasma Handling tab has the ability to create multiple copies of a form (repeating form feature).

Plasma Handling – Plasma Return

This form is used for plasma units returned to inventory. This can refer to plasma returned from the clinic to the local blood bank, or from the local blood bank back to the study's central suppliers (Delmarva, Northshore, etc). A few possible reasons for a plasma return include: transfusion reactions, withdrawing consent, or sponsor request.



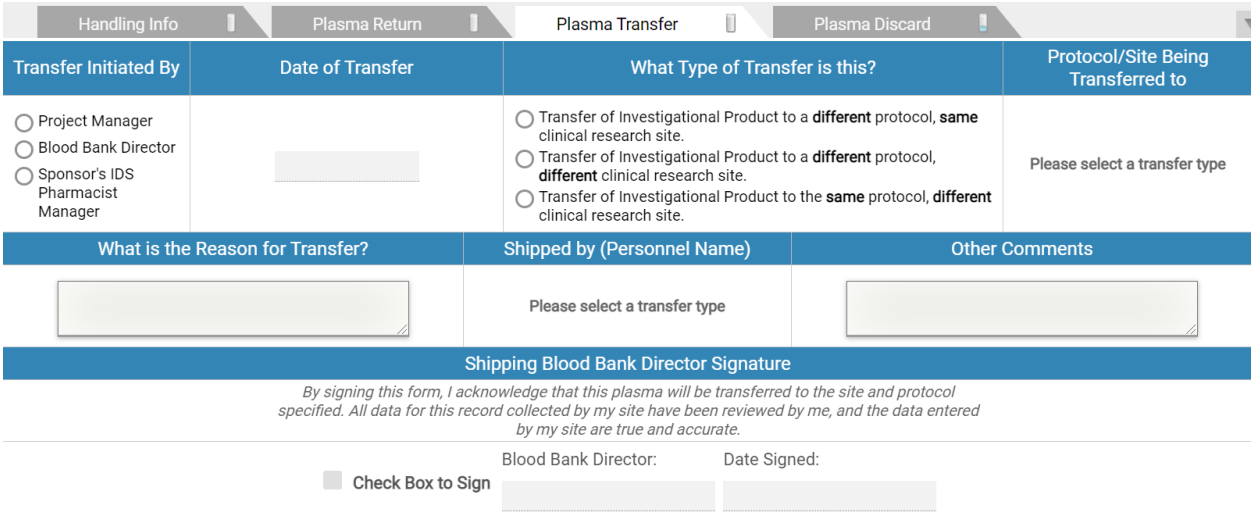
The following fields in this form are as follows:

- **Receipt Date of the Returned Plasma**: The date in which the plasma unit was received by the recipient. In most cases, the local blood bank will be receiving the returned unit.
- **Return Reason**: The reason in which the return was requested.
- **Received by**: Who was the one to receive the plasma unit?

Similar to other forms in the Plasma Handling tab, multiple Plasma Return forms can be created using the "Add New Form" on the bottom of the page.

Plasma Handling – Plasma Transfer

The Plasma Transfer form is used when units are transferred to either a different site or a different study. If the unit is moved to a different site, same protocol, then completing this form allows the project managers to electronically move the unit to another site's page. The form has two different sections; the former is to be filled out by the original blood bank, while the latter is to be filled out by the receiving blood bank.

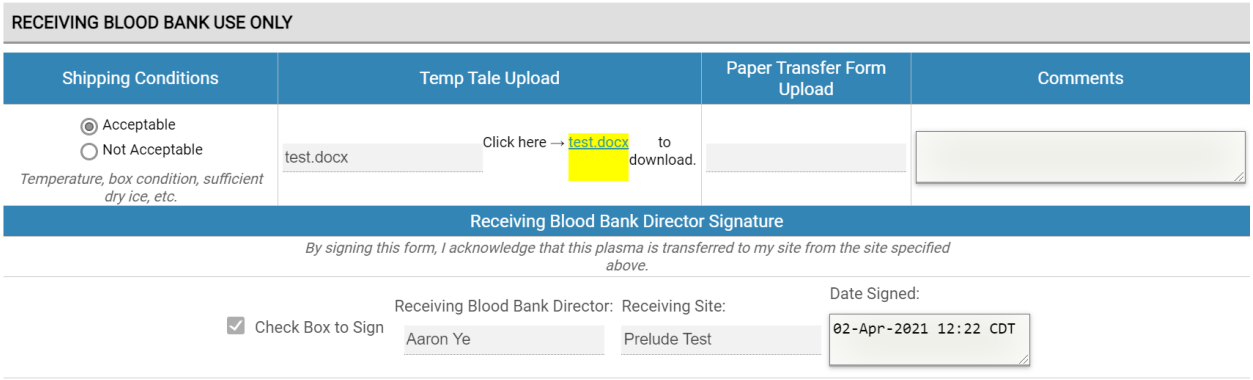


In the first section (image above), there are multiple fields for the shipping blood bank to fill out. The fields are as follows:

- **Transfer Initiated By**: Who was the one that requested the transfer?
- **Date of Transfer**: The date of the transfer/shipment.
- **What Type of Transfer is this?**: Indicate if it is the same or different protocol or site.
- **Protocol/Site Being Transferred to**: Depending on what type of transfer this is (previous question), you will be prompted to fill in a site or protocol number.
- **What is the Reason for Transfer**: The reason in which this transfer was initiated, i.e. sponsor request.
- **Shipped by (Personnel Name)**: The name of the person who conducted the shipment. This field is only required if the plasma unit was transferred to a different clinical site.
- **Other Comments**: Optional field for comments or note-keeping.
- **Shipping Blood Bank Director Signature**: By checking the box and hitting "save", LOCATOR will automatically fill in the name and date of the current user's signature. This field should be filled out by the blood bank director.

Once all the fields are filled out for all units being transferred, it is important to notify Anusha Yarava (ayarava1@jhu.edu) of the completion of the form. Please also send a list of units.

This next section is for the receiving blood bank.



Once a plasma unit has been moved to the new site's LOCATOR page, the receiving blood bank will have to fill out the rest of the form (image above). This part of the form will only be visible if the transfer was to a new site.

