

Exhibit B

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 2023 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
- Washington University, St. Louis, MO
- University of Michigan, Ann Arbor, MI

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)
- 30000 - 39999: Beth Israel Deaconess Medical Center (Site ID: BI)

Exhibit B

- 40000 - 49999: Northwestern Medical Faculty Foundation (Site ID: NW)
- 50000 - 59999: University of Utah (Site ID: UU)
- 60000 - 69999: Kansas University (Site ID: KU)
- 70000 - 79999: Washington University, St. Louis, MO (Site ID: WU)
- 80000 - 89999: University of Michigan, Ann Arbor, MI (Site ID: UM)

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.

Patients with other identified causes for their peripheral nerve damage are not eligible, in 2023 that includes patients with chemotherapy-induced neuropathy (CIPN), or PN associated with HIV/AIDS which were previously 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.

4. PNRR Visit Information Forms

The PNRR database includes seven 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. Metabolic Syndrome Evaluation (MetS)**
- F. Supplemental Data - OPTIONAL**
- G. 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/studies/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.

A. Physician Examination Form (PEF)

Exhibit B

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.

All data captured on the PEF form is considered mandatory information and part of the Minimum Data Set (MDS), with the exception of cold sense and monofilament evaluations which are considered optional. The PEF information is to be entered into REDCap by the PNRR site personnel.

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. Starting in 2023, all patients enrolled in PNRR must have either sural SNAP or skin biopsy testing on record as part of the MDS. Patients without NCS nor skin biopsy testing on record, or those with NCS or skin biopsy testing older than 36 months are no longer eligible for enrollment.

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. Second tier testing results are highly desired, and should be also provided as available. 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, exceptions to the 36 months window are genetic and HIV testing as well as nerve or lip biopsies. 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.

D. Patient History Questionnaire (PHQ)

The PHQ discusses symptoms associated with polyneuropathies and their severity, as well as medical and family history. 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.

Exhibit B

E. Metabolic Syndrome Evaluation (MetSyn)

The MetSyn form evaluates the presence and severity of the five criteria that define metabolic syndrome. The form was added to the PNRR data set in 2020 and shall be completed for all new enrollments.

F. Supplemental Data – OPTIONAL

The Supplemental Data contains additional data points collected for all patients enrolled at Johns Hopkins, including muscular strength in reference to the MRC scale, additional laboratory testing and a neuropathy severity score. The supplemental data set is considered OPTIONAL, and it is within the discretion of each site how much information captured in the supplemental data CRF they may provide.

G. Blood Collection and Processing Form

Plasma, serum and buffy coat should be collected from all new enrolled patients and shipped to the PNRR biorepository located at Indiana University (IU). 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.

5. Minimum Data Set

IU-personnel checks the PNRR database once a week for newly completed records (all six required 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, NCS and PNW forms have a defined MDS data set. The MDS is considered the absolute minimum of information that has to be provided on those forms

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.

Exhibit B

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 DQA status of new enrollments is included in the monthly enrollment report forwarded to the sites at the end of each month.

The enrollment site is expected to address all DQA comments no later than 30 days after the Quarterly Progress Report due date.

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.

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 MDS violations not caused by other medical conditions of the patient, or (c) DQA comments were not addressed by the enrollment site within 30 days of Quarterly Progress Report due date.

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

10. Follow-Up Visits

Exhibit B

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. The recommended time elapse for follow-up visit information is 4-6 years.

For each Follow-Up visit, the PEF and PHQ forms must be completed as a minimum. NCS, PNW and MetSyn forms should be completed if additional testing results are available. Blood samples should not be collected during follow-up visits unless the site has been notified of a re-draw request for the patient or no blood has been collected for the patient previously.

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 a summary enrollment report to the consortium members at the end of each calendar month.

11.b. DQA Status Report

DQA status for each new enrollment is part of the monthly enrollment report distributed to the consortia sites. At the end of each quarter, the Foundation will resend copies of that report with changes in the DQA status of new enrollments as appropriate to inform consortia sites for which enrollments DQA is considered completed.

11.c. Quarterly Enrollment Reports by Consortium Members

All actively enrolling consortium member sites shall send quarterly progress 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:

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.

Exhibit C
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.

Exhibit C

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

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

0. When did you notice the first symptoms associated with your peripheral neuropathy?

Number of years since patient noticed the first PN symptoms, recorded with one decimal, e.g. 3.5

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 8)

Exhibit C

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

Patient Instruction:

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

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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.”

Exhibit C
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.**

Exhibit C

PNRR SOP for Patient History Questionnaire (PHQ)

- **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.

- l. 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

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

- 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."

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

- 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 <input type="checkbox"/> Insurance coverage <input type="checkbox"/> No longer effective <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)

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

- Neck:** area of numbness located in neck area

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

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

▶ 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.

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 “charley 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:

Exhibit C

PNRR SOP for Patient History Questionnaire (PHQ)

Possible Answers:

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

If answered with yes:

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

Possible Answers:

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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

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

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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
-

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)

Exhibit C

PNRR SOP for Patient History Questionnaire (PHQ)

- 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.

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.

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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 had new medical issues, diagnoses, or surgeries since your last PNRR visit, Questionnaire is complete.

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 ddl, d4T, or ddc?
 - Yes
 - No
 - Don't know

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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
- 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.

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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:

- 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.”

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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?

AND

For how many years?

Less than 1 pack

Less than 10 years

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 (below). 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

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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

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

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

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

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 50s” or “mid 60s” or a similar statement.

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

If “mid 50s” 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:

- 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.

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**.

Exhibit C

PNRR SOP for Patient History Questionnaire (PHQ)

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:

- 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
-

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

Exhibit C

PNRR SOP for Patient History Questionnaire (PHQ)

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.

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

Exhibit C
PNRR SOP for Patient History Questionnaire (PHQ)

ATTACHMENT 1: Medication Frequency Codes

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

Exhibit D
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.

INCLUSION / EXCLUSION CRITERIA:

The enrolling physician should use the inclusion and exclusion criteria to determine if a patient with peripheral polyneuropathy is eligible for enrollment into the PNRR study.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Patients with distal, symmetrical, axonal polyneuropathies and patients with length- or non-length dependent small fiber neuropathy	Patients with predominantly demyelinating polyneuropathies
Patients with diabetic neuropathies, as determined by the enrolling physician	Patients with any identified cause of polyneuropathy besides diabetes
Patients with idiopathic polyneuropathy, for which other common causes of PN have been excluded through past evaluations	Patients with upper neuron involvement
Patients with symptoms exclusively in the peripheral nervous system	Patients diagnosed with a second conditions confounding PN symptoms in PEF data set

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

Exhibit D

PNRR SOP for Physician Examination Form (PEF)

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:** Patients with chemotherapy induced neuropathy are no longer considered valid enrollments.
- c. **HIV/AIDS:** Patients with HIV-induced neuropathy are no longer considered valid enrollments.
- 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:** For patients for which a cause of neuropathy other than Diabetes Mellitus or Prediabetes is identified after enrollment, the enrollment category should be changed to “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.

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:

Exhibit D

PNRR SOP for Physician Examination Form (PEF)

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

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+/3/3-	Active movement against gravity but not against resistance
	2+/2/2-	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.

Exhibit D

PNRR SOP for Physician Examination Form (PEF)

DEEP TENDON REFLEXES

The following reflexes shall be examined:

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

Exhibit D

PNRR SOP for Physician Examination Form (PEF)

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

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

Exhibit D

PNRR SOP for Physician Examination Form (PEF)

database, when the test was performed under less than ideal 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)

Exhibit D

PNRR SOP for Physician Examination Form (PEF)

Values: **2 = Normal:** joint position sense is not impaired
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		Deep pressure sensation only
	300	6.65		

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		

Exhibit D

PNRR SOP for Physician Examination Form (PEF)

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

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (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 before or after enrollment visit should be reported in the PNW form, with the exception of genetic and HIV testing.

The FIRST TIER testing is considered the Minimum Data Set (MDS) and must be provided for all PNRR subjects.

The SECOND TIER testing is considered high desired, and all available testing results should be entered into REDCap.

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 can be waived if the diagnosis is supported by PEF and PHQ information or skin biopsy results are provided.

NOTE: If a patient had NCS testing outside of the 36 months window, the NCS interpretation should still 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. Must be within 36 months to visit.

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):

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

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

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

For patients who have a normal NCS/EMG result, skin biopsy testing results should be provided.

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, should be within 36 months of visit

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

Creatinine level from the most recent Comprehensive Metabolic Panel (CMP) should be reported in milligram per deciliter (mg/dL). Creatinine levels ≥ 1.4 mg/dL should be reported as abnormal. Creatinine levels reported in nmol/L should be converted into mg/dL.

