

# PNRR Standard Operating Procedure

## EXHIBIT C

### Standard Operating Procedure (SOP) for Peripheral Neuropathy Research Registry (PNRR)

The Peripheral Neuropathy Research Registry (PNRR) is a research project that was initiated by *the* Foundation *for* Peripheral Neuropathy (the “Foundation”) to advance the knowledge about peripheral neuropathies.

The PNRR General Standard Operating Procedures provide additional information about enrollment proceedings, specifically detailing when recruited participants count as fully enrolled patients.

All PNRR data is entered into a REDCap database maintained by Indiana University School of Medicine (IU); the collected biospecimen are cataloged and maintained by the Indiana University Genetic Biobank (IUGB). Access to the PNRR data (in full or partly) and distribution of blood samples for research is at the discretion of the Foundation and has to be requested in form of a written research proposal.

#### 1. PNRR Consortium Members

The Foundation has organized a consortium of research institutions to enroll patients into the study, entering the relevant medical information into the REDCap database, and collecting and processing blood samples from each participant. The contract between the consortium members and the Foundation is renewed on an annual basis.

Active (enrolling) consortium members for the 2018 year include:

- Johns Hopkins University, Baltimore, MD
- Icahn School of Medicine at Mount Sinai Medical Center, New York, NY
- Northwestern University, Evanston, IL
- University of Utah, Salt Lake City, UT
- University of Kansas Medical Center, Kansas City, KS

Consortium members no longer enrolling new patients:

- Beth Israel Deaconess Medical Center, Boston, MA

The consortium agreement between the consortium members and *the* Foundation *for* Peripheral Neuropathy are renewed on an annual basis, detailing the enrollment allocations for each consortium member.

#### 2. Individual Subject IDs

Only de-identified data is entered into the PNRR REDCap database, and a unique individual ID must be assigned to each participant at the time of enrollment. Each site will be assigned a block of 10,000 Individual IDs. The blocks of IDs have been assigned as follows:

- 10000 - 19999: Johns Hopkins University (Site ID: JH)
- 20000 - 29999: Mount Sinai Hospital Medical Center (Site ID: MS)

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- 30000 - 39999: Beth Israel Deaconess Medical Center (Site ID: BI)
- 40000 - 49999: Northwestern Medical Faculty Foundation (Site ID: NW)
- 50000 - 59999: University of Utah (Site ID: UU)
- 60000 - 69999: Kansas University (Site ID: KU)

The PNRR site coordinators will be responsible for assigning Individual IDs and ensuring that each participant is assigned a unique ID.

All data entry forms need to be completed using the same subject ID for the individual. The same ID should also be used for follow-up visit data entries.

### 3. Inclusion Criteria

Patients diagnosed with distal, symmetrical polyneuropathy without an identified cause for the nerve damage (idiopathic), and patients with polyneuropathy caused by diabetes mellitus, the exposure to chemotherapy-drugs with known nerve-toxicity, or PN associated with HIV/AIDS are eligible to be enrolled in the study.

Patients with other identified causes for their peripheral nerve damage are not eligible. Patients with other medical conditions superimposing their polyneuropathy – such as patients with severe spinal stenosis or myopathies – are also not eligible. Patients with predominantly demyelinating neuropathies should only be enrolled when they are diagnosed with DPN, CIPN or HIV/AIDS associated PN.

### 4. PNRR Visit Information Forms

The PNRR database includes five visit information forms:

- A. Physician Examination Form (PEF)**
- B. Nerve Conduction Studies Form (NCS)**
- C. Peripheral Nerve Work-Up Form (PNW)**
- D. Patient History Questionnaire (PHQ)**
- E. Blood Collection and Processing Form**

All five forms must be complete in order for a patient to be considered as fully enrolled.

Printable versions of all forms are available on the PNRR website ([https://thepnrr.org/study\\_resources.html](https://thepnrr.org/study_resources.html)).

Per HIPPA regulations, the PNRR site personnel under the supervision of the site Principal Investigator may maintain paper or electronic copies of the data entry forms (source material) together with the Informed Consent Form signed by each PNRR participant.

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### A. Physician Examination Form (PEF)

The Physician Examination Form (PEF) captures the results of routine examinations to diagnose and evaluate peripheral neuropathies. The examination is to be performed by a trained neurologist familiar with the PNRR study.

The PEF information is to be entered into REDCap by the PNRR site personnel. No field on this form should be left blank. If some assessments were not performed by the examining physician, the data entry fields should be labeled as "Not Done". Unpopulated data entry fields result in a data query error when the form is exited in REDCap.

The PEF form has a Minimum Data Set (MDS) of evaluations that are required to be performed for each patient by the enrolling physician.

The SOP's for the PEF form are detailed in Appendix A, a printable copy of the PEF-Form is available on the PNRR web site ([https://thepnrr.org/study\\_resources.html](https://thepnrr.org/study_resources.html)).

### B. Nerve Conduction Study Form (NCS)

The results of Nerve Conduction Studies performed on major motor and sensory nerves in arms and legs are captured in the Nerve Conduction Study (NCS) form. Only NCS testing information from trusted sources should be entered in this form.

This form must be entered in the REDCap database by the PNRR site personnel. Unanswered questions will result in a data query error when the form is exited in REDCap.

Patients without NCS testing performed are still eligible for PNRR enrollment, but the reimbursement may be reduced for patients without neither NCS nor skin biopsy information on file. The NCS Form does not have a MDS.

The SOP's for the NCS form are detailed in Appendix B, a printable copy of the NCS-Form is available on the PNRR web site ([https://thepnrr.org/study\\_resources.html](https://thepnrr.org/study_resources.html)).

### C. Peripheral Nerve Work-Up Form (PNW)

The findings and results from diagnostic laboratory tests are captured in the Peripheral Nerve Work-Up (PNW) Form. Laboratory tests listed in the first tier are part of the MDS for new enrollments. The MDS testing for the PNW form is considered the absolute minimum. It is expected that all enrollment centers are putting forward their best effort to provide as much information about conducted laboratory testing as possible.

Only laboratory testing performed within 36 months prior to enrollment and 12 months after enrollment should be entered into the PNW form in REDCap. The laboratory testing results must be entered into the PNW form in the REDCap database by the PNRR site personnel. Unanswered questions will result in a data query error when the form is exited in REDCap.

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The SOP's for the PNW form are detailed in Appendix C, a printable copy of the PNW-Form is available on the PNRR web site ([https://thepnrr.org/study\\_resources.html](https://thepnrr.org/study_resources.html)).

### D. Patient History Questionnaire (PHQ)

The PHQ may be completed by the participant alone (on paper) or with the assistance of the site coordinator. The answers of the patient provided in the PHQ must be entered in the REDCap database by the PNRR site personnel.

The SOP's for the PHQ are detailed in Appendix D of this document. A printable copy of the PHQ is available on the PNRR web site ([https://thepnrr.org/study\\_resources.html](https://thepnrr.org/study_resources.html)).

### E. Blood Collection and Processing Form

The Blood Collection and Processing Form captures details about the collected blood sample. A paper copy of the Sample Collection and Processing Form is included in each collection kit.

The blood collection and processing information is entered into REDCap by PNRR site personnel, but the form should not be marked as completed by the PNRR site personnel. After the samples are received by IU, IU-personnel will enter information about the condition of the samples and mark the form as complete.

The SOP's for the Biospecimen Collection, Processing and Shipment are detailed in Appendix E of this document, printable copies of the Biospeciment Collection-Forms are available on the PNRR web site ([https://thepnrr.org/study\\_resources.html](https://thepnrr.org/study_resources.html)).

## 5. Minimum Data Set

IU-personnel checks the PNRR database once a week for newly completed records (all five data entry forms are marked as complete in REDCap). All newly completed records are checked for any MDS-violations and a report is generated. Missing MDS information due to other medical conditions are reported by the site and will not be considered MDS violations that prevent reimbursement.

The PEF and PNW forms have a clearly defined MDS data set. The MDS is considered the absolute minimum of information that has to be provided for both forms. It is expected that the patients are providing answers to all questions, and unanswered question are also considered MDS violations. The NCS does not have a defined MDS, and the minimum requirement for blood samples is specified below.

## 6. Minimum Blood Sample

Plasma, Serum and DNA are required for a patient to count as fully enrolled. Ideally, samples are collected the day of the neurological examination. If that is not feasible, it is acceptable that the blood sample is collected within three months of the visit.

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For a blood sample to be considered complete, a minimum of three (3) serum aliquots (total of 2.5 ml or more), five (5) plasma aliquots (total of 4.5 ml or more), and one (1) buffy coat specimen have to be received by IU in good condition.

### **6.a. DNA Yield**

After buffy coat aliquots arrive at IU, the DNA is extracted and a DNA yield is recorded for each PNRR participant in the OnCore Sample Management System. IU will include a list of buffy coats extracted with insufficient DNA yield in each quarterly report. The enrollment sites are then expected to contact these patients and ask for an additional saliva sample.

## **7. Data Quality Assessment (DQA)**

For all new PNRR enrollments, the PNRR Project Manager (PNRR-PM) will perform a remote Data Quality Assessment (DQA) within 30 days of the record being reported as complete by IU. The date of DQA completion is entered into the Data Quality Assessment (DQA) form in REDCap by the PNRR-PM with a summary of the DQA comments. The PNRR-PM shall also notify the lead PNRR-personnel at the enrollment site about the DQA status and any comments.

The enrollment site then has 30 days to respond to the DQA comments by either updating the information in the database or by providing a justification for non-compliance. After the information update is completed, the PNRR site personnel shall report the date of update completion in the DQA form and inform the PNRR-PM accordingly.

The PNRR-PM shall then review the updates and mark the DQA as completed with a recommendation to the foundation regarding payment.

## **8. Fully-Enrolled Records**

A fully-enrolled record is an initial visit for which (a) sufficient serum, plasma and DNA samples were received by IU in good condition; (b) all required forms were completed and no MDS-violations were reported, and (c) the DQA process was completed.

### **8.a. Fully Enrolled Records with missing NCS information**

The information entered in the NCS form is important for the full evaluation of peripheral neuropathy, and should be provided for all PNRR participants. However, sometimes NCS testing is not clinically necessary for the diagnosis or NCS testing has been done at an outside institution and does not need to be repeated. Patients with missing NCS information will still count as fully enrolled, but the reimbursement amount will be reduced.

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## 9. Incomplete Records

Valid Incomplete Records are all enrollments for whom (a) an insufficient or damaged serum, plasma, and DNA sample was received by IU; or (b) have PNW and/or PEF MDS violations not caused by other medical conditions of the patient, or an incomplete PHQ; or (c) DQA comments were not addressed by the enrollment site within 30 days.

Valid Incomplete Records count towards the overall PNRR enrollment numbers, but the enrollment sites will not necessarily be reimbursed for their efforts.

A report of incomplete records older than 90 days will be generated at the end of each quarter and the enrollment centers will be informed accordingly for resolution.

## 10. Follow-Up Visits

Follow-up data entries for returning patients shall be entered into the PNRR database on a regular base, as long as at least 12 months have elapsed since the last visit information was entered.

For each Follow-Up visit, the PEF and PHQ forms must be completed. NCS and PNW forms should only be completed to report additional laboratory results or additional NCS testing that was not reported in previous data entries. Blood samples should not be collected during follow-up visits unless more than three years have elapsed since the previous blood collection, or the site has been notified of a re-draw request for the patient.

## 11. Reporting

### 11.a. New Enrollment Reports

IU generates a report of new completed enrollments on a weekly basis, which is provided to the Foundation and the PNRR-PM; the Foundation distributes the enrollment reports to the consortium members and the FPN board at regular time intervals.

### 11.b. DQA Status Report

At the end of each quarter, the PNRR-PM shall send a DQA report to the consortium members and the foundation, reporting when the initial DQA was performed, if the DQA was completed, and recommendations for payment.

### 11.c. Quarterly Enrollment Reports by Consortium Members

All actively enrolling consortium member sites shall send quarterly enrollment reports to the foundation. The reporting template shall be sent to the consortium members at the end of each quarter with the date when the reports are due.

The general template for these reports is as follows:

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| Quarter        | End of Quarter | Report Due Date |
|----------------|----------------|-----------------|
| First Quarter  | March 31       | April 15        |
| Second Quarter | June 30        | July 15         |
| Third Quarter  | September 30   | October 15      |
| Fourth Quarter | December 31    | January 15      |

### 12. Funding and Payments

The number of patients which can be enrolled into PNRR may vary each calendar year will be detailed in the annual Consortium Member Agreement, together with the details about reimbursement of the consortium members for each new enrollment.

**Attachment A**  
**PNRR SOP for Physician Examination Form (PEF)**

**Physician Examination Form (PEF)**

- **ALL DATA ENTRY FIELDS OF THE PHYSICIAN EXAMINATION FORM MUST BE POPULATED. Only Cold Sense and Monofilament evaluations are considered optional, all other tests are required for all PNRR participants.**
- All abnormalities reported in the Physician Examination Form should be related or caused by Peripheral Neuropathy.

**GENERAL INFORMATION**

1. **Physician:** name of examining physician (last name only)
2. **Year of Visit:** calendar year the exam was performed
3. **Sex:** genetic sex of patient – male or female
4. **Year of birth:** year patient was born
5. **Weight:** weight measured on the day of exam in English pounds (lbs)
6. **Height:** last measured height in inches

*Note: the entered weight and height information will automatically be converted into kilograms (kg) and centimeters (cm) and Body Mass Index (BMI) will be calculated*

**NEUROPATHY CLASSIFICATION**

**7. Type of PN (Peripheral Neuropathy):**

Evaluation if patient experiences pain associated with the peripheral neuropathy

Scale: Painful: patient has pain symptoms which are caused by PN

Non-Painful: patient does not experience pain sensations associated with PN

**8. Primary Diagnosis:**

- a. **Diabetic PN:** shall be chosen as the category if the patient is diagnosed with diabetes mellitus or pre-diabetes and examining physician determines that this condition is most likely the cause of the neuropathy.

**Type of diabetes mellitus** must be identified for all study participants with diabetic PN:

Values: **Type 1** – diabetes mellitus type 1

**Type 2** – diabetes mellitus type 2

**Pre-diabetic** – patients diagnosed with either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) can be categorized as pre-diabetic at the physician's discretion.

- b. **Chemotherapy-Induced PN:** shall be chosen as the category if the patient received chemotherapy treatment and the examining physician agrees that the chemotherapy drugs most likely cause the neuropathy.



