Standard Operating Procedure (SOP) for
Peripheral Neuropathy Research Registry - 2 (PNRR-2)

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 distal, and predominantly sensory, axonal 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 submitted through the request portal posted on the Foundation's website https://www.foundationforpn.org/research-registry-for-researchers/.

1. PNRR Consortium Members

The Foundation has organized a consortium of academic research institutions to identify eligible participants and enroll them into the study, enter the collected information into the REDCap database, and collect and process blood or saliva samples from each participant.

Active (enrolling) consortium members for the 2026 year include:

- Johns Hopkins University School of Medicine, 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
- University of North Carolina, Chapel Hill, NC

The individual consortium agreements between the consortium members and the Foundation 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)
- *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)
- *90000 - 99999*: University of North Carolina, Chapel Hill, NC (Site ID: NC)

The consortia sites are 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

Participants diagnosed with distal, symmetrical polyneuropathy without an identified cause for the nerve damage (idiopathic), and participants with polyneuropathy caused by hyperglycemia in form of diabetes mellitus or prediabetes are eligible for enrollment.

Participants with any other identified causes for their peripheral polyneuropathy are not eligible. In addition, participants with other medical conditions superimposing their polyneuropathy – such as participants with severe spinal stenosis or myopathies – are also not eligible. Participants with predominantly demyelinating neuropathies should only be enrolled when their PN is caused by DM.

4. PNRR Visit Information Forms

The PNRR database includes seven case report forms (CRF's):

A. Physician Examination Form (PEF)
B. Nerve Conduction Studies Form (NCS)
C. Peripheral Nerve Work-Up Form (PNW)
D. Participant History Questionnaire (PHQ)
E. Metabolic Syndrome Evaluation (MSE)
F. Supplemental Data (SUP) - OPTIONAL
G. Blood Collection and Processing Form

PEF, NCS, PNW, PHQ and MSE CRF's must be marked as complete in the REDCap database and a biospecimen must have been shipped to PNRR biorepository in order for a new research participant to be considered fully enrolled.

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

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

A. Physician Examination Form (PEF)

The Physician Examination Form (PEF) captures the examination findings that are most likely abnormal in participants with distal, symmetrical, axonal polyneuropathies. The examination must be performed by a trained neuromuscular specialist familiar with the PNRR study.

All data captured on the PEF-CRF is considered mandatory information and part of the Minimum Data Set (MDS), with the exception with exception for the foot abnormalities examination.

B. Nerve Conduction Study Form (NCS)

The results of electrophysiological testing of the peroneal motor nerve and the sural sensory nerve in the leg is recorded in the Nerve Conduction Study (NCS) CRF. Only NCS testing data from trusted sources should be recorded in PNRR.

Only participants with NCS testing of at least one sural sensory nerve on record are eligible for PNRR enrollment, with the exception of participants with either pathological or clinical confirmed pure Small Fiber Neuropathy (SFN). For information from the skin biopsy pathology report should be provided.

C. Peripheral Nerve Work-Up Form (PNW)

The results from diagnostic laboratory testing are captured in the Peripheral Nerve Work-Up (PNW) Form. The first tier includes all laboratory testing recommended by the American Academy of Neurology (AAN) to identify the most common causes of PN, plus lipid profile which is critical information to evaluate research participants for the presence of metabolic syndrome. All first tier testing with exception of the lipid profile are part of the MDS for new PNRR enrollments with idiopathic PN, for new enrollments with diabetic PN the SIFE/SPEP testing is desired but not required.

Second tier testing results should be 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 or after PNRR enrollment should be entered into the PNW CRF, with the exception of genetic testing results.

D. Participant History Questionnaire (PHQ)

The Participant History Questionnaire (PHQ) is divided into eight sections, capturing information about demographics, presence and severity of the most common symptoms associated with PN, including autonomic symptoms and the effects of PN on the quality of life. It also captures medication and supplement intake, medical and family history as well as life style habits such as smoking history and alcohol consumption and exercises.