The following fields are:

- **Shipping Conditions**: Upon inspection of the package, are conditions acceptable? This includes temperature, box condition, sufficient dry ice, etc.
- **Temp Tale Upload**: Upload the temperature tale file that came with the shipping container, which tracks the temperature throughout shipment.
- **Paper Transfer Form Upload**: A corresponding paper transfer form should have been filled out for this shipment. Please upload it here.
- **Comments**: Optional comments.
- **Receiving Blood Bank Director Signature**: By checking the box and hitting "Save", LOCATOR will automatically store the signature of the user. This field should be filled out by the receiving blood bank director.

Once this portion is completed, please submit the form for review so that the monitors can finalize the form. Repeat this process for all units transferred to your site.

If multiple transfers occur, a new Transfer form can be added by the "Add New Form" button on the bottom. The procedure is exactly the same for any subsequent transfers.

Plasma Handling – Plasma Discard

The discard form is used when a unit has been discarded for any reason. Please refer to your hospital's SOP in discarding plasma. This form is not meant for any removal of units out of the inventory, but specifically when it is removed via discard.

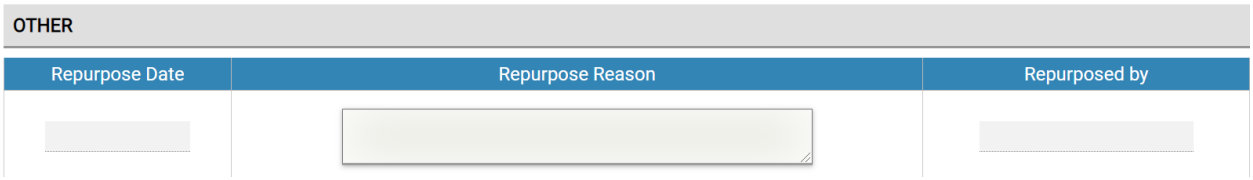
The following fields are:

- **Date**: The date of discard.
- **Reason**: The reason for discard.
- **Discarded by**: The name of the person who conducted the unit discard.

Similar to other forms, you can create multiple discard forms.

Plasma Handling – Other

The Other form is used when a unit is removed from inventory for any other reason that is not a dispense, return, or discard. Similar to the return and discard forms, the Other form asks for a date, reason, and name of staff.

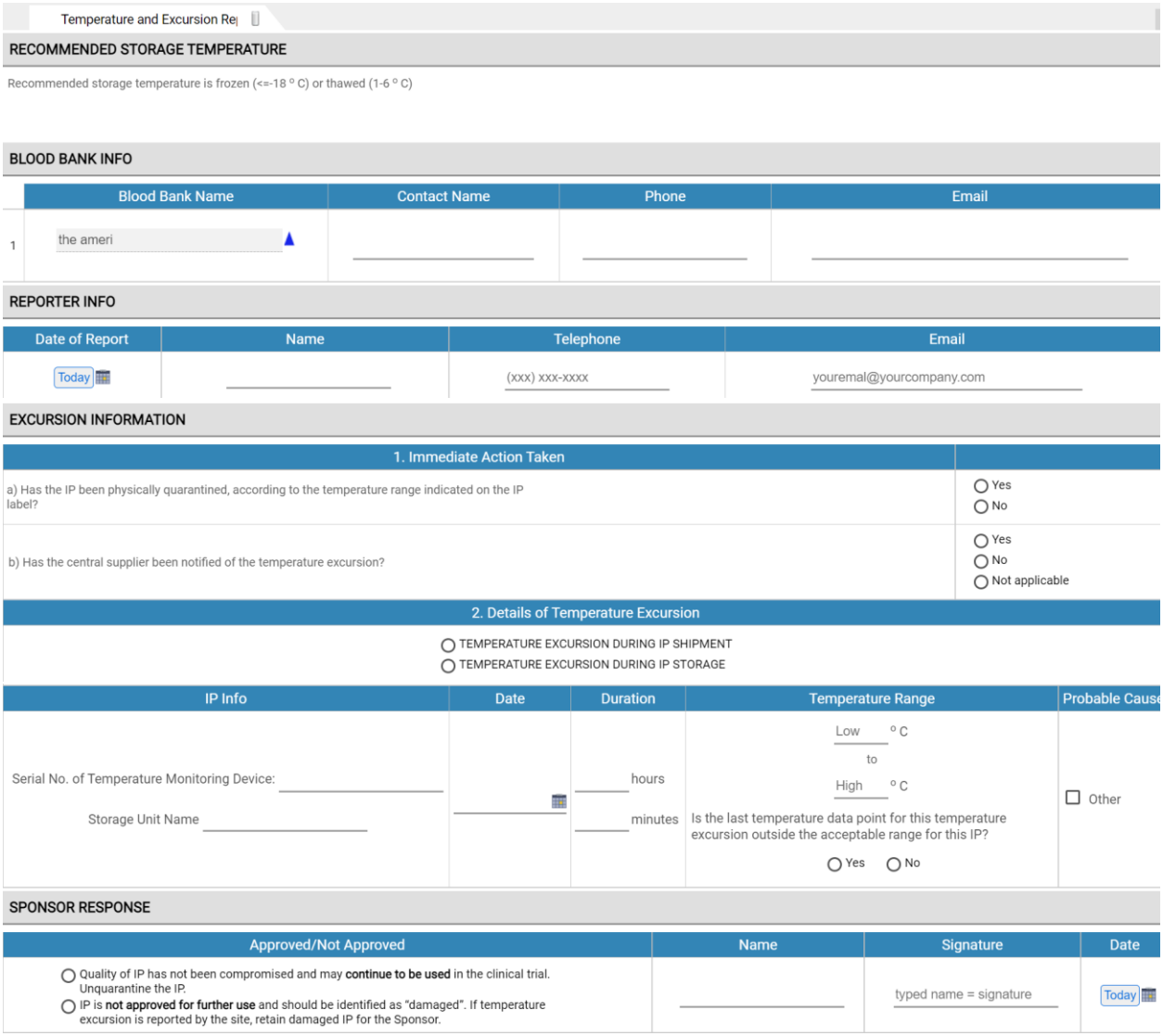


The following fields are:

- **Repurpose Date**: The date of removal from inventory.
- **Repurpose Reason**: The reason for removal from inventory.
- **Repurposed by**: The name of the person who removed this unit from inventory

This form is not on-demand or repeating.

