

STOP CP
WIRB Protocol # STOP CP001
Manual of Operations

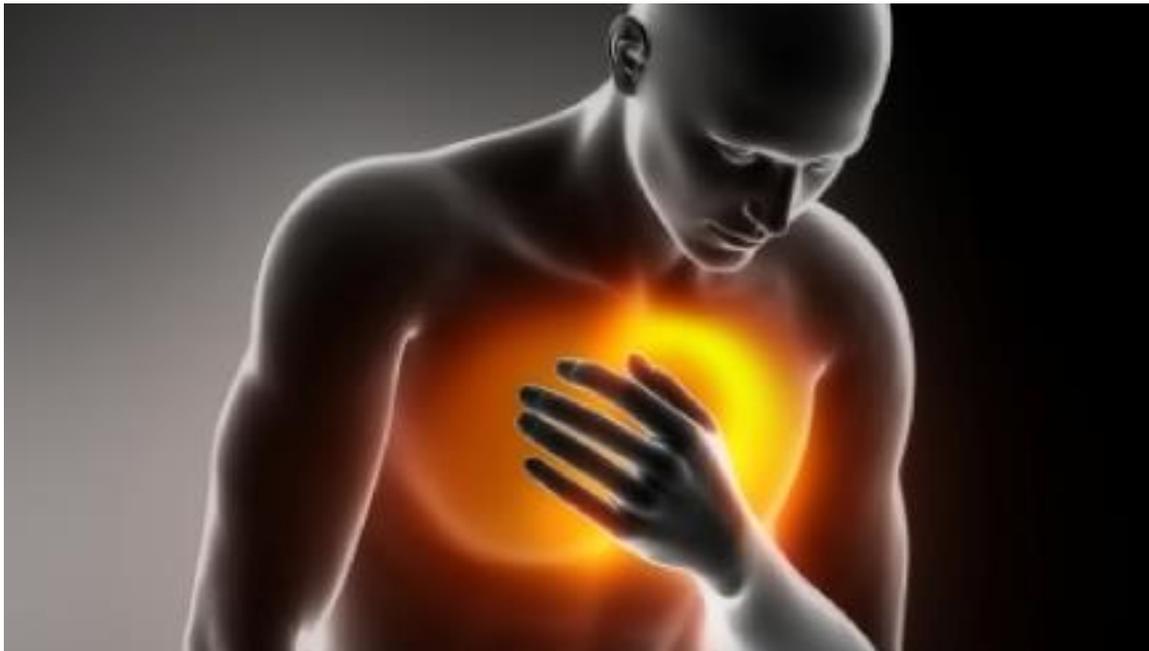


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1.0 Study Contacts

	Name	Address	Email	Phone
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Co-Principal Investigator	Simon Mahler, MD	Meads Hall Medical Center Blvd Winston-Salem, NC 27157	STOPCP-L@lists.ufl.edu	(336) 716-4626
Protocol	Clinical Coordinating Center Coordinator Bambi Arnold-Bush, MPH, PMP	1329 SW 16 th Street P.O. Box 100186 Gainesville, FL 32608	STOPCP-L@lists.ufl.edu	(352) 265-5911
Data Management and REDCap	Bioinformatics Bambi Arnold-Bush, MPH, PMP	1329 SW 16 th Street P.O. Box 100186 Gainesville, FL 32608	STOPCP-L@lists.ufl.edu	(352) 265-5911
Specimen Collection, Processing, and Shipping	University of Maryland Central Processing Laboratory Heather Rebeck	685 W Baltimore Street Baltimore, MD 21201	hrebuck@som.umaryland.edu	(410) 706-7734

1.1 Site Listing

Site Number	Site Name	Site ID
1	University of Florida	UF
2	Wake Forest University	WFU
3	University of Maryland	UMB
4	Henry Ford Health System	HFH
5	University of California, Davis	UCD
6	University of Utah	UTAH

2.0 Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria should be assessed prior to obtaining informed consent. Patients that meet any exclusion criteria should not be consented. If any of the exclusion criteria are met after the patient signs the informed consent the patient will remain in the study and will not be withdrawn.

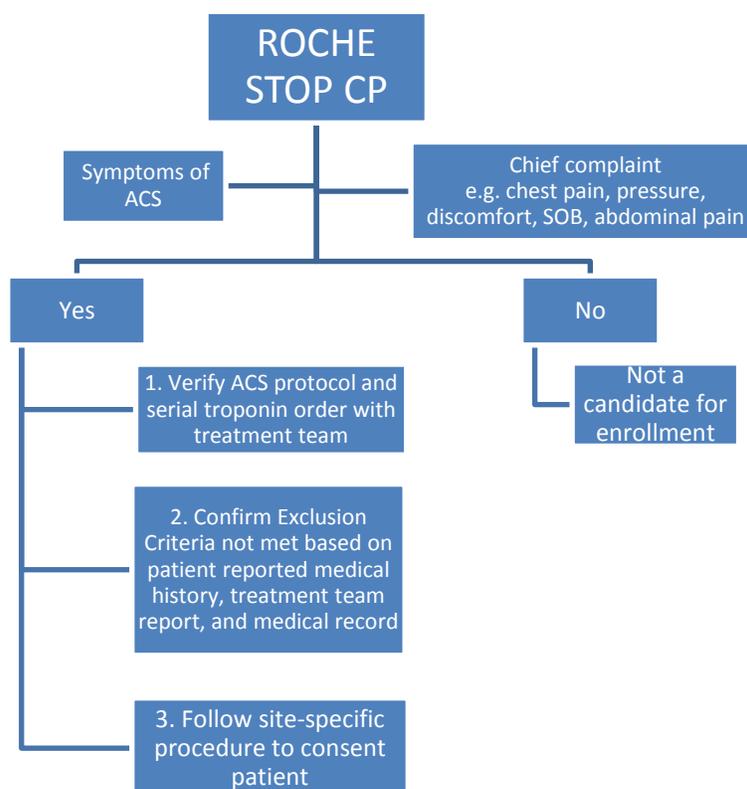
Study Criteria	<p>Inclusion Criteria</p> <ol style="list-style-type: none"> 1. Age greater than or equal to 21 years of age at the time of enrollment in the ED. 2. Chest discomfort or other symptoms consistent with possible ACS in which the treating physician plans to obtain an ECG and cTn for the patient's evaluation in the ED. <p>Exclusion Criteria</p> <ol style="list-style-type: none"> 1. New ST-segment elevation consistent with myocardial infarction. 2. Evidence of shock identified by the provider at the bedside and/or the PI. 3. Terminal diagnosis with life expectancy less than 90 days. 4. A non-cardiac medical, surgical, or psychiatric illness determined by the provider to require admission. 5. Prior enrollment in the STOP CP study. 6. Lack of capacity to provide consent and comply with study procedures. 7. Inability to be reliably reached after the index visit for follow-up. 8. Non-English speaking. 9. Pregnant patients. 10. Provider does not intend on obtaining serial cTn assays for evaluation of ACS. 11. The first study draw (T0) will exceed 1 hour after the site-specific standard of care troponin draw. 12. Unable or unwilling to authorize medical records release.
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3.0 Patient Recruiting and Retention

3.1 Patient Identification and Selection

All patients must be enrolled from the site's emergency department (ED). Study staff must be knowledgeable of the study, HIPAA-trained, and IRB-approved to screen presenting patients using a partial waiver of authorization to access medical records. Patients are to be screened and enrolled as early as possible following presentation at the ED. A screening log should be kept to track the reasons why patients were not selected for enrollment. No identifying information should be recorded on the screening log. A copy of the screening log is available on the study website.