Data Entry:

Normal: creatinine value is within normal range (≤ 1.3 mg/dL)

Abnormal: creatinine value is outside the normal range (≥ 1.4 mg/dL)

ND/NA: no Chemistry panel was done in the past 36 months, or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Creatinine level: enter measured creatinine value in 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) or prediabetes as the cause of neuropathy.

a. Glycated Hemoglobin (HbA1C)

The glycated hemoglobin value is an indicator for hyperglycemia. If HbA1C value was analyzed within the past 36 months, it should be reported here in % glycated hemoglobin. For PNRR, HbA1c of 5.7% or higher is considered abnormal.

Data Entry:

Normal: measured HbA1c % was within the reference range ($\leq 5.6\%$)

Abnormal: measured HbA1c % was higher than the reference range ($\geq 5.7\%$)

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (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 of visit.

HbA1C Level: enter measured HbA1c level in % of total hemoglobin

b. Blood Glucose (fasting)

Expresses the amount of glucose in blood after a minimum of 8 hour fasting, abnormal testing results should only be provided if study personnel can verify that blood was collected while patient was fasting. For PNRR, fasting blood glucose levels ≥ 100 mg/dL are considered abnormal. Fasting glucose levels reported in mmol/L shall be converted to mg/dL.

Data Entry:

Normal: fasting glucose within normal range (≤ 99 mg/dL)

Abnormal: fasting glucose outside the normal range (≥ 100 mg/dL)

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

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Fasting Glucose level: enter measured fasting glucose level in mg/dL

c. Oral Glucose Tolerance test

Blood glucose levels measured 2 hours after patient drank glucose syrup should be reported in milligram per deciliter (mg/dL). Both abnormal high (hyperglycemic, ≥ 140 mg/dL) and abnormal low (hypoglycemic, ≤ 70 mg/dL) test results should be reported as abnormal. Testing results reported in mmol/L should be converted to mg/dL.

Data Entry:

Normal: test result within normal range (70-139 mg/dL)

Abnormal: blood glucose levels after 2 hours were abnormal low (≤ 70 mg/dL) or abnormal high (≥ 140 mg/dL).

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

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Glucose level: measured 2-hour glucose in mg/dL)

5.a. Serum Immunofixation (SIFE) and/or

5.b Serum Protein Electrophoresis (SPEP)

Both tests evaluate Immunoglobulin (antibodies) and protein levels in serum. If Serum Immunofixation (SIFE) results are reported abnormal, 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 within the last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

If SIFE and/or SPEP were abnormal:

Identification of type of abnormality:

- Monoclonal gammopathy – presence of paraprotein (abnormal high levels)
- Hypoglobulinemia – one or more values are in abnormal low range

And 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 reported in picogram per milliliter (pg/mL). Reported values below the normal range (180 pg/mL) should be reported as abnormal in PNRR. High values are of little concern and are common in patients who take Vitamin B supplements and should not be reported as abnormal. Vitamin B12 levels measured in pmol/L should be converted to pg/mL before entered into the database.

Data Entry:

Normal: Vitamin B12 values in normal range or elevated

Abnormal: Vitamin B12 value is below normal range < 180 pg/mL

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

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Vitamin B12 Value: enter measured Vitamin B12 value in pg/mL

SECOND TIER

The Second Tier lists standard laboratory tests which are commonly done to check for other causes of Peripheral Neuropathy and other factors that influence the phenotype. All second tier testing should be completed as testing results are available.

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 during past 36 months or test results are not available.

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

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 pending 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

9. Thyroid Stimulating Hormone (TSH)

Measures amount of Thyroid Stimulating Hormone (TSH) in blood reported in milli-International Units per Liter (mIU/L). The normal range may differentiate between laboratories and the range information provided by the laboratory which conducted the test should be consulted, however most common standard is 0.5-5 mIU/L.

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 as abnormal

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

Year of Test: calendar year test was performed. Must be within 36 months of visit.

TSH value: measured TSH level should be entered in mIU/L.

10. Lipid Profile

Lipid profile or lipid panel is a series of blood tests that serves as an initial broad medical screening tool for abnormalities in lipids, such as cholesterol and triglycerides. Lipid profile is critical component for the evaluation of the presence of metabolic syndrome and should be obtained for all PNRR enrollments. If information is not available in the medical records, the study team shall contact the Primary Care Physician to obtain the information. Laboratory testing results for lipid profile should be reported in milligram per deciliter (mg/dL).

Data Entry:

Normal: all measured lipids were in the normal range

Abnormal: one or more measured lipids were outside of normal range (cholesterol \geq 200 mg/dL, triglycerides \geq 150 mg/dL, HDL $<$ 30 mg/dL for men or $<$ 40 mg/dL for women)

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 of visit.

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

- **Cholesterol:** measured cholesterol level in mg/dL
- **Triglycerides:** measured triglyceride level in in mg/dL

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

- **HDL:** measured HDL-cholesterol level in mg/dL
- **LDL:** measured LDL-cholesterol level in 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

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 of 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 found, titer <1:10

Abnormal: positive, one or more ANA's found, titer >1:10

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 of visit.

13.a Urine Immunofixation (UIFE) and/or

13.b Urine Electrophoresis (UPEP)

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

Data Entry:

Normal: monoclonal immunoglobulins are not found

Abnormal: monoclonal immunoglobulin(s) are detected

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

Year of Test: calendar year test was performed. Must be within 36 months of visit.

If Abnormal, report abnormality: _____

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

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.

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

Data Entry:

Normal: MMA level considered to be within normal range

Abnormal: elevated MMA levels above normal range

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 of 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 the ratio between kappa and lambda chains is calculated. If the concentration of either kappa or lambda chains is outside of the normal range, or if the kappa/lambda ratio is outside of the normal range, an abnormal test result should be reported.

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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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

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 of visit.

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

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

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

Data Entry:

Normal: negative result for Anti ds-DNA Ab

Abnormal: positive result

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 of visit.

18. Anti-Endomysial Immunoglobulin G antibodies

Screening test for autoimmune diseases, including celiac disease.

Data Entry:

Normal: negative result

Abnormal: positive result

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 of visit.

19. Anti-Ganglioside Antibodies (GM-1)

Screening test for autoimmune neuropathies.

Data Entry:

Normal: negative screening result

Abnormal: positive screening result

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 of visit.

20. Anti-Gliadin Antibodies (IgA / IgG)

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

Data Entry:

Normal: negative screening test

Abnormal: positive screening test

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 of visit.

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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

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 autoimmune diseases, and both need to be elevated for positive diagnosis for Sjögren’s. SSA testing is sometimes referred to as Ro52 or Ro60 testing.

Data Entry:

Normal: negative screening test

Abnormal: positive screening test for either SSA or SSB antibodies or both

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 of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

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

Screening test for peripheral neuropathy caused by IgM monoclonal gammopathy with high anti-MAG titers with purely sensory or mixed sensory and motor neuropathy and predominantly demyelinating features.

Data Entry:

Normal: negative screening test

Abnormal: positive screening test

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 of visit.

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

Abnormal: positive screening test

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 of visit.

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

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

Abnormal: positive test (antibodies found)

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 of 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

Abnormal: elevated levels of RF detected

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 of 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

Abnormal: positive screening test

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 of visit.

29. Cryoglobulins

Screening for vasculitis and other autoimmune diseases.

Data Entry:

Normal: negative screen

Abnormal: positive screen

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 of visit.

INFECTIOUS:

30. Human Immunodeficiency Virus (HIV) screen

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

Screening test for HIV antibodies. For patients with positive HIV test, the first positive HIV test should be reported. 36 months limitation does not apply to HIV testing.

Data Entry:

Normal: negative screen

Abnormal: positive screen

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 of visit.

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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

32. Rapid Plasma Reagin Antibodies (RPR Ab)

Screening test for syphilis.

Data Entry:

Normal: negative screen

Abnormal: positive screen

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 of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

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

Genetic testing results screening for inherited forms of polyneuropathy. 36-months limitation does not apply for genetic testing results. If patients are diagnosed with CMT, their enrollment category should be changed to "Other" in the PEF, as they are no longer eligible enrollments.

Data Entry:

Normal: negative screening test

Abnormal: positive screening test (confirmation of CMT)

ND/NA: genetic screening test was never done

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

PARANEOPLASTIC:

37. Anti-Ri antibody screen

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

Data Entry:

Normal: negative screen

Abnormal: positive screen (antibodies present)

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 of 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 indicated small cell carcinoma of the lung.