## Attachment A

### PNRR SOP for Physician Examination Form (PEF)

- c. **HIV/AIDS:** PN shall be categorized as caused by HIV/AIDS if the patient is diagnosed with HIV and the examining physician agrees that either HIV or the intake of HIV-suppressing drugs are most likely the cause for the neuropathy.
- d. **Idiopathic PN:** if the cause of the neuropathy is unknown and all common causes of neuropathy are negative, the examining physician may categorize the PN as idiopathic.
- e. **Other:** If patients with known causes of neuropathy other than Diabetic, Chemotherapy, or HIV/AIDS were enrolled in the study, the primary diagnosis should be "Other".

#### 9. Secondary Diagnosis:

If patient has a secondary diagnosis for peripheral neuropathy, it should be listed here. For example, if a patient has a mild inherited neuropathy which was significantly worsened by diabetes mellitus, then the Primary Diagnosis should be Diabetic, and the Secondary Diagnosis should be Inherited.

If a patient has two identified causes of neuropathy, which are both listed under primary diagnosis, then it will be to the discretion of the examining physician to determine which diagnosis should be considered primary and which one secondary.

### CRANIAL NERVE EXAM

#### 10. Facial sensation:

Method of evaluation at physician's discretion. Findings from exam are reported as Normal or Abnormal. Only observations with relevance to Peripheral Neuropathy should be considered.

Values:    **Normal:** physician examination suggests normal facial sensation  
              **Abnormal:** physician examination reveals abnormal or absent facial sensations caused by peripheral neuropathy  
              **Not Done:** facial sensation was not evaluated

#### 11. Facial movement:

Method of evaluation at physician's discretion. Only observations with relevance to Peripheral Neuropathy should be considered for the score.

Values:    **Normal:** physician examination suggests normal facial movements  
              **Abnormal:** physician examination reveals abnormal or absent facial movements caused by peripheral neuropathy  
              **Not Done:** facial movements were not evaluated

#### 12. Hearing:

Method of evaluation at physician's discretion; "finger rubbing" is recommended.

Values:    **Normal:** patient can hear finger rubbing or similar noise  
              **Abnormal:** patient not able to hear finger rubbing or has reduced hearing of finger rubbing  
              **Not Done:** hearing was not evaluated

**Attachment A**  
**PNRR SOP for Physician Examination Form (PEF)**

**MUSCLE EXAMINATION**

**Upper Extremities:**

- 13. Arm abduction
- 14. Elbow flexion
- 15. Elbow extension
- 16. Wrist extension
- 17. Wrist flexion
- 18. Finger extension
- 19. Interossei and Abductor Digiti Minimi (ADM)
- 20. Abductor Pollicis Brevis (APB)

**Lower Extremities:**

- 21. Hip flexion
- 22. Knee extension
- 23. Knee flexion
- 24. Ankle dorsiflexion
- 25. Great toe dorsiflexion
- 26. Great toe plantar flexion

The method how muscular function is evaluated shall be at the physician’s discretion. The findings from the exam shall be transferred into the PNRR data base using a simplified Medical Research Council (MRC) scale.

**Table 1: PNRR Reference Scale for Muscle Examination**

| PNRR Scale | MRC Scale | Description of Muscular Power  |
|------------|-----------|--|
| 2          | 5/5-      | Normal muscular power  |
| 1          | 4+/4/4-   | Active movement against gravity with reduced movement against resistance |
|            | 3         | Active movement against gravity but not against resistance               |
|            | 2         | Movement against gravity eliminated                                      |
| 0          | 1         | Only flicker of movement   |
|            | 0         | No movement  |

**Not Done:** ND shall be entered if the muscle strength of a particular muscle was not evaluated.

**DEEP TENDON REFLEXES**

The following reflexes shall be examined:

- 27. Biceps
- 28. Triceps
- 29. Brachioradialis
- 30. Patellar

**Attachment A**  
**PNRR SOP for Physician Examination Form (PEF)**

**31. Achilles**

The method of examination is at the discretion of the examining physician.

The following Tendon Reflex Scale shall be used to transfer the examination results into the PNRR Physician Examination Form:

**Table 2: PNRR Reference Scale for Tendon Evaluation**

| PNRR Database Scale | Tendon Reflex Rating Scale | Description of Reflex Response  |
|---------------------|----------------------------|---|
| 0                   | 0                          | Reflex absent with reinforcement  |
| 1                   | 1                          | Reflex present but decreased in amplitude and velocity and only elicit with reinforcement         |
| 2                   | 2                          | Normal amplitude and velocity without reinforcement   |
| 3                   | 3                          | Increase in amplitude and velocity without any pathological symptoms                              |
| Exclusion Criteria  | 4                          | Increase in amplitude and velocity, spreading to other sites and/or duplication of jerk or clonus |

**Not Done:** ND shall be entered if a certain reflex was not evaluated

**LOCOMOTION AND BALANCE**

**32. Gait:**

Observation of regular walking pattern at the discretion of the physician.

Only gait abnormalities related to Peripheral Neuropathy should be considered when determining if gait is normal/abnormal on this form.

Values: **Normal:** gait is considered normal or abnormalities are not related to PN  
**Abnormal:** gait is abnormal and symptoms are (expected) caused by PN  
**Not Done:** gait was not evaluated

**33. Tandem gait:**

Toes of the back foot touch the heel of the front foot at each step. Observation of ability to tandem walk at the discretion of the physician.

Values: **Able:** patient is able to perform tandem gait without problems.  
**Not Able:** patient unable to perform five (5) steps in tandem gait  
**Not Done:** tandem gait was not evaluated

**34. Toe walk:**

Patient is asked to walk across the room on toes.

Values: **Able:** patient is able to walk on tiptoes  
**Not Able:** patient unable to take more than five (5) steps while on tiptoes  
**Not Done:** toe walk was not evaluated

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**35. Heel walk:**

Patient is asked to walk on heel (with toes lifted off the ground) across the room.

Values: **Able:** patient is able to walk on heels

**Not Able:** patient unable to take more than five (5) steps on heels

**Not Done:** heel walk was not evaluated

**36. Romberg:**

Patient is asked to stand in middle of room and maintain standing position for at least five (5) seconds after closing eyes. The examining physician may determine if Romberg is present or absent.

Values: **Absent/Negative:** if patient is able to stand with eyes closed for five (5) seconds or longer.

**Present/Positive:** patient falls or demonstrates excessive swaying after closing eyes.

**Not done:** Romberg was not evaluated

**SENSORY EXAMINATION**

Testing sites for all sensory examinations include toes (hallux), ankle and fingers (digit 2). If examination of the toe reveals normal sensory responses, evaluation at the ankle is NOT required.

**37. Pinprick:**

Sharp needle-like object should be used for pinprick examination. Needle-like object is then used to place on skin and apply some pressure so skin is “slightly dented” but not pierced. During the test the patient should close eyes and reports whenever he/she feels needle-like object touching.

Testing Locations:

**Toes:** Dorsum of hallux at IP joint

**Ankle:** Front of ankle between the internal and external malleolus

**Fingers:** Dorsum of index finger at DIP joint

**2 = Normal:** regular sensation to pinprick (Note: if patient is hypersensitive to pinprick, it should also be marked as normal and the hypersensitivity should be mentioned in the Notes data entry field)

**1 = Reduced:** patient feels pinprick, but sensation is reduced (less sharp)

**0 = Absent:** patient cannot differentiate between sharp or dull objects touching

**Not Done:** pinprick was not evaluated

**38. Cold sense (optional):**

Testing should be performed with a cold turning fork. Testing protocol and results at the discretion of the examining physician. Data from the cold sense test should not be entered into the PNRR database, when the test was performed under less than ideal

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### PNRR SOP for Physician Examination Form (PEF)

conditions and the results are compromised, e.g. the patient had very cold extremities when test was performed.

Testing Locations:

**Toes:** Dorsum of hallux at IP joint

**Ankle:** Front of ankle between the internal and external malleolus

**Fingers:** Dorsum of index finger at DIP joint

Values: **2 = Normal:** regular sensation to cold touch

**1 = Reduced:** patient has reduced cold sensation

**0 = Absent:** patient unable to detect "cold"

**Not Done:** cold sense evaluation was not performed

#### 39. Vibration sense:

Rydel-Seiffer tuning fork (64 Hz) should be used for evaluation of vibration sense. The patient is asked to report when he/she no longer feels the "vibration" from the fork at the testing site. The physician shall read the value off the black triangle on the left damper as soon as the patient reports that he no longer can feel any vibration (scale 0-8).

After the tuning fork is put into motion its base shall be positioned at the following testing sites:

**Toes:** dorsum of hallux at IP joint

**Ankle:** internal or external malleolus

**Finger:** dorsum of index finger, over DIP joint

Values: **2 = Normal** (see Table below): All readings equal or higher than the listed values

**1 = Reduced:** For readings below the "normal values" as long as the patient still detected some of the vibrations from the fork.

**0 = Absent:** patient was unable to detect any vibrations from the tuning fork

**Not Done:** vibration sense evaluation was not performed

Table 3: Normal values for Rydel-Seiffer tuning fork

| Age   | Upper Limbs | Lower Limbs |
|-------|-------------|-------------|
| ≤40   | ≥6.5        | ≥4.5        |
| 41-60 | ≥6.0        | ≥4.0        |
| 61-85 | ≥6.0        | ≥3.5        |
| >85   | ≥5.5        | ≥3.0        |

#### 40. Joint position sense:

Movement of toes, fingers and ankle by physician. Patient has to identify upwards or downwards movement of limb while eyes are closed. Exam result at physician discretion.

The identified testing sites for the joint position sense are:

**Toes:** IP joint of hallux

**Ankle:** ankle joint

**Finger:** DIP joint of Digit 2 (index finger)

Values: **2 = Normal:** joint position sense is not impaired

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### PNRR SOP for Physician Examination Form (PEF)

- 1 = Reduced:** impaired joint position sense, but patient still able to detect movement
- 0 = Absent:** patient unable to reliably identify joint movements
- Not Done:** joint position sense was not evaluated

#### 41. Monofilaments (optional):

Testing should be done using Semmes-Weinstein Monofilaments. Patient should look away while test is performed. Avoid areas of callus, abrasions, scars or other blemishes. During testing the monofilaments shall be pressed against the skin at a 90 degree angle until the monofilament bows. The monofilament should be held in place for about 1.5 seconds. For smaller monofilaments (0.07 to 1 gram) the stimulus should be applied three times until it is determined that the test is negative. One single positive response out of the three trials shall be considered a positive test.

The identified testing sites for the monofilaments are:

- Toes:** Hallux, dorsum side of IP joint
- Ankle:** testing to be done in front of ankle between internal and external malleolus
- Fingers:** Index finger, dorsum side of DIP joint

- Values:
- 2 = normal:** patient able to detect touch of fine filaments (see tables 4+5 below)
  - 1 = reduced:** patient able to feel medium size monofilaments (see tables 4+5 below)
  - 0 = absent:** patient can only feel very large monofilaments (see 4+5 tables below)
  - Not Done:** monofilament testing was not performed

Table 4: PNRR Reference Table to Monofilament Evaluation - **Index Finger**

| PNRR Scale | Force (grams) | Size | Color  | Description                     |
|------------|---------------|------|--------|---------------------------------|
| 2          | 0.07          | 2.83 | Green  | Normal                          |
| 1          | 0.4           | 3.61 | Blue   | Diminished light touch          |
|            | 1.0           | 4.08 | Purple | Diminished protective sensation |
|            | 2.0           | 4.31 |        |                                 |
| 0          | 4.0           | 4.56 | Red    | Loss of protective sensation    |
|            | 10.0          | 5.07 |        |                                 |
|            | 300           | 6.65 |        | Deep pressure sensation only    |

**Attachment A**  
**PNRR SOP for Physician Examination Form (PEF)**

Table 5: PNRR Reference Table to Monofilament Evaluation - **Toes and Ankle**

| PNRR Scale | Force (grams) | Size | Color  | Description                     |
|------------|---------------|------|--------|---------------------------------|
| 2          | 0.07          | 2.83 | Green  | Normal                          |
|            | 0.4           | 3.61 | Blue   | Diminished light touch          |
| 1          | 1.0           | 4.08 | Purple | Diminished protective sensation |
|            | 2.0           | 4.31 |        |                                 |
|            | 4.0           | 4.56 | Red    | Loss of protective sensation    |
| 0          | 10.0          | 5.07 |        | Deep pressure sensation only    |
|            | 300           | 6.65 |        |                                 |

**42. NOTES:**

Additional information should be entered here. For example, if some evaluations were not performed due to other injuries or medical conditions which are not associated with neuropathy, those should be explained in the Notes.

**43. Date Data Entry Completed:**

Date should be entered when data entry was **completed**.

**44. Physician Examination Form (PEF) Status:**

- **Incomplete:** not all data is entered yet
- **Unverified:** all data is entered, but waiting for confirmation for some data (for example, when waiting for confirmation about primary diagnosis pending lab results, the form should be considered unverified)
- **Complete:** all information is verified, no additional edits are anticipated

**Attachment B**  
**PNRR SOP for Nerve Conduction Study Form (NCS)**

**Nerve Conduction Study Form (NCS)**

The Nerve Conduction Study Form (NCS) should be submitted every time a Nerve Conduction Study (NCS) is performed with a PNRR participant. **It is required that a NCS data entry form is completed in the PNRR data base for the initial (enrollment) visit.** For follow-up visits, a NCS form should only be filled out when a nerve conduction evaluation was performed.

It is highly desired that NCS/EMG information is available for each PNRR participant. However, for patients with predominantly small fiber neuropathy, NCS/EMG testing information may be waived at the physician's discretion if clinically not required. If no NCS/EMG information is available, the reason for not performing the testing should be reflected in the NOTES of the NCS data entry form.

**GENERAL INFORMATION:**

**Physician:** last name of examining physician

**Sex (circle one):** genetic sex of the PNRR participant

**Year of visit:** year of the visit this NCS form is associated with

**Year of birth:** year the PNRR participant was born

**Year of NCS Testing:** year the NCS test was performed. Must be within 36 months prior or 12 months after visit.

**MEDIAN MOTOR NERVE:**

**Median Motor Nerve Conduction Velocity (MNCV):**

Calculated motor nerve conduction velocity (MNCV) for median nerve in meter per second (m/s). The median nerve is stimulated at two locations: (1) just above the wrist and (2) just below the elbow. For both stimulation sites, the evoked potential is measured above the Abductor Pollicis Brevis (APB) muscle.