Pre-screening may be performed using the following presenting characteristics:



3.2 Screen Failures and Screening Log

The screening log documents the effort of the study staff during the pre-enrollment process. Patients who are reviewed for inclusion/exclusion criteria and/or approached for the study should be recorded. No identifying information should be recorded in the screening log.

A patient who signed the informed consent form and ultimately met exclusion criteria, but did not undergo any study procedures (i.e., collection of a study blood draw) is a screen failure.

A patient who signed the informed consent form and did undergo study procedures (i.e., collection of a study blood draw) can be withdrawn if at the discretion of the site PI with consultation with the coordinating center.

The Participant Status form should be completed for patients that have signed the informed consent and are ultimately deemed screen failures or request to withdrawal from the study.

If medical records were reviewed and it was determined that the patient met exclusion criteria the patient is also considered a screen failure. No participant ID should be assigned, but the reason he patient met exclusion criteria should be documented in the screening log.

An electronic copy of the Screening Log template can be found on the STOP CP website.

3.3 Informed Consent, Banking Addendum, and Medical Records Release

Each site is responsible for conducting the informed consent discussion using a WIRB/IRB approved informed consent form (ICF). Potential participants must be able to consent for themselves. There is no Legally Authorized Representative (LAR) designated on the authorization of informed consent page. The Banking Addendum should also be signed with a clear indication of whether or not the participant consents to allow their leftover blood to be used for future research.

After the participant signs the ICF, an Authorization for Release of Medical Records (ARMR) form should be signed. Only the patients name should be printed on the top portion of the ARMOR, the rest should be left blank for now, as this will be completed at the time of requesting the release of medical records.

After the ICF, Banking Addendum, and Authorization for Release of Medical Records form are signed each site must:

1. Maintain the original signed ICF and ARMOR in a locked cabinet
2. Upload the signed ICF and ARMOR in REDCap using the appropriate field on the Patient Information form.
3. Provide a copy of the signed ICF and ARMOR to the participant
4. Scan the signed ICF and ARMOR into medical record (if applicable to your site specific regulatory requirements)

3.4 Assignment of Participant ID

Participant ID's should be assigned in sequential order in REDCap. Participant ID's are unique participant identifiers and cannot be re-assigned if a participant withdraws from the study. The Enrollment Log report (sorted in descending order) in REDCap should be used to identify the next available participant ID. Every patient that signs an ICF should be assigned a Participant ID.

3.5 Criteria for Exclusion from Primary Analysis, Withdrawal and Replacement

Criteria for exclusion from the study primary analysis include:

1. Inability to obtain a serial cTn measure 2-12 hours after the initial blood draw as part of routine clinical care, except in patients with an initial positive cTn measure.
2. Failure to obtain at least two study-specific blood samples within the protocol timeframe detailed in protocol section 7.4-7.8 and 8.1-8.4.

We will replace any participants that meet the criteria for exclusion from analysis until the goal enrollment of 1,500 participants is reached across all sites. The Participant Status form should be completed for any participant that meets the criteria for exclusion from the primary analysis.

If there is any concern regarding a participant's ability to remain in the study due to safety concerns related to the required blood draws (e.g. anemia, participant will be receiving a blood transfusion, etc.) the treating provider should be consulted regarding the participants ability to provide blood for the study. If the treating provider recommends that further blood samples should not be drawn the site PI and coordinating center should be notified prior to withdrawing the participant.

Once a participant has been excluded from primary analysis or withdrawn their participant ID cannot be used again. The Participant Status form in REDCap must be completed for any participant that requests to be withdrawn or is withdrawn at PI discretion.

3.6 Lost to Follow-up

If a participant is unable to be contacted at the 30 day follow-up and again at the 90 day follow-up via all provided means of communication (three attempted phone contacts, email, and letter) the ARMR form should be used to obtain more information about the participant's status and medical history since completion of their Index Visit. The ARMR form can be used to obtain the participant's medical records from their primary care provider or other local hospital or healthcare facility in order to obtain follow-up medical history for the participant since completion of their Index Visit.

If a participant's follow-up history is unable to be obtained via the methods described above, then the participant will be considered lost to follow-up. Participants that are lost to follow-up will not be replaced in this study, therefore every attempt should be made to reach the participant and/or obtain their medical records since the completion of the Index Visit.

4.0 Blood Sample Collection

4.1 Blood Sample Collection Kits

Blood sample collection kits are sent to your facility from the University of Maryland, Baltimore CCRL (UMB CCRL). Each site is responsible for ordering kits as needed. Kits can be ordered by emailing hrebuck@som.umaryland.edu.

4.1.1 Kit Components

One participant kit is packaged in a large bag that contains four smaller bags, each with the following components in each of the smaller bags:

