

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

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- 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:

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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.

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- 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

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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

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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

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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.

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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

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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

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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