Temperature Excursion



Temperature and Excursion Re

RECOMMENDED STORAGE TEMPERATURE

Recommended storage temperature is frozen (<=-18 ° C) or thawed (1-6 ° C)

BLOOD BANK INFO

	Blood Bank Name	Contact Name	Phone	Email
1	the ameri			

REPORTER INFO

Date of Report	Name	Telephone	Email
Today		(xxx) xxx-xxxx	youremal@yourcompany.com

EXCURSION INFORMATION

1. Immediate Action Taken	
a) Has the IP been physically quarantined, according to the temperature range indicated on the IP label?	○ Yes ○ No
b) Has the central supplier been notified of the temperature excursion?	○ Yes ○ No ○ Not applicable

2. Details of Temperature Excursion

○ TEMPERATURE EXCURSION DURING IP SHIPMENT
○ TEMPERATURE EXCURSION DURING IP STORAGE

IP Info	Date	Duration	Temperature Range	Probable Cause
Serial No. of Temperature Monitoring Device:		hours	Low ° C to High ° C	☐ Other
Storage Unit Name		minutes	Is the last temperature data point for this temperature excursion outside the acceptable range for this IP? ○ Yes ○ No	

SPONSOR RESPONSE

Approved/Not Approved	Name	Signature	Date
○ Quality of IP has not been compromised and may **continue to be used** in the clinical trial. Unquarantine the IP. ○ IP is **not approved for further use** and should be identified as "damaged". If temperature excursion is reported by the site, retain damaged IP for the Sponsor.		typed name = signature	Today

Upon a failure to maintain the proper storage temperature for frozen units, the temperature excursion form must be filled out to alert the sponsor. Specific details regarding the excursing must be filled out, along with notifying the sponsor IP team. The sponsor will then determine, at the bottom of the form, if the unit is acceptable for continued use, or must be discarded.

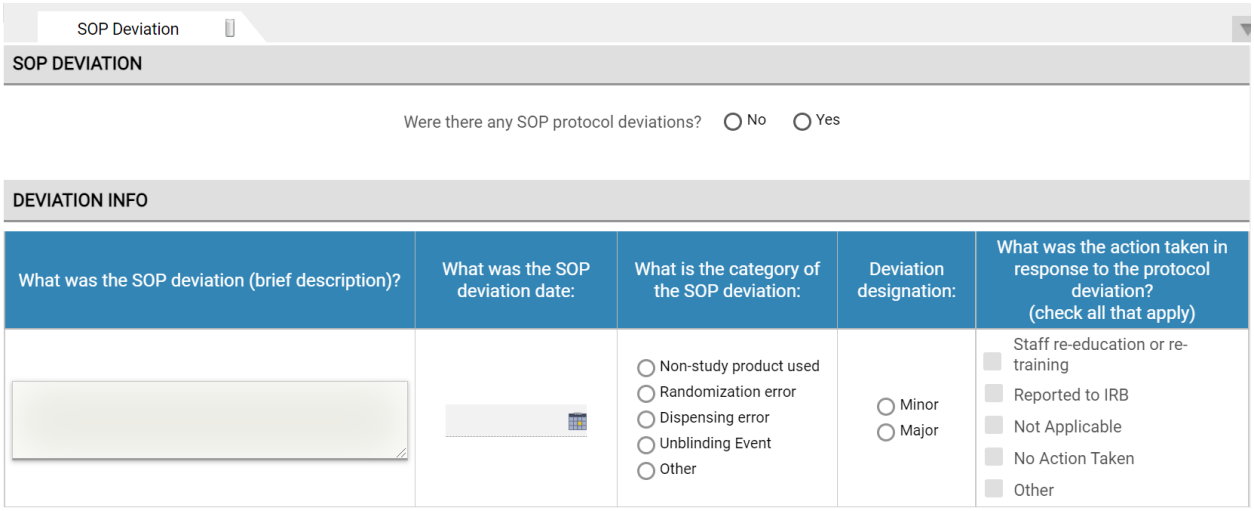
Below are the fields to fill out in the form:

- **Blood Bank Info - Blood Bank Name**: The name of the supplier. For centrally supplied plasma, some information will be automatically filled out in this row, such as Delmarva. However, unless the field is automatically filled out, Enter in the supplier name here.
- **Blood Bank Info - Contact Name**: The contact name associated with the supplier. This field may also be automatically filled out depending on what supplier was entered in the Screening tab.

- **Blood Bank Info - Phone**: The phone number associated with the supplier. This field may also be automatically filled out depending on what supplier was entered in the Screening tab.
- **Blood Bank Info – Email**: The email associated with the supplier. This field may also be automatically filled out depending on what supplier was entered in the Screening tab.
- **Reporter Info – Date of Report**: The date of when the temperature excursion was discovered and reported.
- **Reporter Info – Name**: The name of the person reporting the excursion.
- **Reporter Info – Telephone**: A phone number that can reach the person reporting the excursion.
- **Reporter Info – Email**: An email for the person reporting the excursion.
- **Has the IP been physically quarantined, according to the temperature range indicated on the IP label?** Mark Yes/No depending on if the unit has been quarantined separate from the main stock of plasma units reserved for the CSSC study. It must also be sequestered in the appropriate temperatures as indicated at the top of the form [frozen (<=-18 C) or thawed (1-6 C)].
- **Has the central supplier been notified of the temperature excursion?** The form, upon being filled out and saved, will send an automated email to the sponsor. However, it is still required for the blood bank to contact the sponsor IP team to notify them of the temperature excursion. This question is a reminder to contact the sponsor IP team.
- **Details of Temperature Excursion**: Indicate if the temperature excursion occurred during shipment or storage of the plasma unit.
- **IP Info - Serial No. of Temperature Monitoring Device**: Provide the serial number of the monitoring device that alerted staff of the temperature excursion.
- **IP Info – Storage Unit Name**: If the temperature excursion occurred during IP storage, provide the storage unit name.
- **Date**: The date of the temperature excursion (not to be confused with the date of report).
- **Duration**: Enter in the number of hours and minutes the temperature excursion lasted.
- **Temperature Range**: Indicate the highest and lowest temperature during the time entered in the “Duration: field.
- **Is the last temperature data point for this temperature excursion outside the acceptable range for this IP?**: Was the last recorded temperature from the monitoring device outside the acceptable temperature range as indicated at the top of the form [frozen (<=-18 C) or thawed (1-6 C)]?
- **Sponsor Response – Approved/Not Approved**: The fields under “Sponsor Response” should be filled out by the sponsor, not the blood bank. Once the rest of the form is completed, inform the sponsor via phone or email and our IP pharmacist will indicate whether the product has permission for continued use or not.
- **Sponsor Response – Name**: To be filled out by the sponsor. This field records the name of the IP Pharmacist who determined if the unit can be used for the study.
- **Sponsor Response – Signature**: A signature from the IP pharmacist indicating that the information and decision has been acknowledged.
- **Sponsor Response – Date**: The date of sponsor signature.

