

CRANE: Reducing Falls with Varenicline in Hypocholinergic Parkinson Disease Manual of Procedures

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Section	Change
Document Footer	Updated to “Version (March 2025)”
Section 3.1	Added general BioSEND phone number
Section 6.1	Updated specimen and kit label format



National Institute of Neurological Disorders and Stroke
Biorepository:

BioSpecimen Exchange for Neurological Disorders, BioSEND

Biospecimen Collection, Processing, and Shipment Manual
for Reducing Falls with Varenicline in Hypocholinergic
Parkinson Disease

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1.0 PURPOSE

The purpose of this manual is to provide collection site staff (PIs, study coordinators, and the sample collection and processing teams) at various study sites with instructions for collection and submission of biological samples. It includes instructions for biospecimen submission to the BioSpecimen Exchange for Neurological Disorders (BioSEND) located at Indiana University.

This manual includes instructions for the collection, processing, aliquoting and shipping of the following samples:

- Whole Blood (one for DNA extraction)

These procedures are relevant to all study personnel responsible for processing blood specimens to be submitted to BioSEND.

2.0 ABBREVIATIONS

BioSEND	BioSpecimen Exchange for Neurological Disorders
IATA	International Air Transport Association Parkinson's
PDBP	Disease Biomarkers Program
RBC	Red Blood Cells
RCF	Relative Centrifugal Force
RPM	Revolutions Per Minute

3.0 BioSEND INFORMATION

3.1 BioSEND Contacts

Tatiana Foroud, PhD, Principal Investigator

Claire Wegel, Project Manager

Email: cwegel@iu.edu

General BioSEND Contact Information

Phone: 317-278-6158

Email: biosend@iu.edu

Website: www.BioSEND.org

Sample Shipment Mailing Address

BioSEND

Indiana University School of Medicine 351

W. 10th Street. TK-217

Indianapolis, IN 46202-5188

3.2 Hours of Operation

Indiana University business hours are from 8 AM to 5 PM Eastern Time, Monday through Friday.

Frozen samples must be shipped Monday- Wednesday only.

Check the weather reports and the shipping courier website to make sure impending weather events (blizzards, hurricanes, etc.) will not impact the shipping or delivery of the samples. Couriers often report anticipated weather delays on their website.

3.3 Holiday Schedules

- Please note that courier services may observe a different set of holidays. Please be sure to verify shipping dates with your courier prior to any holiday.

3.4 Holiday Observations

Date	Holiday
January 1	New Year's Day
3 rd Monday in January	Martin Luther King, Jr Day
4 th Monday in May	Memorial Day
June 19	Juneteenth (observed)
July 4	Independence Day (observed)
1 st Monday in September	Labor Day
4 th Thursday in November	Thanksgiving
4 th Friday in November	Friday after Thanksgiving
December 25	Christmas Day

Please note that BioSEND has extended closures to inbound shipments around the Thanksgiving and Christmas holidays. In addition to sending advance notification of these closures to sites, dates will be posted on the BioSEND website. Frozen specimens collected during this period should be held at your site to ship after the first business day in January. If you are ever unsure if it is safe to ship samples, please email biosend@iu.edu to confirm.

For up-to-date holiday closure information and instructions, please visit <https://biosend.org/holiday-closures>.

4.0 BIOSEND SAMPLE REQUIREMENTS

NINDS approves each study for a specific biospecimen collection protocol. Studies and study sites should make every effort to meet their approved biospecimen collection requirements. The expected number of samples from each site that should be returned to BioSEND are listed in [sections 4.1-4.2](#).

If a sample is not obtained at a particular visit, this should be recorded in the notes section of the Specimen Collection and Processing Form (**see Appendix I**). This form is submitted with your frozen sample shipment to BioSEND.