Data Entry:

Normal: negative screening test

Abnormal: positive screening test

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

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

Year of Test: calendar year test was performed. Must be within 36 months of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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⁺ Channel Ab, S
- OTHER Other: _____

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

OTHER:

41. Creatine Kinase (CK)

Also referred to as creatine phosphokinase (CPK) is a screen test for inflammation, particularly myositis. CK levels of 24-204 IU/L are generally regarded as normal. 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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. Testing results should be reported in milligram per liter (mg/L). Lab testing results reported in µg/mL or any other units should be converted to mg/L before entered into REDcap.

Data Entry:

Normal: Vitamin E levels in normal range or elevated

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

Abnormal: Vitamin E levels below normal range

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 of visit.

Vitamin E value: measured Vitamin E value should be entered in 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. Vitamin B1 is usually measured in nanomole per liter (nmol/L) but some laboratories report their results in microgram per deciliter ($\mu\text{g}/\text{dL}$). The normal range is generally 74-222 nmol/L or 2.5-7.5 $\mu\text{g}/\text{dL}$. For PNRR, laboratory testing reported in $\mu\text{g}/\text{dL}$ should be converted to nmol/L before the value is entered into REDcap.

Data Entry:

Normal: Vitamin B1 within normal range or elevated

Abnormal: Vitamin B1 deficiency

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 of visit.

Vitamin B1 value: enter measured Vitamin B1 level in 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. B6 testing results are either reported as nanogram per milliliter (ng/mL), microgram per liter ($\mu\text{g}/\text{L}$) or deciliter ($\mu\text{g}/\text{dL}$), or in nanomole per liter (nmol/L). Normal Vitamin B6 ranges from 5.3-46.7 ng/mL. Vitamin B6 testing results should be reported in ng/mL and test results reported in $\mu\text{g}/\text{L}$, $\mu\text{g}/\text{dL}$ or nmol/L should be converted into ng/mL before data is entered.

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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Vitamin B6 value: enter measured Vitamin B6 value in 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

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

Abnormal: elevated sweating response

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 of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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 within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of 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.

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.

Exhibit E
Peripheral Neuropathy Research Registry (PNRR)
Standard Operating Procedure (SOP) for Peripheral Nerve Workup Form (PNW)

Data Entry:

Normal: negative for Sjörger's syndrome

Abnormal: positive for Sjörger's syndrome

ND/NA: no lip biopsy was previously performed.

Year of Test: calendar year test was performed

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

Exhibit F
PNRR-SOP for NCS Form 2022

NERVE CONDUCTION STUDY FORM

Nerve Conduction Study (NCS) testing results from major motor and sensory nerves should be available for each enrollment record. NCS information should not be older than 36 months and ideally NCS testing was done at the time of enrollment visit. However, for patients with predominantly small fiber neuropathy, NCS testing information is not required as long as skin biopsy results are provided. For all other patients, sural nerve action potential (SNAP) of at least the right or left leg is expected to be provided for all new enrollments.

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 (should be within 12 months of 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:

Consortia Site	Normative value 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
University of Kansas	>49 m/s
Washington University	>49 m/s
University of Michigan	>49 m/s

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done. Value to be left blank.

Exhibit F PNRR-SOP for NCS Form 2022

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:

Consortia Site	Normative value for Median 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
University of Kansas	<4.5 msec
Washington University	<4.4 msec
University of Michigan	<4.4 msec

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done. Value to be left blank.

Median Distal Compound Muscle Action Potential (CMAP):

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

Data Entry:

Consortia Site	Normative values for Median CMAP
Johns Hopkins	>4.0 mV
Mount Sinai	≥4.0 mV
Beth Israel	≥4.0 mV
Northwestern	>6.0 mV for patients <60, >5.0 mV for patients ≥60
University of Utah	>4.0 mV
University of Kansas	>4.5 mV
Washington University	>4.0 mV
University of Michigan	>4.0 mV

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

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.

Exhibit F PNRR-SOP for NCS Form 2022

Data Entry:

Consortia Site	Normative values for Median F-wave
Johns Hopkins	<32 msec
Mount Sinai	≤31 msec
Beth Israel	≤31 msec
Northwestern	<31 msec
University of Utah	<31 msec
University of Kansas	<32 msec
Washington University	<31 msec
University of Michigan	<31 msec

- NR – Not Recordable. “0” 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.

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:

Consortia Site	Normative value for Ulnar MNCV
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
University of Kansas	>49 m/s
Washington University	>49 m/s
University of Michigan	>49 m/s

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

Exhibit F
PNRR-SOP for NCS Form 2022

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:

Consortia Site	Normative value for Ulnar 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
University of Kansas	<3.6 msec
Washington University	<3.5 msec
University of Michigan	<3.5 msec

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

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:

Consortia Site	Normative values for Ulnar CMAP
Johns Hopkins	>4.0 mV
Mount Sinai	≥6.0 mV
Beth Israel	≥6.0 mV
Northwestern	>8.0 mV for patients <30, >7.0 mV for patients ≥30
University of Utah	>6.0 mV
University of Kansas	>5.0 mV
Washington University	>6.0 mV
University of Michigan	>6.0 mV

- NR – Not Recordable. “0” 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).

Exhibit F
PNRR-SOP for NCS Form 2022

Data Entry:

Consortia Site	Normative values for Ulnar F-wave
Johns Hopkins	<33 msec
Mount Sinai	≤33 msec
Beth Israel	≤32 msec
Northwestern	<32 msec
University of Utah	<31 msec
University of Kansas	<33 msec
Washington University	<32 msec
University of Michigan	<31 msec

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

PERONEAL MOTOR NERVE:

Motor Nerve Conduction Velocity (MNCV):

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.

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:

Consortia Site	Normative values 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
University of Kansas	>41 m/s
Washington University	>41 m/s
University of Michigan	>41 m/s

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

Exhibit F
PNRR-SOP for NCS Form 2022

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:

Consortia Site	Normative value for Peroneal 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
University of Kansas	<6.6 msec
Washington University	<6.1 msec
University of Michigan	<6.1 msec

- NR – Not Recordable. “0” 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:

Consortia Site	Normative values for Peroneal CMAP
Johns Hopkins	>2.0 mV
Mount Sinai	≥2.0 mV
Beth Israel	≥2.0 mV
Northwestern	>3.0 mV for patients <50, >2.5 mV for patients ≥50
University of Utah	≥2.0 mV
University of Kansas	>2.0 mV
Washington University	>2.0 mV
University of Michigan	>2.0 mV

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

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).

Exhibit F PNRR-SOP for NCS Form 2022

Data Entry:

Consortia Site	Normative values for Peroneal F-wave
Johns Hopkins	<56 msec
Mount Sinai	Dependent on height, range from ≤48 to ≤58 msec
Beth Israel	≤56 msec
Northwestern	<56 msec
University of Utah	<55 msec
University of Kansas	<57 msec
Washington University	<56 msec
University of Michigan	<55 msec

- NR – Not Recordable. “0” 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:

Consortia Site	Normative value for Sural SNCV
Johns Hopkins	>39 m/s
Mount Sinai	≥40 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
University of Kansas	>41 m/s
Washington University	>38 m/s
University of Michigan	>41 m/s

- NR – Not Recordable: “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

Sensory Nerve Action Potential (SNAP) for Sural Nerve:

Action potential (amplitude) measured for Distal Sural Sensory Nerve in microVolts (μV).

Exhibit F
PNRR-SOP for NCS Form 2022

Data Entry:

Consortia Site	Normative values for Sural SNAP
Johns Hopkins	dependent on age, range from >5.0 to >9.0 μV
Mount Sinai	$\geq 6.0 \mu\text{V}$
Beth Israel	dependent on age, range from ≥ 3 to $\geq 14 \mu\text{V}$
Northwestern	>6 μV for patients <30, >5 μV for patients 30-49, >4 μV for patients 50-59 and >3 μV for patients ≥ 60
University of Utah	$\geq 6.0 \mu\text{V}$
University of Kansas	>6.0 μV for patients <60 years, >3.0 μV for patients >60 years
Washington University	>5.0 μV
University of Michigan	>6.0 μV

- NR – Not Recordable: “0” 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:

Consortia Site	Normative value for Median SNCV
Johns Hopkins	>49 m/s
Mount Sinai	$\geq 50 \text{ m/s}$
Beth Israel	$\geq 50 \text{ m/s}$
Northwestern	>51 m/s for patients <50, >50 m/s for patients ≥ 50
University of Utah	>50 m/s
University of Kansas	>48 m/s
Washington University	>44 m/s
University of Michigan	>48 m/s

- NR – Not Recordable: “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

Sensory Nerve Action Potential (SNAP) for Median Nerve:

Action potential (amplitude) measured for Distal Median Sensory Nerve in microVolts (μV).

