

Exhibit H
PNRR SOP for Biospecimen Collection, Processing and Shipment

Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for
Biospecimen Collection, Processing and Shipment

This Standard Operating Procedure (SOP) provides instructions for PNRR site personnel how to order supplies, collect and process the biospecimen samples and ship the collected biospecimen samples to the Indiana University Genetic Biobank (IUGB) for long-term storage and further processing.

I. Blood Collection Kits

All blood collection kits are assembled at Indiana University (IU) and are shipped to each site upon request. The PNRR site personnel will be responsible for informing IU of the number of required blood collection kits, shipping supplies, and the requested date of arrival, with at least 10 business days advanced notice via the PNRR-portal at <http://kits.iu.edu/pnrr>.

Each blood collection kit contains the following items:

1. Sample Collection and Processing Form

A paper copy of the Sample Collection and Processing Form pre-labeled with the kit number.

2. Sealable plastic biohazard bag

Clear sealable plastic bag, marked with the red/orange BIOHAZARDOUS MATERIAL symbol. The bag is pre-labeled with the kit number. A sheet of absorbent material will be included in the bag.

3. Blood collection tubes

Each blood collection kit includes two (2) 10ml EDTA (purple-top) tubes and two (2) 5ml SST (gold-top) tubes for blood collection.

4. Sterile pipettes and mixing vial

Four (4) sterile 1ml disposable pipettes and one (1) sterile mixing vial.

5. Cryovials

Seventeen (17) 2ml aliquot tubes (cryovials) for long-term cold storage of the serum, plasma, and buffy coat aliquots. The cryovials are pre-labeled with the blood kit number and barcode, as well as the specimen type. Furthermore, they have colored tops for easy identification of the type of specimen collected in each of them:

Sample Type	Cryovial Color
serum	yellow
plasma	purple
buffy coat	clear

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6. Cryobox

25-cell cryobox for freezing and shipping the aliquot tubes.

7. Extra Labels

1. Five general labels with lines for the PNRR site coordinator to write in the Site ID and Individual ID. These labels should be applied to the EDTA and SST tubes prior to blood collection.
2. One additional kit number label.
3. Two extra specimen labels for additional plasma cryovials, if needed.
4. One extra specimen label for additional serum cryovial, if needed.

NOTE: All blood kit supplies can also be ordered separately through the PNRR portal at <http://kits.iu.edu/pnrr>.

II. Blood Collection and Processing

II.a. General Remarks

- Blood should be collected from study participants at the initial (enrollment) visit. Ideally, the blood sample is collected on the same day the patient is examined by the enrolling physician. If that is not feasible, then the blood sample must be collected within three months of the enrollment visit.
- Blood is collected via standard venipuncture procedure at the enrollment site. Two (2) 10ml EDTA (purple-top) and two (2) 5 ml SST (gold-top) tubes are included in each blood collection kit provided by IU. The serum and plasma must be centrifuged, aliquoted, and placed in the freezer within 2 hours of the blood draw.
- Serum and plasma aliquots should be filled to 1ml, with the final aliquot being a residual (less than 1ml); see diagram below. This may result in extra, unused cryovials.

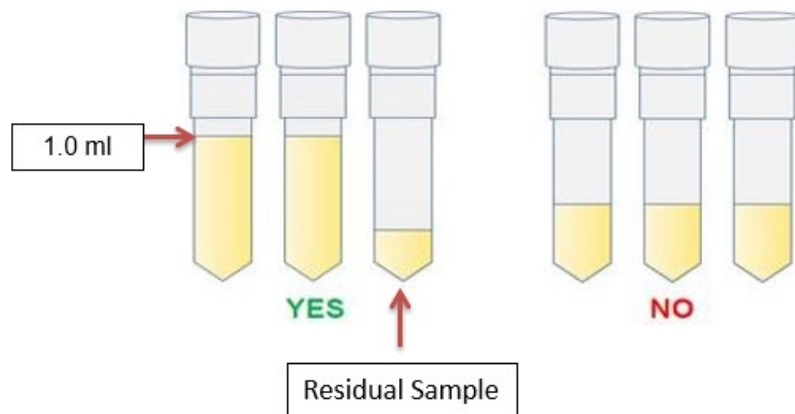


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II.b. Blood Collection

1. Prior to the blood draw, each collection tube should be labeled with the Site ID and the participant's Individual ID using the blank labels provided in the blood collection kits. Do not label the aliquot tubes with the Site ID or Individual ID.
2. Collect blood into the SST tubes and EDTA tubes using your institution's recommended procedure for standard venipuncture technique. Collect the blood into the SST tubes first. Per standard laboratory testing procedures, serum tubes should be filled prior to EDTA tubes to prevent anticoagulant contamination.
3. Immediately after blood collection, gently invert/mix the blood collection tubes 8-10 times.
4. Record the date and time of draw on the Blood Collection and Processing Form. Also record the date and time the patient last ate. Some biomarkers are influenced by the time elapsed since the last meal, so it is important to have that information available.