4.1 Protocol Schedule for Biospecimen Submission to BioSEND – CRANE

Visit (month)	BL
Whole Blood, 6ml	2

5.0 SPECIMEN COLLECTION KITS, SHIPPING KITS AND SUPPLIES

Research specimen collection kits (except dry ice and equipment listed in Section 5.7) will be provided by BioSEND. BioSEND will provide a sufficient number of labels only for those specimens that are to be shipped back to the BioSEND repository. Any specimens that will remain at the collection site should be labeled accordingly. Ensure that all tubes are properly labeled during processing and at the time of shipment according to [Section 6.2](#).

Links to each study's kit request module, sample submission forms, and other information can be found at <https://biosend.org/coordinate-studies/active-studies>.

5.1 Kit Supply to Study Sites

Kits and individual kit components (ie, “Extra Supplies”) can be ordered as required through the kit request module. Sites are advised to proactively confirm kits are on hand ahead of study visits.

The link to the kit request module is shown below:

- CRANE: <https://redcap.link/CRANEKits>

Please allow **TWO weeks** for kit orders to be processed and delivered.

5.2 Specimen Collection Kit Contents

Collection kits contain the following (for each subject) as designated per your protocol and/or NINDS resource development agreement. Do not replace or supplement any of the tubes or kit components provided with your own supplies unless you have received approval from the NINDS/BioSEND Study team to do so. Please store all kits at room temperature until use

CRANE Blood Collection Kit	
Supply	Quantity
EDTA (plastic) tube, 6ml	2
Label set (kit & specimen labels)	1

CRANE Shipping Kit	
Plastic Biohazard bag with absorbent sheet	6
UPS Airbill Sleeve	1
Shipping box/Styrofoam container	1
UN3373 Category B Label	1
Fragile label	1
Dry ice label	1

5.4 Site Required Equipment

The following materials and equipment are necessary for the processing of specimens at the collection site and are to be **supplied by the local site**:

- Personal Protective Equipment: lab coat, nitrile/latex gloves, safety glasses
- Tourniquets
- Alcohol Prep Pads
- Gauze Pads
- Bandages
- Butterfly needles and hubs
- Microcentrifuge tube rack
- Test tube rack
- Sharps bin and lid

In order to process samples consistently across all projects and ensure the highest quality samples possible, project sites must have access to the following equipment:

- Centrifuge capable of ≥ 1500 rcf ($1500 \times g$) with refrigeration to 4°C
- -80°C Freezer

In order to ship specimens, you must provide:

- Dry ice (minimum 10 pounds per shipment)

6.0 SPECIMEN LABELS

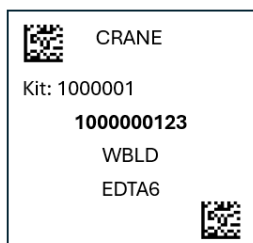
Labels must be affixed on all collection and aliquot tubes to ensure unique specimen identity. BioSEND provides labels for all samples being collected and returned to BioSEND. The site is responsible for providing labels for biospecimens that will be retained at the site. If labels are provided but the sample is not collected, please discard the unused labels.

6.1 Types of Labels

Each kit contains all labels required for the return of biospecimens to BioSEND.



The **Kit Labels** do not indicate a specimen type, but are affixed on BioSEND forms and on packaging materials. See shipping appendices for further instructions.

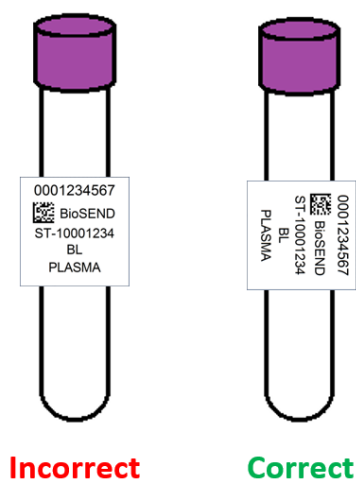


The **Specimen Labels** are placed on all sample collection and aliquot tubes. See processing appendices for further instructions.

6.2 Affixing Labels

In order to ensure the label adheres properly and remains on the tube, follow these instructions:

- Place specimen labels on **ALL** collection tubes and cryovials **BEFORE** sample collection, sample processing, or freezing. This will help to ensure the label properly adheres to the tube before exposure to moisture or different temperatures.
- The blood collection tube labels contain a 2D barcode on the left hand side of the label. When turned horizontally, the barcode should be closer to the top (cap end) of the tube.
- Place label **horizontally** on the tube (wrapped around sideways if the tube is upright); see below.