Data Entry:

Consortia Site	Normative values for Median SNAP
Johns Hopkins	>9.0 μV
Mount Sinai	$\geq 20.0 \mu\text{V}$
Beth Israel	$\geq 20.0 \mu\text{V}$

Exhibit F
PNRR-SOP for NCS Form 2022

Northwestern	>20 μ V for patients <50, >15 μ V patients 50-59, >10 μ V patients \geq 60
University of Utah	\geq 20.0 μ V
University of Kansas	>15.0 μ V
Washington University	>7.0 μ V
University of Michigan	>20.0 μ V

- NR – Not Recordable: “0” 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:

Consortia Site	Normative value for Ulnar SNCV
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
University of Kansas	>48 m/s
Washington University	>44 m/s
University of Michigan	>48 m/s

- NR – Not Recordable: “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

Sensory Nerve Action Potential (SNAP) for Ulnar Nerve:

Action potential (amplitude) measured for distal sensory ulnar nerve in microVolts (μ V).

Data Entry:

Consortia Site	Normative values for Ulnar SNAP
Johns Hopkins	>9.0 μ V
Mount Sinai	\geq 17.0 μ V
Beth Israel	depending on age \geq 20.8 to \geq 11.0 μ V
Northwestern	>18.0 μ V for patients <30, >12.0 μ V for patients 30-49, >10.0 μ V for patients \geq 50
University of Utah	\geq 10.0 μ V

Exhibit F
PNRR-SOP for NCS Form 2022

University of Kansas	>10.0 μV
Washington University	>5.0 μV
University of Michigan	>10.0 μV

- NR – Not Recordable: “0” 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:

Consortia Site	Normative value for Radial SNCV
Johns Hopkins	>49 m/s
Mount Sinai	≥ 50 m/s
Beth Israel	≥ 50 m/s
Northwestern	>51 m/s for patients <50, >50 m/s for patients ≥ 50
University of Utah	>50 m/s
University of Kansas	>48 m/s
Washington University	>50 m/s
University of Michigan	>48 m/s

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

Sensory Nerve Action Potential (SNAP) for Radial nerve:

Action potential (amplitude) measured for distal radial nerve in microVolts (μV).

Data Entry:

Consortia Site	Normative values for Radial SNAP
Johns Hopkins	>9.0 μV
Mount Sinai	≥ 15.0 μV
Beth Israel	depending on age, range from ≥ 12 to ≥ 25.5
Northwestern	>18 μV for patients <50, >14 μV for patients 50-59 and >10 μV for patient ≥ 60
University of Utah	≥ 20.0 μV
University of Kansas	>15.0 μV for patients <60 years, >10.0 μV for patients >60 years
Washington University	>10.0 μV
University of Michigan	>15.0 μV

- NR – Not Recordable. “0” should be entered as value and “NR” should be chosen as evaluation.
- ND – Not Done

Exhibit F PNRR-SOP for NCS Form 2022

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.

Date Data Entry Completed:

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

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

Exhibit G
PNRR SOP for Metabolic Syndrome Evaluation Form
Standard Operating Procedure for
Metabolic Syndrome Evaluation Form (MetSyn)

Subject ID: Subject ID is populated automatically.

I. HYPERGLYCEMIA

HbA1C value entered in the PNW file is displayed

1. Diagnosis of hyperglycemia:

- **Yes:** patient fulfills one of these criteria:
 - i. Recorded clinical diagnosis of Diabetes Mellitus type 1 or type 2,
 - ii. Recorded clinical diagnosis of impaired glucose tolerance (IGT),
 - iii. past impaired fasting glucose (IFG) of ≥ 100 mg/dL (with confirmed fasting),
 - iv. past HbA1C $\geq 5.7\%$,
 - v. past elevated 2-hour blood glucose levels ≥ 140 mg/dL during Oral Glucose Tolerance Test
- **No:** patient does not have a diagnosis of DM type 1 or 2, or diagnosis of prediabetes
- **Unknown:** should only be chosen if no fasting glucose or HbA1C laboratory testing results are available and no medical history is entered into EPIC and medication intake is not verified

2. Type/severity of hyperglycemia:

- **Pre-diabetes:** patient fulfills one of these criteria:
 - i. has diagnosis of IGT (2-hr glucose ≥ 140 , but < 200 mg/dL),
 - ii. past IFG (≥ 100 but ≤ 125 mg/dL) was confirmed fasting,
 - iii. elevated current or past HbA1c (≥ 5.7 , but never > 6.4),
 - iv. does not take any other glycemic control medications besides metformin,
 - v. enrolling physician indicates that patient has prediabetes in exam note
- **DM Type 2:** patient fulfills one of these criteria:
 - i. past HbA1C of $\geq 6.4\%$,
 - ii. past IFG > 125 mg/dL with confirmed fasting,
 - iii. taking ≥ 1000 mg Metformin QD, or
 - iv. taking any other medication to treat hyperglycemia besides metformin
- **DM Type 1:** patient carrying diagnosis of DM type 1
- **Unknown:** should only be selected if no information is available in regard to type of hyperglycemia

Depending on which type of hyperglycemia was selected, questions 3 and 4 will be tailored towards the type of hyperglycemia. If DM Type 1 is selected, question 3 does not appear because DM Type 1 patients have to use insulin.

Exhibit G

PNRR SOP for Metabolic Syndrome Evaluation Form

3.a Medications taken by patient for Pre-diabetes:

- **No medications:** patient does not take any medications to control blood sugar levels.
- **Low dose Metformin:** patient takes Metformin 500 mg QD or BID, but no other medications to control blood sugar levels.
- **Unknown:** daily medication intake is unknown

If patient takes any other hyperglycemia-controlling medications on a regular basis, the “type/severity of hyperglycemia” data entry should be changed to DM type 2 (or possibly type 1 if the medication is insulin)

3.b Medications taken by patient for DM type 2:

- **No medications:** patient does not take medication for hyperglycemia
- **Metformin only:** hyperglycemia is controlled with only taking metformin; no other medications regularly prescribed to lower blood sugar levels
- **Metformin and other medications (not insulin):** patient takes metformin and at least one more medication to lower blood sugar levels, but patient is not prescribed insulin
- **Insulin (and other hyperglycemic medications):** patient has prescription of at least one insulin-containing medication.
- **Unknown:** medication prescriptions are unknown

Common Diabetes / Prediabetes Medications:

Brand Name	Generic Name	Indication
Actos	Pioglitazone	Prediabetes or DM type 2
Alogliptin	Alogliptin	DM type 2
Amaryl	Glimepiride	DM type 2
Bydureon, Byetta	Exenatide	DM type 2
Diabeta	Glyburide	DM type 2
Farxiga	dapfliflozin	DM type 2
Glucotrol	Glipizide	DM type 2
Glumetza	Metformin hydrochloride	DM type 2
Humalog	Insulin lispro	DM type 2
Invokana	Canagliflozin	DM type 2
Janumet	Sitagliptin and metformin	DM type 1 or DM type 2
Januvia	Sitagliptin	DM type 2
Jardiance	Empagliflozin	DM type 2
Lantus, Basaglar, Toujeo	Insulin glargine	DM type 2
Levemir	Insulin detemir	DM type 2
Novolin N, Humulin N	Insulin N	DM type 2
Novolin R, Humulin R	Insulin R	DM type 2

Exhibit G
PNRR SOP for Metabolic Syndrome Evaluation Form

Novolog	Insulin aspart	DM type 1 or DM type 2
Onglyza	Saxagliptin	DM type 2
Ozempic	Semaglutide	DM type 2
Prandin	Repaglinide	DM type 2
Semglee	Insulin glargine-yfgn	DM type 2
Starlix	Nateglinide	DM type 2
Symlin Pen	Pramlintide	DM1
Tradjenta	Linagliptin	DM type 2
Tresiba	Insulin Degludec	DM type 1 or DM type 2
Trulicity	Dulaglutide	Prediabetes or DM type 2
Victoza, Saxenda	Liraglutide	DM type 2

4. Time elapsed since patient was diagnosed with diabetes or prediabetes:

Number of years to be entered, with one decimal, e.g., 5.5 years

If information is not available in the medical records, patient should be asked to estimate the time since his/her diagnosis and that information should be entered (e.g., patient answer “at least 6 years,” 6.0 should be entered)

Enter “unknown” if information is not available – this option only applies when information is backfilled for older records.