Note: Use the later time if a patient gives a time frame, e.g. record 7:00 am when a patient indicates that the last meal was "sometime between 6:30 and 7:00 am".

II.c. PLASMA processing (EDTA tubes)

5. The plasma collection tubes should be centrifuged as soon as possible after the blood draw (max. 30 minutes after draw) for 15 minutes at 1500 x g. If a centrifuge with refrigeration capabilities is available, the temperature should be set at 4°C. **It is critical that the EDTA tubes are centrifuged at the appropriate speed to ensure proper plasma separation and the formation of the buffy coat layer.**

Note: most standard blood centrifuges allow speed settings in either Relative Centrifugal Force (RCF) or Revolutions Per Minute (RPM). If RCF is used, the speed should be set at 1500; for RPM setting the required speed depends on the radius of the centrifuge. The PNRR site personnel shall verify the required RPM-setting to reach 1500 x g (for table-top centrifuges the RPM setting is between 2000-3000).

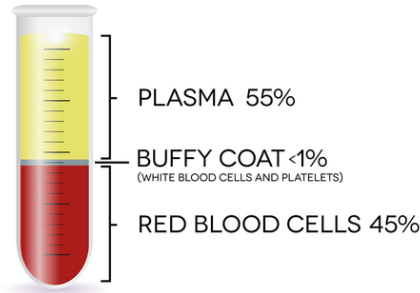
6. While centrifuging, record the start time and temperature of centrifugation on the Sample Form.

Note: If a refrigerated centrifuge is not available, the EDTA tubes may be centrifuged at room temperature and the room temperature should be recorded on the form.

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7. After centrifugation is complete, the EDTA tubes should be carefully removed from the centrifuge to avoid disturbing the cell layers and placed in a test tube rack.
8. There are three distinct layers after centrifugation: plasma, buffy coat (includes white blood cells) and the red blood cells (RBCs).



NOTE: if no buffy coat is visible at the plasma / RBC border, please check the centrifuge setting. If the centrifuge setting was lower than 1500 x g, please place the EDTA tubes back into the centrifuge and spin the samples for another 10 minutes at the correct centrifugation speed.

9. Verify that the blood kit number on the pre-labeled aliquot tubes matches the number on the Blood Collection and Processing Form.
10. Using a clean transfer pipette, transfer 1 ml aliquots of plasma into each pre-labeled plasma (purple-capped) cryovial. Each EDTA tube should yield, on average, 4.5 ml of blood plasma for a total of 8-10 plasma aliquots per subject. Record the number of aliquots created on the Blood Collection and Processing Form. If the final aliquot is less than 1ml (residual aliquot), record the volume of the residual aliquot and the last four digits of the barcode for that vial.
11. Using a clean transfer pipette, transfer the buffy coat from each EDTA tube into the 2 individual cryovials (clear-capped). Record the number of buffy coat aliquots created on the Blood Collection and Processing Form.
Note: The buffy coat is a layer of white blood cells used to extract DNA. To ensure that the DNA yield is sufficient, the entire layer must be collected, which usually means that some RBC's are also collected, which explains why buffy coat samples usually appear red or pink. An instruction video for buffy coat collection is posted on the PNRR website.
12. Place the filled plasma and buffy coat vials into the provided cryobox cap-side up. Discard all unused purple-top cryovials.

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II.d. SERUM processing (SST tubes)

13. After the blood draw, allow the blood inside the SST tubes to clot for at least 20-30 minutes. Centrifuge the SST tubes (with appropriate balanced tubes) at room temperature for 15 minutes at 1500 x g. **It is critical that the tubes be centrifuged at the appropriate speed to ensure proper filtering of the serum from the red blood cells.**

***Note:** most standard blood centrifuges allow speed settings in either Relative Centrifugal Force (RCF) or Revolutions Per Minute (RPM). If RCF is used, the speed should be set at 1500; for RPM setting the required speed depends on the radius of the centrifuge. The PNRR site personnel shall verify the required RPM-setting to reach 1500 x g (for table-top centrifuges the RPM setting is between 2000-3000).*

14. While centrifuging, record the start time of centrifugation on the Sample Form.
15. After centrifugation is complete, the SST tubes should be carefully removed from the centrifuge and placed it in a test tube rack.