**Data Entry:**

- The calculated numeric value (m/s) shall be entered into the data entry fields labeled "Right" or "Left" pending if the test was conducted with the median nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Median MNCV:
  - Johns Hopkins: >49 m/s
  - Mount Sinai: ≥49 m/s
  - Beth Israel: ≥50 m/s
  - Northwestern: >51 m/s for patients <50, >50 m/s for patients ≥50
  - University of Utah: >49 m/s
  - Kansas University: >49 m/s



## **Attachment B**

### **PNRR SOP for Nerve Conduction Study Form (NCS)**

- NR – Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

#### **Median Distal Motor Latency:**

Expresses the time it takes an electrical impulse to travel from the stimulation point to the recording site measured in milliseconds (msec). The onset latency should be recorded in this data entry field, reflecting the conduction along the fastest fibers in the median nerve.

#### **Data Entry:**

- The measured onset latency shall be entered into the data entry fields labeled “Right” or “Left” pending if the test was conducted with the median nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Median Distal Motor Latency:
  - Johns Hopkins: <4.3 msec
  - Mount Sinai: ≤4.4 msec
  - Beth Israel: ≤4.0 msec
  - Northwestern: <3.9 msec for patients <50, <4.0 msec for patients ≥50
  - University of Utah: <4.4 msec
  - Kansas University: <4.5 msec
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

#### **Median Distal Compound Muscle Action Potential (CMAP):**

Highest measured action potential evoked for the median nerve during NCS testing, in milliVolts (mV).

#### **Data Entry:**

- The calculated value of the amplitude of evoked response shall be entered as a numeric value into the data entry fields labeled “Right” or “Left” pending if the test was conducted with the median nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Median CMAP:
  - Johns Hopkins: >4 mV
  - Mount Sinai: ≥4 mV
  - Beth Israel: ≥4.0 mV
  - Northwestern: >6 mV for patients <60, >5 mV for patients ≥60
  - University of Utah: >4 mV
  - Kansas University: >4.5 mV
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

## **Attachment B**

### **PNRR SOP for Nerve Conduction Study Form (NCS)**

#### **Median F-wave latency:**

Time elapse until the second voltage change after supramaximal nerve stimulation in milliseconds (msec). The F-wave onset is usually 25-32 msec in the upper extremities, including the median nerve.

#### **Data Entry:**

- The measured time elapse in milliseconds (msec) shall be entered as a numeric value, using the data entry field labeled “Right” or “Left” pending if the test was conducted with the median nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Median F-wave:
  - Johns Hopkins: <32 msec
  - Mount Sinai: ≤31 msec
  - Beth Israel: ≤31 msec
  - Northwestern: <31 msec
  - University of Utah: <31 msec
  - Kansas University: <32 msec
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done.

#### **ULNAR MOTOR NERVE:**

##### **Ulnar Motor Nerve Conduction Velocity (MNCV) for distal ulnar nerve:**

Nerve Conduction velocity calculated for the distal ulnar nerve in meter per second (m/s). The ulnar nerve is stimulated at two locations: (1) just above the wrist and (2) just below the elbow. For both stimulation sites, the evoked potential is measured at the Abductor Digiti Minimi (ADM) muscle.

#### **Data Entry:**

- The calculated numeric value shall be entered into the data entry fields labeled “Right” or “Left” pending if the test was conducted with the ulnar nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Ulnar MNCV between wrist and elbow:
  - Johns Hopkins: >49 m/s
  - Mount Sinai: ≥49 m/s
  - Beth Israel: ≥50 m/s
  - Northwestern: >51 m/s for patients <30, >50 m/s for patients ≥30
  - University of Utah: >49 m/s
  - Kansas University: >50 m/s
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

## Attachment B

### PNRR SOP for Nerve Conduction Study Form (NCS)

#### Ulnar Motor Nerve Conduction Velocity (MNCV) around elbow:

Nerve conduction velocity calculated for the ulnar nerve around the elbow in meter per second (m/s) from two stimulation sites: (1) an action potential is evoked just below the elbow and (2) just above the elbow, to evaluate for cubital tunnel syndrome. For both stimulations, the evoked potential is recorded above the Abductor Digiti Minimi (ADM) muscle.

#### Data Entry:

- The calculated numeric value in meters/second shall be entered into the data entry fields labeled “Right” or “Left” pending if the test was conducted with the ulnar nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Ulnar MNCV around elbow:
  - Johns Hopkins: >49 m/s
  - Mount Sinai: ≥49 m/s
  - Beth Israel: ≥50 m/s
  - Northwestern: >51 m/s for patients <30, >50 m/s for patients ≥30
  - University of Utah: >49 m/s
  - Kansas University: >49 m/s
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

#### Ulnar Distal Motor Latency:

The recorded onset latency for the distal ulnar nerve should be recorded in this data entry field in milliseconds (msec). The onset latency records the time it takes an electrical impulse to travel from the stimulation point to the recording site, reflecting the conduction along the fastest fibers.

#### Data Entry:

- The calculated onset latency shall be entered into the data entry fields labeled “Right” or “Left” pending if the testing was conducted with the ulnar nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Ulnar onset latency:
  - Johns Hopkins: <3.5 msec
  - Mount Sinai: ≤3.3 msec
  - Beth Israel: ≤3.3 msec
  - Northwestern: <3.0 msec for patients <30, <3.1 msec for patients ≥30
  - University of Utah: <3.5 msec
  - Kansas University: <3.6 msec
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

**Attachment B**  
**PNRR SOP for Nerve Conduction Study Form (NCS)**

**Ulnar Distal Compound Muscle Action Potential (CMAP):**

Highest measured action potential evoked for the ulnar nerve during the NCS testing, in millivolts (mV).

**Data Entry:**

- The calculated value of the amplitude of evoked response shall be entered as a numeric value into the data entry fields labeled “Right” or “Left” pending if the test was conducted with the ulnar nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Ulnar CMAP:
  - Johns Hopkins: >4 mV
  - Mount Sinai: ≥6 mV
  - Beth Israel: ≥6 mV
  - Northwestern: >8 mV for patients <30, >7 mV for patients ≥30
  - University of Utah: >6 mV
  - Kansas University: >5 mV
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

**Ulnar F-wave latency (msec):**

Recorded time elapse until the second voltage change after supramaximal nerve stimulation of distal ulnar nerve, in milliseconds (msec).

**Data Entry:**

- The measured time elapse in milliseconds (msec) shall be entered as a numeric value, using the data entry field labeled “Right” or “Left” pending if the test was conducted with the ulnar nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Ulnar F-wave latency:
  - Johns Hopkins: <33 msec
  - Mount Sinai: ≤33 msec
  - Beth Israel: ≤32 msec
  - Northwestern: <32 msec
  - University of Utah: <31 msec
  - Kansas University: <33 msec
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

**Attachment B**  
**PNRR SOP for Nerve Conduction Study Form (NCS)**

**PERONEAL MOTOR NERVE:**

**Motor Nerve Conduction Velocity (MNCV) for Distal Peroneal Nerve:**

Nerve conduction velocity calculated for the peroneal nerve in meter per second (m/s). Value is calculated from two stimulations: (1) an action potential is evoked at the ankle and (2) just below the knee (fibular head). For both stimulations, the evoked potential is recorded above the Extensor Digitorum Brevis (EDB) muscles.

**Data Entry:**

- The calculated numeric value (meter per second) shall be entered into the data entry field labeled “Right” or “Left” pending if the peroneal nerve in the right or left leg was evaluated.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Peroneal MNCV:
  - Johns Hopkins: >39 m/s
  - Mount Sinai: ≥44 m/s
  - Beth Israel: ≥40 m/s
  - Northwestern: >41 m/s for patients <30, 40 m/s for patients ≥30
  - University of Utah: >41 m/s
  - Kansas University: >41 m/s
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

**Motor Nerve Conduction Velocity (MNCV) for Peroneal Nerve Around Knee:**

Nerve conduction velocity calculated for the peroneal nerve around knee, in meter per second (m/s). Value calculated from two stimulations: (1) an action potential is evoked just below the knee (fibular head) and (2) a second potential is evoked “behind” (above) the knee to evaluate for potential nerve entrapment at the knee. For both stimulations, the evoked potential is recorded above the Extensor Digitorum Brevis (EDB) muscles.

**Data Entry:**

- The calculated numeric value (meter per second) shall be entered into the data entry fields labeled “Right” or “Left” pending if the peroneal nerve in the right or left leg was evaluated.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for peroneal MNCV:
  - Johns Hopkins: >39 m/s
  - Mount Sinai: ≥44 m/s
  - Beth Israel: ≥40 m/s
  - Northwestern: >41 m/s for patients <30, 40 m/s for patients ≥30
  - University of Utah: >41 m/s
  - Kansas University: >41 m/s

## **Attachment B**

### **PNRR SOP for Nerve Conduction Study Form (NCS)**

- NR - Not Recordable. "NR" should be entered as value and "NR" should be chosen as evaluation.
- ND – Not Done

#### **Distal Motor Latency for Peroneal Nerve:**

Measured time it takes an electrical impulse to travel from the stimulation point to the recording site, in milliseconds (msec). The onset latency should be recorded in this data entry field, reflecting the conduction along the fastest fibers in the peroneal nerve.

#### **Data Entry:**

- The calculated onset latency shall be entered into the data entry fields labelled "Right" or "Left" pending if the peroneal nerve in the right or left leg was evaluated.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for peroneal distal motor latency:
  - Johns Hopkins: <5.6 msec
  - Mount Sinai: ≤6.5 msec
  - Beth Israel: ≤6.5 msec
  - Northwestern: <5.5 msec for patients <50, <6.0 msec for patients ≥50
  - University of Utah: <6.1 msec
  - Kansas University: <6.6 msec
- NR - Not Recordable. "NR" should be entered as value and "NR" should be chosen as evaluation.
- ND – Not Done

#### **Distal Compound Muscle Action Potential (CMAP) for Peroneal Nerve:**

Highest measured action potential evoked in the peroneal nerve, in millivolts (mV).

#### **Data Entry:**

- The calculated value of the amplitude of evoked response shall be entered as a numeric value into the data entry fields labeled "Right" or "Left" pending if the peroneal nerve in the right or left leg was evaluated.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Peroneal CMAP:
  - Johns Hopkins: >2 mV
  - Mount Sinai: ≥2 mV
  - Beth Israel: ≥2 mV
  - Northwestern: >3 mV for patients <50, >2.5 mV for patients ≥50
  - University of Utah: ≥2 mV
  - Kansas University: >2mV
- NR - Not Recordable. "NR" should be entered as value and "NR" should be chosen as evaluation.
- ND – Not Done

## **Attachment B**

### **PNRR SOP for Nerve Conduction Study Form (NCS)**

#### **F-wave Latency for Peroneal Nerve:**

Time elapse until the onset of the second voltage change after supramaximal nerve stimulation of the peroneal nerve, in milliseconds (msec).

#### **Data Entry:**

- The measured time elapse in milliseconds (msec) shall be entered as a numeric value, using the data entry field labeled “Right” or “Left” pending if the peroneal nerve in the right or left leg was evaluated.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for peroneal F-wave latency:
  - Johns Hopkins: <56 msec
  - Mount Sinai: Dependent on height, range from ≤48 to ≤58
  - Beth Israel: ≤56 msec
  - Northwestern: <56 msec
  - University of Utah: <55 msec
  - Kansas University: <57 msec
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

## **SENSORY NERVES**

### **SURAL NERVE**

#### **Sensory Nerve Conduction Velocity (SNCV) for Sural Nerve:**

Calculated nerve conduction velocity for Sural Sensory Nerve in meter per second (m/s) for distal sural nerve between calf and ankle.

#### **Data Entry:**

- The calculated nerve conduction velocity for the Sural Sensory Nerve in meters per second (m/s) shall be entered as a numeric value into the data entry field labeled “Right” or “Left” pending if the test was conducted with the sural nerve on the right or left leg.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Sural SNCV as normal or abnormal:
  - Johns Hopkins: >39 m/s
  - Mount Sinai: ≥40 m/s
  - Beth Israel: ≥40 m/s
  - Northwestern: >41 m/s for patients <30 y, >40 m/s for patients ≥30 y
  - University of Utah: >41 m/s
  - Kansas University: >41 m/s
- NR – Not Recordable: “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

## **Attachment B**

### **PNRR SOP for Nerve Conduction Study Form (NCS)**

#### **Sensory Nerve Action Potential (SNAP) for Sural Nerve:**

Action potential (amplitude) measured for Distal Sural Sensory Nerve in microVolts ( $\mu\text{V}$ ).

#### **Data Entry:**

- The calculated value of the amplitude of evoked response shall be entered as a numeric value into the data entry fields labeled “Right” or “Left”, pending if the test was conducted with the sural nerve on the right or left leg.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Sural SNAP as normal or abnormal:
  - Johns Hopkins: dependent on age, range from  $>5$  to  $>9$   $\mu\text{V}$
  - Mount Sinai:  $\geq 6$   $\mu\text{V}$
  - Beth Israel: dependent on age, range from  $\geq 3$  to  $\geq 14$   $\mu\text{V}$
  - Northwestern:  $>6$   $\mu\text{V}$  for patients  $<30$ ,  $>5$   $\mu\text{V}$  for patients 30-49,  $>4$   $\mu\text{V}$  for patients 50-59 and  $>3$   $\mu\text{V}$  for patients  $\geq 60$
  - University of Utah:  $\geq 6$   $\mu\text{V}$
  - Kansas University:  $>6$   $\mu\text{V}$  for patients  $<60$  years,  $>3$   $\mu\text{V}$  for patients  $>60$  years
- NR – Not Recordable: “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

#### **MEDIAN NERVE**

#### **Sensory Nerve Conduction Velocity (SNCV) for Median Nerve:**

Calculated Nerve Conduction Velocity for Distal Median Sensory Nerve, in meter per second (m/s). Preferably, the entered value should reflect the SNCV between Digit II and above the wrist.

#### **Data Entry:**

- The measured time elapse in meters per second (m/s) shall be entered as a numeric value into the data entry field labeled “Right” or “Left” pending if the test was conducted with the median nerve on the right or left hand.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Median SNCV as normal or abnormal:
  - Johns Hopkins:  $>49$  m/s
  - Mount Sinai:  $\geq 50$  m/s
  - Beth Israel:  $\geq 50$  m/s
  - Northwestern:  $>51$  m/s for patients  $<50$ ,  $>50$  m/s for patients  $\geq 50$
  - University of Utah:  $>50$  m/s
  - Kansas University:  $>48$  m/s
- NR – Not Recordable: “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done



## **Attachment B**

### **PNRR SOP for Nerve Conduction Study Form (NCS)**

#### **Sensory Nerve Action Potential (SNAP) for Median Nerve:**

Action potential (amplitude) measured for Distal Median Sensory Nerve in microVolts ( $\mu\text{V}$ ).

