

Determining Best or Inferior Drug(s) Using an Adaptive Platform for Cryptogenic Sensory Polyneuropathy (BEAT CSPN)

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PCORI RESEARCH PLAN: Phased Large Awards for Comparative Effectiveness Research

RESEARCH STRATEGY

A. Research Question/Background and Significance

Significance: Chronic pain and the opioid epidemic continue to dominate public health concerns in the US.¹⁻³ The World Health Organization has estimated that 22% of the world's primary care patients have chronic pain making this condition a problem to be addressed by all physicians and health professionals.⁴ Peripheral neuropathy is a common, chronic pain problem encountered by neurologists and primary care physicians, and while there are many causes, no cause can be identified for a large percentage of patients.⁵ Many peripheral neuropathies are secondary to identifiable causes, such as diabetes, alcohol abuse and the use of certain medications. However, once known etiologies are excluded, **at least 25% of neuropathies remain idiopathic. This is the case for 5 million people (of the estimated 20 million people with neuropathy) in the United States.** We refer to these remaining cases as Cryptogenic Sensory Polyneuropathy (CSPN, commonly pronounced as C SPAN).⁶⁻¹⁶ **The research question is: What is the best available medication(s) to treat pain due to CSPN?** There is only one comparative effectiveness study of medications most used to treat painful CSPN, conducted by the investigators involved in this application.¹⁷ This larger, open-label, pragmatic trial will paint a more complete picture of medication effectiveness, testing six new non-opiate medications and creatively blending the results from the prior four drug trial in an elegant statistical analysis. This study adds critical components that address barriers to diagnosis and barriers to implementation of study results in clinical practice.

Description and diagnosis: Prior reports describing CSPN have used other terms such as idiopathic neuropathy or small fiber sensory peripheral neuropathy, but we prefer CSPN. The assigned ICD-10 code is G60.8. The diagnostic criteria for CSPN were established by Dr. Barohn and colleagues.¹³ Our retrospective review of databases from two North and one South American tertiary neuropathy clinics (NA-SA study) showed that CSPN represented at least one-quarter of all referred peripheral neuropathy patients and was the most common form of neuropathy evaluated at these sites (Table 1).¹⁸ The mean age of patients in prior publications ranges from 51 to 63 years.^{8,9,13,18}

Table 1. North America South America Study Results Major category	NA # of pts (%)	SA # of pts (%)
Immune-mediated	215 (19.7%)	191 (18%)
Diabetes	148 (13.5%)	236 (23%)
Hereditary/degenerative	292 (26.7%)	103 (10%)
Infection/inflammation	53 (4.8%)	141 (14%)
Syst./metab./toxic (Non-diabetic)	71 (6.5%)	124 (12%)
Cryptogenic (CSPN)	311(28.5%)	239 (23%)
Total # of cases	1090	1034

CSPN is usually diagnosed based on pain (a presenting symptom in 70-80% of patients), numbness and/or tingling in the distal extremities. There are equal numbers of men and women with this condition, and it occurs in all races/ethnicities and all geographic regions. The most common symptoms are pain (as noted above), sensory loss (86%), and paresthesia (86% to 100%).^{6-10,13-16,18-22} Lower extremity symptoms usually precede upper extremity symptoms.^{13,14,18} Approximately one-third to one-half of patients will have symptoms confined to their lower

extremities. The average time for symptoms to spread to the upper extremities appears to be about five years. Worsening of sensory symptoms with contact, heat exposure, activity, or fatigue commonly is reported. Based on symptom presentation, our group and others have found that patients with CSPN constitute a homogeneous group of elderly women and men for whom a similar approach can be taken regarding diagnosis and treatment.^{13,14,18}

Patient-centered problem: According to a poll obtained by the Neuropathy Association, 87% of patients rated pain management as the greatest challenge in managing their neuropathy. These patients are treated with a variety of medications including opioids, non-narcotic oral medications, topical creams, devices such as neurostimulators, as well as with behavior and exercise modalities. Of grave concern is the use of opioids. Review of electronic health records at one site showed that **21% (118 of 552) of people with CSPN are prescribed narcotics.** This represents a group of individuals for whom finding a non-opioid alternative for their CSPN pain would be both safer and more beneficial.

Physician-centered problem and clinical decisional dilemma: In a preliminary poll taken for this application, primary care

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

physicians report being unfamiliar with the term CSPN, unclear of its diagnostic criteria, and unsure of which among many non-opioid treatment options works best for peripheral neuropathic pain, and frustration with lack of effectiveness and side effects of current treatment approaches. For this study, the strategy is to empower primary care clinicians and neurologists with the information needed to select non-opioid choices to treat CSPN. Specifically, we will uncover, document, and recommend how to surmount barriers to implementation to provide best model therapies with substantially **greater patient-centered precision**. To establish comparative effectiveness among available drug alternatives yet fail to address implementation barriers yields less than desirable results relative to translational research and to improved clinical medicine. Removing barriers and resolving therapeutic choice decisional dilemmas for clinicians and patients will improve efficiency, quality of life, and health.

Leveraging PCORnet: This study makes full use of PCORnet. **Using the PCORnet Clinical Research Network (CRN) infrastructure and a Front Door (MDQ) query, we engaged 42 sites and now know that there are 28,814 people with the ICD 10 code for CSPN** (from 1/2016-6/2021). The University of Missouri leads the Greater Plains Collaborative (GPC) which is one of the CRNs of PCORnet. The leader of the GPC, Dr. Russ Waitman, is the co-PI on this application and his team will lead the Data Coordinating Center. He is perfectly positioned to partner with the other CRNs, and this will further enhance the representativeness and scale of this trial (see letters of support). Our PCORnet Front Door-sponsored webinar (held on 12/13/21) and summary materials provided wide-spread attention to the study that resulted in additional clinician engagement and study participation. In addition, Dr. Barohn personally reached out to neurologists at PCORnet sites to seek their support and engagement; see letters of support.

We have developed a comprehensive approach to improving the care of people with CSPN. We will: address the under-recognition of CSPN in clinical care; continue our ongoing dialog with patients as part of every step of the study (including dissemination); thoroughly study and then offer solutions to implementation barriers of adopting trial outcomes in both neurology and primary care settings; encourage durable, collaborations between neurology and primary care, thereby empowering primary care clinicians to care for these patients and indirectly addressing the general neurologists shortage^{23,24} which leads to long delays in specialty care referral; and find non-opioid solutions to CSPN pain relief. This study has the potential capacity to improve the quality of lives of literally millions of Americans. Until our recently completed PCORI study (see below), there had been no large CSPN prospective treatment trial. Furthermore, we are not aware of any pharmaceutical/industry trials with CSPN as a disease target, despite its prevalence. The exception is a recent trial by Vertex of a new sodium channel inhibitor drug for a subclass of CSPN.

Nearly all studies of non-opioid drugs for painful neuropathy have involved either diabetic distal sensory neuropathy, post herpetic neuralgia or trigeminal neuralgia.^{11,12,15,16,25,26} The drugs that have been studied usually fall in the class of antidepressants that interfere with neuronal serotonin or norepinephrine uptake and anticonvulsants that interfere with neuronal excitability (Table 2). A number of these drugs have been approved by the FDA for various pain syndromes, but none have been approved for CSPN. Two of these drugs are FDA approved for painful diabetic neuropathy, pregabalin and duloxetine.^{27,28} The American Academy of Neurology (AAN) has produced guidelines for first, second- and third-line drug therapy for *diabetic* neuropathy.²⁷ Table 2 outlines the most common drug therapies used for CSPN, with full discussion in the Research Strategy section. The advantage of using these drugs is that they are alternates to opioids.

PRESCRIPTION THERAPIES	Route	Starting Dose	Maintenance Dose	Positive RCT	FDA approval for pain
First Line:					
Tricyclic Anti- Depressants	Oral	10-25 mg at bedtime	Increase by increments of 10-25 mg to 100-150 mg at bedtime	Yes	Chronic pain
GABAPENTIN (Neurontin)	Oral	300 mg tid	Increase by 300-400 mg increments to 2400-6000 mg daily divided in 3-4 doses	Yes	Post herpetic neuralgia

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

TOPICAL LIDOCAINE PATCH	Skin	Same as maintenance	Apply over painful skin 12 hrs of 24 hrs period	Yes	Post herpetic neuralgia
Tramadol (Ultram)	Oral	50 mg bid or tid	Increase by 50 mg increments to a maximum of 100 mg qid	Yes	Moderate & mod- severe pain
Duloxetine (Cymbalta)	Oral	30 mg/d	Increase by increments of 30-60 mg up to 120 mg/d	Yes	Diabetic peripheral neuropathy
Pregabalin (Lyrica)	Oral	75 mg bid	Increase by 75 mg tid to 2400-6000 mg daily divided in 3-4 doses	Yes	Diabetic peripheral neuropathy
Second Line:					
VENLAFAXINE XR (Effexor)	Oral	37.5 - 75 mg once a day	Increase by 75 mg increments to 150-225 mg a day	Yes	No
Valproate	Oral	250 mg bid to tid	Increase by 250 mg increments to 1500 mg/d	Yes	No
Carbamazepine	Oral	200 mg bid	Increase by 200 mg increments to 200-400 mg 3 to 4 times a day; follow drug levels on doses greater than 600 mg/d	Yes	Trigeminal neuralgia
Oxcarbazepine (Trileptal)	Oral	150-300 mg bid	Increase by 300 mg increments to 600-1200 mg 2 times a day	No	No
Lamotrigine (Lamictal) [^]	Oral	25 mg once a day or bid	Increase by 25 mg increments weekly to 100- 200 mg bid	Yes	Post herpetic neuralgia
TOPIRAMATE (Topamax)	Oral	25-50 mg at bedtime	Increase by 50 mg increments weekly to 200 mg bid	Yes	No
Third Line:					
Bupropion SR (Wellbutrin)	Oral	150 mg/d	After 1 week, increase to 150 mg twice a day	Yes	No
Tiagabine hydrochloride (Gabitril)	Oral	4 mg/d	Increase to 4-12 mg tid	No	No
LEVETIRACETAM (Keppra)	Oral	250 mg at bedtime	Increase by increments of 250-500 mg to 1500 mg twice a day	Yes	No
Zonisamide (Zonegran)	Oral	100 mg at bedtime	Increase by increments 100 mg to 400-600 mg at bedtime	Yes	No
Mexiletine	Oral	200 mg once a day	Increase by 200 mg increments to a maximum of 200 mg tid	Yes	No
Phenytoin	Oral	200 mg at bedtime	Increase by 100 mg increments to 300-400 mg daily divided in 1-2 doses, following drug levels	Yes	No
Milnacipran (Savella)	Oral	12.5 mg at bedtime x 1 d	12.5 mg bid x 2 d then 25 mg bid x 4 d, then stay on 50 mg bid. May increase up to 100 mg bid	Yes	Fibromyalgia
LACOSAMIDE (Vimpat)	Oral	50 mg by mouth bid	In 1 wk, go to 100 mg bid. May increase up to 200 mg bid	Yes	No

There are two important challenges in treating CSPN. First, we have established that **CSPN is underdiagnosed in primary care where many of these patients first seek pain relief**. Second, while primary care clinicians are acutely aware of the opioid epidemic, they may also be **unaware of the utility of the medications in Table 2 for peripheral neuropathic pain**.

We recently completed a comparative effectiveness study comparing four non-narcotic drugs in a 402 patient/40 sites study called Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTROLS).¹⁷ The four drugs studied in PAIN-CONTROLS I (Table 2 (blue shade)) were nortriptyline, duloxetine, pregabalin and mexiletine. Each drug has a different mechanism of action. We found overall that nortriptyline and duloxetine outperformed pregabalin and mexiletine (see below for more details). For the proposed study, we plan to extend our findings and test six additional drugs commonly used to treat painful peripheral neuropathy in a similar,

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

successful, comparative effectiveness manner. This new study is called ‘Determining **B**est or Inf**E**rior Drug(s) Using an **A**daptive Pla**T**form for **C**ryptogenic **S**ensory **P**oly**n**euro**p**athy – **BEAT CSPN**. The new drugs we will study are oral **gabapentin, topiramate, levetiracetam, lacosamide and venlafexine** and topical **lidocaine**. We will include the two superior medications (nortriptyline and duloxetine) to be able to statistically link results between the two studies. It should be emphasized that the six drugs we have selected provisionally will be thoroughly discussed in the feasibility phase by all stakeholders including patients, clinicians, and investigators. We will confirm the final selection of the study drugs following these discussions. As in the previous PAIN-CONTRoLS study, we will not use a placebo group. We expect participants to fill their prescription for the study medication as they would for any other drug to ensure that the study is as real-world as possible. This CER study will engage primary care physicians as partners in the identification and improved care of patients with CSPN. This engagement has the potential to keep these patients in their primary care medical home, which yields economic advantage to the clinic, the safety conferred by continued primary care awareness of the context of their existing medications and chronic conditions and is the location where people with CSPN prefer to receive their care. For neurologists in the study, patients referred to them for care can be better managed and the study encourages new partnership(s) with the primary care clinicians making the referrals.

B. Specific Aims (Feasibility and Full-Scale Study)

The scale and ambition of this study requires the full feasibility period to ensure successful outcomes. Patient advisors are especially supportive of the plan to participate in and assist with the **completion of a comprehensive, multi-level project plan during this time. The feasibility period aims also include:** developing a computable phenotype for CSPN (using PCORnet data resources for further identify potential participants at CRN sites); refining and pilot testing our practice/clinician enrollment process; development of a patient video to augment the informed consent process; developing and testing the patient and the practice remuneration process; develop physician/clinician-facing checklists, templates and materials for use during neurologist/primary care dyad in-service sessions; development/modification of reporting forms for both participating clinics and for participants’ to provide patient reported outcomes (questionnaires, journaling, etc.); expansion of the Patient Advisory Council and Stakeholder Advisory Council; establish workflows, communication and conduct routine steering committee and councils’ meetings; establish terms and contracts with firms that will conduct genetic testing; develop training materials, guided interview content and other tools needed for coordinators at each participating site for outreach to study participants (patient and clinician); plan and complete dissemination of start-up findings across PCORnet and to relevant professional societies and advocacy organizations that includes/is led by patients and other stakeholders; seek guidance from other PCORnet resources (i.e., the PCORnet Engagement Coordinating Center) to improve various aspects of the study; and establish publicly facing communication channels (like social media YouTube and Facebook) to encourage information sharing and dissemination efforts.

Full Study Specific Aim 1: Determine which non-opioid drug is most effective in producing pain relief and improving quality of life in patients with CSPN. The six drugs we will use are oral gabapentin, topiramate, levetiracetam, lacosamide and venlafexine and topical lidocaine, and we will include the two best performing drugs from the PAIN-CONTRoLS study, nortriptyline, and duloxetine in the first randomization group of participants. Adding these two “winner” drugs from the PAIN CONTRoLS trial permits a comprehensive statistical analysis that takes into account both study’s results. This pragmatic, open label study will be done during routine primary care visits and in real time. Patients will be engaged, consented, and randomized to one of medications at their baseline clinic visit and clinicians will order the drug to which they are randomized at that time. As a pragmatic trial, participants will be responsible for filling their study prescription like any other they would receive from their doctor. Initial pain scores at 30- and 60-day periods will indicate how quickly the medications show an effect; the primary measure for efficacy will use the 90-day metric. Data from months 4-12 will inform the long(er)-term effectiveness of the medications in a secondary analysis. Safety labs taken at 30 days will be monitored as part of the protocol.