- Take a moment to ensure the label is **completely affixed** to each tube. It may be helpful to roll the tube between your fingers after applying the label.

7.0 SPECIMEN COLLECTION AND PROCESSING PROCEDURES

Consistency in sample collection and processing is essential for biomarker studies. All samples are drawn in the same order and then processed in a uniform fashion. **Please read the instructions before collecting any specimens. Have all your supplies and equipment out and prepared prior to drawing blood.**

7.1 Blood Collection Protocols

- Appendix E: Whole Blood Collection for Isolation of DNA (No Processing)

8.0 Packaging and Shipping Instructions

ALL study personnel responsible for shipping should be certified in biospecimen shipping. If not available at your institution, training and certification is available through the CITI training site (Course titled “Shipping and Transport of Regulated Biological Materials” at <https://www.citiprogram.org/>).

We encourage all studies to use our custom UPS shipping interface to create shipping waybills and schedule package pickups. More information can be found at <https://biosend.org/shipping-resources>.

8.1 Specimen Collection and Processing Form

The Specimen Collection and Processing Form should be completed for all samples submitted to BioSEND. Please see Appendix I for further instructions.

8.2 Shipping Instructions

Please reference Appendix K for frozen shipping instructions and Appendix Q for generating airway bills and scheduling pick-ups.

8.3 Shipping Address

All samples are shipped to the BioSEND laboratory:

BioSEND
Indiana University School of Medicine
351 W. 10th Street. TK-217
Indianapolis, IN 46202-5188

9.0 Reconciliation and Non-Conformance

Appendix I must be completed the day that samples are collected to capture information related to sample collection and processing. This form includes information that will be used to reconcile sample collection and receipt, as well as information essential to future analyses.

BioSEND will contact the site as soon as possible when a discrepancy or issue is found with either the samples or paperwork.

Common non-conformance issues that will result in BioSEND staff contacting your site include:

- Missing samples (samples documented on the sample form that are not physically present in the shipment)
- Incorrect samples collected and shipped
- Damaged or incorrectly prepared samples
- Unlabeled or mislabeled samples
- Samples frozen and stored longer than three months at the site

10.0 APPENDICES

Appendix E: Whole Blood Collection for Isolation of DNA (No Processing)

Appendix I: Specimen Collection and Processing Form

Appendix K: Frozen Shipping Instructions

Appendix Q: UPS ShipExec™ Thin Client Instructions

Appendix E – Whole Blood Collection for Isolation of DNA (No Processing)

Two 6 ml Purple-Top EDTA tubes are provided by BioSEND for the collection of Whole Blood from which DNA will be extracted from one tube. These tubes should be shipped to BioSEND FROZEN; no processing required).