***NOTE:** If only a small amount of serum is separated from the RBC layer, or if the gel is still sitting on the bottom of the blood tube, the tube was not centrifuged at the appropriate setting. Check the centrifugation speed and time. Re-centrifuge the SST tubes at the correct speed for an additional 10 minutes.*

16. Using a clean transfer pipette, carefully transfer the serum from both SST tubes into the mixing vial provided in the blood collection kit.
17. Mix the collected serum in the mixing vial by drawing the serum up into the pipette 4-6 times. Alternatively, cap the mixing vial tightly and carefully invert 4-6 times.
18. Using a clean transfer pipette, transfer 1 ml aliquots of serum into the pre-labeled serum cryovials (yellow-capped). Each serum tube should yield, on average, 2.5 ml of blood serum for a total of 4-5 serum aliquots per subject. Record the number of aliquots created on the Sample Form. If the final aliquot is less than 1ml (residual aliquot), record the volume of the residual aliquot and the last four digits of the barcode on the Blood collection and processing form.
19. Transfer all serum aliquots into the cryobox, cap-side up. Discard all unused yellow-cap cryovials.
20. Place the cryobox into the biohazard bag remove the air and seal the biohazard bag for storage/freezing. Place the samples into a -80°C freezer immediately after processing is complete. Be sure to freeze the samples cap-

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side up. Record the time that aliquots were placed into the freezer on the Blood Collection and Processing Form.

NOTE: *If a -80°C freezer is not immediately accessible, the aliquots may be stored in a -20°C freezer or on dry ice for several hours prior to being transferred to the -80°C freezer.*

21. Discard the SST and EDTA collection tubes and processing materials according to site guidelines for disposing of biomedical waste.

III. Sample Shipments

III.a. Shipment Supplies

- Required materials to transfer specimens from the enrollment center to IU will be assembled at IU and shipped to each site. The PNRR site coordinators will be responsible for informing IU of the materials the site requires at least ten (10) business days in advance, using the PNRR-portal: [http:// kits.iu.edu/pnrr](http://kits.iu.edu/pnrr).
- The provided shipping materials include:
 1. Styrofoam insulated shipping boxes
 2. Pre-addressed shipping labels
 3. Dry ice shipping labels
 4. “UN3373: Biological Substance, Category B” stickers
 5. “Fragile” stickers
- Insulated shipping boxes are available in two sizes. Small shippers hold samples from one to four individuals (plus dry ice). Large shippers should be used to send samples from four to eight individuals.

NOTE: *All PNRR samples must be shipped on dry ice. The enrollment centers are responsible for providing the required dry ice for the shipments.*

III.b. Shipping Instructions

- **All blood samples MUST be shipped to IU within 2 weeks of collection.**
- Samples can be shipped to IU on Monday, Tuesday, or Wednesday. Do not ship samples on Thursday or Friday.
- The blood kits and shipping materials provided by IU are designed to comply with all Department of Transportation rules regarding the shipment of blood samples. Please assemble the shipment as instructed to assure compliance.
- Notify IU of incoming sample shipments via email prior to shipment using the pnrr@iupui.edu email address. The shipment tracking number should be included in the shipment notification.

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1. Packaging the blood sample

1. Only one participant's blood sample should be included in each cryobox. Multiple cryoboxes may be sent in one shipping container as long as there is room for an adequate amount of dry ice, but please request a bulk shipper if sending more than three cryoboxes in a shipment.
2. Verify that there is an absorbent sheet in the biohazard bag with the cryobox, and ensure that the biohazardous bag is sealed.
3. The insulated shipping container should be filled first with a layer of dry ice, followed by a layer of cryoboxes, another layer of dry ice and another layer of cryoboxes, topped with a thick layer of dry ice to ensure that the samples stay frozen even if the shipment takes longer than 24 hours.
4. Copies of the sample forms for the specimens should be included in the shipment and should be placed outside the Styrofoam liner.
5. Ensure the Styrofoam lid is in place (shut) before placing tape on the outside cardboard shipping box to close it securely.
6. Weigh the package to determine the weight of the dry ice used in the shipment in kg.

NOTE: *The weight of the dry ice should always be rounded up. It is better to report a higher amount of dry ice than to underestimate the amount.*

2. Shipment labeling and paperwork

7. Log in to the IU UPS ShipExec™ portal at: <https://kits.iu.edu/UPS>
8. Find the "Shipping" dropdown menu in the top left corner of the screen and click on "Shipping and Rating."
9. Once the Indiana University page loads, look for the "Study Group" dropdown menu under "Shipment Information" on the right side of the screen. Choose "PNRR" from the dropdown menu.
10. After selecting "PNRR," click on the magnifying glass icon on the left side of the screen under "Ship From."
11. An address book and filter function will appear on the screen. A list of all the PNRR site addresses should appear on the right side of the screen
 - a. Once you have found your site address, click on the "Select" button to the left of the address.