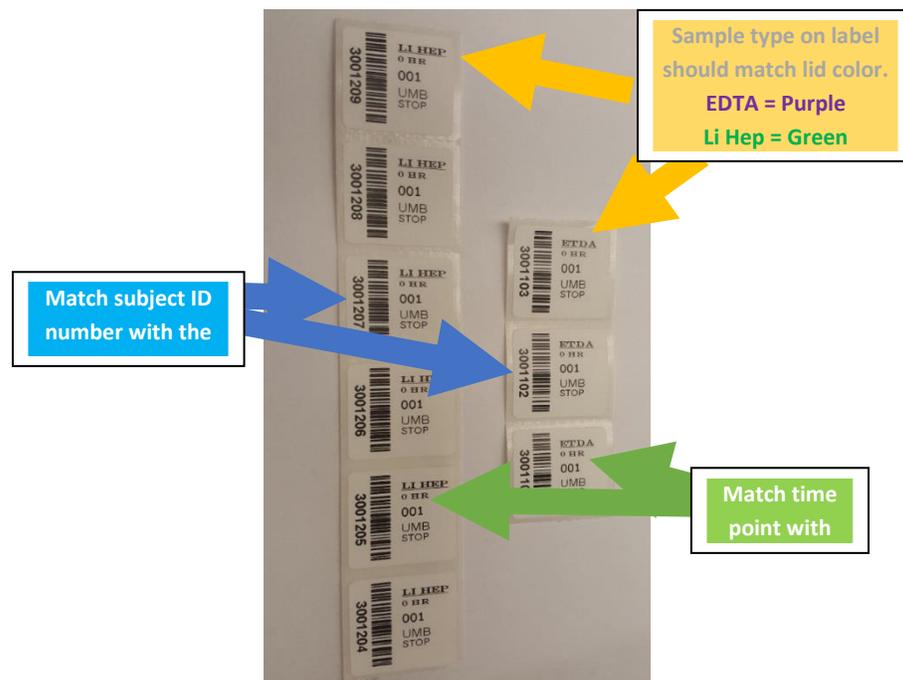
- (1) One - 6.0ml EDTA vacutainer
- (1) One – 5.5ml Lithium Heparin vacutainer
- (2) Two graduated disposable pipettes
- (12) Twelve sample vials
 - (6) Six purple or pink caps
 - (6) Six green caps

Use one participant kit with the components listed above for each one enrolled participant at draw time – T0, T1, T2, and T3. All kits are identical.

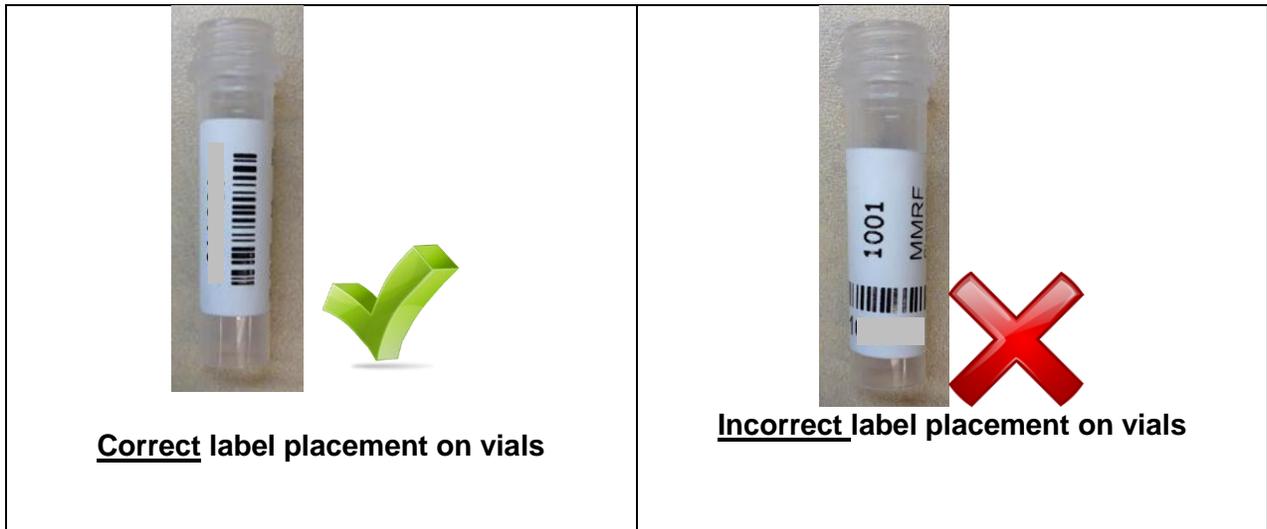
4.1.2 Labeling Vials

Use the roll of labels provided to label the vials. Be sure to match the correct label, paying attention to the anticoagulant for your aliquots!

Each label will have a seven digit number under the barcode. The first number indicates your site number, the next three numbers correspond to the participant ID. The next number identifies the tube as an EDTA (1) or a Lithium Heparin (2) tube, followed by the number identifying the time point of the blood draw (0-3) and the final number is the aliquot number (1-6).

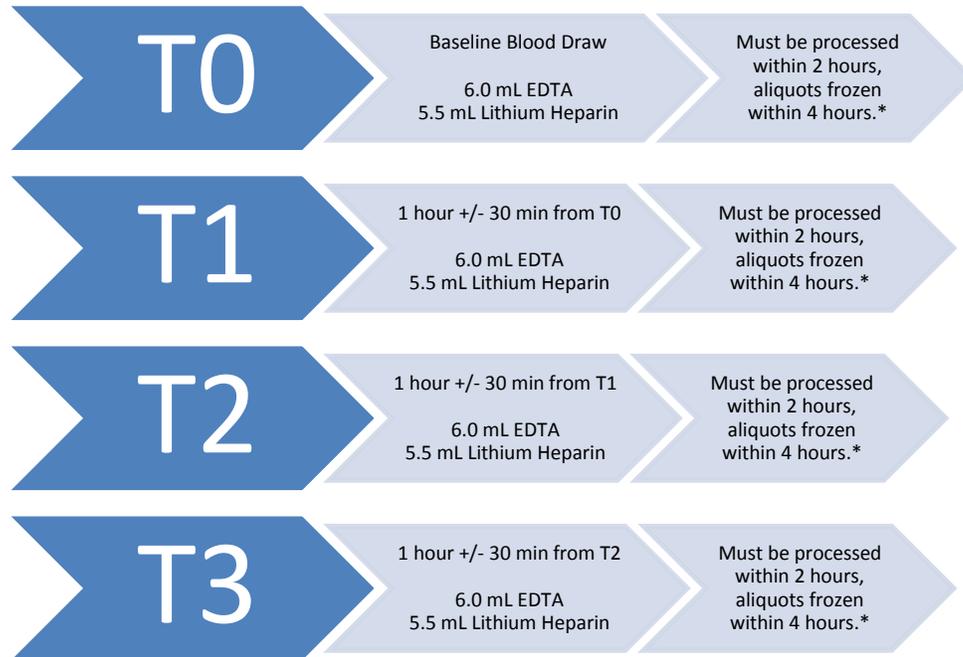


Place the label on the vial so that the barcode is **vertical** along the side of the vial **NOT horizontal**. Otherwise, the barcode will not be able to be scanned*.



4.2 Blood Draws and Processing

Samples should be obtained using the kit provided by University of Maryland, Baltimore CCRL. The Blood Collection form should be completed in conjunction with each timed blood draw.



4.2.1 Blood Draw Procedure

Use standard venipuncture techniques in accordance with institutional standards and requirements to collect blood. The maximum amount of blood drawn from any participant will not exceed 48 mL.

Note that the time of draw is calculated from the time of the previous blood draw, i.e. T1 is calculated from T0, T2 from T1, and T3 from T2.