Once the form is saved, an automatic email will be sent to the central IP team.

SOP Deviation



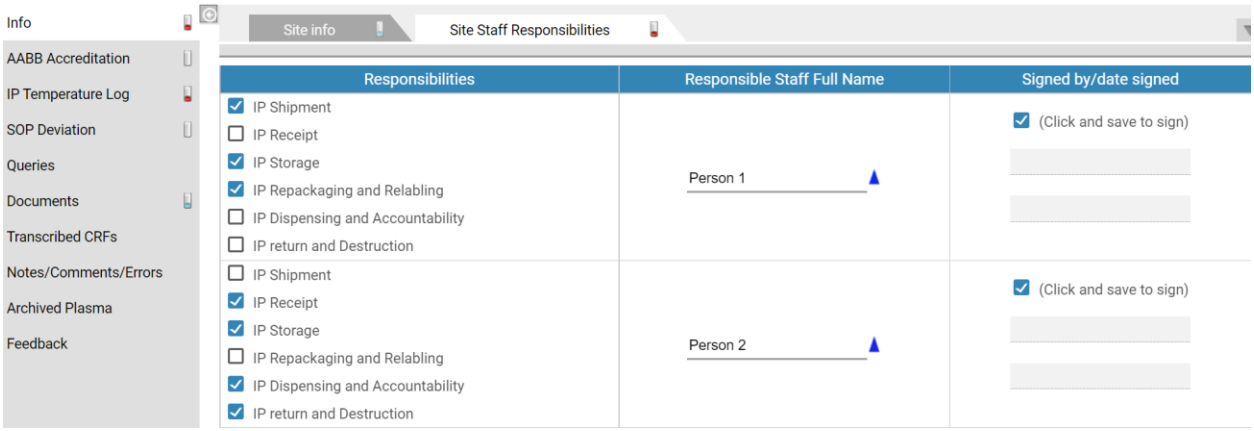
The SOP Deviation is filled out once a deviation from the described protocol IP SOP Manual occurs. Details regarding the deviation is recorded. Please inform the sponsor IP Operations team via phone or email upon completion of this form.

The following fields are as follows.

- **Were there any IP SOP protocol deviations?** Indicate if an SOP deviation occurred.
- **What was the SOP Deviation (brief description)?**: In a few sentences, explain what the deviation was and how it occurred.
- **What was the SOP deviation date?**: The date in which the SOP deviation occurred.
- **What is the category of the SOP deviation?**: Select from the options, or “other”.
    - Non-study product used: A unit outside of the study was transfused to a patient in the CSSC study.
    - Randomization error: A patient in the study was incorrectly randomized.
    - Dispensing error: A product was dispensed and thawed under incorrect procedures.
    - Unblinding event: A blinded study staff was unblinded.
- **Deviation Designation**: Was the deviation a major or minor deviation? Does this affect patient safety?
- **What was the action taken in response to the protocol deviation? (check all that apply)**: What responses were taken as a result of the SOP deviation?
    - Staff re-education or re-training: The blood bank staff was re-trained on the SOP and study protocol.
    - Reported to IRB: The SOP deviation was reported to the IRB.
    - Not Applicable: No action is required.
    - No Action Taken: Action is required but not taken.

Upon the event of an SOP deviation, please also inform the central IP team.

Site Level – Site Staff Responsibilities



In addition to the unit-level data, there are a number of site-level documentations that we require from sites. The first form that needs to be filled out is the Site Staff Responsibilities form. You can find this form by clicking on “Sites” on the top left of LOCATOR, selecting your site, then selecting “Site Staff Responsibilities” at the top.

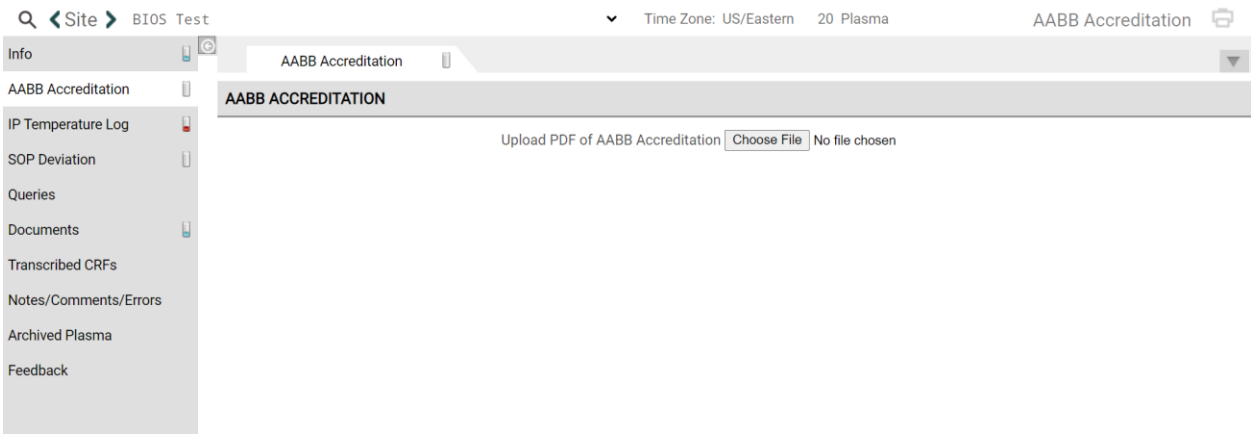
This form requires every member of your blood bank who is participating in the study or handling study IP product to enter his or her name in a separate row. The form requires 3 fields to be filled out by each blood bank person:

- **Responsibilities**: Select the duties that this person will perform. Multiple options can be selected.
    - IP Shipment: The shipping of IP product to other sites.
    - IP Receipt: The receipt of plasma sent to your site from our central suppliers, or from another site.
    - IP Storage: Responsible for the storage of IP product in the blood bank, ensuring that proper temperatures are maintained according to the SOP and protocol, and that IP temperature logs are uploaded weekly to the LOCATOR database.
    - IP Repackaging and Relabeling: Modifying the product (such as thawing) and relabeling it in preparation for a patient transfusion in the study.
    - IP Dispensing and Accountability: Dispensing the IP product after relabeling and responsible for the accountability of the IP product to ensure it reaches the patient safely and under proper conditions/temperatures. This person is also responsible for filling out the Handling Info form in LOCATOR.
    - IP Return and Destruction: In the event that an IP is requested to be returned to the blood bank or the sponsor central supplier, or is required to be destroyed for any reason, this person will be responsible for returning or discarding the IP product and appropriately marking it in LOCATOR.
- **Responsible Staff Full Name**: The name of the blood bank person.
- **Signed by/date signed**: Click the checkbox and click “Save” at the bottom of the form. The database will automatically record a signature and date of the user.