5. Patient’s medical complications from diabetes or pre-diabetic hyperglycemia:

To be checked if the patient has medical record evidence of each diagnosis, regardless of when it was diagnosed with regard to the onset of hyperglycemia

- **None:** patient has none of the diagnosis on records, takes no medication to treat any of the conditions and lab testing results are in normal range
- **Renal insufficiency:** to be checked if patient fulfills one of the following criteria:
 - i. entered creatinine level is above 1.3 mg/dL,
 - ii. glomerular filtration rate (GFR) <60 mL/min/1.73m²,
 - iii. patient has diagnosis of kidney or renal failure on record,
 - iv. patient takes medication to treat renal failure
- **Retinal, macular or lens-based eye disease:**
 - i. patient has diagnosis of retinopathy, macular edema, or cataracts (or past cataracts surgeries),
- **Coronary artery disease:**
 - i. patient has diagnosis of coronary artery disease (CAD), atherosclerosis, angina or arrhythmia,
 - ii. patient had past heart attack, stent or bypass surgeries
 - iii. patient takes medications to treat CAD
- **Vasculopathy:**

Exhibit G

PNRR SOP for Metabolic Syndrome Evaluation Form

- i. patient carries diagnosis of common vascular disorders such as deep vein thrombosis (DVT), stroke, pulmonary embolus (PE), peripheral arterial disease (PAD), or livedoid vasculopathy
 - ii. patient takes medication to treat vasculopathy.
- **Unknown:** information not available

Glaucoma

Name	Generic Name
Betaxolol	n/a
Betimol	Timolol
Betoptic	Betaxolol
Bimatroprost	n/a
Istalol	Timolol
Latanoprost	n/a
Latanoprostene	n/a
Lumigan	Bimatroprost
Tafluprost	n/a
Timolol	n/a
Timoptic	Timolol
Travatan	Travoprost
Travoprost	n/a
Vyzulta	Latanoprostene
Xalatan	Latanoprost
Zioptan	Tafluprost

Renal Insufficiency

Name	Generic Name
Demadex	Torseamide
Edecrin	Ethacrynic acid
Ethacrynic acid	n/a
Furosemide	n/a
Lasix	Furosemide
Torseamide	n/a
Sodium Edecrin	Ethacrynic acid

Vasculopathy

Name	Generic Name
Apixaban	n/a
Arixtra	Fondaparinux
Betrixaban	n/a
BEVYXXA	Betrixaban
Coumadin	Warfarin
Dabigatran	n/a
Edoxaban	n/a
Eliquis	Apixaban
Fondaparinux	n/a
Heparin	n/a
Pentoxifylline	n/a
Pradaxa	Dabigatran
Rivaroxaban	n/a
Savaysa	Edoxaban
Trentol	Pentoxifylline
Warfarin	n/a
Xarelto	Rivaroxaban

Coronary Artery Disease

Name	Generic Name
Aspirin (>81 mg)	n/a
Clopidogrel	n/a
Eptifibatide	n/a
Integrilin	Eptifibatide
Nitroglycerin	n/a
Plavix	Clopidogrel
Ranolazine	n/a
Ticlid	Ticlopidine
Ticlopidine	n/a

6. Physician assessment of glycemic control:

For new enrollments, the enrolling physician should provide this assessment. For past enrollments, the following criteria should be used if no assessment about hyperglycemic control can be found in the medical records:

- Well controlled: HbA1c consistently <7.0
- Moderately controlled: HbA1c 7.0 - 9.0
- Poorly controlled: past HbA1c >9.0

Exhibit G

PNRR SOP for Metabolic Syndrome Evaluation Form

- Unknown: should only be used if no past HbA1c information can be found in the medical records.

7. Past HbA1C testing:

Past glycemic haemoglobin (HbA1c) values should be entered as available together with the year of testing. Ideally, past HbA1c testing should provide information about the glycemic control history of the patient – if glycemic control fluctuated over the years, the entered values should reflect this. If patients have a long-standing diagnosis of diabetes, the entered HbA1c values should span the entire duration (e.g., if a patient has DM type 2 for the past 10 years, then ideally, HbA1c from 4, 7 and 10 years ago would be entered – plus the most recent HbA1c value entered in the PNW file).

II. HYPERTENSION

1. Medication(s) taken by patient for hypertension:

- **None:** patient does not take any blood pressure lowering drugs
- **One HTN medication:** patient takes one blood pressure lowering drug
- **Two HTN medications:** patient takes two blood pressure lowering drugs
- **Three or more HTN medications:** patient takes three or more blood pressure lowering drugs
- **Unknown:** medication prescriptions are unknown. **Unknown should not be entered for new enrollments, only when information is backfilled for older enrollment records.**

Medications routinely prescribed to treat hypertension:

Brand Name	Generic Name		Brand Name	Generic Name
Sectral	Acebutolol		Prinivil, Zestril	Lisinopril
Aldactazide	Aldactone + HCTZ		Cozaar	Losartan
Tekturna	Aliskiren		Toprol XL	Metoprolol Succinate
Tenormin	Atenolol		Lopressor	Metoprolol Tartrate
Edarbi	Azilsartan		Corgard	Nadolol
Lotensin	Benazepril		Bystolic	Nebivolol
Bumex	Bumetanide		Procardia, Adalat	Nifedipine
Atacand	Candesartan		Inderal	Propranolol
Coreg	Carvedilol		Accupril	Quinapril
Hygroton	Chlorthalidone		Altace	Ramipril
Catapres	Clonidine		Aldactone	Spirolactone
Cardiazem, Tiazac, Dilacor	Diltiazem		Micardis	Telmisartan
Cardura	Doxazosin		Dyrenium	Triamterene
Vasotec	Enalapril		Dyazide, Maxide	Triamterene + HCTZ
Monopril	Fosinopril		Diovan	Valsartan

Exhibit G

PNRR SOP for Metabolic Syndrome Evaluation Form

Lasix	Furosemide		Micardis	Telmisartan
Apresoline	Hydralazine		Verelan, Calan	Verapamil
Avapro	Irbesartan			

2. Systolic BP on day of PNRR visit:

Systolic blood pressure reading on the day of visit in mmHg, or within 3 months of visit if blood pressure was not measured at the actual visit date.

3. Diastolic BP on day of PNRR visit:

Diastolic blood pressure reading on the day of visit in mmHg, or within 3 months of visit if blood pressure was not measured at the actual visit date.

III. OVERWEIGHT / OBESITY

BMI, calculated from entered weight and height in PEF file is displayed

1. Is the patient overweight or obese?

- **No:** patient has a BMI <27
- **Yes, overweight (BMI ≥27)**
- **Yes, obese (BMI ≥30)**
- **Unknown:** patient has no BMI or height/weight information on record. *This option is for older enrollments when MetSyn data is backfilled and information cannot be obtained through medical records or by asking the patient.*

For patients who are considered obese, both “obese” and “overweight” should be checked and time elapse since diagnosis should be provided for both conditions. If a patient is considered obese, both years of being obese and years of being overweight should be captured if possible.

2.a Years since patient was diagnosed as being overweight

Number of years to be entered, e.g., 33 years. If, based on record review or participant recall, the absolute time is unknown, but a minimal time overweight can be confidently stated (e.g., “at least 10 years,” this should be provided). Enter “unknown” if information is not available.

2.b Years since patient was diagnosed as being obese

Number of years to be entered, e.g., 33 years. If, based on record review or participant recall, the absolute time is unknown, but a minimal time obese can be confidently stated (e.g., “at least 10 years,” this should be provided).

Exhibit G

PNRR SOP for Metabolic Syndrome Evaluation Form

Enter “unknown” if information is not available.

BMI calculator:

Can be utilized to calculate BMI based on past weight measurements found in the medical records to determine when patient was first considered overweight or obese. Calculator automatically uses height entered in PEF file.

IV. DYSLIPIDEMIA

Triglycerides and high-density cholesterol (HDL) testing results are displayed if they were previously entered into the PNW file.