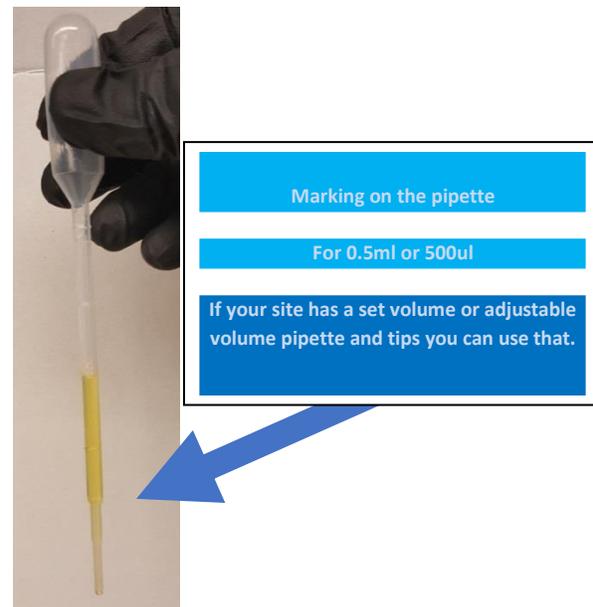
The timeframe for each sample collection is outlined in sections 7.4-7.8 and 8.1-8.4 of the protocol. Missing a draw should be avoided, however, in the event that one of the sample collections is missed the next sample in sequence should be collected within the timeframe required for the next sample collection (e.g., if T1 is missed then T2 should be collected within 1 hour (+/- 30 minutes) of the time when T1 should have been collected).

If the participant cannot provide enough blood to fill the 5.5ml Li Hep vacutainer or the 6.0ml EDTA vacutainer, a venipuncture should be done on the other arm to try to obtain the full amount of blood required for each draw. If there is still difficulty in obtaining the required amount of blood additional attempts can be made as long as they fall into the collection time window. At a minimum the T0 draw is required followed by at least one additional sample collection within the protocol defined window. The number of aliquot vials filled should be recorded on the blood collection form in REDCap.

4.2.2 Blood Sample Processing

Each sample must be centrifuged within 2 hours of collection, and then aliquotted and frozen within 4 hours of collection.

1. Mix the EDTA and lithium heparin tubes well by inverting 8-10 times to ensure the anticoagulant is dispersed throughout the sample.
Inversion technique: An inversion is one complete turn of the wrist, 180 degrees, and back. Tubes should be inverted according to recommendations.
2. Centrifuge each tube at 1000-1300 x g (g-force) for 10 to 15 minutes. Older centrifuges may only use RPMs and may not automatically convert to g-force. Verify your centrifuge automatically converts RPMs to g-force. If not, locate the User Guide and/or User Manual and check to see if a conversion table is contained within for RPM to g-force. If not, check the manufacturer's website for this information or check with your bioengineering group.
3. Use the **graduated pipette**, transfer **0.5ml** of the resulting pale yellow plasma layer into each cryovial in the kit. Use 1 pipette for each sample type – EDTA and Li Hep
4. Cap the EDTA vials with the **PURPLE/PINK** lids
5. Cap the lithium heparin vials with the **GREEN** lids



4.3 Recording Samples on the Specimen Tracker

All aliquots must be recorded on the Specimen Tracker as illustrated below. This form is downloadable and located on the STOP CP website. The completed Specimen Tracker form is required to be included in the shipment of vials to the UMB CCRL. The Specimen Tracker report in REDCap can be generated into an Excel file and then relevant information can be copied into this spreadsheet.

Enter site number and shipping date here.

At each time point – 0hr, 1hr, 2hr, and 3hr – enter the number of aliquots you have for each sample type.

Fill out form as samples are collected.

Send original to UMB lab with Shipping Form and keep a copy for your records

Site # _____		# of cryovials T0		# of cryovials T1		# of cryovials T2		# of cryovials T3			
Shipping date:		EDTA	Lithium Heparin	Total # of cryovials	Cryovial box #						
Subject ID #	Enrollment Date										
7 (EXAMPLE)	11/11/2016	3	6	3	6	3	6	3	6	36	1

Subject number and enrollment date entered here.

Note that there are 2 sample types that need to have the aliquots recorded.

Record the total number of aliquots you are sending for the subject and the box in which they are located.

START WITH BOX 1 after each shipment.

FEDEX Tracking number: _____

Enter FedEx number at bottom of form.

4.4 Blood Sample Placement in Cryovial Box

Place all cryovials from each participant in consecutive order (as depicted below) by placing the time points one after the other, from left to right in each row, in the sample box. Start with the EDTA vials for each time point. Participant cryovials may carry over into another box as long as the same sequence is maintained.

See **Table A** below for a visual aid.

(back of box)

EDTA Subject 2 time 2hr	Li Hep Subject 2 time 2hr	Li Hep Subject 2 time 2hr	Li Hep Subject 2 time 2hr					
EDTA Subject 2 time 1hr	EDTA Subject 2 time 1hr	EDTA Subject 2 time 1hr	Li Hep Subject 2 time 1hr	Li Hep Subject 2 time 1hr	Li Hep Subject 2 time 1hr	Li Hep Subject 2 time 1hr	Li Hep Subject 2 time 1hr	Li Hep Subject 2 time 1hr
Li Hep Subject 2 time 0	EDTA Subject 2 time 1hr	EDTA Subject 2 time 1hr	EDTA Subject 2 time 1hr					
Li Hep Subject 1 time 3hr	Li Hep Subject 1 time 3hr	Li Hep Subject 1 time 3hr	EDTA Subject 2 time 0					
EDTA Subject 1 time 3hr	Li Hep Subject 1 time 3hr	Li Hep Subject 1 time 3hr	Li Hep Subject 1 time 3hr					
EDTA Subject 1 time 2hr	EDTA Subject 1 time 2hr	EDTA Subject 1 time 2hr	Li Hep Subject 1 time 2hr	Li Hep Subject 1 time 2hr	Li Hep Subject 1 time 2hr	Li Hep Subject 1 time 2hr	Li Hep Subject 1 time 2hr	Li Hep Subject 1 time 2hr
Li Hep Subject 1 time 1hr	EDTA Subject 1 time 2hr	EDTA Subject 1 time 2hr	EDTA Subject 1 time 2hr					
Li Hep Subject 1 time 0	Li Hep Subject 1 time 0	Li Hep Subject 1 time 0	EDTA Subject 1 time 1hr					
EDTA Subject 1 time 0	Li Hep Subject 1 time 0	Li Hep Subject 1 time 0	Li Hep Subject 1 time 0					

(front of box)

TABLE A

Start here!