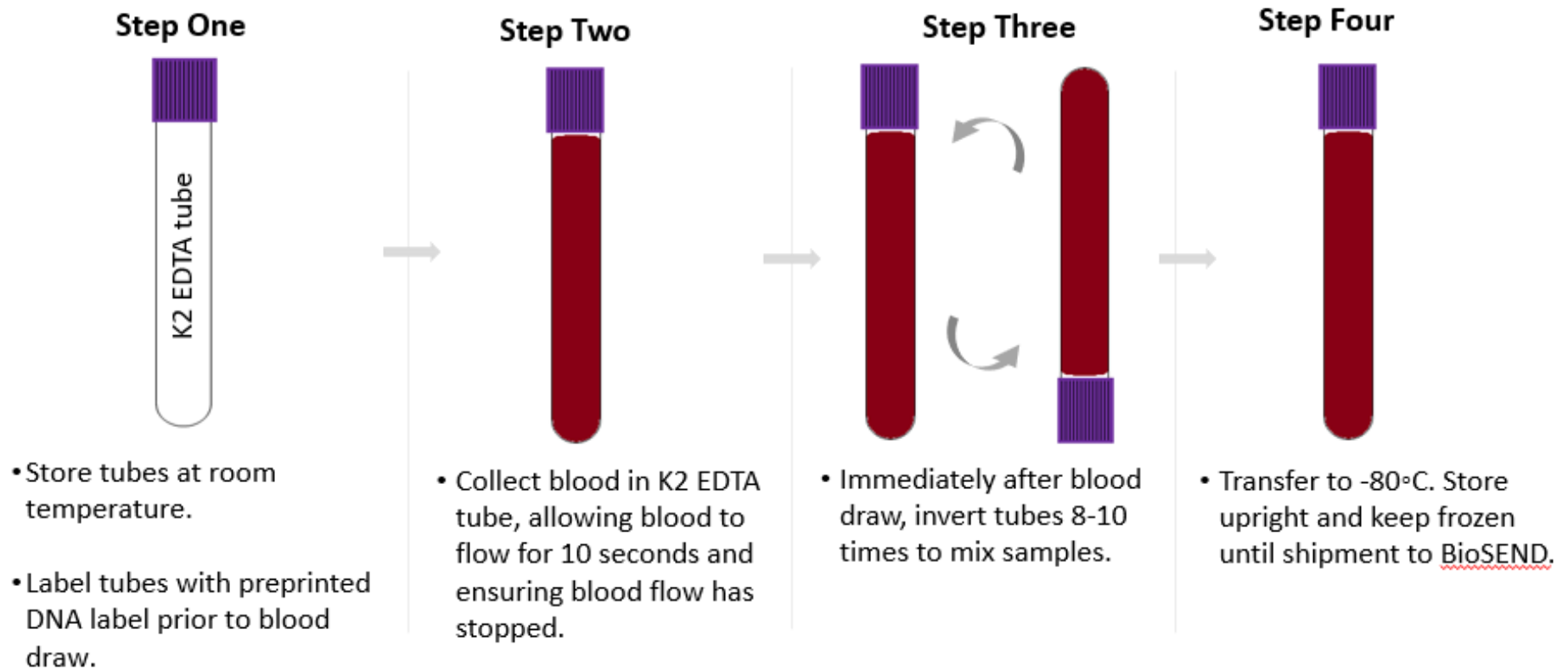


1. **CRITICAL STEP:** Store empty Whole Blood EDTA tubes at room temperature, 64°F - 77°F (18°C to 25°C) before use.
2. Place pre-printed Collection and Aliquot “DNA” labels on the **6 ml EDTA tubes** prior to blood draw.
3. Using a blood collection set and a holder, collect whole blood into the 6 ml purple top whole blood tubes using your institution’s recommended procedure for standard venipuncture technique.



The following techniques shall be used to prevent possible backflow:

- a. Place donor's arm in a downward position.
 - b. Hold tube in a vertical position, below the donor’s arm during blood collection.
 - c. Release tourniquet as soon as blood starts to flow into tube.
 - d. Make sure tube additives do not touch stopper or end of the needle during venipuncture.
4. **CRITICAL STEP:** Immediately after blood collection, gently invert/mix (180 degree turns) the EDTA tubes 8-10 times.
 5. Complete the **Sample Record and Shipment Notification form (Appendix I)**.
 6. Place the Purple-Top EDTA tubes in a **WIRE** or **PLASTIC** rack. Do **NOT** use a Styrofoam rack. This will cause the Purple-Top EDTA tube to crack when frozen. Place the Purple-Top EDTA tubes immediately to a **-80°C Freezer**.
 7. Ship the whole blood tubes to BioSEND according to **Appendix K - Frozen Shipping Instructions**.



Appendix I – Sample Collection and Processing Form

A Sample Collection and Processing Form must be completed for each subject-visit submitted to BioSEND. This form includes a Frozen Shipping Manifest that should be completed in advance of shipping to BioSEND also be physically included in the shipper. The form can be completed via REDCap by following the bellow link:

- **Link to Sample Collection and Processing Form:**
<https://redcap.link/CRANESampleForm>

Please note that there is a Save & Return option at the bottom of the survey. This may be used if, for example, you are ready to complete the Collection and Processing portion of the form, but not yet ready to complete the Frozen Shipping Manifest.

