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

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

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

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

1. PNRR Consortium Members

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

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

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

Consortium members no longer enrolling new patients:

- Beth Israel Deaconess Medical Center, Boston, MA

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

2. Individual Subject IDs

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

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

- *30000 - 39999*: Beth Israel Deaconess Medical Center (Site ID: BI)
- *40000 - 49999*: Northwestern Medical Faculty Foundation (Site ID: NW)
- *50000 - 59999*: University of Utah (Site ID: UU)
- *60000 - 69999*: Kansas University (Site ID: KU)
- *70000- 79999:* Washington University, St. Louis, MO (Site ID: WU)

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

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

3. Inclusion Criteria

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

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

4. PNRR Visit Information Forms

The PNRR database includes five visit information forms:

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

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

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

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.

PNRR Standard Operating Procedure

A. Physician Examination Form (PEF)

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

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

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

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

B. Nerve Conduction Study Form (NCS)

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

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

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

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

C. Peripheral Nerve Work-Up Form (PNW)

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

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

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

D. Patient History Questionnaire (PHQ)

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

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

E. Blood Collection and Processing Form

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

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

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

5. Minimum Data Set

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

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

6. Minimum Blood Sample

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

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

6.a. DNA Yield

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

7. Data Quality Assessment (DQA)

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

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

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

8. Fully-Enrolled Records

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

8.a. Fully Enrolled Records with missing NCS information

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

9. Incomplete Records

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

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

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

10. Follow-Up Visits

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

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

11. Reporting

11.a. New Enrollment Reports

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

11.b. DQA Status Report

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

11.c. Quarterly Enrollment Reports by Consortium Members

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

The general template for these reports is as follows:

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.