Note: If there are any questions about any of the processing components, do not hesitate to contact the UMB CCBL at email: hrebuck@som.umaryland.edu or call **410-706-7734**.

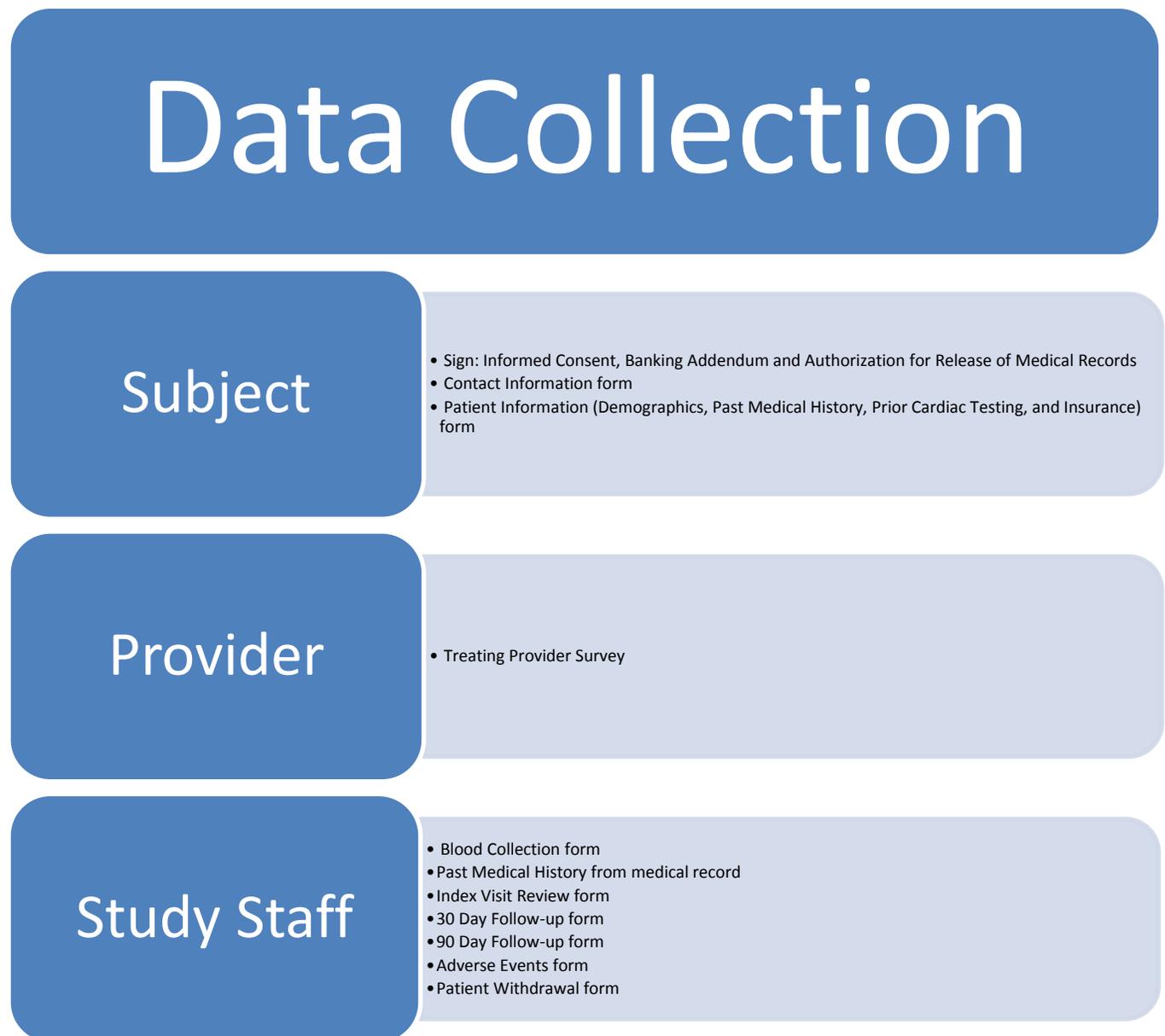
4.5 Destruction of Blood Samples

If sample specimens must be destroyed for any reason (e.g. participant calls after enrollment to withdraw from study), then contact Heather Rebeck (hrebuck@som.umaryland.edu) at the University of Maryland Core Lab and copy the clinical coordinating center (stopcp-1@lists.ufl.edu) on the correspondence.

5.0 Data Entry

All study electronic case report forms (eCRFs) and the Provider Survey are required to be completed on the electronic data capture platform, REDCap (<https://redcap.ctsi.ufl.edu/redcap/>). Printed versions of the eCRFs can be used, but all information recorded on the printed CRFs must be transcribed into REDCap within seven business days of enrollment. All completed paper forms are considered source documents and should be kept in a secure location, accessible to the study monitor or auditor upon request. Printable versions of the eCRFs and the Provider Survey can be found on the study website.

A more detailed description of each of the required eCRFs for this study is included in this section. The appropriate person that should provide the information being collected on each form is outlined in the diagram below.



5.1 Contact Information and Patient Information Forms

The participant should be the primary source of information when completing the Contact Information and Patient Information forms. A family member or relative may supplement information. These forms should be completed at the time of arrival in the ED. Past Medical history should be collected from participant reported medical history for the past year only. The medical record should not be used to supplement this information.

5.2 Treating Provider Survey

The treating provider should complete the Treating Provider Survey during the Index Visit. The treating provider may be a PGY I-IV, an attending, advance practice provider (i.e., PA or ARNP), or a fellow. If any clarification on data completion of the survey is needed, the treating provider should be contacted.

5.3 Blood Sample Collection Form

The Blood Sample Collection Form should be updated in REDCap as the blood samples are collected in real time. A STOP CP Time Log can be printed to assist with keeping track of blood sample collection times and blood draw windows. The STOP CP Time Log is available on the study website.

5.4 Past Medical History from EMR and Index Visit Review Form

The Past Medical History from the Medical Record form should be completed using the participant's current medical record as the source for this information. Testing results should be collected from the past year.

The Index Visit is defined as the time starting when the patient was admitted to the hospital and ends when they are discharged. The review includes past medical history, results from testing, and other outcomes from the index visit.

5.5 Follow-up Call and Chart Review Forms: 30 and 90 Day Forms

The 30 and 90 Day Follow-up Call forms should be completed as the telephone calls are completed. Each successful or unsuccessful telephone call attempt should be recorded on these forms. The Follow-up Chart Review form for 30 day follow-up can be completed at 30 days or along with the 90 day follow-up chart review. Follow-up chart review should only be conducted on participants that indicated they were re-hospitalized or saw a provider after their Index Visit.