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12. Make sure your address appears 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 “PNRR” again from the “Study Group” menu and click on the magnifying glass icon again to search for your correct address.

13. 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.

14. 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 15-16 can be skipped if you do not need to schedule a pickup)**

15. After entering the weights, click on the blue “Pickup Request” button.

16. 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”
 - ii. Enter times in 24-hr format (Ex: 14:00 for 2pm)
 - 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 up to 8 characters.
 - d. Click “Save” when done.

17. Once you are certain that all the correct information has been entered, click the “Ship” button in the bottom right corner of the screen.

18. If no red error messages pop up at the top of your screen after clicking on “Ship”, then two PDF files should have downloaded: “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 for scheduled pickups

19. Print out the UPS air waybill label that downloads to your computer, fold it in half, place it inside the clear UPS sleeve.

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20. Peel the backing off the clear sleeve, and affix the clear sleeve to the top of the outside cardboard of the dry ice shipping container.
21. Fill out the dry ice label by providing both shipper and recipient information (see below) and the amount of dry ice used to keep the blood samples frozen. Affix the dry ice label to the front of the outside cardboard box of the dry ice shipping container.

Recipient Information:

PNRR at IUGB
351 West 10th Street, TK-217
Indianapolis, IN 46202
Phone: 317-278-6158

NOTE: *The courier may refuse to accept the shipment if the dry ice weight is not recorded correctly. Ensure that the same amount of dry ice is recorded on both the airway bill and the dry ice label.*

22. Affix the “UN 3373: Biological Substance, Category B” and “Fragile” stickers to the front of the outside cardboard of the dry ice shipper, next to the dry ice label.
23. Place your package in the spot designated in your pickup request, or wherever your daily UPS pickups occur.

NOTE: If you need to reprint your air waybill 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 air waybill, 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”

IV. Saliva Collection

If PNRR site personnel receives notification of an insufficient DNA yield, personnel at the enrollment center should attempt to collect a saliva specimen from the patient.

Saliva collection kits can be ordered via the PNRR-portal at <http://kits.iu.edu/pnrr>

Each saliva collection kit includes the following items:

1. Saliva collection kit with instructions
2. PNRR Biological Sample Form
3. Biohazard bag
4. Pre-labeled and postage-paid shipping envelope
5. UN 3343 exempt sticker

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IV.a Saliva Collection Instructions

***Note:** each saliva collection kit contains an insert with detailed instructions including diagrams how to collect a viable saliva sample.*

For saliva collections at the enrollment center:

1. The patient cannot eat, drink, smoke or chew gum for 30 minutes before the saliva collection.
2. Using a blank Subject/Site ID label from the IU-provided kit, label the saliva collection tube with the subject's ID.
3. Ask the patient to spit into funnel until the amount of liquid saliva (not bubbles) reaches the fill line. It takes approximately 5 minutes to collect a sufficient amount of saliva.
4. Close the funnel lid by firmly pushing the lid downwards until the liquid inside the lid is released into the tube.
5. Hold the tube upright. Remove the funnel and screw the small blue cap on the tube. Ensure cap is secured tightly.
6. Invert sample several times to mix saliva with stabilization liquid.
7. Label the saliva sample with the subject ID.
8. Place the tube in the bio-specimen bag, peel off the blue liner and seal the bag by pressing down on the glue line.

Shipment instructions (from enrollment center):

9. Complete the "PNRR Biological Sample Form" and place form in shipment envelope together with the saliva sample itself.
10. Mail envelope to PNRR@IUIGB within 48 hours after collection using the provided postage-paid padded envelopes. Verify the address and ensure that an "exempt human specimen" sticker is on the envelope.

PNRR @ IUIGB
351 W 10th Street, TK217
Indianapolis, IN 46202
Phone: 317-278-6158

Mailing saliva collections kits to the subjects:

1. Using a blank Subject/Site ID label from the IU-provided kit, label the saliva collection tube with the subject's ID.

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2. Fill out the PNRR Biological Sample Form (contact information should be for the PNRR site personnel sending the saliva collection kit to the patient).
3. Mail the saliva collection kit to patient, in combination with a letter summarizing the request and instructions. A letter template is provided on the PNRR website.