E. Metabolic Syndrome Evaluation (MSE)

In recent years, metabolic syndrome has been identified as a potential cause of PN. This CRF evaluates the presence and severity of the five components that define metabolic syndrome which are hyperglycemia, hypertension, overweight/obesity, hypertriglyceridemia and low high density cholesterol levels.

F. Supplemental Data (SUP) – OPTIONAL

The Supplemental Data (SUP) contains additional data points that are of interest to the research team located at Johns Hopkins University School of Medicine. The supplemental data CRF completion is optional for all other consortia members.

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 biospecimen.

If it is not possible to collect plasma, serum and buffy coat, or if the DNA yield from the buffy coat is determined insufficient by IU, a saliva sample should be collected.

Only participants with either plasma, serum and buffy coat or saliva collection on record are considered completed PNRR enrollments.

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5. Minimum Data Set (MDS)

The Minimum Data Set (MDS) is defined as the following for each CRF:

- **PEF:** entire CRF except for foot evaluation
- **NCS:** sural SNAP from at least one leg or skin biopsy pathology report information
- **PNW:** chemistry, glucose, vitamin B12 and SIFE/SPEP for idiopathic PN enrollments; chemistry, glucose and vitamin B12 for diabetic PN enrollments
- **MSE:** entire CRF
- **PHQ:** entire CRF except those questions the participant refused to answer
- **SUP:** not part of MDS
- **Biospecimen:** plasma/serum/buffy coat or saliva sample

The REDCap database is screened once a week by IU personnel for completed new PNRR enrollments – all six CRF's that are part of MDS must be marked as completed in REDCap and biospecimen must have been shipped to biorepository in order for IU to report new enrollments as completed. All new enrollments are checked for MDS violations. If MDS data points are missing due to circumstances outside of the enrollment centers control, an explanatory note should be added to that data entry field in REDcap.

6. Minimum Blood Sample

Plasma, Serum and buffy coat are collected for new PNRR enrollments. Ideally, the biospecimen are collected on 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.

If it is not possible to collect blood, then a saliva sample should be collected from the PNRR research participant for DNA extraction.

6.1 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. If DNA yield is considered low by IU, this will be reported and the enrollment site is expected to reach out to the patient and ask for additional DNA in form of a saliva sample.

7. Data Quality Assessment (DQA)

A Data Quality Assessment (DQA) will be conducted for all new PNRR enrollments within 30 days of the record being reported as complete by IU. The DQA includes a check for data completeness, MDS violations as well as data quality and consistency.

The DQA status of new enrollments will be reported back to all consortia sites as part of the PNRR enrollment report forwarded to the sites at the end of each calendar month.

All DQA comments/actions should be addressed by the enrollment sites prior to submitting the quarterly Progress Report. However, if additional time is required DQA comments can be addressed up to 30 days after Progress Report due date.

8. Follow-Up Visits

The MDS for follow-up visit includes the PEF, PNW, MSE and PHQ CRF's. A minimum of 12 months must elapse between enrollment visit and the first follow-up visit. Ideally follow-up visits are conducted 4-6 years after initial enrollment, and every 4-6 years after that. No biospecimen collection shall occur during follow-up visits.

9. Reporting

9.1 Monthly Status Report

A status report of new PNRR enrollments shall be generated and reported to all consortia sites at the end of each calendar month. The report must include subject ID, date of enrollment completion, MDS status as well as DQA status. The consortia sites shall review the monthly status reports for correctness and shall report any discrepancies to IU or the Foundation.

9.2 Quarterly Progress Reports

Each actively enrolling consortium sites shall send a quarterly progress report to the Foundation, reporting all new enrollments together with the MDS and DQA status.

The template for the progress reports is part of the annual consortia agreement and the quarter end dates and report dates are listed in the table below:

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

10. Funding and Payments

The number of participants which can be enrolled into PNRR may vary between calendar years and enrollment numbers will be detailed in the annual Consortium Member Agreement together with the details about reimbursement amounts.