Site Level – AABB Accreditation

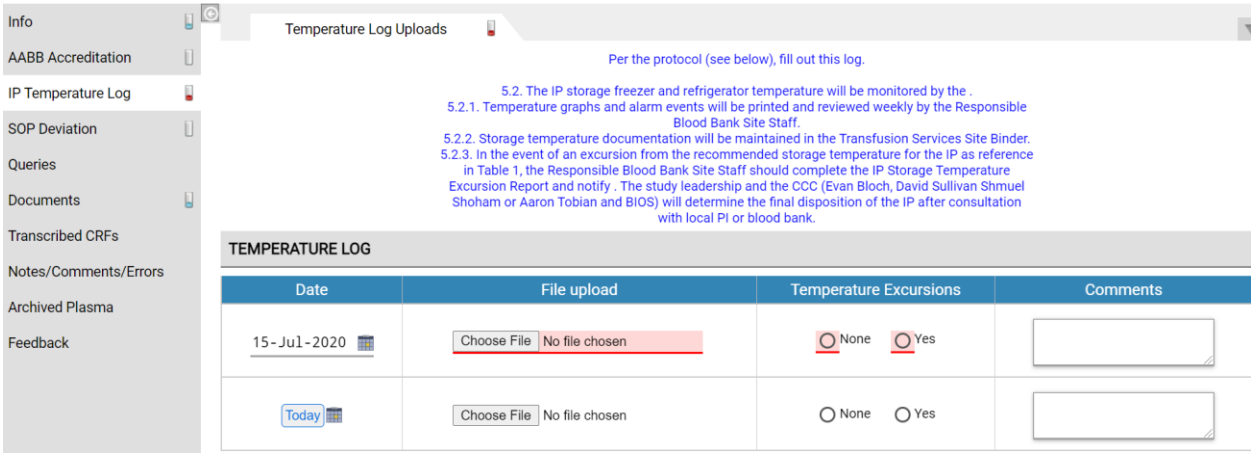
This form is a single upload field that records your blood bank's AABB Accreditation. If your blood bank has an alternative accreditation (such as CAP), please upload that in replacement. Be sure that the document uploaded in this field is up-to-date and current. If your accreditation expired and you need to replace it, please upload a new document in the same upload field, then upload the expired certificate in the "Other Docs" form (more information on "Other Docs" in the coming sections).

You can navigate to the AABB Accreditation form by select "Sites" at the top, selecting your site, then selecting the "AABB Accreditation" tab on the left.



Site Level – IP Temperature Log

It is a requirement for blood banks to enter weekly temperature logs onto the site level in the LOCATOR database. You can navigate to this form by selecting the "IP Temperature Log" tab on the left after navigating to the site level in LOCATOR.



For each freezer used to store the study's IP product, a temperature log covering the entire span of time must be uploaded *weekly*.

This form contains a repeating table. Once the form is saved, another row will appear for further uploads.

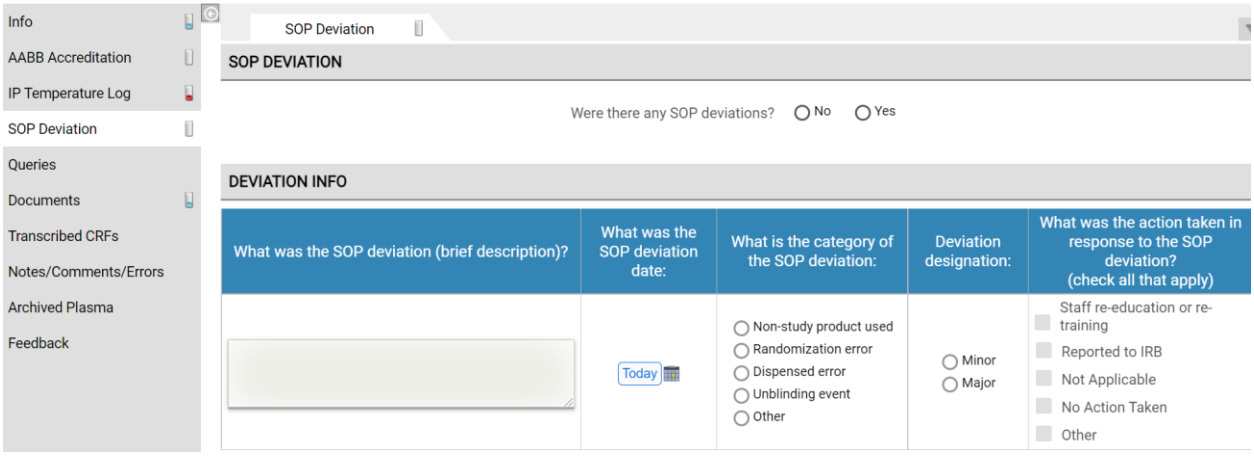
The form has the following fields:

- **Date**: The date of upload.
- **File Upload**: Contains an upload button which you can use to upload a temperature log.
- **Temperature Excursions**: During the period of time in which this temperature log covers, were there any temperature excursion events? If so, fill out the Temperature Excursion form on the site level for each unit that has been affected.
- **Comments**: Optional comments that you would like to inform the monitors of.

Monitors will be checking for temperature logs every week to ensure that the week's logs have been properly uploaded and maintained.

Site Level – SOP Deviation

In the event of an SOP or protocol deviation, please fill out the SOP Deviation form. This can be found on the site level after selecting "SOP Deviation" on the left. The form looks similar to the SOP Deviation form on the plasma unit level, but this form's purpose is to cover site level deviations. If a deviation occurs at your sitewide instead of for an individual unit, please fill out this form and inform the central IP team through email or phone call.