5.6 Adverse Event Form

As this is an observational study with minimal risk, a serious adverse event (SAE) related to study procedures is unlikely. Only adverse events possibly related to the blood draws (i.e., hematoma, excessive bleeding, infection at the venipuncture site, thrombophlebitis, lightheadedness, fainting or syncope) will be collected on the Adverse Event form. See section 8.5 for additional information on safety reporting for this study.

5.7 Participant Status Form

The Participant Status form must be completed for every participant that signed an ICF and is considered a screen failure, requests to withdraw from the study, dies during the study, or completes the study.

5.8 Window for Completing Data Entry

If paper forms were used for initially capturing study data, the information must be transcribed to the REDCap forms according to the timeframe outlined below.

- Data from enrollment/baseline should be entered within 3 business days.
- Data from index hospitalization should be entered within 7 business days from discharge.
- Data from follow-up should be entered within 7 business days.

6.0 Follow-up Phone Contact

Study staff will conduct telephone follow-up and/or medical chart review at 30 days and 90 days after the date of enrollment. At the time of enrollment, the participant's telephone number, email, emergency contact, and physical mailing address will be collected on the Contact Information form for follow-up purposes. The follow-up form for each visit is available on REDCap, and the follow-up telephone script is available on the STOP CP website. Due to limitations of the follow-up survey, only English-speaking patients will be able to participate in this study.

Participants are to be contacted by telephone within three attempts, and then resort to email, text, and emergency contact number. An attempt is defined as making contact with all numbers (not including emergency contact) provided by the participant one time per day. Participants may be contacted a maximum of three different days with each contact number attempted a maximum of one time each. The follow-up must be completed by the participant. If a participant is admitted to a facility at the time of follow-up, then the same guidelines apply.

If a participant discloses an adverse event that is related to the study blood draw, then the event should be reported using the Adverse Event form on REDCap. If the event is serious, this should be reported within 24 hours and reported to WIRB and the coordinating center. Please see section 8.5 Safety Reporting for additional information. If a participant discloses healthcare-related events at another facility, then records will be requested using the Authorization for Medical Records Release form (see section above).

Follow-up phone calls should NOT be conducted on withdrawn participants.

6.1 Follow-up Day 30 (+10 days)

Study staff will contact participants to further determine clinical outcomes and determine healthcare utilization since enrollment. The follow-up form is available on REDCap. Please note all telephone follow-up attempts on the form in REDCap.

If these methods of contact are deemed unsuccessful, then a letter will be mailed to the participant. The WIRB approved template for this letter is available on the STOP CP website. Below is the suggested timeline for completing follow-up attempts at the 30 day follow-up time point.

1st attempt done on Day 31 (+/-1 day)

2nd attempt done on Day 33 (+/-1 day)

3rd Attempt done on Day 35 (+/-1 day)

If after the 3rd attempt is unsuccessful, the emergency contact number can be utilized in an additional attempt to reach the participant.

Letter sent on Day 36 (+/-1 day)

6.2 Follow-up Day 90 (+30 days)

Study staff will contact participants to further determine clinical outcomes and determine healthcare utilization since the previous 30-day follow-up, or since enrollment if contact was not established. Follow-up phone contact will still be conducted if the 30-day follow-up was unsuccessful, unless the methods of contact are deemed invalid. Participants who are unable to be contacted will be searched for in the Social Security Death Master File.

The Follow-up Day 90 form is available on REDCap. Please note all telephone follow-up attempts in REDCap.

6.3 Authorization for Medical Records Release

Participants reporting potential cardiac-related events at other facilities should have their records requested from that facility, and the data will be reviewed by adjudicators using the same structured data abstraction template. The Authorization for Medical Records Release form can also be used to obtain medical history since the Index Visit for any participant that is lost to follow-up (see section 3.6 for more information about participants that are lost to follow-up). The template for the Authorization for Medical Records Release form is available on STOP CP website.

7.0 Adjudication

Adjudicators will review participants on a case-by-case, outcome-based basis. The clinical coordinating center will notify participating sites to supplement more information, including but not limited to emergency department notes, index visit ECGs, index visit H&P, index visit discharge summary, cardiology consult notes (if applicable), subsequent ED visits for MACE or death, subsequent ECG from ED visit for MACE or death, stress tests, and angiography (CT and invasive) results in a redacted, HIPAA-compliant format.

8.0 Regulatory Requirements

8.1 Institutional Review Board (IRB) or Western IRB (WIRB)

Each site is responsible for submitting the protocol, informed consent documents, and recruiting materials for approval at the local IRB or Western IRB (WIRB). Approved documents and official approval letter should be filed in the Regulatory File/Site Study Binder. Forward regulatory correspondence (i.e. approvals, continuing reviews) to the clinical coordinating center at arnoldb@ufl.edu.

8.2 Regulatory Files / Site Study Binder

The following essential documents must be included in each participating site's regulatory binder:

- IRB/WIRB
 - IRB/WIRB Approval Letters
 - IRB/WIRB Approved Consents (all versions)
 - IRB/WIRB Membership List
- Protocol
- Investigator Agreement
- Financial Disclosure
- Correspondence
 - IRB/WIRB
 - Sponsor
 - Study Memos
- Current Clinical License of Site PIs, Sub-Is until study closeout
- Curriculum Vitae (may be in electronic format) for all study staff. Signature and dated within 2 years at any given time
- GCP and HIPAA Training GCP current within 3 Years
- IATA Training certificates for staff shipping blood samples
- Shipping Logs (if applicable)
- Laboratory
 - Laboratory Normal Reference Ranges
 - Laboratory Certifications
- Documentation of a Federal Wide Assurance (FWA)
- Delegation of Authority Log
- Documentation of Site Staff Training
- Temperature Logs
- AEs, Deviation Logs, Note to Files
- Source Documents
- Site Monitoring Visit Log
- Notes from Monitoring Visit

The GCP definition of source documentation (ICH E6 1.51) that should be maintained throughout a clinical study includes original documents, data, and records involved in the clinical trial. Any paper source documents used in this study should be locked in a secure location.

8.3 Site Protocol Compliance Monitoring

At least one person on the study staff should be delegated to monitor study procedures and ensure they are performed correctly. Protocol deviations should be reported to the coordinating center and IRB/WIRB in accordance with institution requirements. Forward correspondence, including any reports and IRB/WIRB response, to the clinical coordinating center.

If there are any questions about the protocol, contact the clinical coordinating center at STOPCP-L@lists.ufl.edu. The personnel are available to assist and can provide an answer within 24 hours (Monday-Friday).

8.4 Monitoring Plan

Monitoring visits will be conducted in-person and/or teleconference. Information and documents requested for review during the monitoring visit will be specified in the monitoring confirmation visit letter.