It is preferred that you complete the form online via the REDCap link above. However, a copy of the printed form is available on the following pages, should you need a back-up option. Please note that if you do not complete the form online, you will need to email a copy of the form directly to biosend@iu.edu prior to shipment.

For links to your sample processing form, to download the most recent version of of this manual, and access recordings of BioSEND trainings, please visit <https://biosend.org/coordinate-studies/active-studies> and choose your study from the drop-down list.

CRANE Sample Record and Shipment Notification Form

Please complete the Specimen Collection and Processing Form, below, to ship samples to BioSEND for Reducing Falls with Varenicline in Hypocholinergic Parkinson Disease (CRANE). Copies of the completed forms will be automatically emailed to you after submission.

BioSEND CRANE Study

Study Site

☐ University of Michigan

Email address of staff member completing this form

Note: A copy of the completed sample form and the shipping manifest will be sent to this address.

CRANE Study ID

Kit Number

Sex (used for DNA quality control)

☐ Male
☐ Female
☐ Other

Visit

☐ BL

Date of venipuncture blood collection

Time of venipuncture blood collection

(Use 24 Hour clock)

WHOLE BLOOD EDTA

Number of WBLD tubes shipped:

(Two 6ml EDTA tubes expected)

NOTES

Please record any issues with collection/processing:

Shipping Information - Please complete.

Frozen shipments should be sent Monday-Wednesday only. Please check for holiday closures and weather issues prior to shipping. Contact us at biosend@iu.edu if you are unsure whether or not it is safe to ship.

Date of shipment:

Did/will you use the IU UPS interface (ShipExec©) to generate the shipping label?

- ☐ Yes
☐ No

Which shipping service did you use?

- ☐ UPS
☐ FedEx
☐ World Courier
☐ Other

What is the shipment tracking number?

Appendix K – Frozen Shipping Instructions

IMPORTANT!

Frozen samples must be shipped Monday – Wednesday only,
 using Next Day Air delivery

Please be aware of holidays and inclement weather and plan your shipments accordingly. Reach out to biosend@iu.edu if you have any questions

Specimens being shipped to BioSEND are Category B UN3373 specimens and as such must be triple packaged and compliant with IATA Packing Instructions. *See the latest eEdition of the IATA regulations for complete documentation.*

Triple packaging consists of a primary receptacle(s), a secondary packaging, and a rigid outer packaging. The primary receptacles must be packed in secondary packaging in such a way that, under normal conditions of transport, they cannot break, be punctured, or leak their contents into the secondary packaging. Secondary packaging must be secured in outer packaging with suitable cushioning material. Any leakage of the contents must not compromise the integrity of the cushioning material or of the outer packaging.

IATA Packing and Labeling Guidelines

- The primary receptacle (cryovials or blood collection tubes) must be leak proof and must not contain more than 1 L total.
- The secondary packaging (plastic canister or biohazard bag) must be leak proof and if multiple blood tubes are placed in a single secondary packaging, they must be either individually wrapped or separated to prevent direct contact with adjacent blood tubes.
- Absorbent material must be placed between the primary receptacle (cryovials or blood collection tubes) and the secondary packaging. The absorbent material must be of sufficient quantity to absorb the entire contents of the specimens being shipped. Examples of absorbent material are paper towels, absorbent pads, cotton balls, or cellulose wadding.
- A shipping manifest listing the specimens being shipped must be included between the secondary and outer packaging.
- The outer shipping container must display the following labels:
 - ✓ Sender's name and address
 - ✓ Recipient's name and address
 - ✓ Responsible persons (shipper and recipient)
 - ✓ The words "Biological Substance, Category B"
 - ✓ UN3373
 - ✓ Class 9 label including UN 1845, and net weight of dry ice contained