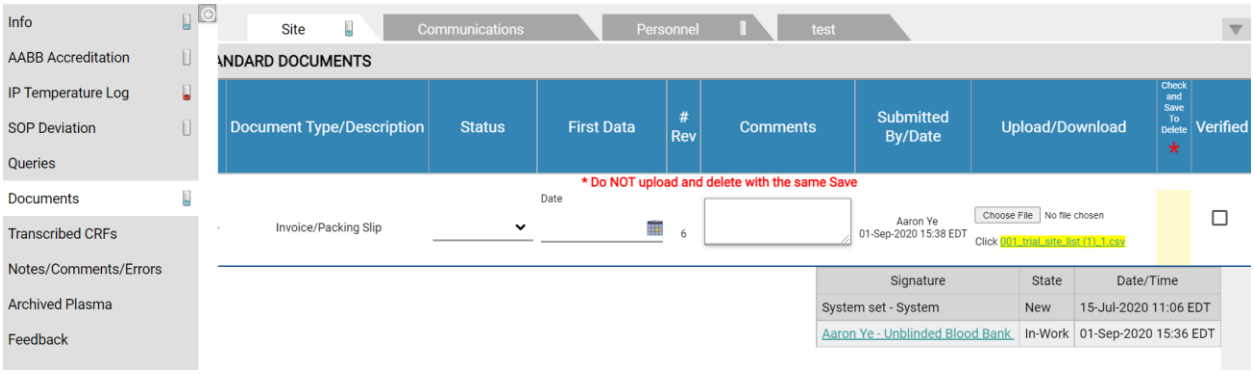


The fields in the form are as follows:

- **Were there any SOP protocol deviations?** Indicate if an SOP deviation occurred.
- **What was the SOP Deviation (brief description)?** In a few sentences, explain what the deviation was and how it occurred.
- **What was the SOP deviation date?** The date in which the SOP deviation occurred.
- **What is the category of the SOP deviation?** Select from the options, or "other".
    - Non-study product used: A unit outside of the study was transfused to a patient in the CSSC study.
    - Randomization error: A patient in the study was incorrectly randomized.
    - Dispensing error: A product was dispensed and thawed under incorrect procedures.
    - Unblinding event: A blinded study staff was unblinded.
- **Deviation Designation**: Was the deviation a major or minor deviation? Does this affect patient safety?
- **What was the action taken in response to the protocol deviation? (check all that apply)**: What responses were taken as a result of the SOP deviation?
    - Staff re-education or re-training: The blood bank staff was re-trained on the SOP and study protocol.
    - Reported to IRB: The SOP deviation was reported to the IRB.
    - Not Applicable: No action is required.
    - No Action Taken: Action is required but not taken.

Site Level – Documents: Site

Blood bank personnel must also upload packing slips for both local and centrally acquired plasma for the study. This serves as a primary source documentation for each unit in the blood bank inventory.



You can navigate to the uploading page by selecting “Documents” on the left. Ensure that you are on the “Site” form on the top.

To upload a packing slip, use the “choose file” button under Upload/Download and save. To upload a second document, use the same “choose file” button. It may appear as if the first document is being replaced, but that is not the case. Once you save, a +/- will appear on the left, which can be clicked to view all previous uploads.

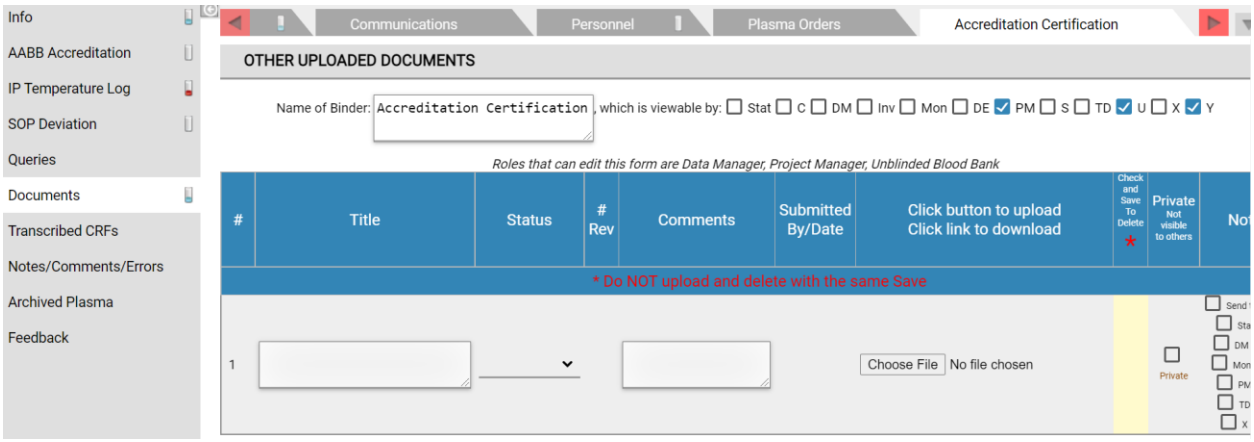
The following fields are:

- **Document Type/Description**: Automatically populated to be Invoice/Packing Slip.
- **Status**: You may select between Draft, Preliminary, or Final. If you will not be making any changes to the packing slip, use “Final”.
- **First Data**: Enter the date of the packing slip (not to be confused with date of upload).
- **Comments**: Optional comments.
- **Submitted By/Date**: Once the form is saved with a new upload, this field will record the user and the date of upload.
- **Upload/Download**: The upload field where you can upload your document. Clicking the link of an existing file will allow the download of the packing slip.
- **Click and Save to Delete**: To delete an uploaded document, select this checkbox and click “save”. This will not delete the entry itself, but it will delete the document upload to prevent others from viewing or downloading.
- **Verified**: A field for the central IP team to mark a packing slip as verified against the entered units in the LOCATOR page.

To ensure compliance with IP Accountability regulations, please sign your name and temperature upon receipt for each packing slip before uploading it to the LOCATOR database.

Site Level – Other Docs

The “Other Docs” form is used to store documentation of various forms. It is organized into binders which can be created and shared. There are two main binders that will be created: Plasma Orders and Accreditation Certifications. To access the forms, navigate to “Documents” and select the appropriate form from the top.