Full Study Specific Aim 2: Determine which drug has the fewest and which has the most side effects and determine the efficacy of each drug, combining data regarding pain reduction and quits. We will use the MedDRA adverse event coding system and count the number of dropouts due to side effects or other patient-reported burden. Both prescribing

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

clinician and patient need to know what medication they are taking to maintain clear, trusted communication and to reflect real-life, so this is an open label study. If, for example, a patient decides not to take the randomized medication for some reason or decides when they go to fill their prescription that the drug is too expensive, then they are counted as a drop out (“a quit”) from that arm of the study. As in the prior PAIN CONTRoLS study, adherence to a medication is not solely related to its efficacy; other real-life factors influence the abilities of patients to use a prescribed therapy.

Full Study Specific Aim 3: Determine efficacy and quit rate for selected non-opioid drugs for CSPN. We will build on the data obtained in the recently completed PAIN-CONTRoLS study and combine those data with new data from this study of six additional medications to calculate the grand winner(s) and losers.

Full Study Specific Aim 4: Improve CSPN recognition by educating primary care health professionals and neurologists of CSPN and supporting their need to select appropriate, effective, non-opioid drugs for CSPN treatment. A neurologist and primary care physician team will develop, and a dyad will deliver CSPN information designed specifically for busy prescribing clinicians. They will use an online, academic mentoring/academic detailing model used successfully in prior studies.²⁹ Clinician pre-/post- knowledge of CSPN and the frequency of diagnosis will be measured as well as clinicians’ satisfaction with the education provided. Further, we will explore whether the computable phenotype and machine learning analysis can be used to estimate CSPN in a clinician’s panel.

Full Study Specific Aim 5 (exploratory): Using pharmacogenomics and genetic data, analyze intra- and inter-arm profiles that may indicate different effectiveness among the study drugs. A low-burden collection of a cheek swab sample from participants will enable an exciting, precision medicine aim to enhance our understanding of medication effectiveness for CSPN. If associations between a participant’s genetic profile and their study drug’s effectiveness can be detected, an even more personalized, precise process to determine a best “match” medication could be made.

C. Outcomes

We have presented the case for the need to fill the gap in the identification and subsequent treatment of CSPN. To close this gap, we intend to provide educational content to address the under-diagnosis of CSPN and to highlight the capacity of primary care to routinely treat patients with CSPN without needing to refer them to neurology. Especially because of the limited availability in most settings of neurologists and the usual 4-6 month waiting period for an appointment, it is both financially viable and patient-centered to strengthen primary care’s capacity to care for people with CSPN.

Improving the identification of CSPN is one objective to meet Criterion 1. The other gap this study addresses is the need for a comprehensive comparative effectiveness study to improve selection of medications for CSPN treatment. **Closing both gaps will have tremendous utility and impact for the five million individuals who suffer with CSPN.**

We have selected a Bayesian adaptive design to accelerate our ability to arrive at “winner” and “loser” medications for the treatment of CSPN pain. **A decisive advantage of this design is that randomization moves at the speed of study outcomes;** this means that medications causing substantial patient burden like side-effects or that impact quality of life and that offer poor pain control will be weeded out more quickly, allowing the more successful medications to emerge from the trial. This approach can result in a shorter duration trial, saving money and alleviating patient participation burdens. Additionally, **the selection of outcomes for the trial was accomplished by and with people living with CSPN.**

This engagement process ensures that outcomes are relevant to their lived experience. The primary outcome of this study will be change in pain score. Secondary outcomes will assess the fatigue, sleep, pain interference and self-reported impact of pain on daily life by using specific measures NIH fatigue scale, sleep disturbance scale, pain interference scale and SF-12. A subgroup analysis to assess the possible difference in efficacy and outcomes of these medications with sex, age, race/ethnicity, and genetic profile will be performed as exploratory outcomes. The same measures used in the study for primary and secondary outcomes will be used to assess the exploratory outcomes.

The most patient-centered, relevant, primary outcome in the effective treatment of CSPN is the reduction of pain caused by this condition. Patients shared the daily burden of living with CSPN during the previous study and the development of this proposal, and their stories are heartbreaking. Unrelenting pain diminishes their quality of life, hampers their ability to fulfill daily activities that matter most to them and has a debilitating and demoralizing ripple effect on partners, family members and caregivers. What matters most to patients is the personal empowerment effective medication gives them to lead the lives they choose. Therefore, it is imperative that medication effectiveness be a top priority to establish and then implement in the care settings most often visited for treatment– primary care.

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

People with CSPN also noted that pain has important influence over other aspects of their lives. Focus group participants achieved consensus and selected pain interference, fatigue, and sleep disturbance as secondary outcomes (Table 3). Focus group participants all said that CSPN impacts their ability to sleep soundly, and it often is so intense that it wakes them after only a few hours of rest. This pattern leads to exhaustion and fatigue. One participant shared that their fatigue was so significant, it interfered with their ability to stay alert and awake at work, and they lost their job.

Primary or Secondary	Name of Outcome	Specific measure to be used	Timepoints
Primary	Participant-reported Pain	Likert Pain Scale	Monthly x 12 months
Secondary	Pain Interference	PROMIS Pain Interference Scale	Monthly
Secondary	Fatigue	PROMIS Fatigue Interference Scale	Monthly
Secondary	Sleep Disturbance	PROMIS Sleep Disturbance Scale	Monthly
Secondary	Overall Health and Quality of life	SF-12 and/or NeuroQOL-DM	Monthly
Secondary	Clinician Experience	Generalized Self-Efficacy (GSE) ³⁰	Baseline/End of Study
Secondary	Clinician CSPN Knowledge	CSPN Knowledge Survey	Baseline/End of Study
Secondary	CSPN recognition and diagnosis	ICD 10 code G60.8	Monthly
Exploratory	Demographic Factors	Participant sex, age and race/ethnicity	sub-analysis/End of Study
Exploratory	Qualitative Reflections	Content analysis of participants' journaling	Variable ³¹
Exploratory	CSPN risk phenotypic profile and Expected CSPN prevalence by site	Machine learning analysis of participant data to test & develop phenotypic profile; predict expected prevalence by clinician panel	Midpoint/End of Study
Exploratory	Pharmacogenomics and genetics	Conduct genomic analysis ³²⁻³⁴	Secondary analysis/End of Study

Another strength of the selected outcomes is that almost all have validated survey instruments, and the ones intended to be used with participants use scales familiar to people with chronic pain. Furthermore, the patient-reported outcomes were used successfully in the prior PAIN CONTROLS trial with the same population of participants. While few chronic pain patients are satisfied with the 10-point Likert Pain Scale, they all acknowledged that it is a standardized, common way for them to share the level of pain they experience with their providers. Furthermore, most drug studies in the literature use the Likert Pain Scale for FDA approval. Focus group participants with CSPN initiated conversation about and recommended both the sleep disturbance and the fatigue PROMIS measures. These dimensions of secondary impact of pain are vitally important to people with CSPN and are of intense interest to them as stakeholders in the trial. Some shared that even if their pain levels did not decrease, changes that indicate improved sleep and less fatigue would be of substantial value to them and could influence their medication preference. Finally, we also know that the use of journaling assists with self-monitoring which is an essential patient-centered element of the study's design.³⁵

D. Study Design and Methods

Research Strategy including Conceptual Frameworks: The model that anchors the significance of this study rests on the fundamental premise that effective treatment and comprehensive care for five million people with CSPN depends on expanding comparative effectiveness research. Frequently the conceptual framework aims to identify factors that influence adherence, with little focus on the mechanism of drug action, out of pocket cost, side effects and quality of life issues that affect patients. We designed a patient-centered, patient-partnered, stakeholder-informed, rapid comparative effectiveness research study using a design – Bayesian adaptive randomization – that will safely and dependably identify best performing medications for the treatment of CSPN chronic pain. We will augment this design with the use of Normalization Process Theory³⁶⁻³⁸ as a framework to explore themes that may contribute to understanding medication performance in the context of the daily lives and experiences of people with CSPN by using patient journaling entries during their enrollment. Journaling is a reliable and informative strategy³⁹ that will enrich and expand the model of the study. Importantly, we will design effective implementation strategies for primary care practice, a step often omitted that further limits the delivery of many effective, patient-centered interventions. This study adheres to the PCORI methodology standards (see Checklist).

Comparators: Six medications used to treat painful peripheral neuropathy will be studied in a head-to-head comparison.

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

Two previously studied medications will be included as arms in the initial randomization but will drop out or remain in the group of tested medications depending on patient outcomes. Including them in the initial randomization permits statistical analysis that will result in a comprehensive profile of 10 commonly used medications. Below we provide comparator technical descriptions.

1. *Gabapentin (Neurontin)*

Gabapentin interacts with a high-affinity binding site in brain membranes, which recently was identified as an auxiliary subunit of voltage-sensitive Ca²⁺ channels. However, the functional correlate of gabapentin binding is unclear and remains under study. Gabapentin crosses several lipid membrane barriers via system L amino acid transporters. In vitro, gabapentin modulates the action of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD) and the glutamate synthesizing enzyme, branched-chain amino acid transaminase.

Gabapentin is among the most used anticonvulsants for neuropathic pain.⁴⁰ Results with human and rat brain NMR spectroscopy indicate that gabapentin increases GABA synthesis. Gabapentin increases non-synaptic GABA responses from neuronal tissues and reduces the release of several mono-amine neurotransmitters in vitro.

Although gabapentin may have several different pharmacological actions, it appears that modulation of GABA synthesis and glutamate synthesis may be important. The established therapeutic dosing for gabapentin in neuropathic pain is 1800-3600 mg/day in 3 divided doses in patients with normal renal function. This means the minimum effective dose is 600 mg, 3 times a day. Renal adjustments are recommended in patients with CrCl below 60 mL/min.⁴¹ Several cross-sectional studies have reported it being used in subtherapeutic doses among most patients. In a retrospective analysis of 939 patients with post-herpetic neuralgia, the mean daily dose of gabapentin was 826 mg.⁴²

2. *Lidocaine (Lidoderm)*

Lidocaine is an amide class 1-b anti-arrhythmic medication and an anesthetic agent. It was first approved in US in 1940s.⁴³ Structurally, it contains an amide group as well as a tertiary amine. It is a stable, crystalline, colorless solid. The uncharged, free base of lidocaine can readily penetrate the lipid matrix of the outer layer of the skin. Basic conditions will favor formation of the free base and increase penetration. It has an n-octanol/water coefficient that makes it favorable for distribution in tissues. The distribution depends on the total dose administered, the route of delivery, the thickness of the skin, surface area of stratum corneum at the site of application and the blood supply to the site.⁴⁴ Lidocaine works by reversible blockade of nerve fiber impulse firing. Lidocaine is rapidly metabolized by the liver and has a half-life of 1.5-2 hours.

Lidocaine is available in gels, ointments (creams), sprays and patches. The patches have been recognized by FDA as a "topical delivery system" dosage form. Prescription lidocaine has many indications including production of local or regional anesthesia by topical application, infiltration, infusion, and nerve blocks. However, patch formulation has only been approved for the treatment of post herpetic neuralgia.^{45,46} Topical lidocaine is generally safe with most common side effects include skin irritation which is mild and transient. Adverse effects with systemic lidocaine include dizziness, drowsiness, muscle twitches, seizures, respiratory distress, loss of consciousness and cardiac arrest.⁴⁵⁻⁴⁷ Class 1 anti-arrhythmic drugs should be avoided while using lidocaine as the toxic effects are additive.

Lidoderm is the first 5% prescription lidocaine patch that received FDA approval in 1999, indicated for neuropathic pain in PHN. The patches consist of an aqueous adhesive material (hydrogel) containing 5% lidocaine by weight, with 700 mg of lidocaine in 14 g of the adhesive material applied to a non-woven backing material and non-perforated polyethylene terephthalate (PET) release liner. Up to three patches can be applied to the painful area, 12 h on, followed by 12 h off. The patches can be cut to conform to localized painful areas. Analgesic data from PHN studies suggest that some people using lidocaine patches achieved pain relief within 30 minutes.⁴⁶

3. *Topiramate (Topamax)*

We are potentially considering two drugs that inhibit sodium channels in this study, and one is topiramate. Sodium channel inhibitors that were developed primarily for treatment of epilepsy improve neuropathic pain in some patients. Over the last decade, we have discovered that some patients with painful neuropathy of unknown cause can have a mutation of the SCN11A gene.⁴⁸⁻⁵¹ In some patients with prominent neuropathic pain, a sodium channel mutation leads to increased sensory axon irritability, suggesting a pharmacological role for sodium channel

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

inhibition. It is possible that patients with other forms of neuropathy may share this dysfunctional sodium pathway. Patients with this mutation maybe more likely to respond to a drug such as topiramate or lacosamide. We will explore the relationship between this drug, quits and trough the study's exploratory pharmacogenetics aim. It is likely that analogous acquired altered sodium channel function is linked to other forms of neuropathy, including diabetic and chemotherapy induced neuropathies. Topiramate has been shown to reduce peripheral nerve excitability, likely via inhibition of voltage gated sodium channels.⁵²⁻⁵⁴ While topiramate has multiple potential mechanisms of action (weight loss, improved insulin sensitivity, sodium channel modulation), each of these mechanisms would be expected to have potential benefit in CSPN. Alterations in cellular excitability may both increase pain and lead to axon loss and progressive neuropathy.

While topiramate doses used in diabetic neuropathy trials have varied from 100-400 mg daily, data from two small trials suggest 100 mg/day is associated with improvement in both IENFD and neuropathy specific quality of life.⁵⁵⁻⁵⁷ Doses above 100mg daily are more likely to be associated with neuro-cognitive side effects. A Cochrane Review of the use of topiramate for headache suggests there is no additional benefit to doses over 100 mg daily⁵⁷ which supports the dose we selected. This drug is currently being studied to learn if it can change the natural history of CSPN in addition to reducing pain (U01 NS095388 – G. Smith PI, NCT02878798).

4. *Levetiracetam (Kepra)*

Levetiracetam is a medication used to treat epilepsy. It is used for partial-onset, myoclonic or tonic-clonic seizures. The exact mechanism of action is unclear. The drug binds SV2A, a synaptic vesicle glycoprotein and inhibits presynaptic calcium channels, reducing neurotransmitter release and acts as a neuromodulator. This impedes impulse conduction across synapses. It does not undergo extensive metabolism, and the metabolites formed are not active and do not exert pharmacological activity. Metabolism of levetiracetam is not by liver cytochrome P450 enzymes, but through other metabolic pathways such as hydrolysis and hydroxylation. In addition to its use in epilepsy, this has also been shown to have benefit in other pain conditions. A Cochrane review of levetiracetam for chronic neuropathic pain was performed by Wiffen, et al.⁵⁸ This included six studies with total of 174 participants treated with 2000 to 3000mg /day of levetiracetam or placebo. Their conclusion was that the evidence was of low quality, due to small size of the treatment arms and there was insufficient data for pooled analysis. A migraine headache study⁵⁹ showed its benefit in migraine. Reda and colleagues showed that levetiracetam produced antiallodynic and antihyperalgesic effect in diabetic mice with favorable effects on sciatic nerve and spinal cord, thus providing promise in alleviating neuropathic pain in diabetic patients.⁶⁰ In a single center, prospective, randomized study of levetiracetam in chronic neuropathic pain in 20 Multiple sclerosis patients, Rossi et al showed that this was well tolerated with significant difference between levetiracetam and placebo in all study outcomes including pain.⁶¹ Another study looked at 7 patients with various pain conditions and improvement in pain condition after the addition of levetiracetam with VAS scores decreasing from 8-9/10 to 0-3 out of 10 within two to 14 days of starting the therapy.⁶² In this case series of three patients with neuropathy, Price showed improvement of pain and sleep with levetiracetam.⁶³ Some of the side effects reported in these studies included suicidal behavior or ideation, somnolence, fatigue, dermatological reactions, coordination difficulties, withdrawal seizures and hematological abnormalities.

