PNRR SOP for Supplemental Data

SUPPLEMENTAL DATA FORM (SUP)

The supplemental data form contains additional data points that are collected by Johns Hopkins for planned data analysis projects. Completing the supplemental data set is voluntary. All data entered in the supplemental data form will be included in the DQA review.

SUPPLEMENTAL SENSORY EXAMINATIONS

1. Pinprick at wrist

Prinprick is evaluated in lower extremities and fingers as part of 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 participants with moderate to severe polyneuropathies.

0 = Normal: regular sensation to pinprick (Note: if participant 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: participant feels pinprick, but sensation is reduced (less sharp)
2 = Absent: participant cannot differentiate between sharp or dull objects touching
Not Done: pinprick was not evaluated for knee or wrist

2. 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 participant 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 tight or higher
Not Done: pinprick border evaluation was not done

3. 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 participant starts to have normal pinprick sensation should be captured.

Values:

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

4. Vibration sense evaluation with 128 Hertz Tuning fork at toe level

Assessment of vibration sense at the great toe level using a 128 Hz Tuning Fork. Currently UENS is validated for 128 Hz Tuning Fork, but PNRR-2 is using Rydel-Seiffer Tuning Fork. 128 Hz Tuning Fork evaluation is collected in near future with the goal to validate UENS with Rydel-Seiffer Tuning Fork and do comparison of the two data collected with both tuning forks.

Table 1: Assessment of vibration sense with 128 Hz tuning fork

PNRR Scale	Short Description	Exact Description
0	Normal	Participant has normal vibration sense (detects vibration for minimum of 8 seconds)
1	Diminished	Participant can initially detect 128 Hz tuning fork vibration, but duration is less than 8 seconds
2	Absent	Participant no longer able to detect vibrating sensation provided by tuning fork

5. Monofilament

Testing should be done using Semmes-Weinstein Monofilaments. Participant 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 degrees ankle until the monofilament bows. For smaller monofilaments (0.07 to 1 gram) the stimulus should be applied three times until it is determined that the test is negative. For larger monofilaments, that cannot be bent, the the monofilament should be hold in place for about half a second with mild pressure on the skin. 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
Fingers: Index finger, dorsum side of DIP joint

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

Table 2: PNRR Reference Table to Monofilament Evaluation - **Index Finger**

PNRR Scale	Force (grams)	Size	Color	Description
0	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		
2	4.0	4.56	Red	Loss of protective sensation
	10.0	5.07		
	300	6.65		Deep pressure sensation only

Table 3: PNRR Reference Table to Monofilament Evaluation - **Hallux**

PNRR Scale	Force (grams)	Size	Color	Description
0	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
2	10.0	5.07		
	300	6.65		Deep pressure sensation only

TOTAL NEUROPATHY SCORE REDUCED (TNSr)

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

6. 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

7. Pin sensibility:

Evaluates the extension of reduced or absent pinprick.

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

8. Vibration sensibility:

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

Values:
- **0:** Normal
- **1:** Reduced at DIP joint on great toe
- **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

9. Strength:

Assesses muscular strength / weakness in one or more muscle group(s). Loss of strength needs to 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)

10. 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

11. Total Neuropathy Score 5-items (TNS-5 score)

The Total Neuropathy 5-items score is calculated automatically as a sum of values from symptom extension, pinprick sensibility, vibration sensibility, strength, and tendon reflexes.

12. Peroneal Compound Muscle Action Potential (CMAP):

Assesses if peroneal CMAP is within normal range or reduced; and if reduced if the reduction is mild, moderate, severe or if peroneal nerve is not responsive

Values: **0:** peroneal CMAP >1.9 mV
1: peroneal CMAP 1.6 – 1.9 mV
2: peroneal CMAP 1.1 – 1.5 mV
3: peroneal CMAP 0.6 – 1.0 mV
4: peroneal CMAP 0 – 0.5 mV

13. Sural Sensory Nerve Action Potential (SNAP)

Assesses if sural SNAP is within normal range or reduced; and if reduced if the reduction is mild, moderate or severe in nature. Two separate scales differentiate between research participants younger than 65 and those 65 years and older.