The following forms are as follows:

- **Plasma Orders**: For each reorder form request sent to the central IP team, the request form will be uploaded to keep track of all plasma units requested for your site’s inventory.
- **Accreditation Certification**: Upload your FDA registration, CAP or AABB Accreditation, and other expired certifications.

The following fields for each form are as follows:

- **Title**: The name of the document.
- **Status**: The status of the document, either Draft, Preliminary, or Final.
- **Comments**: Any optional comments.
- **Submitted By/Date**: Automatically records the upload date of the document and user name.
- **Click button to upload, Click link to download**: If there is no document uploaded yet for the row, use the “Choose File” button to upload a new document from your device. If a document already exists for the row, click the link to download it.
- **Click and Save to Delete**: Check the box and save the form to delete this upload entry. Note: this will not delete the row, but rather delete the document itself and prevent it from being viewed or downloaded.
- **Private (Not visible to others)**: Check this box and save the form to make it invisible to others.
- **Notify**: Check this box when uploading the document in order to notify users in certain database roles that the document has been uploaded.

Blood Bank Steps and Procedures

Upon receipt of the plasma unit, the unblinded blood bank staff should verify the IP shipping/invoice documentation and Documentation of receipt against the blood products shipped and receive them into inventory as defined by hospital procedures. This must be done immediately to prevent product damage. A new entry on the plasma level of your site must be created per unit received into the blood bank CSSC inventory. Select “Add Plasma” on the bottom of the Plasma Overview page to create a new unit. This will bring you to a blank Plasma Intake form.

Each unit will be automatically assigned by the EDC a discrete number that will be used for tracking the product within the VISION system.

Upon the completion of the plasma intake form, you will enter the unit information into the LOCATOR database. The other necessary form to fill out immediately is the Plasma Info form, where you will record all relevant information regarding the specific unit. Once completed, please submit both forms for review.

During or after entering all relevant units into LOCATOR for a particular shipment, upload the packing slip/documentation of receipt into the Documents section in the site level. This source document is important for IP accountability purposes. LOCATOR will keep track of all shipping documentation and packing slips.

It is expected that blood bank personnel will complete the tasks listed above within 48 hours of plasma receipt.

When a unit is dispensed to a patient, returned, discarded, transferred, etc, please follow the instructions in this manual for each form regarding how to fill them out. It is also required that you update the LOCATOR database with the appropriate information within 48 hours of the event.

All IP products will be shipped in compliance with appropriate local and federal regulatory agencies. IP products found to be out of compliance must be reported to the supplier and sponsor for notification and final disposition of the IP, as well as marked appropriately in the LOCATOR database (such as the temperature excursion form, discard form, etc., depending on how the unit is out of compliance).

All data in the LOCATOR EDC must have secured access limited to unblinded study staff.

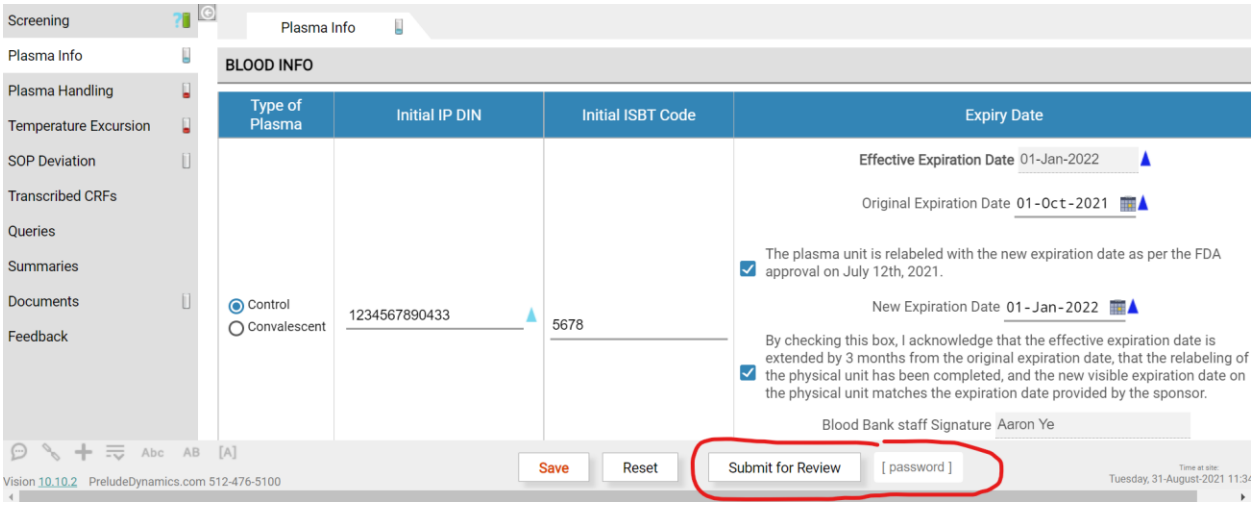
Form Completion

The VISION platform provides a system to track data entry and monitoring progress throughout the study. This is measured by the form completion metric, and visualized via the cylinders on each form.

Cylinder Color	Label	Definition
	In-Work - Errors	The form has been saved, but there are errors on the form that do not satisfy all constraints.
	In-Work	Data has been entered and the form is saved without any constraint errors.
	Submitted	Data has been entered and the form has been submitted for review.
	Reviewed	After the form is submitted, a monitor has reviewed the data.
	Finalized	After final review from the monitor, the form is marked as finalized. The site blood bank can no longer edit the information after form finalization.

After all data for a form is completed and saved, the form will be in-work. If there are errors on the form that do not satisfy constraints, the cylinder will be red. At this stage, please review the form errors, correct them appropriately, and re-save the form so that the cylinder turns blue.

Blood bank staff are required to submit the forms for review so that monitors can review the entered data. To do so, enter your password and utilize the “Submit for Review” button located at the bottom of the form. Before submitting, double-check to ensure that all data is entered correctly and accurately.



After submitting the form for review, the cylinder will turn orange. This will prompt the monitor to review the data and finalize the form. Once a form is reviewed and finalized, it is no longer possible for blood bank staff to edit data on the form, unless the monitor reverts the form status. All forms in the LOCATOR database must be eventually finalized.