8.5 Safety Reporting

The Investigator for each site will be responsible for monitoring the safety of participants who enter this study and for documenting and reporting all Adverse Events to the sponsor. As this is an observational study with minimal risk rather than interventional study a serious adverse event (SAE) related to study procedures is unlikely. If a participant discloses an adverse event that is serious, unexpected and related to the study, or possibly related to the blood draws, the event should be reported within 24 hours of discovery to the coordinating center. Adverse events will be collected on the Adverse Event form on REDCap. Reporting of serious, unexpected, and related adverse events or any unexpected or unanticipated problem should be reported to the coordinating center via email (STOPCP-L@lists.ufl.edu) and as required by your local IRB/WIRB. All reported adverse events should also be submitted to WIRB and/or your local IRB in accordance with their requirements for annual reporting of adverse events.

The patient population in this study may be clinically stable to critically ill. It is expected that critically ill participants will have a number of unrelated adverse health events during the course of their hospital stay. Therefore, we will limit the scope of study AE monitoring and recording to the following:

Adverse Events (AEs) possibly related to blood draws:

- Hematoma
- Excessive bleeding
- Infection at the venipuncture site
- Thrombophlebitis
- Lightheadedness or syncope
- Fainting

Serious Adverse Events (SAEs), defined as:

- Death related to the study/procedures or unexpected due to the acuity of the participant
- A life threatening experience believed to be related to the study or procedure
- Persistent or significant disability or incapacity that is of greater frequency or severity than normally expected in the course of critical illness
- An event that jeopardizes the participant and may require medical or surgical treatment to prevent one of the preceding outcomes and is not expected in the course of illness

Unanticipated Problems (UPs):

An unanticipated problem is an incident, experience, or outcome that is unexpected, related or possibly related to participation in the research, and suggests that the research places participants or others at a greater risk of harm than previously known or recognized. An event is not necessarily considered adverse if no patient is harmed. Ex: a breach of confidentiality (e.g. laptop gets lost).

Unexpected Adverse Events (UAEs):

An Unexpected Adverse Event (UAE) is any Adverse Event and/or reaction, the specificity, severity, or frequency of which is not consistent with the informed consent. Further, it is not consistent with the risk information described in the general investigational plan or proposal and informed consent document on file, or is not consistent with what would be expected in a patient with critical illness.

Expected Adverse Events (EAEs):

Expected Adverse Events are those events that are included as a possible risk in the informed consent document or are expected in the course of care of a patient with critical illness.

Severity Grading

Use the CTCAE version 4 to evaluate each adverse event and grade as appropriate (mild/moderate/severe).

9.0 Shipping Protocol

It is imperative that you collect, process, and store samples according to the directions below.

All human body fluids should be handled as potentially infectious. Personal protective equipment should be used according to local safety regulations.

If there are any questions about any of the processing components, do not hesitate to contact the Core Laboratory at email: hrebuck@som.umaryland.edu or call 410-706-7734.

9.1 Labeling Cryovial Boxes

A page of box labels is included in shipping materials.

Please begin each new shipment numbering at “BOX #1,” meaning after the first shipment each site will re-number the next set of boxes in the freezer with Box #1.

<p><u>FRONT OF BOX</u> </p>	<p><u>NOT TOP OF BOX</u> </p>
	
<p><u>CORRECT:</u> Place labels on front, lower storage portion of cryovial boxes so that the Central Lab is able to read them as they are stacked on top of each other in the freezer.</p>	<p><u>INCORRECT:</u> Do NOT place labels on the top of cryovial boxes. The Central Lab will not be able to read them as they are stacked on top of each other in the freezer.</p>

9.2 Frequency of Shipments

The first shipment should be made after 5 participants. Subsequent shipments should be made after every 20 participants and include all COMPLETE participant sets collected. A complete set

is considered to be T0, T1, T2, and T3. Do not split participants between shipments; it is okay to have participant samples in two different boxes but only for a same-day shipment. E.g. Samples for Participant 003 may be stored in Boxes 1 and 2, and Boxes 1 and 2 must both be shipped on January 1st.

The first shipment should be made after 5 participants. Subsequent shipments should be made after every 20 participants and include all complete participant sets collected. A complete set is considered to be T0, T1, T2, and T3. Do not split participants between shipping boxes or shipments. Ship only participants in complete sample sets even if this means an incompletely filled 9x9 box is being shipped.

Shipments must include the completed Sample Shipping Form as described below (see next page) and the Specimen Tracking Form as described in the sections above. Make a copy of these completed forms to keep on site.

CCRL
685W Baltimore St
MSTF 8-65
Baltimore, MD 21201

**Shipping Form
STOP-CP**

Section 1

Date:	Heather Rebeck	Site #	
To:	University of Maryland	From:	
Org:	685 W. Baltimore St	Address:	
Address:	MSTF RM 8-65	Address:	
	Baltimore, MD 21201	Fax:	
Fax:	410-706-4486	Tel:	
Tel:	410-706-7734		

Section 2

Intended use of samples: Samples will be used for the STOP study

Sample boxes included in shipment:

Box # to Box #

Shipping Form FedEx Tracking #:

Section 3

LAB USE ONLY

Were the samples received on time?	No [if no, explain below]
Were the samples received at appropriate temperatures?	
Was the shipment complete?	Freezer No
Location	

Section 4

Comments

Signature of person receiving shipment _____ Date Received _____

STOP study

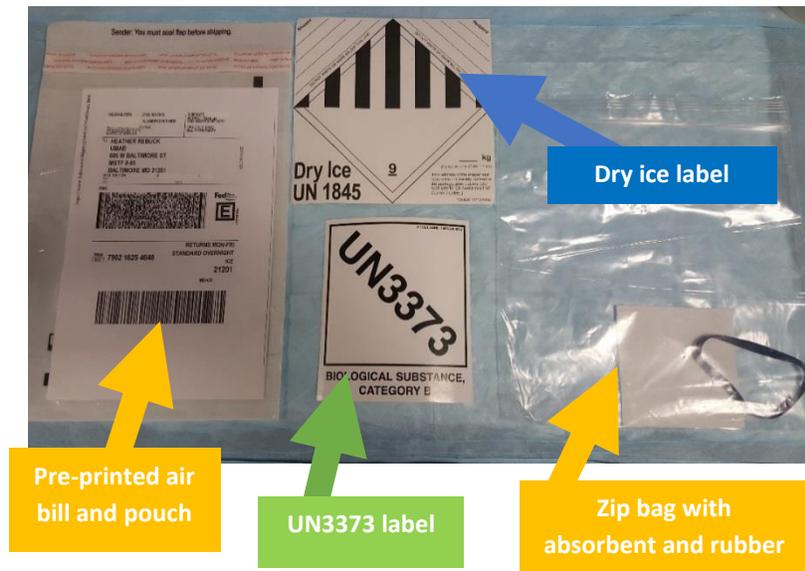
9.3 Packing Instructions for Shipping

Shipping Components

Shipping materials sent to your facility contain the following:

