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

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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:

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.

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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

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

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)

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 ankle until the monofilament bows. The monofilament should be hold 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		
	300	6.65		Deep pressure sensation only

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		
	300	6.65		Deep pressure sensation only

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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