5. *Lacosimide (Vimpat)*

Antiepileptic drugs have been used in pain management since the 1960s and some seem to be especially useful for neuropathic pain. Lacosamide is an antiepileptic drug that has recently been investigated for neuropathic pain relief.⁶⁴ It modulates voltage-gated sodium channels by enhancing their slow inactivation. In addition, Lacosamide seems to interact with collapsin-response mediator protein 2 and thus may mediate neuronal plasticity. Lacosamide has an elimination half-life of 13 hours, no relevant protein binding, and does not induce or inhibit enzymes of the cytochrome P450 system. In one study from 2006 the drug was tested in the streptozotocin rat model of diabetic neuropathic pain. Lacosamide attenuated cold (10, 30 mg/kg, i.p.), warm (3, 10, 30 mg/kg, i.p.) and mechanical allodynia (30 mg/kg, i.p.). Streptozotocin-induced thermal and mechanical hyperalgesia were reduced by lacosamide at doses of 10 and 30 mg/kg, i.p. One 2007 study showed attenuation of pain in diabetic neuropathy in doses up to 400 mg/d and improves quality of life issues.⁶⁵ An 18-week, double-blind, placebo-controlled trial of 1:2:2 to oral

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

lacosamide, 400 or 600 mg/day vs placebo showed reduction in neuropathic pain in patients with diabetes.⁶⁶

6. Venlafaxine

Venlafaxine is an antidepressant that is a serotonin-norepinephrine reuptake inhibitor. It works by helping to restore the balance of serotonin and norepinephrine in the brain. A 2017 review summarized the data in the 11 randomized clinical trials with placebo.⁶⁷ Nine studies reported that the drug was effective against neuropathic pain. One study comparing the drug to a placebo included >200 participants, and another study comparing the drug to pregabalin and carbamazepine had >200 patients. Most of the adverse events reported in the selected studies were consistent with ones already known, and most were mild to moderate. Most of the clinical studies found that this drug was effective for substantial reduction in neuropathic pain in diabetic neuropathy and had less side effects than other treatments.

Study Population and Setting: Adults with either an ICD 10 G80.6 diagnosis or with painful peripheral neuropathy of unknown origin (following rule-out) recruited in primary care or neurology care settings. While the focus of the study is on patient participants, the study also involves their care providers who will be asked to participate in pre- and post-study that will measure changes in their self-efficacy in diagnosis and pain care options for CSPN.

Study Design: Multisite, open label, Bayesian Adaptive Design trial (see details below). Randomization unit is patient.

Randomization: 1:1 randomization across all arms (see details below)

Sample Size and Power: See details below

PCORnet: This study will use PCORnet sites to recruit participants for the study. We used the PCORnet menu-driven query (MDQ) to establish feasibility numbers using the CSPN ICD 10 code at 42 sites. We engaged PCORnet-affiliated site neurologists to participate, and we asked for their assistance to recruit primary care clinician partners at their sites (see letters of support). We will also directly reach out to primary care clinicians using practice-based research networks. During the feasibility phase, we will work with PCORnet to expand the number of PCORnet-participating sites by re-sending network collaborator requests to generate even greater interest in the study.

Statistical Considerations for BEAT CSPN Platform Trial: We chose a Bayesian Adaptive Design with patient participant burden and trial efficiency in mind. Using adaptive randomization, which is updating the treatment allocation ratio during the study based on information gained during the study, not only may allow for substantially smaller sample sizes, but also places more patients on the better performing drugs during the trial to strengthen the conclusions about what treatments are the most effective.⁶⁸ It lets us make changes to our approach or stop the study early if we find strong results before the scheduled end of the study. In preparation for this study design, we conducted extensive trial simulations comparing different designs measuring the resources (time and number of patients required) and the ability to draw conclusions about relative efficacy of the seven drugs. Simulated participants were randomized to one of seven treatment arms (groups) with a maximum total number of patients of 600. Using Bayesian Adaptive Design, at each interim analysis a decision is made to either continue enrolling patients or to stop the trial for success. Further, at the interim analysis, if patient enrollment continued, new patient allocation probabilities are generated using response-adaptive randomization formulas. **All decisions are prespecified. After 2 participants are equally randomized to two veteran arms (nortriptyline and duloxetine) and 120 participants are equally randomized to the six rookie arms (gabapentin, topiramate, venlafaxine, levetiracetam, lidocaine and lacosamide), we begin adapting the randomization structure via response adaptive randomization (RAR).** Specifically, the arm, or drug, that looks to be the best gets more participants allocated to it in the subsequent randomization. An interim analysis that uses up-to-date outcomes data, is performed quarterly (after the first interim analysis), with a new adaptive randomization schedule as appropriate until the trial stops. The trial can stop early for success only after at least 102 patients across all study arms have been enrolled and randomized. The early success stopping criterion is met if the probability of a study arm being the best arm, as measured by a combined utility at 12 weeks, is larger than 0.925. The interim analyses are scheduled for 122, 200, 300, and 500 enrolled with a maximum of 600 enrolled. If enrollment is halted early, we will confirm criterion is met with analysis after all data from all enrolled patients are obtained. **This success criterion was chosen to ensure an overall Type I error rate of 8% for this design that includes multiple statistical testing opportunities through interim**

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

analyses and comparisons across multiple arms. The outcome for the study is called “utility” which is a combination of drug efficacy and quit rates and its construction is detailed in Gajewski et al.⁶⁹ and was used in PAIN-CONTRoLS¹⁷ as $utility = \frac{3}{4} * efficacy + (1 - quit)$ for each drug. Thus, higher utility implies a drug with higher efficacy and/or lower quit rates. Also determined at the final analysis is which of the arms are “losers” defined as an arm that has a probability of being the best arm as measured by a combined utility at 12 weeks as less than 0.0001. This decision rule is extremely important in the absence of one single best drug. If one or more loser is identified, the drug(s) would not be recommended for use in clinical practice.

Justification of a Platform Trial with Multiple Drugs: We chose a platform trial with multiple arms to take advantage of the information we learned in PAIN-CONTRoLS as well as to avoid making an error in “pre-screening” drugs that might actually have high utility. Platform trials are becoming more and more popular because of their efficiency and breadth in choosing treatment regimes.⁷⁰ However, they can be challenging to administer in academic medicine because of the structure of most funding agencies (e.g., 3-5 years). Therefore, we administer a proposed platform design in two stages. The first stage has already been conducted. PAIN-CONTRoLS had four drugs in the study, and it had a type I error of 5% through its rigorous trial design. It was found that two of the drugs were formal “losers” in the study and thus they are no longer recommended as first line treatment for CSPN. Therefore, we graduate the two non-loser drugs to now be in the next stage of the platform proposed here (Table 4). We will compare the two veteran drugs to six rookie drugs in this trial. The veteran drugs will inherit their data from PAIN-CONTRoLS through informative priors.

Next, the rationale for multiple arms is justified. Limited resources are a challenge when planning studies of multiple promising treatments, often prompting a reduction in the sample size to meet the financial constraints. The practical solution is

PAIN-CONTRoLS: Platform Trial				Prospective Trial (nmax=600)						
Medication	n	Pr(Best)	Decision	Medication	Pr(Best)	prior n	First Allocation	n (interim 1)	...	Decision
nortriptyline	134	0.52		nortriptyline		134	0.010	1		TBD
duloxetine	126	0.43		duloxetine		126	0.010	1		TBD
pregabalin	73	0.05	LOSER							LOSER
mexiletine	69	0.00	LOSER							LOSER
				gabapentin		0	0.163	20		TBD
				topiramate		0	0.163	20		TBD
				valproate		0	0.163	20		TBD
				venlafaxine		0	0.163	20		TBD
				levetiracetam		0	0.163	20		TBD
				lacosamide		0	0.163	20		TBD
TOTAL	402									

Table 4. Platform Trial allocation table.

often to increase the efficiency of this sample size by selecting a pair of treatments among the pool of promising treatments before the clinical trial begins (e.g., pre-screening). The problem with this approach is that we may inadvertently leave out the most beneficial treatment. **Rather than having to guess which of two treatments is best, we place more arms in the trial and let response adaptive randomization (RAR) determine better arms.** RAR has clear advantages over adaptive equal randomization (ER), and a fixed design. Given the goals of this trial avoid ‘type III errors’ - inadvertently leaving out the best treatment - with little loss in power compared to a two-arm design, even when choosing the correct two arms for the two-armed design. There are appreciable gains in power when the two arms are pre-screened at random.⁷¹

Statistical Model: Here we describe the statistical model that will be used in the interim analysis/response adaptive randomization that permits us to make a final determination of which drug is “best”. **The best is referred to as the arm of maximum utility – the drug with the best combination of patient reported efficacy and percentage of patients who quit taking the drug.** For this study, these two measures, along with the number of patients who do not quit but for whom the drug was not efficacious are modeled as treatment-specific multinomial distributions. We provide “informative priors” for the veteran arms nortriptyline and duloxetine, Dirichlet (51, 34, 49)) and Dirichlet (47, 29, 50)) respectively. These prior distributions reflect the results found in PAIN-CONTRoLS. In addition, for the six rookie arms we provide “weakly informative” priors, Dirichlet (1/3, 1/3, 1/3)). This prior distribution reflects that before data are collected, for each drug there is 1) an equal probability of a patient being a quit, efficacious, or not efficacious and 2) this information is worth only a single patient (i.e., “weakly informative”). Thus, most of the statistical inference in the rookie

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

arms comes from the data collected from patients in the trial. The statistical inference in the veteran arms comes from data collected in PAIN-CONTRoLS and the data collected from patients in the trial. Once the patient data are collected, we take that data with the multinomial likelihood and combine it with the Dirichlet prior, and using Bayes theorem, calculate a posterior distribution for the model parameters. Specifically, the probability that treatment j is the best treatment is defined as $\Pr(U_j = U_{max}) = \Pr(U_j > U_A; U_j > U_B; \dots; U_j > U_G)$ where $A, B, C, D, E, F,$ and G represent the seven treatments other than treatment j . To make these calculations, we use a program in FACTS similar to the program found in Gajewski et al (2015).⁶⁹

Adaptive Randomization: Allocation: After each interim analysis in which we continue enrollment, the next round of patients is randomized using a formula that takes advantage of the information gained from our analyses up to that point in time. The new randomization probabilities take into account the probability that a treatment is the best, while also accounting for the observed sample size for that treatment at the appropriate interim analysis. Using this formula, each arm (drug) is allocated a portion of the next patients to be enrolled, which in the j th arm would be proportional to $V_j^* = \sqrt{\frac{\Pr(U_j=U_{max})Var(U_j)}{n_{j+1}}}$, where $\Pr(U_j = U_{max})$ is defined as above, $Var(U_j)$ is the posterior variance, and n_j is the sample size, all for the j th treatment drug (arm).

Longitudinal Model: As the randomization is updated during the study, some patients will have provided some follow-up data, but had not completed the study intervention. The longitudinal model predicts patients' 12-week data from data at early time points (4 and 8 weeks). The model is used to estimate transition probabilities from an outcome state at an early time point to final outcome. The number of transitions to the final outcome state given early outcome is distributed as multinomial with the following parameters. The approach uses posterior distribution draws in the MCMC, so it accounts for the pending patient values using multiple imputation. Details of the longitudinal model and the priors can be found in Brown et al., 2016.⁷² (One slight modification is the use of priors Dirichlet (1/3, 1/3, 1/3)).

Virtual Participant Responses Used for Power and Sample Size Simulations

For the purposes of this study, we looked at several virtual responses to determine the power, sample size and time (duration) needed for our study. See Table 5 for these virtual response scenarios, shaded regions show the best treatments the non-shaded regions show the loser treatments. Table 6 shows the probabilities of identifying the best as well as identifying a loser for the respective scenarios. These probabilities are calculated with 1,000 simulated clinical trials executed using the procedure described above.

Table 5: Virtual Response Scenarios. ($\Pr(\text{Quit})$ is proportion of participants who quit; $\Pr(\text{Efficacy})$ is proportion of participants efficacious; $\text{Utility} = 3/4 * \Pr(\text{Efficacy}) + (1 - \Pr(\text{Quit}))$). Shaded region is the best treatment for the respective scenario. Scenario 1 has one best treatment, scenario 2 has three losers and three equally best treatments. *nortriptyline and **duloxetine.

		Treatment								
		j=1*	j=2**	j=3	j=4	j=5	j=6	j=7	j=8	
Scenario 1	Pr(Quit)	0.38	0.37	0.42	0.58	0.25	0.58	0.38	0.50	
	One Best	Pr(Efficacy)	0.25	0.23	0.15	0.2	0.4	0.1	0.25	0.25
	Utility	0.81	0.80	0.69	0.57	1.05	0.50	0.81	0.69	
Scenario 2	Pr(Quit)	0.38	0.37	0.5	0.5	0.5	0.5	0.5	.5	
	Six Losers	Pr(Efficacy)	0.25	0.23	0.1	0.1	0.1	0.1	0.1	.1
	Utility	0.81	0.80	0.58	0.58	0.58	0.58	0.58	0.58	0.58

Table 6: Probability Treatment is Best and Probability Loser by Virtual Response Scenarios. $\Pr(\text{Best})$ is the probability the treatment is the best; $\Pr(\text{Loser})$ is the probability the treatment is a loser. Shaded region is the best treatment for the respective scenario. *nortriptyline and **duloxetine.

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

		Treatment							
		j=1*	j=2**	j=3	j=4	j=5	j=6	j=7	j=8
Scenario 1	Pr(Best)	.00	.00	.00	.00	.95	.00	.00	.00
One Best	Pr(Loser)	.41	.45	.50	.74	.00	.88	.14	.47
Scenario 2	Pr(Best)	.03	.01	.00	.00	.00	.00	.00	.00
Six Losers	Pr(Loser)	.00	.00	.43	.42	.42	.43	.42	.42

Power, Sample Size, and Trial Duration

For the simulations we used an average accrual rate of 2.68 patients/week (estimated from PAIN-CONTRoLS). These simulations resulted in identifying power (the probability of success) in two components—one for early success (i.e., being able to stop the trial early) and one for late success of the trial (i.e., after enrolling all 600 patients). First, we highlight the null hypothesis (scenario #0, not shown in Table 1). This is a scenario where there are no differences in efficacy (all 0.25) or in quit rates (all 0.38) among the seven drugs. Therefore, the extent to which this scenario is “successful” reflects our Type I error. For this scenario, we estimated (identified) that 1.0% of the simulated trials had early success, 7% late success. **Thus, this trial scenario produced an appropriate expected Type I error ($\alpha=.07$).** The sample size of this scenario on average was 598 patients and average length of the trial was 235 weeks. Second, (scenario #1), if there is one best drug, we estimated (identified) that 95% of the simulated trials had early success and 5% late success. **Thus, this simulation had 99%+ power, and all these correctly identified the best treatment (Table 2).** The average sample size of this trial scenario was 310 with average trial duration of 128 weeks. About 1/3 of the sample size, 95 participants, received best treatment. Third (scenario #2), if there are two best and six loser drugs, we estimated 2% of the simulated trials had early success and 91% late success. Thus, this simulation had 96% power. **The trial has over 40% probability to correctly identify each of the six loser drugs (Table 2).** The average sample size of this trial scenario was 59 and average trial duration of 235 weeks.