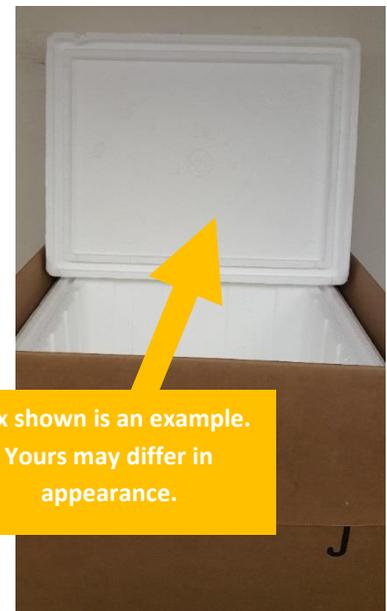
- Styrofoam box with an outer cardboard cover
- FedEx air bill for return shipment – Account Number: 8770-4246-4
- Dry Ice label
- UN3373 label
- Zip bags
- Rubber bands
- Absorbent material

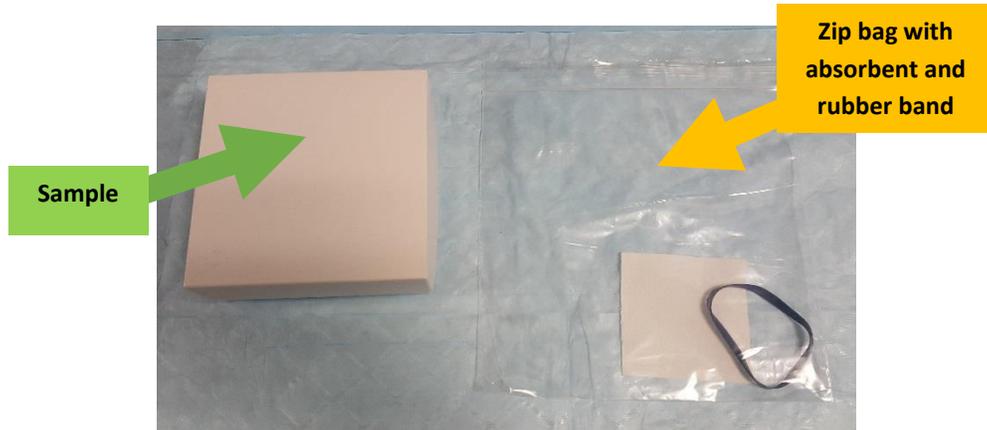
Shipping materials will arrive in the same box used for shipping, so please maintain the cardboard box and styrofoam cooler for re-use.



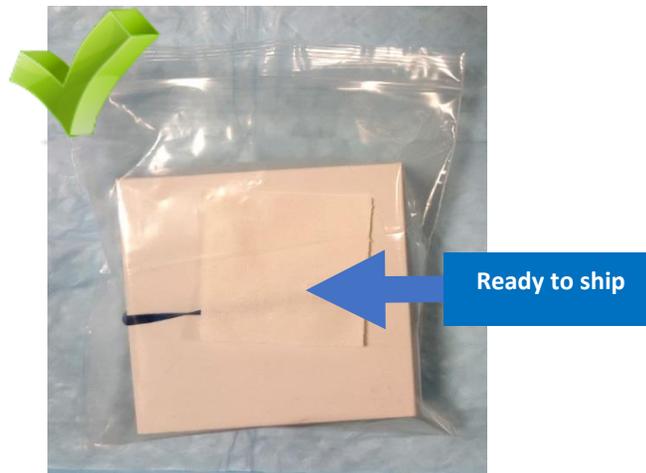
All shipments must be packed with IATA compliance per the directions below:

1. After collecting all required samples, double check all tubes and paperwork to assure that all appropriate barcode labels are attached and records are accurate. Keep a copy of the Specimen Tracking Form and Sample Shipping Form for your records.
2. Place a rubber band around the cryovial storage boxes and place them inside the zip bags with an absorbent sheet in each bag.





3. Place a layer of dry ice on the bottom of the cooler.



4. Place the cryo boxes as packaged in step #2 on top of the ice.
5. Fill the cooler with **at least 15 lbs. of dry ice**, making sure the samples are adequately covered.

6. Add enough padding material (newsprint or another insulating material) on top of the ice to limit air space and to prevent contents from shifting.
7. Close and seal cooler box.
8. Place the Specimen Tracking Form and Sample Shipping Form on the top of the cooler box
9. On the outside of the shipping box place a UN3373 label and a dry ice label (provided inside the shipping box).
10. Be sure that the amount of dry ice on your label matches what is pre-printed on your air bill.
NOTE: The pre-printed amount of dry ice must match what is written on the UN1845 sticker otherwise the shipment may not be processed and shipped by FedEx. The amount of dry ice actually added to the cooler box does not necessarily have to match the amount pre-printed on the air bill, but the pre-printed amount must match what is written on the UN1845 sticker.



11. Place the provided FedEx airbill on the package. Insert the airbill into the pouch and stick the pouch on the box (provided inside the shipping box).

12. If the provided pre-paid airbill is lost, contact the Core Laboratory at hrebuck@som.umaryland.edu for a replacement. If an out of office message is received via email; contact the lab at **410-706-7734**. UMB will create a new FedEx airbill and provide it via email.

Packages should be shipped Monday, Tuesday, or Wednesday.

Heather Rebuck

685 W Baltimore Street

MSTF 8-65

Baltimore, MD 21201

410-706-7734

hrebuck@som.umaryland.edu

For questions: call UM Core Lab at 410-706-7734 or
e-mail Heather Rebuck at hrebuck@som.umaryland.edu

If for any reason you cannot reach someone in the Core Lab,
please call or text Dr. Christenson at 410-218-6454 or Email: rchristenson@umm.edu.

Version Number	Description	Date	Originator
1.0	Original	1/26/2017	Anna Mazzuocolo
2.0	Revised the entire MOP to re-format and add more detail regarding enrollment, study procedures, and data entry	3/9/2017	Bambi Arnold-Bush
3.0	Removed VCU as a participating site and reassigned Henry Ford Health System to site 4. Revised the "Withdrawal Criteria" to "Exclusion from the Primary Analysis" (Pages 5-6). Added clarification to the follow-up call schedule	5/16/2017	Bambi Arnold-Bush
4.0	Added Utah as site 6	8/9/2017	Bambi Arnold-Bush