Table 3: TNS rating for sural SNAP in participants younger than 65 versus those 65 and older

	< 65 years	**65 years and older**
Values:	**0:** SNAP >8.6 µV **1:** SNAP 6.8 – 8.6 µV **2:** SNAP 4.6 – 6.7 µV **3:** SNAP 2.3 – 4.5 µV **4:** SNAP 0 – 2.2 µV	**0:** SNAP >4.9 µV **1:** SNAP 3.8 – 4.9 µV **2:** SNAP 2.6 – 3.7 µV **3:** SNAP 1.3 – 2.5 µV **4:** SNAP 0 – 1.2 µV

14. Total Neuropathy Score 7-items (TNS-7 score)

The Total Neuropathy score is calculated automatically as a sum of values from symptom extension, pinprick sensibility, vibration sensibility, strength, and tendon reflexes (TNS-5) plus peroneal CMAP and sural SNAP evaluations.

Supplemental Laboratory Testing Information

15. 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:

16. Nerve fiber density skin biopsy distal punch site

Interpretation of skin biopsy results for distal punch site near the ankle. As normative values vary between different skin laboratories, the assessments should be made in regard to the normative value indicated on the pathology report.

Values:
Normal density: number of nerve fibers above normative value
Slightly reduced density: below normative value but >50% of normative value
Significantly reduced density: less than 50% nerve fibers detected in regard to normative value
Absent: no nerve fibers were detected in sample
Not done: no information available about nerve fiber density at distal punch site

17. 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 above normative value
Slightly reduced density: below normative value but >50% of normative value
Significantly reduced density: less than 50% nerve fibers detected in regard to normative value
Absent: no nerve fibers were detected in sample
Not done: no information available about nerve fiber density at distal punch site

18. Nerve fibers / mm 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.

19. Does participant have small fiber neuropathy?

Evaluates if participant have pure small fiber neuropathy without any large fiber involvement. For research participant with abnormal NCS/EMG on record, this question should be answered “no”

Values:
Yes – participant has pure Small Fiber Neuropathy (SFN) and no evidence of large nerve fiber involvement (normal NCS/EMG) and enrolling physician confirms that participant presentation is confirm with SFN
No – participant has no confirmed diagnosis of SFN or has large fiber involvement
Unknown – not enough information available to determine if participant has pure SFN

20. Small fiber neuropathy confirmation

Determines if diagnosis if small fiber neuropathy (SFN) is pathologically or clinically confirmed via abnormal skin biopsy report or abnormal sensory evaluations such as abnormal pinprick.

Values:
Pathologically confirmed: diagnosis is confirmed through abnormal skin biopsy evaluation, with IENFD or sweat gland density reported as abnormal low in the pathology report

Clinically confirmed: participant has no or normal skin biopsy report on file, but sensory examination had abnormal findings such as reduced or hypersensitive pinprick

Neither pathologically nor clinically confirmed: participant has no or normal skin biopsy on record and neurological examination did not confirm any sensory deficits

Other: other findings from the skin biopsy report should be reported here

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.

21. 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.

22. Absolute value Immunoglobulin A

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.

23. 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.

24. 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.

25. 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.

26. Absolute value for Rheumatoid Factor

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.

27. Absolute value for Creatinine Kinease (CK)

Creatinine Kinease (CK), formerly known and creatine phosphokinease, is presence in greatest amounts in skeletal muscle, myocardium and brain. It is a biomarker for myopathy (wasting of muscle) in participant with advanced stages of PN, particularly in DPN, when muscular weakness is a common symptom. CK levels are unsually reported in units of enzyme activity per liter (U/L), and the normal range for males is 55-170 U/L, while it is 30-145 U/L for females.

HIV History Information for participants with diagnosis of HIV

28. Does participant have HIV/AIDS?

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

29. Years since diagnosis of HIV

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

30. Most recent viral load value

Viral load of HIV virus from most recently assessment should be entered in absolute number of detected viruses. I 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.

31. 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 participant with HIV. The number of detected cells per cubic-millimeter (mm3) should be reported.

32. Nadir viral load value

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

33. Nadir CD4 value

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

Exercise Information:

34. Calculated METs

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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.

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

Example:

Reported exercises:

1. Cycling: 4 of 14 days, 60 minutes, medium intensity;
2. Yoga/pilates: 2 of 14 days, 35 minutes, low intensity; and
3. Stretching 7 of 14 days, 10 minutes, low intensity.

Calculated METs:

1. Cycling: 4 days x 60 minutes x 8.0 METs/14 = 137
2. Yyoga: 2 days x 35 minutes x 2.5 METs/14 = 12.5
3. Stretching: 7 days x 10minutes x 2.5METs/14 = 12.5

Total METs: 137 + 12.5 + 12.5 = 162 METs/day average

METs for different exercise activities are listed in table below.

Exercise	**METs**	**Compcode**
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

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 METs 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

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