Design for Clinician Team Education: This study is modeled after a number of successful trials including the completed NIDDK R01 study (TRANSLATE CKD).²⁹ Dr. Fox and his team used a remote/online academic detailing model where he and a nephrologist co-delivered education on slowing the progression of chronic kidney disease. Delivered in a low stress, supportive and using a primary-care-informed approach, they provided primary care teams with an improved set of tools to monitor and intervene with patients. The same dyad approach between primary care and specialty care informs this study. The neurologists (Barohn, Pasnoor, Ensrud, Dimachkie) will work with primary care clinicians (Koopman, Misra, Corriveau, Miller) during the first year of the project to co-develop neurology-relevant content, case study examples and other primary care-centric materials to increase accurate CSPN diagnosis, recruit eligible patients into the trial and increase clinician self-efficacy. Proposal preparatory interview data with primary care clinicians include their desire to cover dealing with continued opioid use (and how to taper). Materials will be organized and submitted for continuing medical and nursing education credits to recognize the content, time and effort needed for the site teams to participate in the study. Pre-/post- testing will be used to monitor performance and acceptability of the education. In addition to the clinician team, Drs. Sales and Bartlett have extensive curriculum development experience. They will assist in producing adult-learner-centric, concise materials. These materials will be pilot tested among clinicians who will not be in the study to ensure tailoring and impact are maximized. Final products will include primary care-targeted, evidence-informed clinical algorithms for both diagnosis of neuropathy/CSPN and treatment of CSPN, as well as machine learning-based predictive algorithms for CSPN that can be used to inform EHR clinical decision support.

Exploratory Outcomes: We include three exploratory outcomes. First, we will conduct a sub-analysis using sex, age, race and ethnicity to explore differences that may inform our primary and secondary outcomes. We do not expect to reveal differences based on our previous PAIN CONTRoLS study but given six new medications and a larger population of participants, it remains important to test for impact of these demographic variables. Our training of clinicians will include how to determine if the neuropathy is likely to be small fiber or mixed large and small fiber based on a neurologic exam that they will perform. For example, preservation of ankle reflexes, vibration and proprioception

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

would put the patient in a small fiber category. Therefore, we will collect these data and will be able to do a sub-analysis to determine the effect of the study medications on small vs. large fiber patients.

Second, we intend to analyze participants' experiences using the study drugs from their journaling to describe impact more richly. While we have indications of common and unique factors that influence the lived experiences of people with CSPN, we will explore whether their journaling and storytelling provide any common threads to illuminate conditions leading to drop out or retention in each of the study arms. We will conduct content analysis using Normalization Process Theory.^{36,37,73} The goal of this approach is to find common/unique themes by reviewing the data, coding emergent themes with keywords and phrases, grouping the codes hierarchically and categorizing concepts. We already know that the stories of people living with CSPN are compelling. We anticipate that this work will illuminate the impact of improved medication and care management, self-efficacy and positive interaction with their clinicians. An exploratory outcome involves collecting and analyzing genomic data from the 600 trial participants. To accomplish this work, we will partner with PTC Laboratories, Inc (formerly Paternity Testing Corporation). PTC Labs is the main company and holds all the required laboratory accreditations, WBE and contracts to be a collaborator. While PTC primarily functions in the human identity markets (paternity, kinship, and forensic testing), GeneTrait (a clinical division of PTC) has MedTrait (medtrait.net) which is the Pharmacogenomic (PGx)-assisted medication management application we will specifically use for this study. The Pharmacogenomic (PGx) knowledge and tools available today can lead to safer and more effective prescribing thereby leading to improved outcomes for many patients. But, fulfilling the promise of PGx for every patient and disease remains elusive. A few of the common neuropathy pain medications have robust scientific PGx metabolism information that is clinically actionable. For example, scientifically established relationships for the drug/gene interactions of nortriptyline is available. However, many of the medications in use today have little scientific correlation to specific genetic variations. Currently, the predominant clinical role of PGx is to accurately predict the metabolism of medications (conversion to an active form and/or elimination) by evaluating liver enzymes and transporters. In the case of neuropathy medications, the binding and receptor sites for these medications play a crucial role in the effectiveness of medications. In general, the receptor sites necessary to evaluate the efficacy of these medications remain complex and not well understood from a genetic perspective. A two-pronged approach that evaluates the outcomes of current clinically available testing in patients with neuropathy pain and evaluates newly identified genetic markers that have the potential to develop new companion diagnostic tests for these medications to optimize treatment. The outcomes data of implementing a clinical PGx-assisted medication management program in a neuropathy pain management population may help establish guidelines for the usage of PGx testing in this population.

The prime institution for this study (University of Missouri) has PGx online and has been working on updating the MedTrait knowledge base. We have a list of the current SNPs on the panel and while we believe the whole person medication management offered by MedTrait is a wonderful contribution, we know, and they have advised us, that we are going to need to look at more investigational markers for the medication groups we are studying. They can add up to about 12 markers with little additional expense. We will work with them to make decisions about SNPs and markers during the feasibility phase of this study. Dr. Bartlett has extensive experience looking at pharmacogenomics related to depression and epilepsy treatment, so she will work with study statistician, Dr. Gajewski, to spearhead the secondary analyses and population health framework that will develop with the collection of the genetic data. In addition to pharmacogenomic data, we will be obtaining genetic data to determine if the patient has a mutation of a sodium channel SCN11A gene. We will perform a sub-analysis to determine which drug patients with this gene defect are more likely to respond to. Both pharmacogenomics and genetic studies will be obtained with simple buccal swabs. We include these important data that were not a part of the PAIN CONTRoLS study to widen impact of our findings and understanding of the condition.

E. Analytic Plan

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

Please review the above section that highlights the highly integrated design and analytic plan. To highlight the output we anticipate from this plan, we include the following simulations. These two figures represent example clinical trials that could happen in our proposed trial. In the Figure 1 using simulated data, nortriptyline, and duloxetine (veteran drugs) remained the same in utility but were both better than the five new study drugs. This reflects the number of participants randomized (after the first 102) being much greater in the veteran drugs. This trial enrolled 500 since there was no clear winner, however in this trial the probability of being a winner was all less than .001 for the six new drugs, since they are all very unlikely to be the best, we would not utilize them in clinical practice (e.g., losers). In Figure 2 (also using simulated data), topiramate (one of the new study drugs) emerged to better utility than all the other drugs. This is reflected by the relatively large number of subjects randomized was much greater in topiramate. This trial stopped early at 300 since there was a clear winner, probability topiramate is the best is .99. The conclusion of this trial would be topiramate be recommended in clinical practice.

F. Data Coordinating Center (DCC) Functions

The DCC will use its clinical trials experience to monitor data throughout the study, conduct specified interim analyses, and facilitate the work of the DSMB via periodic reports. The DCC has extensive experience in the analysis and dissemination of Bayesian adaptive trial information. The DCC will promote the trial via active participation in the development of trial-related manuscripts and presentations. See Figure 3 for a schematic representation of the DCC.

Current large, multi-center clinical trials with data management coordinated by the DCC include: ADORE, CTD, HOBIT, and tANBL trials and PCORnet GPC amyotrophic lateral sclerosis characterization studies led by Drs. Barohn and Waitman. The DCC's Clinical Trial Management System (CTMS) encompasses all steps of the data management process, including data capture and verification, subject randomization, programmed data validation, study monitoring and reporting, study calendar functionality, data auditing, and secure data transfer.

The Data Coordinating Center (DCC) activities for the BEAT CSPN trial

will use our REDCap electronic Clinical Trials Management System (CTMS) customized to support this design. **The integrated system facilitates trial management, including data quality, protocol compliance, and trial oversight issues, and represents a shift towards more efficient data and project management processes.** The DCC role is significant because 1) the proposed analysis plan details a statistically innovative and valid approach to addressing the trial's objectives; 2) the CTMS system provides the necessary tools for clinical sites to conduct the research and for the team to *complete its coordination and oversight activities successfully*; and, 3) the data management expertise of the DCC will ensure high-quality data and a trial conducted according to Good Clinical Practice (GCP) guidelines and federal regulations.

Data and protocol information can be entered into CTMS efficiently and in a standardized format compliant with PCORI and PCORnet reporting standards. The system supports participant recruitment, study monitoring, trial design, protocol management, data safety monitoring, case report form construction and dissemination, PCORI Cycle 3 2020 Phased Large Awards for Comparative Effectiveness Research PFA: Research Plan

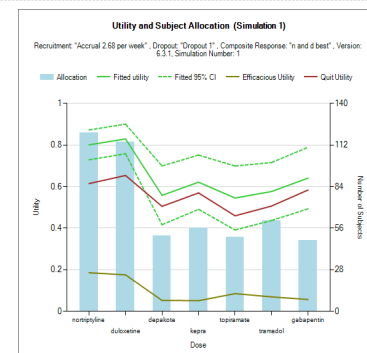


Figure 1. Simulation using PAIN CONTROLS

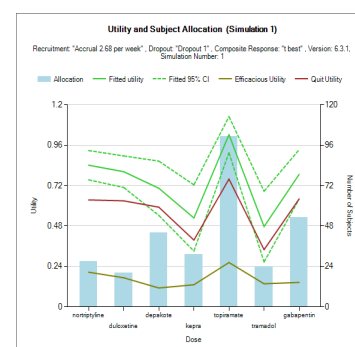


Figure 2. Simulation using

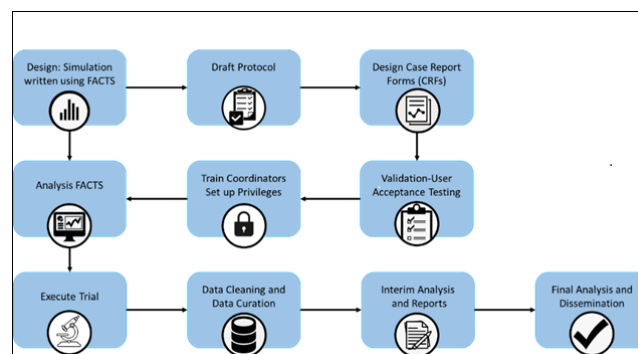


Figure 3. Data Coordinating Center

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

integration of tissue and clinical information, clinical trial execution and query management, and integration with third-party clinical systems. **The DCC team has successfully implemented the Bayesian response-adaptive randomization algorithm using the system in multi-center clinical trials.** The REDCap CTMS will automatically assign the randomization number and the treatment arm to the participant once all the information is entered under the participant's case report form. This functionality enables the clinicians to randomize the patient instantaneously during the clinic visit. The CTMS algorithm helps centralize the randomization process among multiple sites/data coordinators. Sites can easily randomize simultaneously without interrupting the participant recruitment process, which has helped us immensely with our previous studies, including PAIN-CONTRoLS (NCT02260388), etc. The Data Management team has developed and adheres to a comprehensive list of SOPs per FDA guidelines that govern the Software Development Life Cycle (SDLC), established system requirements, proper setup of systems, and system recovery procedures. *Standard Reporting:* Our group provides many different reports, including accrual reporting, ongoing data cleaning, Serious Adverse Event notifications, event window adherence, and others specific to the study's needs. *Data Security:* All servers are housed in the University of Missouri data center, having physical security with 24x7x365 video surveillance system monitoring and controlled by locked doors and an ID card reader or on the University of Missouri's Amazon Web Services environment that is in full compliance with HIPAA and Federal NIST 800.53 standards for obtaining Centers for Medicare and Medicaid Services claims. This AWS environment is also used to manage and store the PCORnet Common Data Models from across the GPC. All database servers are kept behind the KUMC firewall. All servers are encrypted using a 256-bit AES algorithm and backed up nightly offsite in a secure data location with restricted access. If necessary, the data and archive logs can be restored.

The **DCC's goal** is to provide the data management infrastructure for the successful implementation of the BEAT CSPN study, including the creation and maintenance of the study database. The DCC maintains a full set of SOPs covering data management procedures. All data management activities will be conducted in coordination with the PIs using established DCC SOPs. We will develop the following documentation maintain throughout the study: electronic versions of the Case Report Forms (eCRFs) in REDCap, the data collection schedule, data dictionary, Data Management Plan (DMP) that will document all procedures, processes, and methods used during the study that affects the data collection, and CTMS User Manual. The study database will have extensive consistency checks programmed into the electronic REDCap eCRFs (e.g., data type, range, and logic checks) that will provide real-time checks for data accuracy, completeness and timeliness for all essential data elements as defined by the study protocol. Some data entry will occur at the clinical sites via user-friendly data-entry screens of CTMS. The DCC has developed a unique approach to data cleaning to ensure high-quality data. All data submitted to the database undergo a two-stage validation procedure. First, upon completion of data entry, data checks flag items that fail pre-programmed consistency checks, and an on-screen message appears requesting clarification by the site. This approach allows for resolution of discrepant data and has been found to reduce the number of queries when compared to paper-based approaches. Second, throughout the trial, the data manager (DM) is responsible for reviewing submitted eCRFs. Then the DM issues an electronic data clarification request (DCR), which are sent to site personnel for resolution. From the distribution across sites, the DM can identify outlying values and is automatically redirected to the corresponding eCRF for DCR generation, if appropriate. As forms are reviewed and queries generated, the DM adds validation rules to the database to prevent further propagation of erroneous data. This process reduces the time 1) between data entry and cleaning, reducing the burden on the study coordinators, and 2) required to prepare 'clean' data sets, which allows for timely report generation and analysis. Prior to any data freezes (i.e., for preparation of DSMB reports, interim analysis) and at study close-out, the DM will ensure that all data are collected, and all queries resolved. One caveat to web-based data management is its dependence on data entry timeliness at the clinical sites. CTMS posts eCRFs for each participant based on his/her progress in the study. The time-window for sites to submit the eCRF is specified based on the nature of the eCRF. User intuitive interfaces are provided to the site study coordinator and DCC data managers, showing each participant's current data processing status. Site-specific eCRF processing summary reports and detailed missing or late eCRF lists are

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

also provided by CTMS, allowing the DM to monitor the study data collection activities across all sites carefully and ensure that data collection is proceeding uniformly and efficiently. DCC Staffing: Dr. Waitman is the lead of the DCC and co-PI for this study. As a nationally recognized informatician and the leader of the Greater Plains Collaborative PCORnet CRN, he is extremely well suited to lead the Center. Other members of the DCC include faculty and staff (Mosa, Cassone, Mandhadi, Jampani, Niu). DCC investigators are faculty members of the Department of Health Management and Informatics at the University of Missouri while Dr. Gajewski is faculty in the Department of Biostatistics and Informatics at the University of Kansas Medical Center. Dr. Gajewski and Ms. Brown have extensive experience in the conduct, analysis, and application of innovative Bayesian methodology to clinical trials including the study design and analysis of Bayesian adaptive trials PAIN-CONTRoLS.^{17,69,74-77} The DCC statisticians have also served as Data Safety and Monitoring Board (DSMB) members. Drs. Waitman and Gajewski are responsible for DSMB report generation, including all interim safety and efficacy analyses and the final analyses and the creation of public use data sets. Dr. Gajewski and Ms. Brown will collaborate with the DCC research staff during the implementation and analysis of the BEAT CSPN trial. Importantly, the DCC investigators have established an excellent track record of productive collaboration with Dr. Barohn and the other study's investigators.^{69,71,72,78}

The independent Medical Safety Monitor (MSM) and Data Safety Monitoring Board (DSMB) will receive periodic safety reports from the DCC throughout the trial of all adverse events and serious adverse events. This review will aid in identifying any safety issues that may need to be addressed. All MedDRA coded AEs and SAEs will be summarized in terms of frequency of the event, number of subjects having the event, and severity and relatedness to treatment. Unadjusted relative risks will be provided with two-sided 95% Bayesian credible intervals. Stopping the trial or stopping randomization to one of the arms due to harm may be considered by the DSMB at any time. Posterior distributions and their 95% intervals will be calculated. In addition, the cumulative incidences of the specific SAEs and all SAEs will be compared across arms using a main effects model. Dr. Ashraf will serve as the safety monitor throughout the trial.