1. Diagnosis of Dyslipidemia:

- **Yes:** patient fulfills at least one of the following criteria:
 - i. patient has hypertriglyceridemia (triglycerides >150mg/dL),
 - ii. patient has abnormal low high density cholesterol (HDL) levels (for men <40mg/dL, for women <50mg/dL), or
 - iii. patient takes triglyceride-lowering medication, or
 - iv. patient takes high dosage of lipid-lowering drugs (statins)
- **No:** patient does have normal lipid profile and take lower dosages of lipid-lowering drugs as usually prescribed for hypercholesteremia
- **Unknown:** not feasible to determine if patient has dyslipidemia based on the available information

2. Type of dyslipidemia diagnosed in patient:

- **Elevated triglycerides (>150):** patient had elevated triglycerides of >150 mg/dL in at least one lipid profile during the past 36 months
- **Low HDL levels (<40 for men, <50 for women):** patient had low HDL level in at least one lipid profile during the past 36 months
- **Takes triglyceride-lowering medication:** patient takes triglyceride lowering agent
- **Takes low intensity statin dose:** see table below
- **Takes high intensity statin dose:** see table below or if patient takes multiple agents
- **Unknown:** neither lipid profile nor medication list is available for this patient

Lipid-lowering agents – low and high dosages

Generic Name	Brand Name	Low dosage	High Dosage
Atorvastatin	Lipitor	10-20 mg	40-80 mg
Fluvastatin	Lescol	20-40 mg	80 mg
Lovastatin	Mevacor Altoprev	10-40 mg	60-80 mg
Pravastatin	Pravachol	10-40 mg	80 mg
Rosuvastatin	Crestor	5-10 mg	20-40 mg

Exhibit G

PNRR SOP for Metabolic Syndrome Evaluation Form

Simvastatin	Zocor	5-40 mg	80 mg
-------------	-------	---------	-------

Triglyceride lowering agents

Generic Name	Brand Name	
Bezafibrate	Bezalip	<p>*Note: for patients taking Niacin or Omega-3 fatty acids, it should be confirmed that they are taking it to lower their triglyceride levels and not for other reasons such as heart health if triglyceride levels in lipid panel are in normal range.</p>
Ezetimibe	Zetia	
Fenofibrate	Antara Fenoglide Lipofen Tricor Triglide	
Fenofibric acid	Fibricor Trilipix	
Gemfibrozil	Lopid	
Icosapent ethyl	Vascepa	
Niacin*	Vitamin B3	
Omega-3 fatty acids*		

V. EXERCISE

1. Does the patient exercise?

- **Yes:** The activity should be identified as being performed as exercise, rather than, for instance, as a part of the patient’s work activity, yard chores, or housekeeping.
- **No:** patient does not exercise.
- **Unknown:** no information available about exercise habits of this patient.

2. Total number of minutes exercising per week:

Minutes of exercises per week reported by patient – total of all exercises (including aerobic exercise). If patient reports different weekly exercising routines, the average per week should be reported.

3. Total number of minutes of aerobic exercise per week:

Time the patient is performing aerobic exercises, such as jogging, power walking, treadmill, stationary bike, elliptical, swimming, water gymnastics or aerobics. Activities during which the patient “breaks a light sweat” or is a little short of breath are considered aerobic exercise. The weekly average the patient spends on performing aerobic exercises should be reported.

Exhibit H
PNRR SOP for Biospecimen Collection, Processing and Shipment

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

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

I. Blood Collection Kits

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

Each blood collection kit contains the following items:

1. Sample Collection and Processing Form

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

2. Sealable plastic biohazard bag

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

3. Blood collection tubes

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

4. Sterile pipettes and mixing vial

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

5. Cryovials

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

Sample Type	Cryovial Color
serum	yellow
plasma	purple
buffy coat	clear

Exhibit H

PNRR SOP for Biospecimen Collection, Processing and Shipment

6. Cryobox

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

7. Extra Labels

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

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

II. Blood Collection and Processing

II.a. General Remarks

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

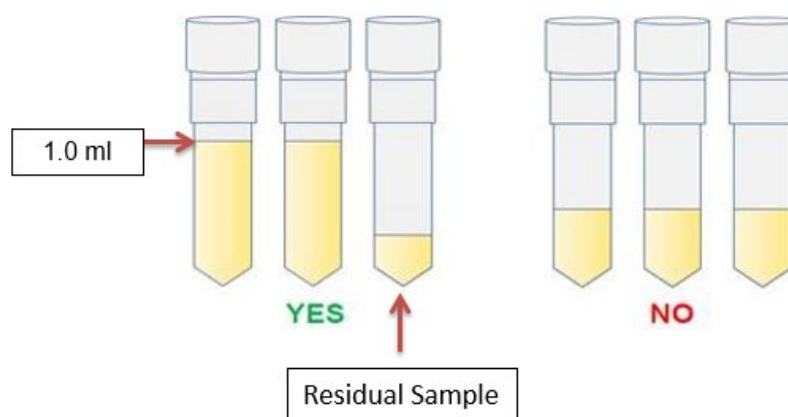


Exhibit H
PNRR SOP for Biospecimen Collection, Processing and Shipment

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).

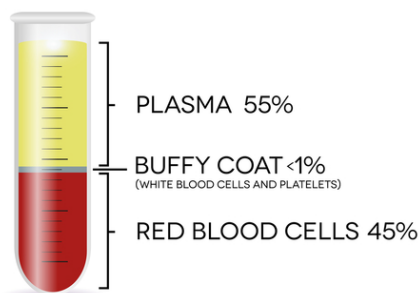
6. While centrifuging, record the start time and temperature of centrifugation on the Sample Form.

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.

Exhibit H

PNRR SOP for Biospecimen Collection, Processing and Shipment

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



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

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

Exhibit H
PNRR SOP for Biospecimen Collection, Processing and Shipment

II.d. SERUM processing (SST tubes)

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

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

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

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

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

Exhibit H

PNRR SOP for Biospecimen Collection, Processing and Shipment

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

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

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

III. Sample Shipments

III.a. Shipment Supplies

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

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

IV.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@iu.edu email address. The shipment tracking number should be included in the shipment notification.

Exhibit H

PNRR SOP for Biospecimen Collection, Processing and Shipment

1. Packaging the blood sample

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

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

2. Shipment labeling and paperwork

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

Exhibit H

PNRR SOP for Biospecimen Collection, Processing and Shipment

12. Make sure your address appears in the fields under “Ship From” on the main page.
 - a. If you accidentally selected the wrong address, click on the “Reset” button on the bottom right of the screen. After the page reloads and clears the information, select “PNRR” again from the “Study Group” menu and click on the magnifying glass icon again to search for your correct address.
13. Enter the total weight of your package in the “Weight” field on the right side of screen under the name of your study.
 - a. Leave the “Dry Ice Weight” field empty or enter “0” if shipping an ambient sample.
14. Enter the weight of the dry ice for frozen shipments in the “Dry Ice Weight” field.
 - a. The “Dry Ice Weight” field can never be higher than the “Weight” field.
 - b. (Steps 15-16 can be skipped if you do not need to schedule a pickup)**
15. After entering the weights, click on the blue “Pickup Request” button.
16. When the “Create Pickup Request” box pops up, enter information into all the fields provided.
 - a. Enter the “Earliest Time Ready” and “Latest Time Ready” in 24-hour format.
 - i. Schedule pickup at a minimum 1 hour before the “Earliest Time Ready”
 - ii. Enter times in 24-hr format (Ex: 14:00 for 2pm)
 - b. Choose a name and phone number that is the best contact if the UPS driver has question related to picking up your package
 - c. Entering the “Room Number” and “Floor” will help the UPS driver locate your package
 - i. The “Floor” field only allows numerical characters while the “Room Number” field is free text up to 8 characters.
 - d. Click “Save” when done.
17. Once you are certain that all the correct information has been entered, click the “Ship” button in the bottom right corner of the screen.
18. If no red error messages pop up at the top of your screen after clicking on “Ship”, then two PDF files should have downloaded: “Shipment Receipt” & “UPS Package Label”
 - a. Shipment Receipt will list a “Pickup No.” that references your specific package if there is ever an issue with UPS picking up your package for scheduled pickups
19. Print out the UPS air waybill label that downloads to your computer, fold it in half, place it inside the clear UPS sleeve.

Exhibit H

PNRR SOP for Biospecimen Collection, Processing and Shipment

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

Recipient Information:

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

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

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

NOTE: If you need to reprint your air waybill or void your shipment, click on “History” at the top of the main screen.

- a. If your shipment does not automatically pop up, enter the date of shipment and then click “Search”.
- b. To reprint your air waybill, click on the printer icon to the far left under “Action”
- c. To void your shipment, click on the “X” icon to the far left under “Action”

IV. Saliva Collection

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

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

Each saliva collection kit includes the following items:

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

Exhibit H
PNRR SOP for Biospecimen Collection, Processing and Shipment

IV.a Saliva Collection Instructions

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

For saliva collections at the enrollment center:

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

Shipment instructions (from enrollment center):

9. Complete the "PNRR Biological Sample Form" and place form in shipment envelope together with the saliva sample itself.
10. Mail envelope to PNRR@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
351 W 10th Street, TK217
Indianapolis, IN 46202
Phone: 317-278-6158

Mailing saliva collections kits to the subjects:

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

Exhibit H

PNRR SOP for Biospecimen Collection, Processing and Shipment

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.