BioSEND Packaging and Shipment Instructions – Frozen Shipments

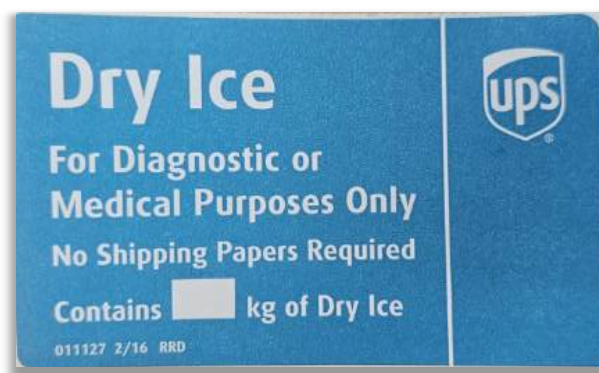
1. Generate airway bill and schedule courier pick-up, as needed.
 - For instructions on generating airway bills and scheduling using the UPS ShipExec™ Thin Client system, see Appendix Q.
2. Record the tracking number onto the Sample Record and Shipment Notification form (Appendix I).
3. Make a copy of the Sample Record and Shipment Notification form.
4. Place all frozen labeled cryotubes in the cryobox. Only include specimens from one subject in each cryobox.
5. Place the cryobox in a clear plastic biohazard bag (do NOT remove the absorbent material found in the bag), and seal the biohazard bag according to the instructions on the bag. Affix a Case Label to the outside of the biohazard bag.



6. Place approximately 2-3 inches of dry ice in the bottom of the Styrofoam® shipping container.
7. If your protocol is collecting frozen whole blood, DNA, or RNA, place labeled tubes in bubble sleeves and seal.
8. Place the tubes in a clear plastic biohazard bag (do NOT remove the absorbent material found in the bag), and seal the biohazard bag according to the instructions on the bag. Affix a Case Label to the outside of the biohazard bag.
9. Place the biohazard bag containing the cryobox into the provided Styrofoam® shipping container on top of the dry ice. Please ensure that the cryobox is placed so that the cryovials are upright in the shipping container (as pictured).



10. Fully cover the cryobox with approximately 2 inches of dry ice. Do not include more than 2 subjects' worth of samples in a single shipper.
11. If including additional biohazard bags in package, include a layer of dry ice (approximately 2 inches) between each biohazard bag.
12. The inner Styrofoam® shipping container must contain approximately 10 lbs (or 4.5 kg) of dry ice. The dry ice should entirely fill the inner box to ensure the frozen state of the specimens.
13. Replace the lid on the Styrofoam® container. Place the completed Sample Record and Shipment Notification form in the package on top of the Styrofoam® lid for each patient specimen, and close and seal the outer cardboard shipping carton with packing tape.
14. Print a copy of your UPS® airway bill generated through the UPS ShipExec™ Thin Client system (see Appendix Q). Place airway bill into the provided airway bill envelope and affix envelope to package.
15. Complete the UPS Dry Ice Label with the following information:
 - Net weight of dry ice in kg (this amount must match the amount recorded on the airway bill)



- Do not cover any part of this label with other stickers, including pre-printed address labels.

IMPORTANT!
Complete the required fields on your airway bill and Class 9 Dry Ice labels, or courier may reject or return your package.

16. Apply all provided warning labels (UN3373, Dry Ice Label and Fragile Label), taking care not to overlap labels with each other or with airway bill.
17. Hold packaged samples in -80°C freezer until time of courier pick-up/drop-off.
18. Specimens should be sent to the address below. Frozen shipments should be sent Monday through Wednesday only to avoid shipping delays on Thursday or Friday.

BioSEND
IU School of Medicine
351 W. 10th Street
TK-217
Indianapolis, IN 46202

19. **Notify BioSEND by email (biosend@iu.edu) that a shipment has been sent and attach the Sample Record and Shipment Notification form to your email. Do not ship until you've contacted and notified BioSEND staff about the shipment in advance.**
20. Use courier tracking system to ensure the delivery occurs as scheduled and is received by BioSEND.