Web-Based Real-Time Information Sharing: Reliable and real-time information sharing within the study community is critical for clinical trial operation management and monitoring success. All users will be trained by Ms. Jampani to use REDCap to ensure security and consistency. REDCap was used as our data information tool for PAIN CONTRoLS and worked exceedingly well for all users. REDCap is also widely used across PCORnet for other studies and notably supported site level tracking activities for the ADAPTABLE trial,^{79,80} PCORnet's first demonstration project (n=15,000). Event and schedule-driven emails are used to share information with authorized users. Email notifications/reminders indicating SAE submission, new participant randomization, overdue eCRFs, and pending follow-ups can be sent to targeted users. All notification emails contain minimal information about the event or schedule to ensure data security.

G. Clinical Coordinating Center (CCC) Functions

CCC Staffing: Dr. Barohn and the other clinician co-investigators, engagement leader, lead statistician and the BEAT CSPN project manager will direct the CCC. As a seasoned multi-site trialist, Dr. Barohn has the breadth of experience to direct this center effectively and efficiently (evidenced by the success of the prior PCORI funded PAIN CONTRoLS study). The CCC will: manage all education development and content delivery; provide site training for each site's project coordinator; conduct monthly calls with both the Patient Advisory Council and the Stakeholder Advisory Council; monitor recruitment and offer assistance as needed; review safety labs and consult with clinicians on a case-by-case basis to determine if the participant should drop out of the study; submit and manage central IRB and IRB approvals, and provide overall agenda setting and leadership of the study. The CCC will organize and execute the dissemination activities, working with PCORI and PCORnet to advance the adoption of better CSPN disease management. As the project management hub for the study, the CCC will be responsible for communicating directly with PCORI, overseeing clinical operations, responding to all data and information requests as well as leading milestone and interim reporting requirements. The project manager (Herbelin) has extensive experience in maintaining regulatory documents, developing Standard Operating Procedures (SOPs) and ensuring that all sites are onboarded following common protocol.

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

For the in-service education provided by the BEAT CSPN neurology/primary care dyad to participating practices and providers, the CCC will manage and schedule each of these sessions. **Given the number of participating sites, we have ensured coverage by having four primary care and four neurology clinicians who can pair up as a dyad based on availability and demand.** The project plan includes an anticipated four session series that would be offered at times selected by the participating practices. Subject to input and possible modification during the feasibility phase, content will include: CSPN diagnosis (including what are the minimal laboratory tests needed to perform on a patient to put them in the CSPN category or to determine another known cause for their neuropathy); how to recognize small vs. large fiber neuropathy from information obtained on a targeted neurologic exam that they will conduct; a comprehensive review of non-opioid drugs plus all other treatment modalities for pain beyond those being compared (e.g., biofeedback, relaxation response) plus other topical options through more invasive options like spinal cord stimulation. Our engagement efforts point to the value of including content on how to discuss this painful condition with patients. We will model how to discuss the long-term prognosis of having CSPN with patients. Often the key is to reassure the patient that this is not ultimately a disease that will cause severe mobility impairment or that it will progress rapidly. This type of reassurance is often one of the best therapies, and while patient research partners affirm this to be true, clinicians may not truly recognize the value of this type of counseling.

The CCC will manage all engagement arrangements with participating PCORnet clinic partners including all agreement and payment documents required for the study. The CCC will execute and manage contracting (e.g., firms that will complete the genetic analyses), subaward contracting and maintain all study protocol and procedure manuals secured electronically behind firewalls at the host institution (Missouri).

Regarding patient participation, the CCC will offer ways to address identified barriers to recruitment in the study. For example, many of the patient reported outcomes are available and validated in Spanish, so we could provide support for non-English speaking participants. Decisions regarding primary language that might help representativeness and advance research equity will be led by the CCC and will be a focus of attention on early agendas during the feasibility phase and early enrollment of sites into the study.

Engagement of all stakeholders is a cornerstone of the study, so bi-directional review, input and development of various aspects of the study will be hosted through the CCC to ensure input is heard and acted upon. In deciding between the benefit and burden, patient and other research partners decided to interface through the CCC rather than maintain a membership, standing role on the CCC. It will be the study engagement lead, Dr. Kimminau's duty to bridge among the Councils and the CCC to maintain ongoing dialog.

H. Recruiting Plans for Feasibility and Full-Scale Study Phase

Feasibility Phase: We will review and assess the applicability of the PAIN-CONTRoLS study to inform our approach to recruitment during this planning phase. This step will include a comprehensive review of all strategies used to recruit practices and participants. We feel that it is a wise use of an already CSPN-informed project that can substantially advantage this CER trial. Because of its success in recruitment, we preliminarily have modeled the recruitment plan in a similar way. However, as this proposed study includes seeking CSPN patients seen in primary care (and who may have yet to either receive a CSPN diagnosis or referral and subsequent care by neurology), we must re-examine our approach, develop and apply a PCORnet Common Data Model computable phenotype, and make sure we adapt to a primary care clinic setting. Furthermore, we may be recruiting trial naïve or sites with limited experience using PCORnet, so we recognize that our engagement of these new partners may also call for modifications. See Table 7 for details.

Table 7. Recruitment, Enrollment, and Retention Plans	Number
1. Estimated number of potentially eligible study participants and a description of how this number was determined (PCORnet MDQ FD 1392)	28,814
2. Total number of potentially eligible study participants expected to be screened	3,000
3. Total number of screened study participants expected to be found eligible	2,500
4. Target sample size (use same number stated in Milestones)	600
5. If applicable, total number of practices or centers that will enroll participants	30-60
6. Projected month first participant will be enrolled (month after project initiation)	May 2024

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

7. Projected month last participant is expected to be enrolled (month after project initiation)	Nov 2028
8. Projected rate of enrollment (anticipated number enrolled per month of enrollment period)	10.72/mo
9. Estimated percentage of participant dropout	10

Full-Scale Study Phase: The project Steering Committee (Barohn, Bensman, Pasnoor, Koopman, Waitman, Gajewski, Kimminau, Herbelin) will host monthly recruitment calls (held at two different times to accommodate clinicians' schedules) with all site PIs and their site coordinators to discuss the status of recruitment overall and for their site. This outreach proactively addresses clinician and clinic retention; it permits a safe and open environment to discuss challenges and barriers. In addition to recruiting patients from neurology and FM clinics, each site may be able to advertise using electronic "push" messages through their patient portals and/or use newspaper advertisements. While it may seem like an antiquated approach, we learned that each time a newspaper advertisement would run for the PAIN CONTROLS study, a site would get a spike of approximately 100 phone calls that the research coordinators would then manage. The calls yielded about a rate of 10% eligible patients. Adding primary care clinics will further increase recruitment potential, so we are confident that recruitment will be successful.

I. Engagement Approach

This research team is committed to authentic and ongoing patient and stakeholder engagement. To that end, the following stakeholder groups are engaged in this study and preliminary plans, goals, activities and metrics for their ongoing collaboration and shared leadership are presented below. The groups include primary care clinicians, patients, advocacy organizations and payers.

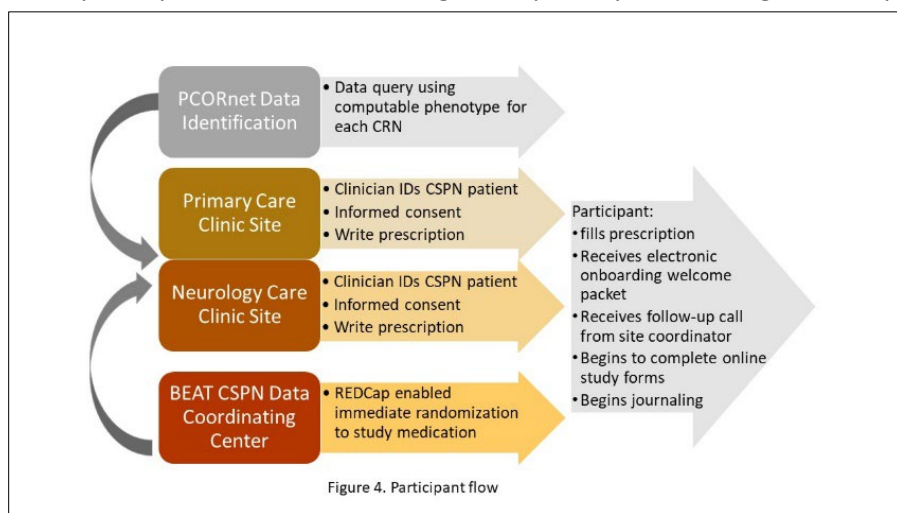
Input from clinician and patient stakeholders: Selecting a medication that can help reduce the pain associated with CSPN represents a decisional dilemma clinicians face and it underscores their need for this study. We interviewed primary care clinicians during proposal development to ensure that specific aims and the planned approach met their needs. They shared a lack of confidence in diagnosing CSPN, choosing appropriate medication and managing care which underscores the importance of offering this study to close care gaps and improve successful CSPN identification. We interviewed people who have peripheral neuropathy during proposal development. It was their lived experience and input that led to the selection and confirmation of primary and secondary outcomes. Our focus groups and interviews discussed the inclusion/exclusion criteria and stakeholders made the strong case that the study should be as open and available as possible. The use of using online options available to enable participant self-reported data collection plus the focus in this study on sharing updates, results and other information electronically was preferred by patients; they are keen to avoid clinic visits. The ability to participate in the trial from home using electronic interfaces were preferred for all stakeholders. They noted, for example, that remote management using telehealth has been shown to be highly effective during the COVID-19 pandemic, resulting in safe and effective patient care. Furthermore, remote engagement for data collection was successful during the prior PAIN-CONTROLS study. From all participants' perspectives (clinicians and patients), remote participation saves time, costs and for patients, it reduces stress involved in attending clinic, especially at large medical centers which they often find overwhelming.

Advisory Committees Engagement: Patient research partner (Janine Bensman) will lead the **Patient Advisory Council (PAC)** that will maintain patient engagement throughout the study. Each participating site will recruit a patient partner for the PAC. We will invite PCORnet CRN leaders, healthcare payers (Sun, Nair), national organization leaders (Graham Center, Foundation for Peripheral Neuropathy, i.e., Colbert) and patient experience experts (O'Connor) to serve on the **BEAT CSPN Stakeholder Advisory Council**. During the feasibility phase of the study, we anticipate identifying additional leading voices that can inform and join these Councils. Our focused attention to encouraging diverse voices during this early phase will galvanize agreement about acceptability, feasibility, rigor, and relevance of the research, and will encourage a comprehensive approach to developing the training proposed for clinicians and the information needed to fully inform and engage patient participants. We provide details on the activities of their work, time and how this will feed ongoing engagement during the study below in Table 8.

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

Table 8. Planned Engagement Goals and Activities			
Stakeholder/Goal	Draft responsibility/work Items	How will they accomplish their work?	Evaluation of impact/ensuring influence
People who live with CSPN/ Ensure experience and insights that can influence study flow freely from stakeholder to research team	Review all patient-facing communications and required documentation; Monitor trial progress	Research team will report progress at each of their monthly meetings and updates shared with the Patient Advisory Council	Track each review and recommendations for modifications; assess impact
	Recommend strategies for recruitment	Monthly review of recruitment target performance	Track reviews and recommendations for modification(s); assess impact
	Craft results messaging	Sub-committee(s) will translate research results into messages relevant to their constituents	Track each message modification and measure uptake based on communication channel selected
	Present research findings	Group will self-identify presenters	Track inclusion of patient presenters
	Participate as co-investigator	Leader (Bensman) will be included in team activities	Monitor communications and consistency of inclusion
Primary care clinicians / Ensure didactic content and delivery is effective and ensure findings are disseminated effectively	Review and approve of training materials	Two extended online meetings (1.5 hr. each) to react to and edit	Track quantity and quality of input
	β-test pre-/post tests	Individual-level testing	Track individual/group (practice) performance and track changes to improve face validity
	Present research findings	Group will self-identify presenters	Track inclusion of clinician presenters
Advocacy organizations / Extend the reach of findings to constituents	Craft results messaging	translate research results into messages relevant to their constituents	Track each message modification and measure uptake based on communication channel
Payers /Impact policy	Review research findings	Group will receive briefings from research team, ranking the merit/demerit of each drug	Track change in eligible coverage, formulary or other policy impacts of findings

Participant Engagement and Flow: Patient participants will be recruited through a primary care or neurology clinic. We are especially interested in recruiting in the primary care setting because patients may be naïve to the study medications



and early in their diagnostic and care journeys. This strategy may address reluctance of more established and/or previously diagnosed CSPN participants from participating if they already have concerns about the effectiveness of medications. We will recruit individuals as they are identified with CSPN and agree to participate in the trial; they will be randomized immediately after consenting to participate. Figure 4 presents the expected participant flow into the study. We will use Wolfe et al⁸¹ inclusion criteria. Exclusion criteria include anyone unable to complete the informed consent process,

women planning pregnancy or lactating; individuals without telephone, internet and/or computer assistance needed to share patient-reported outcomes.

Clinician Engagement: We have three clinician engagement approaches for the study. First, we activated the use of the PCORnet Front Door, holding a webinar and soliciting interest. Second, the PI personally contacted PCORnet site neurologist colleagues to participate in the study. Our third approach specific to engaging primary care clinicians has three prongs – 1) we have asked the neurologists to identify a primary care clinician partner at their local site; 2) we will recruit using the infrastructure of primary care Practice-Based Research Networks (PBRNs). At last update, there are 185

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

PBRNs registered with the AHRQ PBRN Resource Center. One of the investigators for this study, Dr. Kimminau, was the PI for MOSAIC, an AHRQ PBRN Center represent 13 PBRNs with over 3,000 primary care clinicians. This network will activate to recruit academic and community family medicine practices, as needed; 3) two study investigators, Drs. Bartlett and Koopman, hold elected positions in the North American Primary Care Research Group, the recognized leader of primary care research that improves health and health care for patients, families, and communities. Their ability to “get the word out” and seek additional primary care clinicians to participate has enormous potential to engage an even wider group of clinicians beyond PCORnet. This will be especially impactful as the results of the study plan strategies to influence diagnosing and prescribing for CSPN.