Exhibit I

PNRR SOP for Supplemental Data

SUPPLEMENTAL DATA

PURPOSE:

The supplemental data CRF contains a series of data points that were considered of interest for several planned data analysis projects. Providing all or only part of the supplemental data set is voluntary. All data entered in the supplemental data CRF will be included in the DQA review.

MUSCULAR STRENGTH

Evaluation of muscular strength of all major muscle groups for the upper and lower extremities, using the Medical Research Council (MRC) scale.

Table 1: Medical Research Council Scale

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

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

Upper Extremities:

1. Arm abduction
2. Elbow flexion
3. Elbow extension
4. Wrist extension
5. Wrist flexion
6. Finger extension
7. Interossei and Abductor Digiti Minimi (ADM)
8. Abductor Pollicis Brevis (APB)

Lower Extremities:

9. Hip flexion
10. Knee extension
11. Knee flexion

Exhibit I

PNRR SOP for Supplemental Data

- 12. Ankle dorsiflexion
- 13. Ankle plantar flexion
- 14. Great toe dorsiflexion
- 15. Great toe plantar flexion

SUPPLEMENTAL SENSORY EXAMINATIONS

- 16. Pinprick at knee
- 17. Pinprick at wrist

Pinprick is evaluated for toe, ankle and fingers in the Physician Examination Form (PEF). The supplemental data captures pinprick evaluations for knee and wrist in addition to the PEF information, as those can be abnormal in patients with moderate to severe polyneuropathies.

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 for knee or wrist

- 18. Pinprick border leg

This data point captures the border between normal and reduced pinprick sensation in the leg. Testing should start distal to proximal and the area where the patient starts to have normal pinprick sensation should be captured.

Values:

0 – normal: pinprick is intact in toes.

1 – mid foot: pinprick abnormal in toes, but abnormal pinprick does not reach beyond the metatarsophalangeal (MTP) joint.

2 – below ankle: pinprick abnormal in feet, beyond the MTP, but does not involve ankle.

3 – above ankle: abnormal pinprick includes ankle, and maximum up to 2 inches (5cm) above lateral malleolus.

4 – mid shin: abnormal pinprick advanced to mid-calf area

5 – below knee: abnormal pinprick extended to below the knee

6 – above knee: abnormal pinprick extends to above the knee (maximum 2 inches/5 cm)

7 – higher than above knee: abnormal pinprick extends to thigh or higher

Not Done: pinprick border evaluation was not done

- 19. Pinprick border arm

This data point captures the border between normal and reduced pinprick sensation for the arm. Testing should start distal to proximal and the area where the patient starts to have normal pinprick sensation should be captured.

Values:

Exhibit I

PNRR SOP for Supplemental Data

0 – normal: pinprick is intact in fingers.

1 – mid hand: pinprick abnormal in fingers, but abnormal pinprick does not reach beyond the metacarpophalangeal (MCP) joints (knuckles).

2 – below wrist: pinprick abnormal in feet, beyond the MCP, but does not involve wrist.

3 – above wrist: abnormal pinprick includes wrist, and maximum up to 1 inches (3cm) above radial styloid process.

4 – mid forearm: abnormal pinprick advanced to middle of forearm

5 – below elbow: abnormal pinprick extended to 1 inch below the elbow

6 – above elbow: abnormal pinprick extends to above the elbow (maximum 2 inches/5 cm)

7 – higher than above elbow: abnormal pinprick extends to upper arm (more than 2 inches/5 cm above elbow)

Not Done: pinprick border evaluation for arm was not done

20. Vibration sense knee:

Vibration sense at knee is assessed using Rydel-Fork positioned on the tibial tuberosity below the knee. The absolute reading from the white scale is entered (scale from 0 to 8).

Values: **absolute values:** 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8
 Not Done: vibration sense at knee was not done

21. Vibration sense wrist:

Vibration sense at knee is assessed using Rydel-Fork positioned on the ulnar styloid process at the wrist. The absolute reading from the white scale is entered (scale from 0 to 8).

Values: **absolute values:** 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8
 Not Done: vibration sense at knee was not done

TOTAL NEUROPATHY SCORE REDUCED (TNSr)

The Total Neuropathy Score (TNS) is a validated outcome measure to assess severity and progression of peripheral neuropathy symptoms.

22. Symptom extension:

Evaluates the extension of symptoms associated with peripheral neuropathy such as neuropathic pain and numbness.

Values: **0:** Normal
 1: Symptoms are limited to feet
 2: Symptoms extend to legs
 3: Symptoms extend to hands
 4: Symptoms extend to arms

23. Pin sensibility:

Evaluates the extension of reduced or absent pinprick.

Exhibit I PNRR SOP for Supplemental Data

- Values: **0:** Normal
 1: Reduced below mid foot
 2: Reduced above ankle (max. 1 inch above)
 3: Reduced below knee
 4: Reduced above knee

24. Vibration sensibility:

Evaluated using a Rydel-Seiffer tuning fork (64 Hz). Normative values depend on patient age and are specified in the table below.

- Values: **0:** Normal
 1: Reduced over DIP joint on foot
 2: Reduced for malleolus on ankle
 3: Reduced at knee
 4: Reduced in fingers

Table 2: Normative values for Rydel-Seiffer tuning fork in PNRR

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

25. Strength:

Assesses muscular strength / weakness in one or more muscle group(s). Loss of strength needs to be documented bilateral and must be caused by peripheral neuropathy and not other causes such as radiculopathy or past injuries or accidents. The strength score should reflect the lowest bilateral value.

- Values: **0:** Normal
 1: Mild weakness (MRC = 4)
 2: Moderate weakness (MRC = 3)
 3: Severe weakness (MRC = 1 or 2)
 4: Paralysis (MRC = 0)

26. Tendon Reflexes:

Assesses if one or more reflexes are absent.

- Values: **0:** Normal (all reflexes intact)
 1: Ankle reflex reduced
 2: Ankle reflex absent
 3: Ankle reflex absent and others reduced or absent (but some still preserved)
 4: All reflexes absent

Exhibit I PNRR SOP for Supplemental Data

27. TNS score

The Total Neuropathy score is calculated automatically as a sum of values from symptom extension, pinprick sensibility, vibration sensibility, strength, and tendon reflexes.

SKIN BIOPSY

28. Was skin biopsy performed?

Values: **Yes:** skin biopsy was performed
 No: skin biopsy not done

If question is answered YES, the following data entry fields will appear:

29. Nerve fiber density skin biopsy distal punch site

Interpretation of skin biopsy results for distal punch site near the ankle.

Values: **Normal density:** number of nerve fibers is considered normal
 Reduced density: number of nerve fibers is considered abnormal low
 Absent: no nerve fibers were detected in sample
 Not done: no information available about nerve fiber density at distal punch site

30. Nerve fiber density skin biopsy proximal punch site

Interpretation of skin biopsy results for proximal punch site, on outside thigh.

Values: **Normal density:** number of nerve fibers is considered normal
 Reduced density: number of nerve fibers is considered abnormal low
 Absent: no nerve fibers were detected in sample
 Not done: no information available about nerve fiber density at distal punch site

31. Nerve fibers / mm² distally

If provided, absolute number of detected nerve fibers in tissue sample from distal punch site should be entered if provided in skin biopsy report.

SERUM IMMUNOFIXATION RESULTS

Normal and abnormal Serum Immunofixation results are captured in the PNW form. In this section, the absolute levels for the heavy and light chains are recorded in mg/dL or mg/L.

32. Absolute value Immunoglobulin G

The absolute Immunoglobulin G levels as measured by Serum Immunofixation (SIFE) are reported in milligram per deciliter (mg/dL). Normal range varies by laboratory, but are usually around 600-1600 mg/dL.

33. Absolute value Immunoglobulin A

Exhibit I

PNRR SOP for Supplemental Data

The absolute Immunoglobulin A levels as measured by Serum Immunofixation (SIFE) are reported in milligram per deciliter (mg/dL). Normal range varies by laboratory, but are usually around 60-350 mg/dL.

34. Absolute value Immunoglobulin M

The absolute Immunoglobulin M levels as measured by Serum Immunofixation (SIFE) are reported in milligram per deciliter (mg/dL). Normal range varies by laboratory, but are usually around 30-250 mg/dL.

35. Absolute value of kappa light chain

The absolute kappa light chain levels as measured by laboratory testing are reported in milligram per liter (mg/L). Normal range varies by laboratory, but normative range approximate 3-20 mg/L.

36. Absolute value of lambda light chain

The absolute lambda light chain levels as measured by laboratory testing are reported in milligram per liter (mg/L). Normal range varies by laboratory, but is approximate 5-30 mg/L.