#### **Data Entry:**

- The calculated value of the amplitude of evoked response shall be entered as a numeric value into the data entry fields labeled “Right” or “Left” pending if the test was conducted with the median nerve on the right or left hand.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Median SNAP as normal or abnormal:
  - Johns Hopkins:  $>9 \mu\text{V}$
  - Mount Sinai:  $\geq 20 \mu\text{V}$
  - Beth Israel:  $\geq 20 \mu\text{V}$
  - Northwestern:  $>20 \mu\text{V}$  for patients  $<50$ ,  $>15 \mu\text{V}$  patients 50-59,  $>10 \mu\text{V}$  patients  $\geq 60$
  - University of Utah:  $\geq 20 \mu\text{V}$
  - Kansas University:  $>15 \mu\text{V}$
- NR – Not Recordable: “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

#### **ULNAR NERVE**

#### **Sensory Nerve Conduction Velocity (SNCV) for Ulnar Nerve:**

Calculated Nerve Conduction Velocity for Distal Ulnar Sensory Nerve, in meter per second (m/s). Preferably, the entered value should reflect the SNCV between Digit V and above the wrist.

#### **Data Entry:**

- The measured conduction velocity shall be entered as a numeric value into the data entry field labeled “Right” or “Left” pending if the test was conducted with the sensory ulnar nerve on the right or left hand.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Ulnar SNCV as normal or abnormal:
  - Johns Hopkins:  $>49 \text{ m/s}$
  - Mount Sinai:  $\geq 50 \text{ m/s}$
  - Beth Israel:  $\geq 50 \text{ m/s}$
  - Northwestern:  $>51 \text{ m/s}$  for patients  $<50$ ,  $>50 \text{ m/s}$  for patients  $\geq 50$
  - University of Utah:  $>50 \text{ m/s}$
  - Kansas University:  $>48 \text{ m/s}$
- NR – Not Recordable: “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

## **Attachment B**

### **PNRR SOP for Nerve Conduction Study Form (NCS)**

#### **Sensory Nerve Action Potential (SNAP) for Ulnar Nerve:**

Action potential (amplitude) measured for distal sensory ulnar nerve in microVolts ( $\mu\text{V}$ ).

#### **Data Entry:**

- The calculated value of the amplitude of evoked response shall be entered as a numeric value into the data entry fields labeled “Right” or “Left” pending if the test was conducted with the ulnar nerve on the right or left hand.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Ulnar SNAP as normal or abnormal:
  - Johns Hopkins:  $>9 \mu\text{V}$
  - Mount Sinai:  $\geq 17 \mu\text{V}$
  - Beth Israel: depending on age  $\geq 20.8$  to  $\geq 11 \mu\text{V}$
  - Northwestern:  $>18 \mu\text{V}$  for patients  $<30$ ,  $>12 \mu\text{V}$  for patients 30-49,  $>10 \mu\text{V}$  for patients 50-59 and  $>10 \mu\text{V}$  for patients  $\geq 60$
  - University of Utah:  $\geq 10 \mu\text{V}$
  - Kansas University:  $>10 \mu\text{V}$  for patients  $<60$  years,  $>5 \mu\text{V}$  for patients  $>60$  years
- NR – Not Recordable: “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

#### **RADIAL NERVE**

#### **Sensory Nerve Conduction Velocity (SNCV) for Radial Nerve:**

Calculated Nerve Conduction Velocity for Distal Radial Sensory Nerve, in meter per second (m/s). Preferably, the entered value should reflect the SNCV between wrist and mid forearm, using the superficial branch of the radial nerve.

#### **Data Entry:**

- The measured conduction velocity shall be entered as a numeric value into the data entry field labeled “Right” or “Left” pending if the test was conducted with the radial nerve on the right or left arm.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Radial SNCV as normal or abnormal:
  - Johns Hopkins:  $>49 \text{ m/s}$
  - Mount Sinai:  $\geq 50 \text{ m/s}$
  - Beth Israel:  $\geq 50 \text{ m/s}$
  - Northwestern:  $>51 \text{ m/s}$  for patients  $<50$ ,  $>50 \text{ m/s}$  for patients  $\geq 50$
  - University of Utah:  $>50 \text{ m/s}$
  - Kansas University:  $>48 \text{ m/s}$
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

## Attachment B

### PNRR SOP for Nerve Conduction Study Form (NCS)

#### Sensory Nerve Action Potential (SNAP) for Radial nerve:

Action potential (amplitude) measured for distal radial nerve in microVolts ( $\mu\text{V}$ ).

#### Data Entry:

- The calculated value of the amplitude of evoked response shall be entered as a numeric value into the data entry fields labeled “Right” or “Left” pending if the test was conducted with the ulnar nerve on the right or left hand.
- The entered value shall be evaluated in accordance with the normative value established by the enrollment center for Radial SNAP as normal or abnormal:
  - Johns Hopkins:  $>9 \mu\text{V}$
  - Mount Sinai:  $\geq 15 \mu\text{V}$
  - Beth Israel: Dependent on age, range from  $\geq 12$  to  $\geq 25.5$
  - Northwestern:  $>18 \mu\text{V}$  for patients  $<50$ ,  $>14 \mu\text{V}$  for patients 50-59 and  $>10 \mu\text{V}$  for patient  $\geq 60$
  - University of Utah:  $\geq 20 \mu\text{V}$
  - Kansas University:  $>15 \mu\text{V}$  for patients  $<60$  years,  $>10 \mu\text{V}$  for patients  $>60$  years
- NR - Not Recordable. “NR” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

#### NOTES

The following information should be provided at the bottom of the form if applicable:

- If NCS testing was not performed at the enrollment center, the location of the test should be reported. Only NCS data from other trusted NCS-sites should be entered into PNRR.
- Other conditions contributing to the neuropathy and diagnosed during NCS/EMG should be listed in the NOTES together with the vertebrae / disc location where the damage is present; e.g. spinal stenosis L3-L5
- Any technical difficulties encountered during the NCS test that might have influenced / altered the results should be reported here, e.g. severe obesity of the patient preventing sural evaluation.
- If NCS/EMG testing was waived as a requirement because the patient has predominantly small fiber neuropathy, “patient has small fiber neuropathy” should be added to the NOTES.
- If patient had NCS testing done prior to 36 months before PNRR enrollment or later than 12 months after enrollment, the NCS/EMG results should also be reported in the NOTES.

#### Date Data Entry Completed:

Date should be entered when data entry was **completed** (= assumed final).

## Attachment B

### PNRR SOP for Nerve Conduction Study Form (NCS)

#### Physician Examination Form (PEF) Status:

- **Incomplete:** not all data is entered yet
- **Unverified:** all data is entered, but waiting for confirmation for some data (for example, when waiting for confirmation about primary diagnosis pending lab results, the form should be considered unverified)
- **Complete:** all information is verified, no additional edits are anticipated

## Attachment C PNRR SOP for Peripheral Nerve Workup Form (PNW)

### Peripheral Nerve Workup Form (PNW)

The Peripheral Nerve Workup Form (PNW) has to be filled out at the time a new patient is enrolled into the PNRR study. Only testing conducted within 36 months prior and within 12 months after enrollment should be reported in the PNW form, with the exception of genetic tests.

The FIRST TIER testing is considered the Minimum Data Set and must be provided for all PNRR subjects. It is acceptable to report the results from testing conducted outside of the enrollment centers in the PNW form.

#### GENERAL INFORMATION (all fields required):

- **Physician:** last name of the physician performing the study visit
- **Sex:** genetic sex of the PNRR participant
- **Year of visit:** year of the visit this PNW form is associated with
- **Year of birth:** year the PNRR participant was born

#### FIRST TIER

All tests listed in the first tier are part of the minimum data set and are required for new PNRR enrollments. However, for newly enrolled patients with small fiber neuropathy, the requirement for Nerve Conduction Study / Electromyography is waived at the physician's discretion when it is clear that the neuropathy does not involve larger nerve fibers.

If a patient had NCS testing earlier than 36 months prior to visit, the NCS interpretation should be entered into the PNW form, together with the year of testing, but the NCS form itself should not be completed.

#### 1. Nerve Conduction Study / Electromyography (NCS/EMG) diagnosis

The physician interpretation from the NCS/EMG testing should be reported

##### Data Entry:

**Normal:** nerve function is within the normal range.

**Abnormal:** test detected significant nerve dysfunction of one or more nerves

**ND/NA:** no NCS/EMG testing was conducted with this patient

**Year of Test:** calendar year when the test was done.

##### If abnormal (mark one):

**Sensory:** predominantly sensory nerves are affected by neuropathy

**Motor:** predominantly motor nerves are affected by neuropathy

**Sensorimotor:** both motor and sensory nerves are affected by neuropathy

##### AND (mark one):

**Axonal:** the primary process is consistent with axon loss neuropathy

**Demyelinating:** the primary process is consistent with demyelinating neuropathy

**Mixed:** both axonal damage and demyelinating neuropathy

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

#### 2. Skin biopsy (if NCS/EMG is normal):

For patients who have a normal NCS/EMG result, a skin biopsy is requested.

##### Data Entry:

**Normal:** skin biopsy results were normal

**Abnormal:** skin biopsy results were abnormal, confirming small fibers are affected

**ND/NA:** no skin biopsy was performed

**Year of Test:** calendar year skin biopsy was performed up to 60 months (5 years) prior and 12 months after visit. Results from the most recent skin biopsy should be reported if the patient had more than one skin biopsy.

##### If abnormal (mark one):

**Length-Dependent:** nerve fiber density is more reduced at the distal site

**Not Length-Dependent:** nerve fiber densities are reduced at both proximal and distal sites

#### 3. Chemistry 12-18

Results from the most recent Comprehensive Metabolic Panel (CMP) should be reported.

##### Data Entry:

**Normal:** creatinine value is within normal range

**Abnormal:** creatinine value is outside the normal range

**ND/NA:** no Chemistry panel was not done, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**Creatinine level:** enter measured creatinine value in milligram per deciliter (mg/dL)

#### 4. Glucose

The test results of at least one of the three tests approved as glucose screening tests has to be performed with each PNRR participant to exclude or confirm the diagnosis of diabetes mellitus (DM) as the cause of neuropathy.

##### a. Glycated Hemoglobin (HgA1C)

The glycated hemoglobin value is an indicator for diabetes mellitus. The border value can slightly vary between laboratories, and the reference range information should be used to determine if value is normal or abnormal.

##### Data Entry:

**Normal:** measured value was within the reference range

**Abnormal:** measured value was **higher** than the reference range

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

**ND/NA:** test was not performed within last 36 months, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**HgA1C Level:** enter measured HgA1C level in % (of total hemoglobin)

#### b. Blood Glucose (fasting)

Expresses the amount of glucose in blood after a minimum of 8 hour fasting.

*Note: study coordinator should verify that the patient was truly fasting.*

**Data Entry:**

**Normal:** test result within normal range

**Abnormal:** fasting blood glucose levels were outside the normal range

**ND/NA:** test was not performed

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**Fasting Glucose level:** fasting glucose level in milligram per deciliter (mg/dL)

#### c. Oral Glucose Tolerance test

Measured blood glucose levels after two (2) hours should be reported as normal or abnormal. Both higher (hyperglycemic) and lower (hypoglycemic) results should be reported as abnormal.

**Data Entry:**

**Normal:** test result within normal range

**Abnormal:** blood glucose levels after 2 hours were outside the normal range

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**Glucose level:** 2-hour glucose level should be entered in milligram per deciliter (mg/dL)

#### 5.a. Serum Immunofixation (IFE) and/or

#### 5.b Serum Protein Electrophoresis (SPEP)

Both tests evaluate immunoglobulin (antibodies) and protein levels in serum. If Serum Immunofixation (SIFE) results in abnormal result, Serum Protein Electrophoresis (SPEP) is required.

**Data Entry:**

**Normal:** all screened immunoglobulins are within normal range

**Abnormal:** one or more immunoglobulins are outside of normal range

**ND/NA:** test was not performed test results are not available

**Year of Test:** calendar year test was performed; must be within 36 months prior or 12 months after visit.

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

#### If IFE and/or SPEP were abnormal:

Identification of type of abnormality:

- **Monoclonal gammopathy:** presence of paraprotein(s), one or more immunoglobulins or light chains are marked as abnormal elevated. Polyclonal gammopathies should be reported as monoclonal gammopathies.
- **Hypoglobulinemia:** hypoproteinemia, one or more immunoglobulins or light chains are marked as abnormal low

The protein(s) for which abnormal level(s) were detected should be identified.

- Immunoglobulin A (IgA)
- Immunoglobulin G (IgG)
- Immunoglobulin M (IgM)
- Kappa Light Chain
- Lambda Light Chain
- Other

#### 6. Vitamin B12

Measured Vitamin B12 (or cobalamin) levels in blood. Only values below the normal range should be reported as abnormal. High values are of little concern and are common in patients who take Vitamin B supplements and should not be reported as abnormal.

##### Data Entry:

**Normal:** Vitamin B12 values in normal range or elevated

**Abnormal:** Vitamin B12 value is below normal range (200 pg/mL)

**ND/NA:** test was not performed or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**Vitamin B12 Value:** enter measured Vitamin B12 value in picogram per milliliter (pg/mL)

## SECOND TIER

The Second Tier lists standard laboratory tests which are commonly used to diagnose the cause for Peripheral Neuropathy.

#### 7. Complete Blood Cell Count (CBC) with Differential

Results from the most recent CBC test should be reported.

##### Data Entry:

**Normal:** all measured parameters were within normal range

**Abnormal:** one or more parameters were clinically significant outside the normal range

**ND/NA:** Test was not performed or test results are not available.



## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 8. Erythrocyte Sedimentation Rate (ESR)

Measures the rate red blood cells sediment in an anticoagulated blood tube within one hour, expressed in millimeter per hour (mm/h). The normal range values vary depending on the laboratory performing the testing. High ESR values are considered an indication for inflammation.