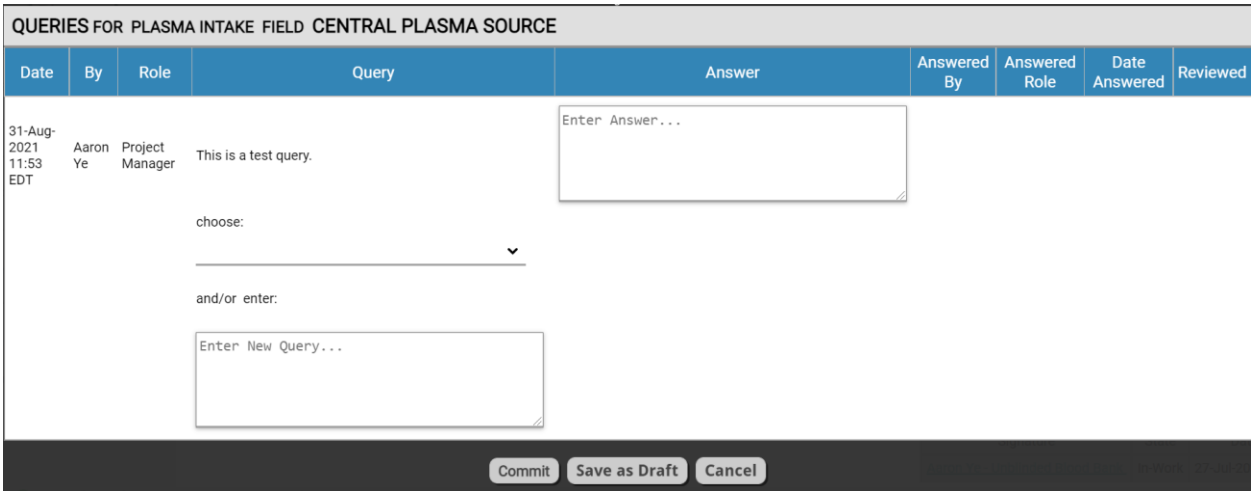
Queries

VISION's query system is utilized to track communications between the blood bank staff and monitors. It also maintains a record of all issues regarding data entry.

Question Color	Label	Definition
?	Unresolved	A new query generated by a monitor. This query has not yet been answered.
?	Resolved	The query has been resolved and answered by the site blood bank, but not yet reviewed.
?	Reviewed	The query answer has been reviewed by the assigned monitor and confirmed to be resolved.

Queries appear next to specific fields on a form. They are generated by the monitors when there is a question or suspicion of incorrect data entered into a field.

To view a query, click the question mark next to the field in question. It will show the query comments and any further discussions from the monitor. To answer a query, type in an answer in the answer box and click "commit" on the bottom of the window. The query will proceed to turn from red to blue.



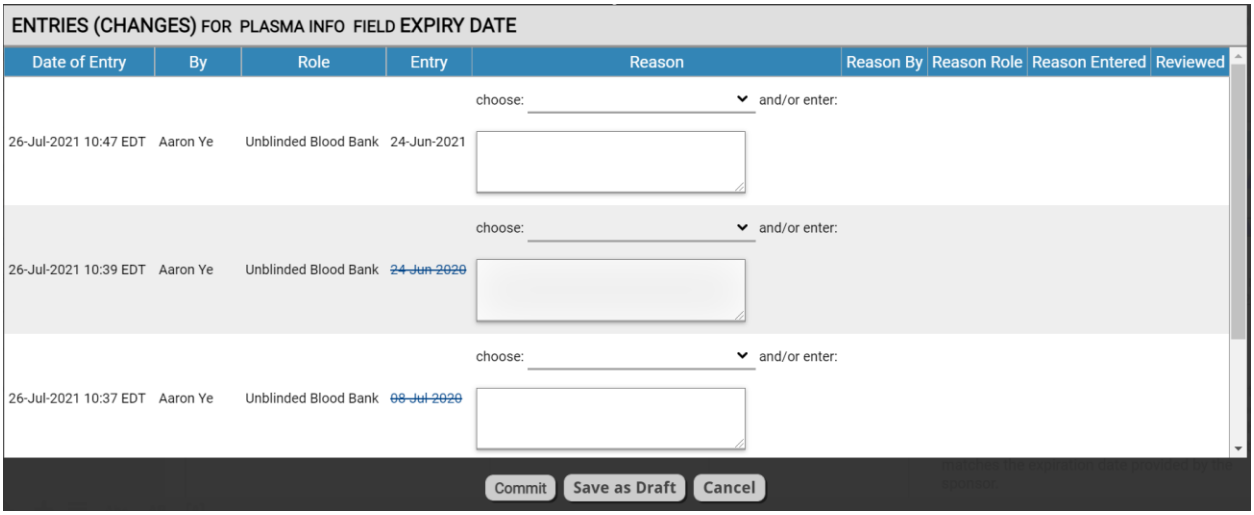
Please ensure to answer all pending queries (red), and check for queries at least once per week on a routine basis.

Audit Trail

Upon the change of any data in LOCATOR, an audit trail is recorded and displayed next to the appropriate field.

Question Color	Label	Definition
	Changed	A change has been made to the field. An answer may or may not have been entered.
	Reviewed	The change has been reviewed by monitors and confirmed.

Once a change has been made and the form re-saved, a blue triangle automatically appears next to the field. To view the specific change that was made, click the triangle to reveal a pop-up screen. The display will show all data that has been previously entered and what they have been changed to. If possible, enter in the reason for the change, so that monitors can review the change and confirm.



Investigational Product Team:

Document Author: Aaron Ye. M.S

Reviewed & Approved: Anusha Yarava, PharmD, MPH.

Date: August 5th 2021.

PROTOCOL TITLE:

Convalescent Plasma to Limit Coronavirus Associated Complications: A Randomized, Double-Blinded, Controlled, Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 non-immune) Plasma Among Adult Outpatients with Symptomatic COVID-19.

PROTOCOL NO.: CSSC-004

DOCUMENT: Investigational Product (SARS-CoV-2 convalescent plasma) Management Standard Operating Procedure

VERSION DATE: August 05, 2021

VERSION Number: 12.

DRAFTED BY:

Anusha Yarava	PharmD, MPH		August 5th 2021
Name	Title	Signature	Date

I have read and agree to this **Investigational Product (SARS-CoV-2 convalescent plasma) Management Standard Operating Procedure**

SITE PRINCIPAL INVESTIGATOR

Name	Title	Signature	Date

SITE BLOOD BANK APPROVAL:

Name	Title	Signature	Date