Site Engagement: It is crucial to keep strong, consistent engagement with clinical sites and the clinicians caring for patients who have painful neuropathy. To do so, Barohn and team will routinely monitor and assess clinic and clinician-level engagement. For example, something as simple as whether sites attend calls and project-related trainings or if attendance diminishes over time is an indicator for action. We will proactively engage with sites to learn how the study can be conducted with minimal disruption to workflows. Site coordinators will receive training from the Clinical Coordinating Center (CCC) and be able to ask the team questions throughout the study. Coordinators will manage site activity including in-clinic recruitment brochures, processes, newsletters, etc. to assist with patient participation. They will conduct follow-up calls and assist any participant who may have problems with submitting their patient-reported outcomes data electronically; in cases where the participant struggles, the site coordinator will be able to interview the patient for information and submit data on their behalf through REDCap.⁸²

Summary of Feasibility Phase Activities (Table 9)

Research element	Which tasks will require <u>significant</u> development or effort in the feasibility phase?
1. Comparators	<ul style="list-style-type: none"> Review preliminary selection and confirm inclusion of each drug and Assess clinician acceptance Review issues around opioids and the study drugs' prescribing with respective stakeholders Document existing workflows, resources, and constraints to ensure no bias regarding any of the study drugs
2. Outcomes	<ul style="list-style-type: none"> Determine additional outcome measures and finalize instruments to assess outcomes Establish REDCap infrastructure to execute data collection and develop SOPs for quality assurance/control Refine exploratory pharmacogenomics data and analytic plan
3. Timing	<ul style="list-style-type: none"> Review/finalize 12-week duration and follow-up intervals post-3-month active study period
4. Setting(s)	<ul style="list-style-type: none"> Determine if all primary care settings are comparable to conduct the trial (i.e., assess common core capacities) Determine how each site's clinics (if both neurology and primary care choose to enroll) will coordinate
5. Analytic plan	<ul style="list-style-type: none"> Determine primary, secondary, or exploratory analyses to finalize the Statistical Analysis Plan Determine power for subgroup analyses Design analyses using genetic data
6. Sample size/power	<ul style="list-style-type: none"> Develop and use computable phenotype Refine estimates of effect size, likely enrollment, attrition, etc.
7. Study design and methods	<ul style="list-style-type: none"> Identify “winner” and “losers” medications for pain control effectiveness Develop instructional slide decks, primary care clinician and neurologist dyad session materials; and pre-test
8. Study population	<ul style="list-style-type: none"> Review inclusion and/or exclusion criteria; assess biases (i.e., race, rurality) Using computable phenotype, estimate candidate pool at each clinic site and at additional PCORnet sites
9. Recruitment potential	<ul style="list-style-type: none"> Assess clinician and/or participant willingness to accept randomized assignment Evaluate estimated percentage enrollment of candidate participants at steps along the recruitment pathway
10. Engagement approach	<ul style="list-style-type: none"> Identify additional patient or stakeholder groups, and review advisory bodies, functions, or roles Obtain stakeholder input to determine research elements (ex. outcome measures, recruitment) Test website to ensure easy to use access of information about study, medications, etc.
11. Site readiness	<ul style="list-style-type: none"> Confirm primary and identify backup sites, if needed negotiate common IRB and contractual arrangements for sites Develop and complete informed consent materials including a patient video; carry out training needed to conduct the study and ensure standardized data collection
12. Research protocol	<ul style="list-style-type: none"> Finalize, and solicit additional stakeholder input for protocol Test acceptability of protocol across key stakeholder groups
13. Various others as appropriate	<ul style="list-style-type: none"> Leverage other PCORnet resources (i.e., Engagement Coordinating Center) to strengthen study Establishing the Medical Safety Monitor (MSM) and DSMB

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

REFERENCES CITED

1. Patel KB, Rushefsky ME. *The Opioid Epidemic in the United States: Missed Opportunities and Policy Failures*. Routledge; 2021.
2. Zelaya CE, Dahlhamer JM, Lucas JW, Connor EM. Chronic pain and high-impact chronic pain among US adults, 2019. 2020;
3. Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. *Pain*. 1998;77(3):231-239.
4. Yawn BP, Wollan PC, Weingarten TN, Watson JC, Hooten WM, Melton III LJ. The prevalence of neuropathic pain: clinical evaluation compared with screening tools in a community population. *Pain medicine*. 2009;10(3):586-593.
5. Smith AG, Singleton JR. Idiopathic neuropathy, prediabetes and the metabolic syndrome. *Journal of the neurological sciences*. 2006;242(1-2):9-14.
6. Amato AA BR. Peripheral Neuropathy. *Harrison's Principles of Internal Medicine*. 2015:2674-2694. New York: McGraw-Hill Professional Publishing. 19th.
7. Amato AA BR. Peripheral Neuropathy. *Harrison's Principles of Internal Medicine*. 2018:3204-3225. New York: McGraw-Hill Professional Publishing. 20th.
8. Barohn R. Approach to muscle and nerve disease. *Cecil's Textbook of Medicine*. 2004:2370-2379. 22nd.
9. Barohn RJ. Approach to peripheral neuropathy and neuronopathy. *Semin Neurol*. 1998;18(1):7-18. doi:10.1055/s-2008-1040857
10. Barohn RJ, Amato AA. Pattern-recognition approach to neuropathy and neuronopathy. *Neurol Clin*. May 2013;31(2):343-61. doi:10.1016/j.ncl.2013.02.001
11. Pasnoor M, Dimachkie MM, Kluding P, Barohn RJ. Diabetic neuropathy part 1: overview and symmetric phenotypes. *Neurol Clin*. May 2013;31(2):425-45. doi:10.1016/j.ncl.2013.02.004
12. Pasnoor M, Dimachkie MM, Barohn RJ. Diabetic neuropathy part 2: proximal and asymmetric phenotypes. *Neurol Clin*. May 2013;31(2):447-62. doi:10.1016/j.ncl.2013.02.003
13. Wolfe GI, Baker NS, Amato AA, et al. Chronic cryptogenic sensory polyneuropathy: clinical and laboratory characteristics. *Arch Neurol*. May 1999;56(5):540-7. doi:10.1001/archneur.56.5.540
14. Wolfe GI, Barohn RJ. Cryptogenic sensory and sensorimotor polyneuropathies. *Semin Neurol*. 1998;18(1):105-11. doi:10.1055/s-2008-1040866
15. Wolfe GI, Barohn RJ. Painful Peripheral Neuropathy. *Curr Treat Options Neurol*. May 2002;4(3):177-188. doi:10.1007/s11940-002-0034-0
16. Wolfe GI, Hotz SE, Barohn RJ. Treatment of painful peripheral neuropathy. *J Clin Neuromuscul Dis*. Dec 2002;4(2):50-9. doi:10.1097/00131402-200212000-00002
17. Barohn RJ, Gajewski B, Pasnoor M, et al. Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTRoLS): Bayesian Adaptive Comparative Effectiveness Randomized Trial. *JAMA Neurol*. Aug 17 2020;doi:10.1001/jamaneurol.2020.2590
18. Pasnoor M, Nascimento OJ, Trivedi J, et al. North America and South America (NA-SA) neuropathy project. *Int J Neurosci*. Aug 2013;123(8):563-7. doi:10.3109/00207454.2013.782026
19. Corvisier N, Vallat JM, Hugon J, Lubeau M, Dumas M. [Neuropathies of unknown etiology. A study of 48 cases]. *Rev Neurol (Paris)*. 1987;143(4):279-83. Les neuropathies de cause indeterminee. Etude de 48 cas.
20. England JD, Gronseth GS, Franklin G, et al. Practice parameter: the evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review).

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

- Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *PM R*. Jan 2009;1(1):14-22. doi:10.1016/j.pmrj.2008.11.011
21. Lindh J, Tondel M, Osterberg A, Vrethem M. Cryptogenic polyneuropathy: clinical and neurophysiological findings. *J Peripher Nerv Syst*. Mar 2005;10(1):31-7. doi:10.1111/j.1085-9489.2005.10106.x
 22. Notermans NC, Wokke JH, van der Graaf Y, Franssen H, van Dijk GW, Jennekens FG. Chronic idiopathic axonal polyneuropathy: a five year follow up. *J Neurol Neurosurg Psychiatry*. Dec 1994;57(12):1525-7. doi:10.1136/jnnp.57.12.1525
 23. Majersik JJ, Ahmed A, Chen I-HA, et al. A Shortage of Neurologists–We Must Act Now: A Report From the AAN 2019 Transforming Leaders Program. *Neurology*. 2021;96(24):1122-1134.
 24. Burton A. How do we fix the shortage of neurologists? *The Lancet Neurology*. 2018;17(6):502-503.
 25. Barohn R. Diabetic Neuropathy. *Decision Making in Pain Management*. 2006:82-83. Elsevier, Inc. 2nd.
 26. Barohn R. *Trigeminal Neuralgia*. 2nd ed. Decision Making in Pain Management. Elsevier, Inc; 2006:146-147.
 27. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *PM R*. Apr 2011;3(4):345-52, 352 e1-21. doi:10.1016/j.pmrj.2011.03.008
 28. Vinik A, Casellini C, Nevoret ML. Diabetic Neuropathies. In: Feingold KR, Anawalt B, Boyce A, et al, eds. *Endotext*. 2000.
 29. Fox CH, Vest BM, Kahn LS, et al. Improving evidence-based primary care for chronic kidney disease: study protocol for a cluster randomized control trial for translating evidence into practice (TRANSLATE CKD). *Implementation Science*. 2013;8(1):1-9.
 30. Tipton RM, Worthington EL, Jr. The measurement of generalized self-efficacy: a study of construct validity. *J Pers Assess*. Oct 1984;48(5):545-8. doi:10.1207/s15327752jpa4805_14
 31. Hayman B, Wilkes L, Jackson D. Journaling: Identification of challenges and reflection on strategies. *Nurse researcher*. 2012;19(3)
 32. Bartlett G, Antoun J, Zgheib NK. Theranostics in primary care: pharmacogenomics tests and beyond. *Expert Rev Mol Diagn*. Nov 2012;12(8):841-55. doi:10.1586/erm.12.115
 33. Bartlett MJ, Shephard EA. The integration and interpretation of pharmacogenomics - a comparative study between the United States of America and Europe: towards better health care. *Drug Metab Pers Ther*. Jun 1 2016;31(2):91-6. doi:10.1515/dmpt-2015-0044
 34. Corponi F, Fabbri C, Serretti A. Pharmacogenetics and Depression: A Critical Perspective. *Psychiatry Investig*. Sep 2019;16(9):645-653. doi:10.30773/pi.2019.06.16
 35. Purtzer MA, Hermansen-Kobulnicky CJ. Optimizing the Benefits of Self-Monitoring Among Patients With Cancer. 2016:
 36. Miller WL, Crabtree BF. Primary care research: A multimethod typology and qualitative road map. 1992;
 37. Burnard P, Gill P, Stewart K, Treasure E, Chadwick B. Analysing and presenting qualitative data. *British dental journal*. 2008;204(8):429-432.
 38. Hsieh H-F, Shannon SE. Three approaches to qualitative content analysis. *Qualitative health research*. 2005;15(9):1277-1288.
 39. Zia JK, Chung CF, Schroeder J, et al. The feasibility, usability, and clinical utility of traditional paper food and symptom journals for patients with irritable bowel syndrome. *Neurogastroenterology & Motility*. 2017;29(2):e12935.

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

40. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. Jun 9 2017;6:CD007938. doi:10.1002/14651858.CD007938.pub4
41. Raouf M, Atkinson TJ, Crumb MW, Fudin J. Rational dosing of gabapentin and pregabalin in chronic kidney disease. *J Pain Res*. 2017;10:275-278. doi:10.2147/JPR.S130942
42. Johnson P, Becker L, Halpern R, Sweeney M. Real-world treatment of post-herpetic neuralgia with gabapentin or pregabalin. *Clin Drug Investig*. Jan 2013;33(1):35-44. doi:10.1007/s40261-012-0030-4
43. Gordh T, Gordh TE, Lindqvist K, Warner DS. Lidocaine: the origin of a modern local anesthetic. *The Journal of the American Society of Anesthesiologists*. 2010;113(6):1433-1437.
44. Weinberg L, Peake B, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine: A review. *World Journal of Anesthesiology*. 2015;4(2):17-29.
45. Pergolizzi Jr JV. Improved Lidocaine Patch Adhesion Expands Treatment Options.
46. Gudín J, Nalamachu S. Utility of lidocaine as a topical analgesic and improvements in patch delivery systems. *Postgraduate medicine*. 2020;132(1):28-36.
47. Purcell A, Buckley T, Fethney J, King J, Moyle W, Marshall AP. The effectiveness of EMLA as a primary dressing on painful chronic leg ulcers: a pilot randomized controlled trial. *Advances in skin & wound care*. 2017;30(8):354-363.
48. Eijkenboom I, Sopacua M, Hoeijmakers JG, et al. Yield of peripheral sodium channels gene screening in pure small fibre neuropathy. *Journal of Neurology, Neurosurgery & Psychiatry*. 2019;90(3):342-352.
49. de Greef BT, Hoeijmakers J, Gorissen - Brouwers C, Geerts M, Faber C, Merkies I. Associated conditions in small fiber neuropathy-a large cohort study and review of the literature. *European journal of neurology*. 2018;25(2):348-355.
50. Persson A-K, Gebauer M, Jordan S, et al. Correlational analysis for identifying genes whose regulation contributes to chronic neuropathic pain. *Molecular pain*. 2009;5:1744-8069-5-7.
51. Brouwer BA, Merkies IS, Gerrits MM, Waxman SG, Hoeijmakers JG, Faber CG. Painful neuropathies: the emerging role of sodium channelopathies. *Journal of the Peripheral Nervous System*. 2014;19(2):53-65.
52. Chong MS, Libretto SE. The rationale and use of topiramate for treating neuropathic pain. *Clin J Pain*. Jan-Feb 2003;19(1):59-68. doi:10.1097/00002508-200301000-00008
53. Erdogan C, Yucel M, Akgun H, Kaskc T, Semai Bek V, Gokcil Z. Effects of topiramate on peripheral nerve excitability. *J Clin Neurophysiol*. Jun 2012;29(3):268-70. doi:10.1097/WNP.0b013e318257c0a0
54. Zuliani V, Rivara M, Fantini M, Costantino G. Sodium channel blockers for neuropathic pain. *Expert Opin Ther Pat*. Jun 2010;20(6):755-79. doi:10.1517/13543771003774118
55. Boyd A, Casselini C, Vinik E, Vinik A. Quality of life and objective measures of diabetic neuropathy in a prospective placebo-controlled trial of ruboxistaurin and topiramate. *J Diabetes Sci Technol*. May 1 2011;5(3):714-22. doi:10.1177/193229681100500326
56. Boyd AL, Barlow PM, Pittenger GL, Simmons KF, Vinik AI. Topiramate improves neurovascular function, epidermal nerve fiber morphology, and metabolism in patients with type 2 diabetes mellitus. *Diabetes Metab Syndr Obes*. Dec 6 2010;3:431-7. doi:10.2147/DMSOTT.S13699
57. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev*. Jun 24 2013;(6):CD010610. doi:10.1002/14651858.CD010610
58. Wiffen PJ, Derry S, Moore RA, Lunn MP. Levetiracetam for neuropathic pain in adults. *Cochrane Database Syst Rev*. Jul 7 2014;(7):CD010943. doi:10.1002/14651858.CD010943.pub2
59. Kashipazha D, Ghadikolaie HS, Siavashi M. Levetiracetam in Compare to Sodium Valproate for Prophylaxis in Chronic Migraine Headache: A Randomized Double-Blind Clinical Trial. *Curr Clin Pharmacol*. 2017;12(1):55-59. doi:10.2174/1574884712666170329094419