**Data Entry:**

**Normal:** sedimentation within normal limits

**Abnormal:** sedimentation elevated to clinical significance

**ND/NA:** test was not performed or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 9. Thyroid Stimulating Hormone (TSH)

Measures amount of Thyroid Stimulating Hormone (TSH) in blood. The normal range may differentiate between laboratories and the range information provided by the laboratory which conducted the test should be consulted.

**Data Entry:**

**Normal:** measured TSH level is within normal range

**Abnormal:** measured TSH level is outside of normal range – both hypo- and hyperthyroidism should be reported

**ND/NA:** test was not performed or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**TSH value:** measured TSH level in milli-International Units per liter (mIU/L)

#### 10. Lipid Profile

Lipid profile or lipid panel is a series of blood tests and the standard medical screening test for lipid levels in the blood.

**Data Entry:**

**Normal:** all measured lipids were in the normal range

**Abnormal:** one or more measured lipids were outside of normal range

**ND/NA:** test was not performed or test results are not available.

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

If a Lipid Profile was created, the following values shall be entered:

- **Cholesterol:** measured cholesterol level in milligram per deciliter (mg/dL)
- **Triglycerides:** measured triglyceride level in milligram per deciliter (mg/dL)

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

- **HDL (high density lipids):** measured HDL level in milligram per deciliter (mg/dL)
- **LDL (low density lipids):** measured LDL level in milligram per deciliter (mg/dL)

#### 11. C-reactive protein (CRP)

Used as a screening test for inflammation: CRP levels rise in response to inflammation in serum. Normal range in healthy humans is usually defined as < 0.5 mg/L blood, but might vary pending on testing laboratory.

**Data Entry:**

**Normal:** CRP level within normal range

**Abnormal:** CRP level above normal range (elevated)

**ND/NA:** test was not performed, or test results are not available.

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 12. Anti-Nuclear Antibody (ANA) test

Also known as Antinuclear Factor or ANF. Test is used to diagnose lupus, Sjörger's syndrome, rheumatoid arthritis, mixed connective tissue disease, polymyositis, dermatomyositis, autoimmune hepatitis and drug induced lupus.

**Data Entry:**

**Normal:** negative, no ANA's are detected

**Abnormal:** positive, one or more ANA's are detected

**ND/NA:** test was not performed or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit

#### 13.a Urine Immunofixation (IFE) and/or

#### 13.b Urine Electrophoresis (UPEP)

Screening for abnormal proteins in urine. If Urine Immunofixation (UIFE) showed an abnormality, Urine Electrophoresis (UPEP) is required.

**Data Entry:**

**Normal:** monoclonal immunoglobulins are not detected

**Abnormal:** monoclonal immunoglobulin(s) are detected

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit

**If Abnormal, report abnormality:** \_\_\_\_\_

The abnormal finding from either UIFE and/or UPEP should be reported.

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

#### 14. Methyl malonic acid (MMA)

Test used to diagnose early or mild Vitamin B12 deficiency. The normal range for MMA levels in blood can slightly vary between laboratories and the reference range information provided by the laboratory should be used to determine if a value is considered Normal or Abnormal.

**Data Entry:**

**Normal:** MMA level considered to be within normal range

**Abnormal:** elevated MMA levels above normal range

**ND/NA:** test was not performed, or test results are not available.

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

### THIRD TIER

#### INFLAMMATORY / AUTOIMMUNE:

#### 15. Kappa / Lambda Light Chains

Test measures amounts of free kappa and free lambda immunoglobulin light chains in blood serum and calculates the ratio between kappa and lambda chains. This test is complementary to SIFE/SPEP, because it determines the exact concentrations while SIFE/SPEP only determine if the amount of light chains in the blood is normal or abnormal.

**Data Entry:**

**Normal:** normal test results, all evaluated parameters are within range

**Abnormal:** either kappa or lambda or K/L ratio are outside of normal range

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 16. Angiotensin-Converting-Enzyme (ACE) (serum)

Also referred to as Serum Angiotensin-Converting Enzyme (SACE)

Elevated levels of ACE are common in people with leprosy, hyperthyroidism, acute hepatitis, primary biliary cirrhosis, diabetes mellitus, multiple myeloma, osteoarthritis, amyloidosis, Gaucher disease, pneumoconiosis, histoplasmosis, miliary tuberculosis and it is used to diagnose sarcoidosis. Lower than normal ACE levels can indicate chronic liver disease, eating disorders, steroid therapy and therapy for sarcoidosis, or an underactive thyroid (hypothyroidism). The normal range for ACE levels varies between laboratories, thus the lab report should be consulted to determine if the test revealed a normal or abnormal result.

**Data Entry:**

**Normal:** measured ACE level in normal range

**Abnormal:** ACE levels are either higher or below normal range

## **Attachment C**

### **PNRR SOP for Peripheral Nerve Workup Form (PNW)**

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### **17. Anti Double-Stranded DNA Antibodies (Anti ds-DNA Ab)**

Screening test for lupus, rheumatoid arthritis, HIV and other autoimmune diseases.

**Data Entry:**

**Normal:** negative result for Anti ds-DNA Ab screening

**Abnormal:** positive result, Anti ds-DNA Ab are present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### **18. Anti-Endomysial Immunoglobulin G antibodies**

Screening test for autoimmune diseases, including celiac disease.

**Data Entry:**

**Normal:** negative result, no antibodies found

**Abnormal:** positive result, antibodies present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### **19. Anti-Ganglioside Antibodies (GM-1)**

Screening test for autoimmune neuropathies.

**Data Entry:**

**Normal:** negative screening result, no antibodies found

**Abnormal:** positive screening result, antibodies present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### **20. Anti-Gliadin Antibodies (IgA / IgG)**

Indication for gluten sensitivity. Anti-Gliadin IgA: present in 80% of people diagnosed with coeliac disease and can be indicator for gluten-sensitive idiopathic neuropathy; Anti-Gliadin IgG: coeliac disease and non-coeliac gluten sensitivity.

**Data Entry:**

**Normal:** negative screening test, no antibodies found

**Abnormal:** positive screening test, antibodies present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

#### 21. Anti-Neutrophil (p-ANCA and c-ANCA)

Screening test for autoimmune diseases, particularly vasculitis

**Data Entry:**

**Normal:** negative screening test

**Abnormal:** positive screening test

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 22. Anti-RO (SSA) Antibodies & Anti-LA (SSB) Antibodies

The screening test is widely used to identify patients with Sjögren's syndrome and/or systemic lupus erythematosus (SLE). But Anti-Ro SSA Antibodies are also present in patients with other auto-immune diseases, and both need to be elevated for positive diagnosis for Sjögren's.

**Data Entry:**

**Normal:** negative screening test, no antibodies found

**Abnormal:** positive screening test, SSA and/or SSB antibodies are present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 23. Anti-68 Kd Antibody (cochlear antigen)

Screening test for sensorineural hearing loss (SNHL), commonly referred to as nerve deafness.

**Data Entry:**

**Normal:** negative screening test

**Abnormal:** positive screening test

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 24. Anti-MAG Dual Antigen (elisa-ather)

Screening test for peripheral neuropathy with purely sensory or mixed sensory and motor neuropathy with predominantly demyelinating features.

**Data Entry:**

**Normal:** negative screening test

**Abnormal:** positive screening test

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

#### 25. Anti-Parietal Cell Antibodies

Screening test that looks for antibodies against the parietal cells of the stomach. Parietal cells are critical for human body to absorb vitamin B12 from food.

**Data Entry:**

**Normal:** negative screening test, no antibodies found

**Abnormal:** positive screening test, antibodies present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 26. Anti-Thyroglobulin Antibodies

Screening test for thyroid antibodies, usually ordered to diagnose an autoimmune thyroid disease or thyroid dysfunction.

**Data Entry:**

**Normal:** negative test, no antibodies found

**Abnormal:** positive test, antibodies present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 27. Rheumatoid Factor (RF)

Screening test, measuring the amount of Rheumatoid Factor (RF) present in serum. Used as a diagnostic test for Rheumatoid Arthritis and Sjögren's syndrome. The reference range of the testing laboratory should be consulted to determine if the test result is considered normal or abnormal.

**Data Entry:**

**Normal:** low levels of RF in blood

**Abnormal:** elevated levels of RF detected

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 28. Tissue Transglutaminase Immunoglobulin A (IgA) Antibodies

Screen for autoantibodies against transglutaminase protein, which are found in patients with celiac disease, juvenile diabetes, inflammatory bowel disease and various forms of arthritis.

**Data Entry:**

**Normal:** negative screening test, no antibodies found

**Abnormal:** positive screening test, antibodies present

**ND/NA:** test was not performed, or test results are not available

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 29. Cryoglobulins

Screening for vasculitis and other auto-immune diseases.

**Data Entry:**

**Normal:** negative screen, no cryoglobulins found

**Abnormal:** positive screen, cryoglobulins present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### INFECTIOUS:

#### 30. Human Immunodeficiency Virus (HIV) screen

Screening test for HIV antibodies.

**Data Entry:**

**Normal:** negative screen, no HIV viruses found

**Abnormal:** positive screen, HIV viruses detected

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Negative HIV screening tests should only be reported when performed within 36 months prior or 12 months after visit. All positive HIV screening tests should be reported, independent of the year they were performed.

#### 31. Lyme screen

Screening test for *Borrelia burgdorferi* antibodies.

**Data Entry:**

**Normal:** negative screen

**Abnormal:** positive screen, must also be confirmed by Western Blot Test

**ND/NA:** test was not performed or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 32. Rapid Plasma Reagin Antibodies (RPR Ab)

Screening test for Syphilis.

**Data Entry:**

**Normal:** negative screen, no RPR antibodies found

**Abnormal:** positive screen, RPR antibodies present

**ND/NA:** test was not performed, or test results are not available

## **Attachment C**

### **PNRR SOP for Peripheral Nerve Workup Form (PNW)**

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### **33. Hepatitis B screen**

Screening test for Hepatitis B antibodies.

**Data Entry:**

**Normal:** negative screen or positive screen due to vaccinations

**Abnormal:** positive screen

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### **34. Hepatitis C screen**

Screening test for Hepatitis C antibodies

**Data Entry:**

**Normal:** negative screen (non-reactive)

**Abnormal:** positive screen (reactive)

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### **GENETIC:**

#### **35. Galactosidase Assay**

Screen test for Fabry's disease.

**Data Entry:**

**Normal:** negative screen

**Abnormal:** positive screen

**ND/NA:** test was not performed or test results are not available

**Year of Test:** calendar year test was performed (no time limit for genetic testing).

#### **36. Charcot-Marie-Tooth (CMT) panel genetic testing**

Screens for known genotypes associated with CMT.

**Data Entry:**

**Normal:** negative screening test

**Abnormal:** positive screening test (confirmation of CMT)

**ND/NA:** genetic screening test was not performed, or test results are not available

**Year of Test:** calendar year test was performed (no time limit for genetic testing).



## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

#### PARANEOPLASTIC:

##### 37. Anti-Ri antibody screen

Screening test for autoantibodies against neuronal nuclei of the central nervous system.

##### Data Entry:

**Normal:** negative screen, no antibodies found

**Abnormal:** positive screen, antibodies present

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

##### 38. Anti-Hu antibody screen

Antineuronal Nuclear Antibody (Anti-Hu) screening test. Anti-Hu is associated with subacute syndrome of encephalomyeloradiculopathy, sensory neuropathy, and autoimmune neuropathy, predominantly affecting the gastrointestinal tract, and can also indicate small cell carcinoma of the lung.

##### Data Entry:

**Normal:** negative screening test

**Abnormal:** positive screening test

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

##### 39. Anti-Purkinje Cell (YO) antibody screen

Screening test for Neuronal Nuclear antibodies affecting Purkinje nerve cells.

##### Data Entry:

**Normal:** negative screening test

**Abnormal:** positive screening test

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

##### 40. Paraneoplastic Panel (MAYO)

Screening for autoantibodies in blood, including Anti-Hu, -Ri and -Yo plus others. For patients who received chemotherapy, a negative Paraneoplastic Panel is considered a confirmation that the neuropathy is caused by chemotherapy drugs.

##### Data Entry:

**Normal:** negative result

**Abnormal:** positive result (autoimmune antibodies present)

**ND/NA:** test was not performed, or test results are not available

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**If Abnormal, list antibodies:** \_\_\_\_\_

All antibodies for which abnormal levels were measured should be listed.

|       |   |
|-------|---|
| ANN1S | Anti-Neuronal Nuclear Ab, Type 1            |
| ANN2S | Anti-Neuronal Nuclear Ab, Type 2            |
| ANN3S | Anti-Neuronal Nuclear Ab, Type 3            |
| AGN1S | Anti-Glial Nuclear Ab, Type 1               |
| PCABP | Purkinje Cell Cytoplasmic Ab Type 1         |
| PCAB2 | Purkinje Cell Cytoplasmic Ab Type 2         |
| PCATR | Purkinje Cell Cytoplasmic Ab Type Tr        |
| AMPHS | Amphiphysin Ab, S                           |
| CRMS  | CRMP-5-IgG, S                               |
| STR   | Striational (Striated Muscle) Ab, S         |
| CCPQ  | P/Q-Type Calcium Channel Ab                 |
| CCN   | N-Type Calcium Channel Ab                   |
| ARBI  | ACh Receptor (Muscle) Binding Ab            |
| GANG  | AChR Ganglionic Neuronal Ab, S              |
| VGKC  | Neuronal (V-G) K <sup>+</sup> Channel Ab, S |
| OTHER | Other: _____                                |

#### OTHER:

##### 41. Creatine Kinase (CK)

Also referred to as creatine phosphokinase (CPK). Screen test for inflammation, particularly myositis. Elevated CK levels are associated with several clinical diagnosis.

#### Data Entry:

**Normal:** CK levels within normal range

**Abnormal:** CK levels outside of normal range

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

##### 42. Homocysteine

Elevated homocysteine levels can be an indicator for low B-vitamin intakes. The normal range may vary between laboratories, and the reference information should be consulted to determine if the homocysteine levels are within normal limits or not. Low homocysteine levels should not be reported as abnormal in PNRR.

#### Data Entry:

**Normal:** within normal range

**Abnormal:** elevated level

**ND/NA:** test was not performed, or test results are not available

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 43. Urine Heavy Metals

Screen for heavy metals in urine.

**Data Entry:**

**Normal:** negative (no elevated levels of heavy metals detected in urine)

**Abnormal:** positive for one or more heavy metals

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### 44. Vitamin E

Vitamin E deficiency is a known cause for peripheral Neuropathy. Normal ranges vary between laboratories and the provided references should be consulted to determine if the measured Vitamin E levels are within normal range or low. Only Vitamin E deficiencies should be reported as an abnormal result.