In addition to tracking and reconciliation of samples, the condition and amount of samples received are tracked by BioSEND for each sample type. Investigators and clinical coordinators for each project are responsible for ensuring that the requested amounts of each fluid are collected to the best of their ability and that samples are packed with sufficient amounts of dry ice to avoid thawing in the shipment process.

Appendix Q - UPS ShipExec™ Thin Client Instructions

***** The shipment label in ShipExec should not be created until the day of shipment *****

- 1) Log in to the UPS ShipExec™ Thin Client website: <https://kits.iu.edu/UPS> or <https://kits.iu.edu/ups>.
 - a. To request an account, complete the following survey:
<https://redcap.uits.iu.edu/surveys/?s=88TTWY3KAF>
- 2) Find the “Shipping” dropdown menu in the top left corner of the screen and click on “Shipping and Rating”.
- 3) Once the Indiana University page loads, look for the “Study Group” dropdown menu under “Shipment Information” on the right side of the screen. Choose your study from the dropdown menu.
- 4) After selecting your study, click on the magnifying glass icon on the left side of the screen under “Ship From”.
- 5) An address book and filters will populate the screen. On the right side of the screen, a list of all the site addresses within the study you selected should populate.
 - a. Filter the list down more by looking to the left side of the screen and searching for their address by filling in the “Company”, “Contact”, or “Address 1” fields. Click on the Search button when ready.
 - b. Once you have found your site address, click on the “Select” button to the left of the address.
- 6) Make sure your address populated in the fields under “Ship From” on the main page.
 - a. If you accidentally selected the wrong address, click on the “Reset” button on the bottom right of the screen. After the page reloads and clears the information, select your study again from the “Study Group” menu and click on the magnifying glass icon again to search for your correct address.
 - b. To change the address for your site and study group, please complete the following survey:
<https://redcap.uits.iu.edu/surveys/?s=88TTWY3KAF>
- 7) Enter the total weight of your package in the “Weight” field on the right side of screen under the name of your study.
 - a. Leave the “Dry Ice Weight” field empty or enter “0” if shipping an ambient sample.
- 8) Enter the weight of the dry ice for frozen shipments in the “Dry Ice Weight” field.
 - a. The “Dry Ice Weight” field can never be higher than the “Weight” field.
 - b. **(Steps 9-10 can be skipped if you do not need to schedule a pickup)**
- 9) After entering the weights, click on the blue “Pickup Request” button.
- 10) When the Create Pickup Request box pops up, enter information into all the fields provided.
 - a. Enter the “Earliest Time Ready” and “Latest Time Ready” in 24-hour format.
 - i. Schedule pickup at a minimum 1 hour before the “Earliest Time Ready”
 - b. Choose a name and phone number that is the best contact if the UPS driver has question related to picking up your package
 - c. Entering the “Room Number” and “Floor” will help the UPS driver locate your package
 - i. The “Floor” field only allows numerical characters while the “Room Number” field is free text.
 - d. Click “Save” when done.
- 11) Once you are certain that all the correct information has been entered, click the “Ship” button in the bottom right corner of the screen.
- 12) If no red error messages pop up at the top of your screen after clicking on “Ship”, then you should have 2 downloaded PDF files: Shipment Receipt & UPS Package Label

- a. Shipment Receipt will list a “Pickup No.” that references your specific package if there is ever an issue with UPS picking up your package
- 13) Print out the UPS airway bill to any printer at your location.
 - a. Fold the UPS airway bill and slide it inside the plastic UPS sleeve.
 - b. Peel the back off the plastic UPS sleeve and stick the sleeve to your package, making sure it is laying as flat as possible along the surface of the package.
- 14) Place your package in the spot designated in your pickup request, or wherever your daily UPS pickups occur.
- 15) If you need to reprint your airway bill or void your shipment, click on “History” at the top of the main screen.
 - a. If your shipment does not automatically pop up, enter the date of shipment and then click “Search”.
 - b. To reprint your airway bill, click on the printer icon to the far left under “Action”
 - c. To void your shipment, click on the “X” icon to the far left under “Action”
 - i. If you created an airway bill that you no longer need, you must void the shipment to ensure your study will not be charged for the shipment.