37. Kappa Lambda Ratio

Kappa Lambda Ratio as determined by laboratory testing. Normal ranges vary by laboratory, but are commonly in the 0.2-1.7 range.

OTHER LABORATORY TESTING RESULTS

38. Erythrocyte Sedimentation Rate Absolute Value

Is an indicator for presence of inflammatory processes and ongoing infections. Measured Erythrocyte Sedimentation Rate to be entered in millimeter/hour (mm/h) as indicated on the lab report. Normal range may vary by laboratory, but is approximately 0-30 mm/h.

39. Titer of Anti-Nuclear Antibody

If Anti-Nuclear Antibody (ANA) was assessed, the titer from the lab report should be entered. Normal findings are usually reported as 1:10 or <1:40, and the number 10 should be entered. For abnormal results the titer should be entered, e.g., for titer of 1:40, the number 40 should be entered for a titer of 1:160 the number 160.

40. Absolute value of Methylmalonic Acid

Elevated Methylmalonic Acid (MMA) levels are an indicator that the body does not have enough Vitamin B12 to support metabolism. The measured amount of MMA should be entered in nanomoles per liter (nmol/L). Normal ranges for MMA vary by laboratory, but are approximately 50-350 nmol/L. If MMA laboratory testing results were provided in another unit than nmol/L, the result should be converted to nmol/L before entering the value into REDCap.

41. Absolute value for Rheumatoid Factor

Exhibit I

PNRR SOP for Supplemental Data

Rheumatoid Factor (RF) is an autoantibody associated with autoimmune diseases such as Rheumatoid Arthritis or Sjögren's. The measured RF levels should be recorded in units per milliliter (IU/mL). Normal results are often reported as RF<20 IU/mL, thus for normal results the value 20 should be entered. For abnormal results the reported RF shall be entered.

42. Absolute value for Homocysteine

Homocysteine is an amino acid that is broken down by Vitamin B12, Vitamin B6 and folate. High blood levels of homocysteine point to vitamin deficiency for one of the three vitamins. Measured homocysteine levels should be reported in micromoles per liter ($\mu\text{mol/L}$), normal range vary by laboratory, but are approximately 4-15 $\mu\text{mol/L}$. If Homocysteine testing results are reported in another unit, the result should be converted and the converted value should be entered in REDCap.

43. Absolute value Vitamin D

Vitamin D is involved in multiple processes in the human body, including bone strength, function of the immune and nervous systems. Measured vitamin D levels should be reported in nanograms per milliliter ng/mL. Normal range is usually reported as >30 ng/mL. Patients with vitamin D levels of 20-29.9 ng/mL are considered having insufficient vitamin D levels, patients with vitamin D levels <20 ng/mL are considered to have vitamin D deficiency. If Vitamin D testing is reported in another unit than ng/mL, the result should be converted into ng/mL and the converted value should be entered in REDCap.

EVALUATION OF PN-CAUSING UNDERLYING ETIOLOGY

44. Does patient have metabolic disease?

Values: **Yes** – patient has metabolic syndrome
 No – patient does not meet criteria for metabolic syndrome
 Unknown – not enough information available to determine if patient has or has not metabolic syndrome

45. Does patient have small fiber neuropathy?

Values: **Yes** – patient has pure Small Fiber Neuropathy (SFN) and no evidence of large nerve fiber involvement
 No – patient has no confirmed diagnosis of SFN or has large fiber involvement
 Unknown – not enough information available to determine if patient has pure SFN

NOTE: currently there is a question if the file if patient has Diabetes Mellitus. Since the presence of DM is covered in the MetSyn file, the questions in regard to DM status in the supplemental data file should no longer be completed. The information that was previously entered here for JH patients is being transferred to the MetSyn file as time permits. After all data entries are transferred these data entry fields will be deleted.

Exhibit I

PNRR SOP for Supplemental Data

46. Does patient have HIV/AIDS?

Values: **Yes** – patient tested positive for HIV
 No – patient never tested positive for HIV

47. Years since diagnosis of HIV

Time elapse in years since patient first tested positive for HIV should be recorded, e.g. 15.0 (years)

48. Most recent viral load value

Viral load of HIV virus from most recently assessment should be entered in absolute number of detected viruses. If lab report states that no viruses were detectable, the number “0” should be entered, if lab report states that viral load was <20, the number “20” should be entered.

49. Most recent CD4 value

CD4+ T cells are white blood cells that fight infection and the CD4 cell count is an indicator of immune function in patients with HIV. The number of detected cells per cubic-millimeter (mm³) should be reported.

50. Nadir viral load value

The highest recorded viral load detected for the patient since initial diagnosis of HIV should be entered (nadir viral load usually occurs at time of diagnosis).

51. Nadir CD4 value

Lowest level of CD4+ T cells detected in patient since initial diagnosis of HIV should be entered (nadir CD4 value usually occurs at time of diagnosis or shortly thereafter).

52. Has patient received chemotherapy?

Values: **Yes** – patient has received chemotherapy, additional questions will pop up
 No – patient has not received chemotherapy

53. Number of completed chemo-therapy cycles

Total number of chemotherapy cycles patient completed (numeric value 1-100)

54. Onset of PN in relation to chemotherapy

Values: **Within first six cycles** – symptoms started before cycle 6 was administered
 Within cycles 6-12 – onset of symptoms after cycle six and before last cycle
 After last dosage – within three months after chemotherapy was completed
 Onset not related to chemotherapy – patient’s symptom onset was not trigger by administration of chemotherapy

55. Year of Chemotherapy

Enter year in which patient received chemotherapy, e.g. 2020

Exhibit I PNRR SOP for Supplemental Data

56. Does patient exercise regularly?

Values: **Yes** – patient exercises in a regular pattern, at least once a month
 No – patient does not exercise

57. Calculated METs

Metabolic equivalents of task is a way to evaluate work out intensity. High intensity workouts such as running receive higher scores than low intensity workouts such as yoga or pilates. METs provide a value that allows to grade the reported exercise habits.

$$\text{METs} = \frac{\text{Activity 1 METs} * \text{Number of Days Activity 1 Performed in Last 2 weeks} * \text{Average Duration of Activity 1}}{14} + \frac{\text{Activity 2 METs} * \text{Number of Days Activity 2 Performed in Last 2 weeks} * \text{Average Duration of Activity 2}}{14}$$

Example:

Patient reported exercise habits in PHQ: Cycling: 4 of 14 days, 60 minutes, medium intensity; Yoga/pilates: 2 of 14 days, 35 minutes, low intensity; and Stretching 7 of 14 days, 10 minutes, low intensity
 METs = (cycling)4 days x 60 minutes x 8.0METs/14 + (yoga)2days x 35minutes x 2.5METs/14 + (stretching)7days x 10minutes x 2.5METs/14 = 137 + 12.5 + 12.5 = 162 METs/day average

METs for different exercise activities are listed in table below.

Exercise	METs	Comcode
Aerobics	6.5	03015
Badminton (Competitive)	7.0	15020
Badminton (Social)	4.5	15030
Bicycling (moderate, leisurly)	8.0	01030
Cycling (intense workout)	10.0	01040
Calisthenics (e.g. pushups, situps)	8.0	02020
Dancing	6.5	03010
Elliptical maching	7.0	02080
Golf	4.8	15255
Gymnastics (general)	4.0	15300
Horseback riding	7.0	11400
Jogging (general)	7.0	12020
Kayaking	5.0	18100
Martial Arts	10.0	15430
Nordic (Power) Walking	3.8	17200
Pilates	3.5	02030
Rope jumping	10.0	15551
Rowing (boat, general)	3.5	18070
Rowing (stationary)	7.0	02072

Exhibit I
PNRR SOP for Supplemental Data

Rowing (boat, vigorous effort/competitive)	12.0	18080
Running (6 mph)	10.0	12050
Stairmaster	9.0	02065
Stretching	2.5	02101
Swimming (laps)	7.0	18240
Tai Chi	4.0	15670
Tennis	7.0	15675
Treadmill (running)	10.0	12050
Volleyball	4.0	15710
Walking	3.0	17170
Water aerobics/gymnastics	4.0	18355
Water jogging	8.0	18366
Weight lifting	3.0	02130
Yoga	2.5	02100

Looking for additional Compcodes, not included in the current list, go to:

[https://journals.lww.com/acsm-
msse/Fulltext/2000/09001/Compendium_of_Physical_Activities_an_update_of.9.aspx](https://journals.lww.com/acsm-msse/Fulltext/2000/09001/Compendium_of_Physical_Activities_an_update_of.9.aspx)

58. 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