**Data Entry:**

**Normal:** Vitamin E levels in normal range or elevated

**Abnormal:** Vitamin E levels below normal range

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**Vitamin E value:** measured Vitamin E value should be entered in milligram per liter (mg/L)

#### 45. Vitamin B1 (Thiamin)

Vitamin B1 deficiencies should be reported as abnormal test result. High values should **not** be reported as abnormal in the PNRR database.

**Data Entry:**

**Normal:** Vitamin B1 within normal range or elevated

**Abnormal:** Vitamin B1 deficiency

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**Vitamin B1 value:** enter measured Vitamin B1 level in nanomol per liter (nmol/L)

#### 46. Vitamin B6

Vitamin B6 is involved in the formation of myelin and both B6 deficiency and chronically elevated B6 levels can cause neuropathy, and both conditions should be reported as abnormal in the database.

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

#### Data Entry:

**Normal:** Vitamin B6 level are within normal range

**Abnormal:** Vitamin B6 levels are either elevated or below normal range.

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

**Vitamin B6 value:** enter measured Vitamin B6 value in nanogram per milliliter (ng/mL)

#### AUTONOMIC:

##### 47. Quantitative Sudomotor Autonomic Reflex Test (QSART)

Test measures the autonomic nerves that control sweating. The test is useful in assessing autonomic nervous system disorders, peripheral neuropathies and some types of pain disorders.

#### Data Entry:

**Normal:** normal sweating response

**Abnormal:** elevated sweating response

**ND/NA:** test was not performed or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

##### 48. Tilt Table

Used to evaluate the cause of unexplained fainting (syncope)

#### Data Entry:

**Normal:** not syncope

**Abnormal:** syncope or pre-syncope

**ND/NA:** test was not performed, or test results are not available

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

##### 49. Sweat Testing

Results from Thermoregulatory Sweat Test (TST) should be reported here. TST evaluates the patient's ability to sweat when stimulated by a warm and humid environment. This test assesses both the central and peripheral autonomic nervous system's control of sweating and body temperature regulation (thermoregulation). Both reduced sweating (anhidrosis) and excessive sweating (hyperhidrosis) patterns shall be reported as abnormal.

#### Data Entry:

**Normal:** normal sweating pattern

**Abnormal:** abnormal sweating pattern detected

**ND/NA:** test was not performed, or test results are not available

## Attachment C

### PNRR SOP for Peripheral Nerve Workup Form (PNW)

**Year of Test:** calendar year test was performed. Must be within 36 months prior or 12 months after visit.

#### BIOPSIES:

##### 50. Nerve biopsy

Nerve biopsy was performed on one or multiple nerves. If a nerve biopsy has been conducted, the result should be reported here. There is no timeframe limitation for nerve biopsy results.

##### Data Entry:

**Normal:** no abnormalities were detected

**Abnormal:** abnormalities were present

**ND/NA:** no nerve biopsy was previously performed

**Year of Test:** calendar year test was performed. No time limit for nerve biopsies.

##### 51. Lip biopsy (Sjögren's)

Diagnostic test for Sjögren's syndrome. Lip biopsy results for other diagnosis such as for malignant cancer should not be reported. There is no timeframe limitation for lip biopsy results.

##### Data Entry:

**Normal:** negative for Sjögren's syndrome

**Abnormal:** positive for Sjögren's syndrome

**ND/NA:** no lip biopsy was previously performed.

**Year of Test:** calendar year test was performed. No time limit for lip biopsies.

#### Date Data Entry Completed:

Date should be entered when data entry was completed.

#### Nerve Workup Form (PNW) Status:

- **Incomplete:** not all data is entered yet
- **Unverified:** data is entered, but not verified
- **Complete:** all information is verified, no additional edits are anticipated

**Attachment D**  
**PNRR SOP for Patient History Questionnaire (PHQ)**

**Patient History Questionnaire (PHQ)**

**NOTE: Instructions for PNRR Study Coordinators are marked in blue ink.**

- The Patient History Questionnaire has to be filled out by each PNRR study participant at enrollment, and the provided information is part of the initial data set.
- During follow up visits a “FOLLOW-UP Questionnaire” should only be filled out, if 12 months have elapsed since the last time the patient filled out a questionnaire
- The FOLLOW-UP Questionnaire is a shortened version of the PHQ, ending with Section III.

**After the patient has completed the questionnaire, the study coordinator should check the answers and make sure that answers were provided to all questions and if some questions were not answered by the patient, the study coordinator shall contact the patient and obtain the missing answers.**

***Patient Instructions (in questionnaire):***

***Please take a moment to read these instructions before completing the Patient History Questionnaire for the Peripheral Neuropathy Research Registry (PNRR).***

- ***Please read each question carefully and answer as thoroughly as possible.***
- ***If you are unsure how to fill out any part of this form, please do not hesitate to ask for help and guidance.***

**Section I. PATIENT INFORMATION**

**Question: *What year were you born?* \_\_\_\_\_: year patient was born**

**Question: *What is your sex?***

Possible Answers:

- Male:** genetic sex of patient is male
- Female:** patient’s genetic sex is female

**Question: *Are you Hispanic or Latino?***

Possible answers:

- Yes:** patient is of Cuban, Mexican, Puerto Rican, South or Central American or other Spanish culture or origin, regardless of race
- No:** patient is not of Cuban, Mexican, Puerto Rican, South or Central American or other Spanish culture or origin.

## Attachment D

### PNRR SOP for Patient History Questionnaire (PHQ)

**Question: *What is your race?***

Possible answers:

- American Indian / Alaska Native:** patient is a descendent of any of the original peoples of North or South America (including Central America) and maintains tribal affiliation or community attachment
- Asian:** patient is of Far Eastern, Indian or Southeast Asian descent
- Black or African American:** patient is a descendent of any of the black racial groups of Africa
- Native Hawaiian or other Pacific Islander:** patient has origins in Hawaii or other Pacific island
- White:** patient is of European, Middle Eastern or North African descent
- More than one race:** patient is of mixed race

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### Section II. CURRENT SYMPTOMS

**Information for Study Coordinator:**

- **All questions should be answered evaluating the neuropathy (symptoms). If a patient experiences pain associated with another medical condition, the questions in section II of the questionnaire should be answered describing only the neuropathic. The study coordinator should make a note of the other painful condition in NOTES data entry field of the PEF.**
- **The patient should describe their CURRENT symptoms, as experienced within the last 7 days. If a patient experiences pain sometimes, but not in the past 7 days, the patient should be instructed to still describe his/her pain as long as pain is experienced on a regular basis.**
- **If the patient is on pain medication, the symptoms should be described as experienced (while on pain medication).**
- **If the pain levels fluctuate, the “average” pain level should be described.**

***Patient Instructions:***

- ***Please provide answers to these questions regarding symptoms due to your peripheral neuropathy only (e.g. pain, numbness, tingling, burning, weakness, balance, etc.)***
- ***Please refer to your “average” pain during the past 7 days. Do not refer to any extreme levels of pain such as “most” painful or “least” painful***

**1. PAIN: Do you have pain?**

Possible Answers:

- Yes:** patient has painful neuropathy
- No:** patient’s neuropathy is not painful
  - ▶ If you do NOT have pain, skip to **Question 2** (on Page 6)

**Attachment D**  
**PNRR SOP for Patient History Questionnaire (PHQ)**

**a. Where is your pain located? Mark all areas that apply.**

Patient to identify the areas of neuropathic pain.

Possible answers:

- Left foot:** neuropathic pain anywhere below left ankle
- Right foot:** neuropathic pain anywhere below right ankle
- Left leg:** neuropathic pain anywhere between ankle and groin of left leg
- Right leg:** neuropathic pain anywhere between ankle and groin of right leg
- Left arm:** neuropathic pain anywhere between shoulder and wrist of left arm
- Right arm:** neuropathic pain anywhere between shoulder and wrist of right arm
- Left hand:** neuropathic pain anywhere below (distal of) left wrist
- Right hand:** neuropathic pain anywhere below (distal of) right wrist
- Torso/trunk:** patient experiences pain on torso/trunk, which is the main part of the body excluding the extremities, head and neck
- Face:** neuropathic pain on face
- Back:** neuropathic pain on back only (not on front of torso/trunk)
- Neck:** neuropathic pain located in neck area

**If patient marks Torso/trunk, face, back or neck, the study coordinator should make sure that this pain is neuropathy related and not associated with another medical condition.**

**b. Is your pain:**

Possible Answers:

- Always present:** patient experiences pain every day
- Sometimes present:** patient experience pain regularly, but not every day
- Rarely present:** patient experiences pain no more than once a week
- Don't know:** patient is unable to provide answer

**c. How long ago did your pain start?**

Possible Answers:

- Within the last week:** neuropathic pain started within the past 7 days
- 2 to 4 weeks ago:** neuropathic pain started within the last month
- 1 to 6 months ago:** neuropathic pain started within the last 6 months
- 7 to 12 months ago:** neuropathic pain started within the last year
- 1 to 5 years ago:** neuropathic pain started more than 1 year, but less than 5 years ago
- 6 to 10 years ago:** neuropathic pain started more than 5 years, but less than 10 years ago
- 11 to 20 years ago:** neuropathic pain started more than 10 years, but less than 20 years ago
- As long as I can remember:** neuropathic pain started more than 20 years ago



**Attachment D**  
**PNRR SOP for Patient History Questionnaire (PHQ)**

***Patient Instruction:***

***For the next set of questions, place an "X" through the number that best describes your pain.***

***d. Please use the scale below to tell us how intense your pain is.***

Pain Scale Interpretation:

- 0:** no pain
- 1, 2, 3:** mild pain, not impacting daily activities
- 4, 5, 6:** moderate pain, mildly impacting daily activities
- 7, 8, 9:** severe pain, impacting daily activities
- 10:** the most intense pain sensation imaginable

***e. Please use the scale below to tell us how sharp your pain feels. Words used to describe sharp feelings include "like a knife", "like a spike", "jabbing", or "like jolts".***

Pain Scale interpretation:

- 0:** pain does not feel sharp
- 1, 2, 3:** pain feels a little bit sharp
- 4, 5, 6:** pain feels moderately sharp
- 7, 8, 9:** pain feels very sharp
- 10:** the most sharp sensation imaginable ("like a knife")

***f. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire".***

Pain Scale interpretation:

- 0:** pain does not feel hot
- 1, 2, 3:** pain feels a little bit hot
- 4, 5, 6:** pain feels moderately hot
- 7, 8, 9:** pain feels very hot
- 10:** the most hot sensation imaginable ("on fire")

***g. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include "like a dull toothache", "dull pain", "aching", and "like a bruise".***

Pain Scale interpretation:

- 0:** pain does not feel dull
- 1, 2, 3:** pain feels a little bit dull
- 4, 5, 6:** pain feels moderately dull
- 7, 8, 9:** pain feels very dull
- 10:** the most dull sensation imaginable

***h. Please use the scale below to tell us how cold your pain feels. Words used to describe very hot pain include "like ice" and "freezing".***

**Attachment D**  
**PNRR SOP for Patient History Questionnaire (PHQ)**

Pain Scale interpretation:

- 0:** pain does not feel cold
- 1, 2, 3:** pain feels a little bit cold
- 4, 5, 6:** pain feels moderately cold
- 7, 8, 9:** pain feels very cold
- 10:** the most cold sensation imaginable (“freezing”)

- i. ***Please use the scale below to tell us how sensitive your skin is to light touch or clothing. Words used to describe sensitive skin include “like sunburned skin” and “raw skin”.***

Pain Scale interpretation:

- 0:** skin is not sensitive to touch
- 1, 2, 3:** skin is a little bit sensitive to touch
- 4, 5, 6:** skin is moderately sensitive to touch
- 7, 8, 9:** skin is very sensitive to touch
- 10:** the most sensitive sensation imaginable (“raw skin”)

- j. ***Please use the scale below to tell us how itchy your pain feels. Words used to describe itchy pain include “like poison oak” and “like a mosquito bite”.***

Pain Scale interpretation:

- 0:** pain does not feel itchy
- 1, 2, 3:** pain feels a little bit itchy
- 4, 5, 6:** pain feels moderately itchy
- 7, 8, 9:** pain feels very itchy
- 10:** the most itchy sensation imaginable (“like poison oak”)

- 
- k. ***Which of the following statements best describes the time quality of your pain?***

Possible answers:

- I feel background pain all the time and occasional flare-ups (break-through pain) some of the time.**
  - **Describe the background pain:** \_\_\_\_\_ Patient to describe background pain using adjectives such as burning, tingling, cold, hot, dull, itchy, etc.
  - **Describe the flare-up (break-through) pain:** \_\_\_\_\_ Patient to describe flare-up pain using adjectives such as burning, tingling, cold, hot, dull, itchy, etc.
- I feel a single type of pain all the time.**
  - **Describe this pain:** \_\_\_\_\_ Patient to describe their pain symptoms using adjectives such as burning, tingling, cold, hot, dull, itchy, etc.
- I feel a single type of pain only sometimes. Other times I am pain free.**

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- **Describe this occasional pain:** \_\_\_\_\_ Patient to describe their pain symptoms using adjectives such as burning, tingling, cold, hot, dull, itchy, etc.