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

60. Reda HM, Zaitone SA, Moustafa YM. Effect of levetiracetam versus gabapentin on peripheral neuropathy and sciatic degeneration in streptozotocin-diabetic mice: Influence on spinal microglia and astrocytes. *Eur J Pharmacol*. Jan 15 2016;771:162-72. doi:10.1016/j.ejphar.2015.12.035
61. Rossi S, Mataluni G, Codeca C, et al. Effects of levetiracetam on chronic pain in multiple sclerosis: results of a pilot, randomized, placebo-controlled study. *Eur J Neurol*. Mar 2009;16(3):360-6. doi:10.1111/j.1468-1331.2008.02496.x
62. Dunteman ED. Levetiracetam as an adjunctive analgesic in neoplastic plexopathies: case series and commentary. *J Pain Palliat Care Pharmacother*. 2005;19(1):35-43.
63. Price MJ. Levetiracetam in the treatment of neuropathic pain: three case studies. *Clin J Pain*. Jan-Feb 2004;20(1):33-6. doi:10.1097/00002508-200401000-00007
64. Shaibani A, Biton V, Rauck R, Koch B, Simpson J. Long-term oral lacosamide in painful diabetic neuropathy: a two-year open-label extension trial. *European Journal of Pain*. 2009;13(5):458-463.
65. Rauck RL, Shaibani A, Biton V, Simpson J, Koch B. Lacosamide in painful diabetic peripheral neuropathy: a phase 2 double-blind placebo-controlled study. *The Clinical journal of pain*. 2007;23(2):150-158.
66. Wymer JP, Simpson J, Sen D, Bongardt S, Group LSS. Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens. *The Clinical journal of pain*. 2009;25(5):376-385.
67. Trouvin A-P, Perrot S, Lloret-Linares C. Efficacy of venlafaxine in neuropathic pain: a narrative review of optimized treatment. *Clinical therapeutics*. 2017;39(6):1104-1122.
68. Berry SM CB, Lee JJ, Müller P. Bayesian adaptive methods for clinical trials. Boca Raton, FL2011.
69. Gajewski BJ, Berry SM, Quintana M, et al. Building efficient comparative effectiveness trials through adaptive designs, utility functions, and accrual rate optimization: finding the sweet spot. *Stat Med*. Mar 30 2015;34(7):1134-49. doi:10.1002/sim.6403
70. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA*. Apr 28 2015;313(16):1619-20. doi:10.1001/jama.2015.2316
71. Gajewski BJ, Meinzer C, Berry SM, et al. Bayesian hierarchical EMAX model for dose-response in early phase efficacy clinical trials. *Stat Med*. Jul 30 2019;38(17):3123-3138. doi:10.1002/sim.8167
72. Brown AR, Gajewski BJ, Aaronson LS, et al. A Bayesian comparative effectiveness trial in action: developing a platform for multisite study adaptive randomization. *Trials*. Aug 31 2016;17(1):428. doi:10.1186/s13063-016-1544-5
73. May CR, Cummings A, Girling M, et al. Using normalization process theory in feasibility studies and process evaluations of complex healthcare interventions: a systematic review. *Implementation Science*. 2018;13(1):1-27.
74. Carlson SE, Gajewski BJ, Valentine CJ, et al. Assessment of DHA on reducing early preterm birth: the ADORE randomized controlled trial protocol. *BMC Pregnancy Childbirth*. Feb 13 2017;17(1):62. doi:10.1186/s12884-017-1244-5
75. Faseru B, Ellerbeck EF, Catley D, et al. Changing the default for tobacco-cessation treatment in an inpatient setting: study protocol of a randomized controlled trial. *Trials*. Aug 14 2017;18(1):379. doi:10.1186/s13063-017-2119-9
76. Gajewski BJ, Statland J, Barohn R. Using Adaptive Designs to Avoid Selecting the Wrong Arms in Multiarm Comparative Effectiveness Trials. *Stat Biopharm Res*. 2019;11(4):375-386. doi:10.1080/19466315.2019.1610044
77. Wick J, Berry SM, Yeh HW, et al. A novel evaluation of optimality for randomized controlled trials. *J Biopharm Stat*. 2017;27(4):659-672. doi:10.1080/10543406.2016.1198367

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard Joel

78. Gajewski BJ, Berry SM, Barsan WG, et al. Hyperbaric oxygen brain injury treatment (HOBIT) trial: a multifactor design with response adaptive randomization and longitudinal modeling. *Pharm Stat*. Sep 2016;15(5):396-404. doi:10.1002/pst.1755
79. Ahmad FS, Ricket IM, Hammill BG, et al. Computable Phenotype Implementation for a National, Multicenter Pragmatic Clinical Trial: Lessons Learned From ADAPTABLE. *Circulation: Cardiovascular Quality and Outcomes*. 2020;13(6):e006292.
80. Jones WS, Mulder H, Wruck LM, et al. Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease. *New England Journal of Medicine*. 2021;384(21):1981-1990.
81. Wolfe GI, Baker NS, Amato AA, et al. Chronic cryptogenic sensory polyneuropathy: clinical and laboratory characteristics. *Archives of neurology*. 1999;56(5):540-547.
82. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics*. 2009;42(2):377-381.

**PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE
SUMMARY STATEMENT
(Privileged Communication)**

Principal Investigator: Richard Barohn

Organization: The Curators of the University of Missouri

Project Title: Determining Best or Inferior Drug(s) Using an Adaptive Platform for Cryptogenic Sensory

Polyneuropathy (BEAT CSPN)

PCORI Funding Announcement: Phased Large Awards for Comparative Effectiveness Research

Review Cycle: Cycle 3 2021

Request ID: 24811

NOTE: PCORI's merit review process includes an initial online and an in-person discussion phase. All applications go through the online written critique phase, but only a subset of competitive applications continue to the in-person discussion phase.

Your Summary Statement below only contains written critiques from the initial online phase of the merit review process. Because your application did not advance to the in-person panel discussion, your application is not being considered for funding.

Online Reviewer Critiques

Reviewer 1:

Criterion 1: Potential for the study to fill important gaps in evidence

Strengths:

- This study proposed to address the problem of patients with chronic sensory polyneuropathy (CSPN) cared for in primary care including the ability of clinicians to recognize it, and the question of what the most effective non-opioid drug treatment is, considering a range of common effective options. (Moderate)
- Opioid drugs were used in 21% of CSPN patients at one site proposed for the trial, although whether they were indicated for CSPN per se was not clear. (Minor)
- Research from this study would have the potential to determine the relative effectiveness of 7 important therapies for CSPN. (Major)
- Findings will likely remain relevant and valuable given the proposed timeline. (Moderate)

Weaknesses:

Although pain is a very common aspect of CSPN, how the impact of CSPN ranks among the many problems prevalent in adults in primary care, and whether it can be effectively addressed at the patient level as a distinct problem (e.g., versus or in combination with other sources of pain) is unclear. (Moderate)

The authors indicate they polled primary care clinicians who confirmed unfamiliarity with key aspects the trial is intended to address. Details of the survey are not described. (Moderate)

Criterion 2: Potential for the study findings to be adopted into clinical practice and improve delivery of care

Strengths:

- The application has identified a range of appropriate end-users (payers, providers, patient advocacy groups) that have the potential to guide the application of and apply study findings. (Major)
- Although the applicant has not identified potential barriers to implementation, the study does include an effort to characterize these issues led by Dr. Anne Sales who will conduct qualitative interviews with "a sample of sites" (see Budget Justification). (Moderate)
- The applicant will be studying some factors that might affect adoption or reflect adoption potential (treatment side effects, benefits, whether the patient picks up the prescribed drug). (Minor)

Weaknesses:

- It's not clear how end-users have been involved in developing the specific questions posed by the trial, other than patients and providers who have been engaged in shaping the question and outcomes. (Moderate)
- The plan to conduct implementation focused qualitative work focused on barriers and facilitators and an "implementation map" is not integrated into the Aims of the study and the methods are not described in the Research Narrative, raising concern about how it will be executed and integrated into study activities. (Moderate)

Criterion 3: Scientific merit (research design, analysis, and outcomes)

Strengths:

- The study is primarily a comparative effectiveness study of 5+2 pharmacologic options for CSPN using a Bayesian adaptive design (Aims 1,2,3), and the Bayesian design is an elegant approach to improve the efficiency of the planned study. (Major)
- How the Bayesian design will be executed and how it may affect power estimates and improve study efficiency is very elegantly described. These provide confidence for the feasibility of Aim 1 analyses for primary outcomes. (Major)
- The patient population is all adults with an appropriate ICD diagnosis seen in either primary care or a neurology setting at 42 potential clinical sites. (Minor)
- The application adequately justifies and describes the primary and secondary outcomes of the study using validated patient-centered measures. (Major)
- Each of the pharmacologic comparator arms is adequately described and justified. (Moderate)
- Sample sizes and power estimates are provided for the Aim 1 comparative effectiveness trial and the primary outcome. (Major)
- The project timeline and milestones seem realistic. (Minor)

DCC:

- The DCC has overseen similar trials in the past that are highly related to the proposed design. (Major)
- How the DCC operates in relationship to other trial components and provides input to trial activities and management is described in the Leadership plan. (P 22)
- DCC activities related to data collection, reporting, and data quality monitoring for errors, omissions, and completeness are adequately described. (Moderate)
- How the DCC will manage adverse events and DSMB reporting is well characterized. (P 16) (Minor)

Feasibility phase:

- An extensive enumeration of the specific goals of the feasibility phase is provided (Section B, p.4) and summarized. (Table 9). These appear to be appropriate and necessary to execute the intended study successfully. (Moderate)
- It seems likely that the feasibility phase will support an adequate recruitment and enrollment strategy given the large number of existing salient diagnoses at the proposed 42 sites (as determined via PCORnet). (Moderate)

Weaknesses:

- The study indicates its framework is "comparative effectiveness" and also invokes Normalization Process Theory (NPT). However, it is unclear how either of these concepts, especially NPT, inform the thrust of the study. (Major)
- How patients and physicians will be approached, consented to, and enrolled in the context of the patient-physician encounter (given that patients are identified apparently pre-visit) and how information about their specific therapeutic randomization (which apparently is done by the Clinical Trials Management System via RedCAP – a system outside of the clinical record keeping) is communicated and executed, including the complexity of doing so across multiple possibly very diverse practices is not adequately described. This is particularly important given that clinicians are expected to order the medication to which their patients were randomized. (Major)
- A better description of the practice sites including their geography and the extent to which the patients represent the broader, diverse population of the United States would inform the generalizability of the study. (Moderate)
- The study is intended to educate primary care providers and improve their ability to identify CSPN (Aim4) Although the study will evaluate changes in the use of the relevant ICD code(s), there is no gold standard against which to understand if the study is actually improving clinician performance with regard to CSPN detection (the proposed measures are pre-post perceived self efficacy). This goal of the study is not well described including how many clinicians at how many sites may be targeted. (Major)
- Exploratory aim (Aim 5) focuses on heterogeneity of effects using genetic data to elucidate outcomes to the study arms. Among the exploratory aims, there is a very brief mention of using machine learning to develop a CSPN phenotype and characterize prevalence in clinicians' panels. The complex methods, time, and resources required to achieve this and how it will advance the study goals are not discussed. Although described in passing, it may be a crucial element in the study's strategy to create a gold standard against which the base population is defined (see Section H p.17). (Major)^[LS1]
- Exploratory Aim (Aim 5) uses NPT as a guiding conceptual framework for content analysis. NPT is typically used to understand provider / organizational implementation. In the case of the proposed study, NPT's sole application is described as guiding a content analysis of patient study journals. Of the three citations associated (36,37,73) the systematic review of NPT application explicitly excluded studies of patients and caregivers. It's not clear how NPT will be informative for this purpose. (Major)
- Some data will be collected at the point of care (p15) but a better description of how monthly assessments (Web based RedCAP), journals, and other relevant analytic data is collected would strengthen the study and understanding of its feasibility. (Moderate)
- The study intends to use ICD codes and also a machine learning informed electronic phenotype to determine eligible patients before potential encounters. How these two sources of enrollment affect study biases and generalizability is unclear – given that ICD codes may be more likely among severe cases, or among those seen by neurologists. Considering how to strike an equipoise on this and how it may affect generalizability and

application of the results would strengthen the study. (Moderate)

- It would strengthen the proposal to provide more specifics about the development of the final protocol and how the DCC contributes throughout that process. (Minor)

Feasibility phase:

- Some of the feasibility phase goals (e.g., developing and applying an electronic phenotype with machine learning) may require significant effort. More description of the specifics of the various activities, the participants, approaches, resources, timeline, and how they are integrated into the final protocol is needed. (Major)
- It is hard to assess the adequacy of the scope and duration of the feasibility phase given sparse detail. (Minor)
- The application does not sufficiently address potential challenges and how to address them in the feasibility phase. (Major)

Criterion 4: Investigator(s) and environment

Strengths:

- The Principal Investigators for the study have conducted a preliminary study with a similar goal and adaptive design that is likely to be highly informative of the comparative effectiveness aims (e.g., Aims 1-3) of the trial. (Major)
- The individuals responsible for leadership of engagement activities have appropriate experience working with diverse stakeholders, resources to support the proposed activities. (Moderate)
- The application describes the availability of and access to appropriate facilities and resources. (Minor)
- The three principal investigators have complementary expertise, one of whom (Waitman) is proposed as head of DCC. Dr. Pasnoor and Barohn have similar expertise but complementary roles which could be a strength given the complexity of executing the trial. (Moderate)
- The investigative team has the experience carrying out similar projects adequate to inform and guide the proposed plan of research. (Moderate)
- The leadership plan supports a governance and organizational structure appropriate to sustain the research including roles and responsibilities. (Major)
- The institutional support is appropriate for the proposed research and for the needs of the DCC. (Minor)

Weaknesses:

- The roster of investigators does not clearly include someone with expertise in the application of machine learning or in the production of electronic phenotypes. This expertise and these methods are critical to the success of the project as it will be used to identify study patients without an existing diagnosis. (Major)

Criterion 5: Patient-centeredness

Strengths:

- The application indicates that patients contributed to decisions about primary and secondary outcomes, and these are addressed in study plans. (Major)
- The study indicates that the seven treatment arms are all "common" therapeutic options. Two of these options reflect superior drugs from the PAIN-CONTRoLS study and will be cross informative. (Moderate)
- The feasibility phase includes plans to re-evaluate the proposed comparator choices including an assessment of "clinician acceptance." (Minor)

Weaknesses:

- How the feasibility phase will elicit and integrate input from multiple stakeholders in reassessing specific choices for the comparator arms is not clear. (Moderate)

Criterion 6: Patient and stakeholder engagement

Strengths:

- The proposed engagement approach which largely focuses on clinic level activities will support the goals of the full study, as will the broader involvement of stakeholders and their engagement in the evaluation and dissemination of study results. (Major)
- The proposed stakeholders are representative of important groups that will be impacted by the study and who can provide diverse perspectives on the research process. (Major)
- There are extensive engagement activities planned at both the patient and clinician stakeholder levels (Table 8, p.19) sufficient to inform and guide the research process. (Major)
- There are clear descriptions of the roles and contributions of the various investigators and how they will collaborate in decision making. (Major)

Weaknesses:

- None noted.

Please provide your overall comments

Please provide your overall narrative here. The narrative should be written in paragraph form and provide a summary of strengths and weaknesses that drove the overall impact score.

This study proposes to evaluate 7 common drugs used to treat cryptogenic sensory polyneuropathy (CSPN). Strengths of the study include the focus on primary care as well as neurology, the use of an efficient sophisticated adaptive trial design, the experience of the team in conducting a closely related preliminary study which is cross informative of the proposal, and the project revision which now includes a strong complement of diverse, engaged stakeholder. Concerns include that the other goals (e.g., educating primary care providers), and exploratory goals are not fully described in methods. One of the “exploratory goals” is the development of an electronic phenotype of CSPN which could be daunting and is otherwise not described, and yet its success is crucial in informing eligibility. A preliminary study of implementation is only described in the budget justification. The steps to be undertaken in the feasibility phase of the project are appropriate but not well described. In summary, this is a project of some merit, but there are concerns that the proposal does not reflect adequate detail for some crucial preparatory aspects.

Protection of Human Subjects (Scientist Reviewers):

Does the application have acceptable risks and/or adequate protections for human subjects?