**Study Coordinator needs to check that pain descriptions are provided.**

**If more than one choice is marked, Study Coordinator should discuss with patient which of the three options is the most fitting.**

- i. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how unpleasant your pain is to you. Words used to describe very unpleasant pain include “miserable” and “intolerable”. Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how unpleasant your pain feels.**

Pain Scale interpretation:

- 0:** pain is not unpleasant
- 1, 2, 3:** pain feels a little bit unpleasant
- 4, 5, 6:** pain feels moderately unpleasant
- 7, 8, 9:** pain feels very unpleasant
- 10:** the most unpleasant sensation imaginable (“intolerable”)

- m. We want you to give us an estimate of the severity of the deep versus surface pain. We want you to rate both location of pain (deep and surface) separately. We realize this can be difficult to make these estimates, and most likely it will be a “best guess”, but please give us your best estimate.**

- i. How intense is your deep pain?**

Pain Scale interpretation:

- 0:** no deep pain
- 1, 2, 3:** deep pain is mild
- 4, 5, 6:** deep pain is moderate
- 7, 8, 9:** deep pain is severe
- 10:** the most intense deep pain sensation imaginable

- ii. How intense is your surface pain?**

Pain Scale interpretation:

- 0:** no surface pain
- 1, 2, 3:** surface pain is mild
- 4, 5, 6:** surface pain is moderate
- 7, 8, 9:** surface pain is severe
- 10:** the most intense surface pain sensation imaginable

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- n. ***Do you experience abnormal perceptions of pain or discomfort from a normally non-painful stimulus? For example, do you experience tingling, burning, discomfort or some other abnormal sensation when lightly touched?***

Possible answers:

- Yes:** patient has experienced at least one abnormal perception of pain or discomfort in the past seven days from an otherwise non-painful stimulus
- No:** patient did not experience an abnormal perception of pain or discomfort from an otherwise non-painful stimulus in the past seven days
- Don't Know**

- o. ***Are you taking medication for your neuropathic pain?***

Possible Answers:

- Yes:** patient takes medication for neuropathic pain
- No:** patient does not take pain medication
  - ▶ If you do NOT take medication, skip to **Question 2** (next Page)

- p. ***How efficient is your pain medication?***

- Not effective
- Somewhat effective
- Very effective
- Was once effective but no longer helps

- q. ***Do you have side effects from your pain medication?***

Possible Answers:

- Sleepiness, drowsiness (somnolence)
- Dizziness
- Weight gain
- Nausea, upset stomach
- Sexual dysfunction
- Other: \_\_\_\_\_
- No side effects

- r. ***Have you taken other medications for your neuropathic pain in the past, and if so please tell us why you stopped taking those medications:***

- The name of the discontinued pain medications should be listed, using either the pharmaceutical drug name or the brand name as listed in the RXNorm medication dictionary. If the option is available, both the pharmaceutical drug name and the brand name should be provided.
- For pain medication that was taken only once a day, the daily dosage should be listed, followed by the letters "QD". For example: "81 mg QD".

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- For pain medications which are taken more than once each day, the medication for each dosage should be listed, followed by the frequency. Example: for a patient taking 300 mg gabapentin three times a day, the data entry should be “300 mg TID”. A list of the medication frequency codes (e.g. TID for three times daily) is provided in Attachment 1

| Name of medication | Dosage of medication | Reason you stopped / switched   |
|--------------------|----------------------|---|
|                    |                      | <input type="checkbox"/> Side effects<br><input type="checkbox"/> Insurance coverage<br><input type="checkbox"/> No longer effective<br><input type="checkbox"/> Other: _____ |

**Patient Instructions:**

**For the following questions, please refer only to those symptoms you have experienced due to your peripheral neuropathy during the past 7 days.**

**2. NUMBNESS: Do you have numbness (loss of sensation)?**

Possible Answers:

- Yes:** patient has areas of numbness
- No:** patient does not experience numbness
  - ▶ If you do NOT have numbness, skip to **Question 3**.

**a. Where is your numbness (loss of sensation) located? Mark all areas that apply.**

Patient to identify the areas of neuropathic pain.

Possible answers:

- Left foot:** area of numbness located below left ankle
- Right foot:** area of numbness located below right ankle
- Left leg:** area of numbness located between ankle and groin of left leg
- Right leg:** area of numbness located between ankle and groin of right leg
- Left arm:** area of numbness located between shoulder and wrist of left arm
- Right arm:** area of numbness located between shoulder and wrist of right arm
- Left hand:** area of numbness located below (distal of) left wrist
- Right hand:** area of numbness located below (distal of) right wrist
- Torso/trunk:** area of numbness located on torso/trunk, which is the main part of the body excluding the extremities, head and neck
- Face:** area of numbness located on face
- Back:** area of numbness located on back only (not on front of torso/trunk)
- Neck:** area of numbness located in neck area

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If patient marks **Torso/trunk, face, back or neck**, the study coordinator should make sure that the numbness is neuropathy related and not associated with another medical condition.

**b. Is your numbness (loss of sensation):**

Possible Answers:

- Always present:** patient experiences numbness every day
- Sometimes present:** patient experience numbness regularly, but not every day
- Rarely present:** patient experiences numbness no more than once a week
- Don't know:** patient is unable to provide answer

**c. How long ago did your numbness (loss of sensation) start?**

Possible Answers:

- Within the last week:** numbness started within the past 7 days
- 2 to 4 weeks ago:** numbness started within the last month
- 1 to 6 months ago:** numbness started within the last 6 months
- 7 to 12 months ago:** numbness started within the last year
- 1 to 5 years ago:** numbness started more than 1 year, but less than 5 years ago
- 6 to 10 years ago:** numbness started more than 5 years, but less than 10 years ago
- 11 to 20 years ago:** numbness started more than 10 years, but less than 20 years ago
- As long as I can remember:** numbness started more than 20 years ago

---

**3. Do you experience spontaneous abnormal sensations (with or without loss of sensation)? Some people might describe these as “pins and needles”, “tingling”, or “like part of a limb fell asleep”.**

Possible Answers:

- Yes, all the time:** patient experiences spontaneous abnormal sensations on average at least once a week or more frequently
- Yes, occasionally:** patient experiences spontaneous abnormal sensation less than once a week on average
- No, never:** patient does not have spontaneous abnormal sensations

**4. WEAKNESS: Do you have weakness (loss of strength or power)?**

Possible Answers:

- Yes:** patient experienced symptoms of weakness within the past week
- No:** patient did not experience symptoms of weakness within the past week
  - ▶ If you do NOT have weakness, skip to **Question 5**.

**a. What is your weakness (loss of strength or power)? What are the types of activities you have difficulty with? Mark all that apply.**

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Possible Answers:

- Feet and ankles (trip easily)**
  - Foot drop**
  - Proximal legs (difficulty going upstairs, getting out of a chair or toilet)**
  - Fine motor tasks with hands (difficulty buttoning, zipping a zipper)**
  - Decreased grip strength**
  - Proximal arms (difficulty lifting heavy objects, shampooing hair)**
  - Other: \_\_\_\_\_**
- 

**5. Do you experience tight, painful contractions of your muscles? These are sometimes referred to as “cramps” or “charlie horse”.**

Possible Answers:

- Yes, frequently:** painful muscle contractions are experienced twice a month or more frequently
- Yes, sometimes:** painful muscle contractions are experience less than twice a month, but more than six times a year
- Yes, but very rarely:** painful muscle contractions are experiences less than 6 times a year.
- No, never:** patient does not have painful muscle contractions
  - ▶ If you do NOT have painful contraction, skip to **Question 6** (next Page).

**a. Are your tight, painful contractions of your muscles controlled with medications?**

Possible Answers:

- Yes:** painful muscle contractions are controlled with medication
  - No, medication does not work**
  - I do not take medication for my muscle cramps**
- 

**6. BALANCE: Do you have trouble with your balance or difficulties walking because of poor balance?**

Possible Answers:

- Yes:** patient has impaired balance or difficulties walking
- No:** patient does not experience balance impairment
  - ▶ If you do NOT have trouble with your balance, skip to **Question 7**

**a. Is your trouble with balance:**

Possible Answers:

- Always present:** patient has balance issues every day
- Sometimes present:** impaired balance only under certain conditions or not every day

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- Rarely present:** patient notices impaired balance occasionally; no more than once a week
- Don't know**

**b. Do you use any assistive devices when walking? Mark all that apply.**

Possible Answers:

- Yes, I use a walker**
- Yes, I use orthotics**
- Yes, I use a wheelchair**
- Yes, I use a cane**
- No, I am bedbound**
- No, I do not use any assistive devices when walking**

**c. Have you had any falls?**

Possible Answers:

- Yes, almost every day**
- Yes, more than once a week**
- Yes, about once per month**
- Yes, more than once over the last year**
- Yes, less than once per year**
- No, I have not fallen**

**7. AUTONOMIC: Now we want to know a little bit about your autonomic system. Your autonomic system regulates things like heart rate, blood pressure, sweating, bowel function and sexual function.**

**a. Do you experience spells of lightheadedness or dizziness as if you were going to faint?**

Possible Answers:

- Yes:** patient experiences spells of lightheadedness or dizziness
- No:** patient does not experience lightheadedness or dizziness
  - ▶ If you do NOT have dizziness, skip to **Question 7b** (next Page)

**If answered with yes:**

**i. Do your spells of lightheadedness or dizziness get worse after the following activities? Mark all that apply.**

Possible Answers:

- After standing up quickly**
- After a hot bath or shower**
- After standing for a long time**
- After a large meal**
- Other: \_\_\_\_\_**



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**ii. Have you ever fainted or “passed out”?**

Possible Answers:

- Yes, at least once per month
- Yes, several time per year
- Yes, about once per year
- Yes, less than once per year
- Yes, but very rarely
- No, I have never fainted

**b. Do you have abnormal sweating? Mark all that apply.**

Possible Answers:

- Yes, I sweat more after eating
- Yes, I sweat less in a warm environment
- Yes, I have other abnormal sweating, please explain \_\_\_\_\_
- No

**c. Do you experience dryness of your eyes or mouth?**

Possible Answers:

- Yes
- No

**d. Do you have abnormal bowel movements? Mark all that apply.**

Possible Answers:

- Yes, I have diarrhea
- Yes, I have constipation
- No

**e. Do you have difficulties with urination? Mark all that apply.**

Possible Answers:

- Yes, I often experience a sudden, immediate need to go to the bathroom (urgency)
- Yes, I have the urge to go to the bathroom frequently (frequency)
- Yes, I lose control of my bladder (incontinence)
- Yes, I have trouble emptying my bladder or initiating urination
- No, I don't have difficulties with urination

**f. MEN ONLY: Has your sexual function changed recently? Mark all that apply.**

Possible Answers:

- Yes, I have been having difficulties with having erections
- Yes, I have been having difficulties having ejaculation
- No

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**8. SLEEP: Have you experienced sleeping difficulties?**

Possible Answers:

- Yes**: patient has some sleeping difficulties
- No**: no sleeping problems
  - ▶ If you do NOT have sleeping difficulties, skip to **Question 9**.

**a. Do you have difficulty falling asleep or staying asleep at night from pain due to your peripheral neuropathy?**

Possible Answers:

- Yes**
- No**

**b. Do you have an urge to move your legs at night, accompanied or caused by unpleasant sensations?**

Possible Answers:

- Yes**
- No**

**c. Are your sleeping difficulties controlled with medications?**

Possible Answers:

- Yes**
- No, medication does not work**
- I do not take sleeping aid medication**

---

**9. Which symptom bothers you the most? Please mark only one.**

Possible Answers:

- Pain**
- Numbness (loss of sensation)**
- Weakness (loss of strength or power)**
- Balance or difficulty with walking**
- Other: \_\_\_\_\_**

**If patient selected more than one answer for Question 9, the study coordinator shall discuss this with the patient to determine which symptom is the most bothersome for the patient and correct the answer for question 9 accordingly.**

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**Section III. MEDICATIONS, VITAMINS, AND SUPPLEMENTS**

***Patient instructions:***

***Please list all medications, vitamins, and supplements that you are currently taking.***

**Medication, Vitamin, or Supplement:**

- The names of all current medications should be listed, using either the pharmaceutical drug name or the brand name as listed in the RXNorm medication dictionary. If the option is available, both the pharmaceutical drug name and the brand name should be provided. Vitamins should be listed by either by using the chemical name or by listing the vitamin name as listed in the RXNorm medication list. If available, both the chemical name and the vitamin name should be provided.
- Supplements: all taken supplements should be listed using the generic description of the supplement, for example “turmeric oil”
- Supplements that are not included in the RXNorm medication list, can be entered by requesting unrestricted medication data entry fields. The number of supplements not found in the RXNorm list should be entered, using the **“How many supplements did the patient list which are not on the RXNorm list?”** The requested number of data entry fields will then be created by REDcap.

**Dosage:**

- For medication taken only once a day, the daily dosage should be listed, followed by the letters QD (latin: quaque die). For example, “81 mg QD”.
- For medications taken more than once each day, the medication for each dosage should be listed, followed by the frequency. For example, a patient taking 500 mg Metformin twice a day, the dosage information should be entered as “500 mg BID”. A list of the medication frequency codes (e.g. BID for twice a day) is provided in Attachment 1
- For multivitamins and supplements, it is acceptable to enter the information in form of volume measurements, e.g. “1 capsule QD”

**Study coordinator to check provided medication list against patient’s medical records. Missing medications and dosages should be added to the PNRR data set.**

**Section IV. MEDICAL HISTORY**

**Question for FOLLOW-UP ONLY:**

***Have you had any new medical issues, diagnoses, or surgeries since your last PNRR visit?***

Possible Answers:

- Yes:** patient has reports new medical issues or surgeries
- No:** no new medical issues or surgeries
  - ▶ If you have NOT have new medical issues, diagnoses, or surgeries since your last PNRR visit, Questionnaire is complete.

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**10. Please mark all that apply:**

**Amyloidosis**

**Anorexia**

**Cancer**

Have you ever received chemotherapy?

Yes

No

Don't know

Name of drug(s): \_\_\_\_\_

**Study coordinator to contact Oncologist if patient is not able to provide name of drug(s). At minimum, drug(s) known to cause nerve damage should be listed.**

**Cardiac disease**

**Celiac Disease**

**Crohn's disease**

**Diabetes Mellitus**

Type I: total lack of insulin or do not produce enough insulin

Type II: cannot use insulin efficiently

**Elevated cholesterol**

**Elevated triglycerides**

**Fibromyalgia**

**Hepatitis**

Hepatitis A

Hepatitis B

Hepatitis C

Have you ever received Interferon treatments?

Yes

No

Don't know

**HIV**

Have you ever received ddI, d4T, or ddc?

Yes

No

Don't know

Have you ever received protease inhibitor?

Yes

No

Don't know

**Irritable bowel disease**

**Kidney disease**

**Leprosy**

**Liver disease**

**Lyme disease**

**Mixed connective tissue disease**

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- Peripheral vascular disease
  - Rheumatoid arthritis
  - Sarcoidosis
  - Scleroderma
  - Shingles
  - Sjögren’s syndrome
  - Syphilis
  - Systemic lupus erythematosus (SLE)
  - Thyroid disease
    - Hyper – patient had iodine treatment or takes methimazole medication
    - Hypo – patient takes levothyroxine sodium (Synthroid) medication
    - Don’t know
  - Ulcerative colitis
  - Vitamin B1 deficiency
  - Vitamin B6 deficiency
  - Vitamin B6 over-dosage
  - Vitamin B12 deficiency
- 

**11. Did you have any vaccinations, infections, or the flu 1 to 3 months before the onset of your neuropathy?**

Possible Answers:

- Yes, I had the flu
- Yes, I had an infection(s) ► if YES, which one(s)? \_\_\_\_\_
- Yes, I had vaccination(s) ► if YES, which one(s)? \_\_\_\_\_
- No
- Don’t know

**12. If you have other medical or infectious conditions, please list below:**

**All medical conditions should be listed here – independent if they are effecting neuropathy or not. Study Coordinator should check medical records and physician notes to ensure that all medical and infectious conditions are captured in the database.**

**13. If you have had major surgery, please list the type of surgery and when it was performed:**

- **Definition for “major surgery”:** a surgery that required anesthesia or an overnight stay at a health care facility
- **Year of surgery:** calendar year the surgery was performed

**14. As a child, did you have difficulties or delays in development?**

Possible Answers:

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- Yes
- No   ▶ If you did NOT have delays, skip to **Section V** (next Page).

a. *As a child did you have difficulty with (mark all that apply):*

Possible Answers:

- Riding a bicycle
- Roller skating / ice skating
- Running
- Keeping up with peers in physical activities
- Don't know

b. *At what age did you begin having developmental delays? \_\_\_\_\_ (years)*

**Section V. SOCIAL AND OCCUPATIONAL HISTORY**

15. *What is your current occupation? \_\_\_\_\_*

16. *What is your past occupation? \_\_\_\_\_*

17. *Have you had (now or in the past) any occupational exposure to excessive amounts of hazardous chemicals? Mark all that apply.*

Possible Answers:

- Yes, herbicides, pesticides or fungicides
- Yes, heavy metals, such as lead, mercury, arsenic or others
- Yes, solvents such as N-hexane, perchloroethylene, trichloroethylene, carbon disulfide or others
- No

Most patients do not remember the brand name of the substance(s) they came in contact with. If they do not remember the exact name, the "function" should be listed. For example: "pesticides routinely used in apple orchards"; "solvents used for photo development".

---

18. *Have you ever smoked? If you have never smoked, mark "No" and skip to Question 18.*

Possible Answers:

- Yes, I currently smoke

If YES, how many packs per day?

- Less than 1 pack

AND

For how many years?

- Less than 10 years

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More than 1 pack  More than 10 years

**Yes, I have smoked in the past, but I do not currently smoke**

If YES, how many packs per day? AND For how many years?  
 Less than 1 pack  Less than 10 years  
 More than 1 pack  More than 10 years

At what age did you stop smoking? \_\_\_\_\_(years)

**No**

---

**19. Have you ever drunk alcohol? If you do not drink alcohol, mark "No" and skip to Question 20 (next page). For this question, one drink is equal to one glass of wine, one bottle of beer, or one mixed drink.**

Possible Answers:

**Yes, I currently drink**

If YES, how many drinks per day? AND For how many years?  
 Less than 2 drinks  Less than 10 years  
 More than 2 drinks  More than 10 years

**Yes, I have drunk alcohol in the past, but I do not currently drink**

If YES, how many drinks per day? AND For how many years?  
 Less than 2 drinks  Less than 10 years  
 More than 2 drinks  More than 10 years

At what age did you stop drinking? \_\_\_\_\_(years)

**No**

---

**20. Have you ever used recreational drugs? If you have never used recreational drugs, mark "No" and skip to Question 20. For this question, "recreational drugs" refer to any drugs taken for a psychoactive rather than medical purpose, such as marijuana, cocaine, or methamphetamine.**

Possible Answers:

**Yes, I currently use recreational drugs**

If YES, which drug(s) do you use? AND For how many years?  
 \_\_\_\_\_  Less than 10 years  
 \_\_\_\_\_  More than 10 years

**Yes, I have used recreational drugs in the past, but I do not currently use recreational drugs**

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If YES, which drug(s) do you use?                      AND                      For how many years?  
 \_\_\_\_\_                       Less than 10 years  
 \_\_\_\_\_                       More than 10 years

At what age did you stop using recreational drugs? \_\_\_\_\_ (years)

No

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### 21. *What is your marital status?*

Possible Answers:

- Single
- Married
- Widowed
- Separated
- Divorced

### 22. *Which best describes your living situation?*

Possible Answers:

- I live alone
- I live with my spouse / partner
- I live with my parent(s) / sibling(s)
- I live with a roommate
- I live with my children

## Section VI. FAMILY HISTORY

In Section VI, the patients are asked about their family history in regard to neuropathy and other diseases, and then list each family member and their disease. One of the questions asked is the age of the family member at the time of diagnosis. Often the patient does not remember the exact age and indicates that the diagnosis was made “in 50’s” or “mid 60’s” or a similar statement.

If only the decade is indicated, the first year of the decade should be entered. For example, for “50’s” the number 50 should be entered.

If “mid 50’s” is used as the age indication, the value “55” should be entered into the database.

### 23. *Do you have family members with peripheral neuropathy?*

Possible Answers:



## Attachment D

### PNRR SOP for Patient History Questionnaire (PHQ)

- Yes:** other (blood-related) family members have neuropathy
- No:** no other (blood-related) family member has neuropathy
  - ▶ If you did NOT have any family members with peripheral neuropathy, skip to **Question 24.**
- Don't know:** patient does not know if any relatives have neuropathy
  - ▶ Skip to **Question 24.**

***Please tell us more about your family members with peripheral neuropathy. In the table below, list their relationship to you, type of neuropathy, and the age at which they were diagnosed with autoimmune disease. See example.***

- **Relationship to you:** relationship to relative with peripheral neuropathy from view of patient.
- **Type of neuropathy:** type of neuropathy (if known), e.g. diabetic neuropathy, otherwise “unknown” or just neuropathy
- **Age at diagnosis:** estimated age at diagnosis or exact age if known.

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**24. Do you have family members with autoimmune disease?** *Examples of autoimmune diseases include rheumatoid arthritis, vasculitis, systemic lupus erythematosus, Sjögren's disease, Hashimoto's thyroiditis, ulcerative colitis and Crohn's disease.*

Possible Answers:

- Yes:** one or more (blood-related) family members have autoimmune disease.
- No:** no (blood-related) family member has an autoimmune disease.
  - ▶ If you did NOT have any family members with autoimmune disease, skip to **Question 25.**
- Don't know:** patient does not know if any relatives have autoimmune diseases.
  - ▶ Skip to **Question 25.**

***Please tell us more about your family members with autoimmune disease. In the table below, list their relationship to you, type of autoimmune disease, and the age at which they were diagnosed with autoimmune disease. See example.***

- **Relationship to you:** relationship to relative with autoimmune disease from view of patient.
- **Type of autoimmune disease:** name of autoimmune disease.
- **Age at diagnosis:** estimated age at diagnosis or exact age if known.

**25. Do you have any family members with the following diseases or conditions: DIABETES, HIGH TRIGLYCERIDES or HIGH CHOLESTEROL?**

Possible Answers:

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### PNRR SOP for Patient History Questionnaire (PHQ)

- Yes:** one or more (blood-related) family members have either diabetes mellitus, elevated triglycerides or elevated cholesterol
- No:** no (blood-related) family member has diabetes or elevated triglycerides or cholesterol
  - ▶ If you did NOT have any family members these diseases/conditions, skip to **Question 26.**
- Don't know:** patient does not know if any relative has diabetes or elevated triglycerides or elevated cholesterol
  - ▶ Skip to **Question 26.**

***Patient Instruction: Please tell us more about your family members with these diseases/conditions. In the table below, list their relationship to you, type of disease/condition, and the age at which they were diagnosed with that disease or condition. See example.***

- **Relationship to you:** relationship to relative with medical condition from view of patient.
- **Type of disease / condition:** if a relative has more than one condition, all applicable conditions should be listed in one line, e.g. diabetes and high cholesterol
- **Age at diagnosis:** estimated age at diagnosis or exact age if known. If patient has more than one medical condition, the age at diagnosis for each condition should be listed, e.g. 62 and 68

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#### **26. Do you have any other family history of disease?**

Possible Answers:

- Yes:** one or more (blood-related) family members have another disease
- No:** no (blood-related) family member has another disease
- Don't know:** patient does not know if any relative has another disease

***Please tell us more about your family history of disease. In the table below, list their relationship to you, type of disease, and the age at which they were diagnosed with that disease. See example.***

- **Relationship to you:** relationship to relative with medical condition from view of patient.
- **Type of disease / condition:** if a relative has more than one disease, they should be all listed in one data entry field
- **Age at diagnosis:** estimated age at diagnosis or exact age if known. If a relative has more than one disease, the age at diagnosis for each disease should be listed, in the same order they are listed in the "type of disease / condition" data entry field.

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### PNRR SOP for Patient History Questionnaire (PHQ)

**Date Submitted:**

Date should be entered when data entry was **completed** (= assumed final).

**Form Status:**

- **Incomplete:** not all data is entered yet
- **Unverified:** all data is entered, but waiting for confirmation for some data (for example, when waiting for confirmation about primary diagnosis pending lab results, the form should be considered unverified)
- **Complete:** all information is verified, no additional edits are anticipated

**Attachment D**  
**PNRR SOP for Patient History Questionnaire (PHQ)**

**PHQ Attachment: Medication Frequency Codes**

| <b>Frequency Code</b> | <b>Frequency Description</b> |
|-----------------------|------------------------------|
| <b>BID</b>            | Twice a day                  |
| <b>BIW</b>            | Twice a week                 |
| <b>CI</b>             | Continuous infusion          |
| <b>HS</b>             | At bedtime                   |
| <b>OTO</b>            | One time only                |
| <b>PRN</b>            | As needed                    |
| <b>QH</b>             | Every hour                   |
| <b>Q12H</b>           | Every 12 hours               |
| <b>Q2WK</b>           | Every 2 weeks                |
| <b>Q3WK</b>           | Every 3 weeks                |
| <b>Q4WK</b>           | Every 4 weeks                |
| <b>Q6WK</b>           | Every 6 weeks                |
| <b>Q4H</b>            | Every 4 hours                |
| <b>Q6H</b>            | Every 6 hours                |
| <b>Q8H</b>            | Every 8 hours                |
| <b>QD</b>             | Once a day                   |
| <b>QID</b>            | 4 times a day                |
| <b>QIW</b>            | 4 times a week               |
| <b>QMO</b>            | Once a month                 |
| <b>QOD</b>            | Every other day              |
| <b>QWK</b>            | Every week                   |
| <b>STAT</b>           | Immediately                  |
| <b>TID</b>            | 3 times a day                |
| <b>TIW</b>            | 3 times a week               |
| <b>OT</b>             | Other, specify               |
| <b>QPM</b>            | Each evening                 |
| <b>QAM</b>            | Each morning                 |

## Attachment E PNRR SOP for Biospecimen Collection, Processing and Shipment

### 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          |

**6. Cryobox**

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

## Attachment E

### PNRR SOP for Biospecimen Collection, Processing and Shipment

#### 7. Extra Labels

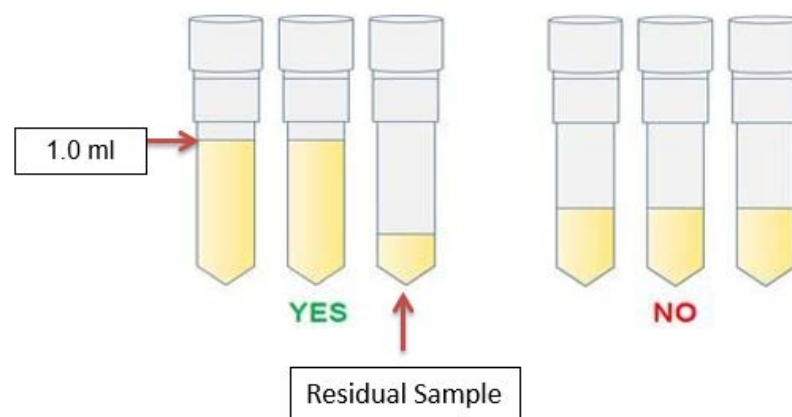
1. Five general labels with lines for the PNRR site coordinator to write in the Site ID and Individual ID. These labels should be applied to the EDTA and SST tubes prior to blood collection.
2. One additional kit number label.
3. Two extra specimen labels for additional plasma cryovials, if needed.
4.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



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### PNRR SOP for Biospecimen Collection, Processing and Shipment

#### 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).

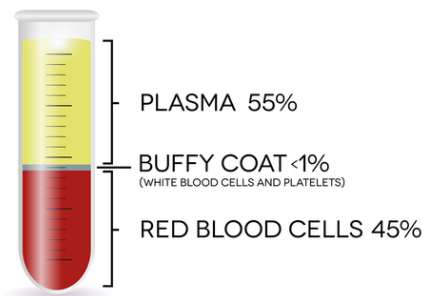
6. While centrifuging, record the start time and temperature of centrifugation on the Sample Form.

**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.

7. After centrifugation is complete, the EDTA tubes should be carefully removed from the centrifuge to avoid disturbing the cell layers and placed it 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).

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### PNRR SOP for Biospecimen Collection, Processing and Shipment



**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.

#### 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).



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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-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).

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### PNRR SOP for Biospecimen Collection, Processing and Shipment

- 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](mailto:pnrr@iupui.edu) email address. The shipment tracking number should be included in the shipment notification.

##### 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.
  
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.

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### PNRR SOP for Biospecimen Collection, Processing and Shipment

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. The shipping waybills provided by IU are pre-filled with the recipient information. Please verify that you are using IU-provided shipping waybills by checking the recipient information:

PNRR @ IUGB  
980 W. Walnut Street, R3-C102  
Indianapolis, IN 46202  
Phone: 317-278-6158

8. PNRR site personnel must complete the required information on the shipping waybill by filling in the shipper information, date of shipment and amount of dry ice used in the shipment.
9. Retain the top copy of the shipping waybill for your records.
10. Affix the completed shipping waybill to the top of the outside cardboard of the dry ice shipping container.
11. Fill out the dry ice label by providing both shipper and recipient information 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.

**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.*

12. 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.
13. If you do not have a regularly scheduled pick-up, call the phone number on the shipping waybill to arrange for pick-up.

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### PNRR SOP for Biospecimen Collection, Processing and Shipment

#### 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

#### 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.

## **Attachment E**

### **PNRR SOP for Biospecimen Collection, Processing and Shipment**

#### **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@IUGB 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 @ IUGB  
980 W. Walnut Street, R3-C102  
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. .
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.