Yes

Please provide comments related to human subjects protections, if any

Reviewer 2:

Criterion 1: Potential for the study to fill important gaps in evidence

Strengths:

- The authors have demonstrated the overuse of opiates in a painful condition that affects 5 million in the US and is often underdiagnosed. Moderate strength
- The authors have demonstrated that CSPN has rarely received attention from the pharmaceutical industry and thus there is a lack of FDA approval for the pharmaceutical management of CSPN. Moderate strength
- The findings should remain relevant in the proposed timeline. Moderate strength

Weaknesses:

- It's not clear that this additional PCORI study is necessary in addition to the recently completed PCORI study by the same authors with a similar design and target condition. Moderate weakness
- It's not demonstrated that additional options for medications are needed beyond those with already demonstrated efficacy. The author notes a gap in understanding of the diagnosis and management of CSPN amongst primary care providers. Their proposal to include an educational series is excellent and likely to fill a needed gap. However, it's not evident how the additional six drug comparisons will improve outcomes in reducing pain for these patients. Moderate weakness
- The scope and magnitude of the including six drug comparison arm is likely beyond what is needed to impact these patients more broadly. For example, the educational series they have proposed is likely to decrease opiate usage and improve pain reduction regardless of the additional comparative effectiveness trial. Moderate weakness

Criterion 2: Potential for the study findings to be adopted into clinical practice and improve delivery of care

Strengths:

- The authors have identified an impressive array of local and national stakeholders who have expressed interest in the outcomes. Moderate strength
- The authors have identified a broad range of methods to disseminate the research findings including national organizations. The authors are well positioned to disseminate the research findings. Major strength

Weaknesses:

- There needs to be increased identification of potential barriers to adoption and strategies. For example, a common barrier in pain is racial and gender bias. This is a barrier that should be addressed in all pain related studies especially ones in which the diagnosis is predominately subjective and does not rely on abnormal tests. Moderate weakness
- The authors have included payers in the study design. However, it is not clear what current barriers to payers exist or how this study will overcome those barriers. Minor weakness

- The authors have demonstrated that stakeholders are interested in the primary outcomes however it is not entirely demonstrated that clinicians or patients have expressed a strong interest in additional medication options instead of education and non-pharmaceutical approaches. Moderate weakness
- The exploratory arm regarding precision medicine is innovative and intriguing. More information is needed on how this could be disseminated and integrated into real world clinical practice. Minor weakness
- More information is needed on how the educational curriculum will be disseminated to general neurologists and primary care physicians. Minor weakness

Criterion 3: Scientific merit (research design, analysis, and outcomes)

Strengths:

- The DCC's planned activities, oversight of data, plans for parity are well thought out and adequate. Major strength
- The feasibility stage is adequately scoped in terms of timeline, enrollment, engagement, and outcomes. It's well thought out with background evidence to suggest a successful feasibility period. Major strength
- The research plan follows PCORI methodology and both study phases are reasonable in scope in terms of timeline, outcomes, and enrollment

Weaknesses:

- Major weakness includes a lack of clarity on who will be excluded based on their severity of CSPN, already "failed" medications, and co-morbidities such as unstable psychiatric disease or kidney stones. The study design implicates inclusion based on CSPN diagnostic criteria and exclusion based predominately on study participation factors. It's not entirely clear if patients will be excluded if they have tried and failed for example 5/6 medications. The randomization does not appear to take into consideration the clinician or patient preference or the patient's medical condition. There is likely to be a strong preference between for example topical lidocaine or vimpat (most primary care doctors have had little experience with vimpat and patients may prefer a non-oral method with less side effect potential) This may be determined during the feasibility stage but will affect the plan for randomization.
- A moderate weakness is the lack of clarity around out-of-pocket costs. Those who can not afford their medication will be considered a "quit" which will be included in the final calculation of results. This could contribute to a few problems. First, there may be inadequate access to all the study arms based on insurance coverage and socioeconomic status. The authors mentioned some money will be reserved for this but it's unclear how it will be used. Second, step therapy without evidence is a problem in the practice of medicine. If there are more "quits" in the more costly medication arms, the results will be skewed to show increased effectiveness/preference for less expensive medications. This does demonstrate real world outcomes in terms of access however it also potentially will confuse the outcomes. For example, if vimpat is quit frequently due to cost currently, this would not be relevant in the future once more generics are available and the price is lower.

Criterion 4: Investigator(s) and environment

Strengths:

- The investigator team and environment is a major strength of this study. The PIs and other study members have a proven record of collaboration and success. The broad range of experts in education development, PCP alignment, patient advisory, and neuromuscular specialists is impressive including the site PIs across the country. They have the experience necessary to make this study successful. The leadership plan and structure are clear, thorough, and appropriate.

- The DCC leadership, capabilities, roles, functions, experience are quite adequate for the study. There is adequate independence of the DCC with clear plans for managing disputes. Major strength

Weaknesses:

- None noted.

Criterion 5: Patient-centeredness

Strengths:

- The authors have demonstrated a clear and authentic engagement of outcomes that are important to patients and these are included in the outcomes for the study plan. Major strength

Weaknesses:

- More evidence is needed that patients' top challenging choices were more medication options. It's clearly stated that patients want pain control but it's not well stated how much of a gap is left with current options and that they wanted medications instead of non-pharmaceutical options. Minor weakness
- More evidence is needed to assess patients' willingness to accept the proposed comparators in terms of risks benefits and burden of time, inconvenience, out-of-pocket costs. As the authors have not finalized their six proposed arms, it is likely this will be done during the feasibility arm. This likely just needs to be more explicitly said in the feasibility phase. Minor weakness

Criterion 6: Patient and stakeholder engagement

Strengths:

- The proposed level of stakeholder support is appropriate and tailored to the study. The frequency of involvement for stakeholders and system partners is appropriate in the feasibility and full-scale study. Major strength
- There are clear descriptions of the roles and contributions of all study collaborators in decision making in ways that are relevant to their field of expertise and interest. Major strength
- The applicants are highly engaged with patient stakeholders with CSPN. Major strength

Weaknesses:

- It's unclear if the patient representation groups include those from underserved areas. Minor weakness
- More evidence of engagement and feedback from primary care clinicians is needed. The inclusion of primary care in this study is excellent and likely to contribute to a more widespread impact earlier in the disease. However, there is a significant gap in PCPs' knowledge of CSPN, diagnosis of CSPN, management of CSPN and most notably they are unlikely to be very familiar with many of the medications proposed. The education curriculum appears to have about 1-2 hours to learn more about these medications which may not be sufficient. More evidence of plans for primary care feedback on medication choices and educational needs is needed. Moderate weakness

Please provide your overall comments

Please provide your overall narrative here. The narrative should be written in paragraph form and provide a summary of strengths and weaknesses that drove the overall impact score.

The investigators are a strong diverse team of accomplished researchers with the experience necessary to conduct this large scale multi-site trial. Patient stakeholders have been clearly incorporated and the investigators have an established relationship with them and other relevant parties. Ultimately, however, it's not entirely clear that this large scale PCORI study is needed in addition to the PCORI study that the same team has recently completed. The applicants have not demonstrated a clear and important gap that remains especially as it's unclear how the demonstration of the previous "two winners" has impacted practice including the use of opiates. The partnership with education development experts and primary care physicians along with the proposed curriculum for improving the diagnosis and management of CSPN is admirable and has the potential for significant impact in increasing access to neurological care with adequate pain management while decreasing the use of opiates. However, it is unclear that additional medication options are needed in the PCP office beyond nortriptyline and duloxetine. Controlling chronic pain in the 5 million patients with CSPN is a highly important target, however, more evidence is needed that this gap in pain control will be served by an additional medication comparative effectiveness trial.

Protection of Human Subjects (Scientist Reviewers):

Does the application have acceptable risks and/or adequate protections for human subjects?

No

Please provide comments related to human subjects protections, if any

No, more evidence is needed that patient's co-morbidities will be considered when randomized to a medication arm, in addition protection for the increased risk of suicidal thoughts after starting medication needs to be more clearly addressed.

Reviewer 3:

Criterion 1: Potential for the study to fill important gaps in evidence

Strengths:

- **[Major strength]** The proposed study focuses on treatment options for painful cryptogenic sensory polyneuropathy (CSPN), previously referred to as idiopathic peripheral neuropathy, a condition that affects approximately 25% of the estimated 20 million people living with peripheral neuropathy in the United States. In the other 75% of cases, the cause of the neuropathy can be attributed to another health condition. Treatment for CSPN is challenging with limited knowledge of which treatment may be effective for which patient. To date, only one large comparative effectiveness study of medications used most often to treat CSPN has been published and it was conducted by the present research team with funding from PCORI. This study will compare a selection of non-opioid treatments — oral gabapentin, venlafaxine, topiramate, levetiracetam, and topical lidocaine — to begin to provide the evidence necessary to improve decision making and prescription options for CSPN for patients, clinicians, health systems, payers, and policymakers.

Weaknesses:

- None noted.

Criterion 2: Potential for the study findings to be adopted into clinical practice and improve delivery of care**Strengths:**

- **[Major strength]** The application clearly identifies interested stakeholders and potential end-users — neurologists, primary care physicians, patients, health system leaders, and payers — who have expressed interest in study findings. Key national stakeholders include the Foundation for Peripheral Neuropathy, American Academy of Family Physicians National Research Network, and the Greater Plains Collaborative (GPC) Clinical Research Network within PCORnet. Representatives of each stakeholder group are included in the study engagement and implementation plans of the study.
- **[Major strength]** Anticipated study findings will provide evidence-based information to help guide treatment decisions for clinicians, policymakers, and payers, as well as treatment recommendations provided by professional and patient advocacy organizations. Adoption of evidence-based treatment guidelines will improve the delivery of care for patients and result in better patient outcomes for those with CSPN.
- **[Major strength]** Study applicants have included a specific aim in the study designed to improve CSPN recognition by primary care professionals and neurologists and to support a need to select appropriate and effective non-opioid drugs for CSPN treatment. Educational content will be designed specifically for and presented to prescribing clinicians with the intent to address the under-diagnosis of CSPN and improve its treatment in the primary care setting.

Weaknesses:

- **[Moderate weakness]** The applicants of this proposal mention committee and several individual study partners who will be responsible for assessing and addressing barriers to study implementation and intervention adoption during the course of the study. However, the applicants do not clearly identify potential barriers to intervention adoption or strategies to address such barriers. A clear list of anticipated barriers and strategies to address those barriers would strengthen the proposal.

Criterion 3: Scientific merit (research design, analysis, and outcomes)**Strengths:**

- **[Major Strength]** Eligible patients with CSPN (or yet to be diagnosed CSPN) will be recruited from 30-60 primary care clinical practices or academic centers. Participants may also be recruited from neurology clinics. The estimated potentially eligible study participants (n=3000) to be screened suggest that enrollment of 600 participants is reasonable over a period of 4.5 years. Both the patient population and study setting(s) are appropriate to support the proposed research question.
- **[Moderate Strength]** The overall study plan for both phases is clear, well justified, and coherent. The application contains significant detail regarding each comparator. It also contains an in-depth justification for the analytic approach for the present study with a timeline and milestones that are realistic.
- **[Moderate Strength]** Activities to be completed during the feasibility stage of the study are clearly detailed, appropriate, and realistic based on the 9-month planned feasibility phase of the study.

Weaknesses:

- None noted.

Criterion 4: Investigator(s) and environment**Strengths:**

- **[Major strength]** The research team has recruited four investigators — Dr. Kimminau, Ms. Bensman, Dr. Pasnoor, Dr. Koopman — to lead engagement activities. Dr. Kimminau, an engagement facilitator, will take the overall lead on engagement. She will work with Ms. Bensman, the lead patient research partner, "to ensure that the patient and stakeholder voice is heard throughout the conduct of the study." Dr. Kimminau will work with and coach Dr. Pasnoor on strategies for engaging neurology clinicians and Dr. Koopman on engaging primary care clinicians. The application states that each of these investigators has experience in team science, working across disciplinary and specialty boundaries, and are excellent communicators/facilitators. Dr. Koopman has connections to the North American Primary Care Research Group. Dr. Pasnoor is connected to the national Muscle Study Group (over 1700 neurologists, many of whom conduct research). Dr. Kimminau has connections to local, regional, and national Practice-Based Research Networks through the National Research Network of the American Academy of Family Physicians and the national PCORnet Engagement Coordinating Center. Each of these professional connections will help to support study goals, levels of engagement, and opportunities for study result dissemination. These enlisted partners have the experience, resources, and time commitments necessary to ensure study success.

Weaknesses:

- **[Fixable weakness]** Stakeholder and patient engagement could be improved by including the lead patient research partner on the Steering Committee to ensure that the study remains patient-centered from the feasibility phase through implementation and dissemination.

Criterion 5: Patient-centeredness**Strengths:**

- **[Major Strength]** The primary outcome in this study is change in pain score. Study outcomes were chosen by people living with CSPN participating in focus groups who selected fatigue, sleep, pain interference, and self-reported impact of pain on daily life as secondary outcomes. Focus group participants also helped to select outcome measures, such as the fatigue PROMIS.
- **[Major strength]** Choosing an effective treatment for CSPN is difficult for patients and clinicians with so many options that may or may not work well. This study aims to "weed out" available medications that are ineffective, cause too many side effects, or surpass a patient's willingness to pay for their out-of-pocket cost. Study results will help inform decision making, improve medication management, and result in better patient-centric outcomes.
- **[Moderate strength]** This study includes an exploratory aim that involves collecting and analyzing genomic data from the 600 trial participants with the intent to find a correlation between certain genomic characteristics and treatment response. Study results have the potential to lead to the development of diagnostic tests to optimize treatment choice.
- **[Moderate strength]** Preliminary interviews of people who have peripheral neuropathy during proposal development led to the decision to use online options for self-reported outcomes data collection to reduce participant burden of attending clinic visits.

Weaknesses:

- **[Minor weakness]** The application is unclear as to whether researchers discussed specific comparators (medications), potential benefits and risks, and out-of-pocket costs with patients living with peripheral neuropathy during the pre-proposal focus group and interview activities. There is no clear indication that further discussion of these factors that might impact study participation will occur as part of the Patient Advisory Council during the feasibility stage of the study.
- **[Minor weakness]** The proposal details that the cost of each enrolled participant is \$7150 which will be paid directly to each site. The applicants also state that "We include budgeting funds to pay participants for their time and recognize their efforts needed to complete the study." However, there is no indication of how much and in what form each enrolled study participant will be compensated.

Criterion 6: Patient and stakeholder engagement**Strengths:**

- **[Major strength]** The proposal includes representatives from each stakeholder group — primary care clinicians, patients, advocacy organizations, and payers — most likely to be impacted by study results in the engagement plan. The research team will establish a Patient Advisory Council (PAC) to be led by patient research partner Janine Bensman. Each participating clinical site will recruit a patient partner to serve on the PAC. The research team will also establish a separate Stakeholder Advisory Council (SAC), the membership of which will include PCORnet CRN leaders, healthcare payers, national organization leaders, and a patient experience expert. During the feasibility phase of the study, researchers anticipate adding individuals to these councils to "encourage diverse voices."
- **[Major strength]** The proposed engagement strategy seems appropriate and tailored to this study while also being informed by experience gained from a previous PCORI-funded study conducted by the present research team. The application outlines clear planned engagement goals and activities for each stakeholder group — people living with CSPN, primary care clinicians, advocacy organizations, payers (Table 8).
- **[Major strength]** A three-pronged strategy for clinician engagement and recruitment is presented that will support study goals. As one of the goals of the study is to increase the awareness of and confidence in diagnosing and treating CSPN in the primary care setting, increased clinician engagement and participation in the study is important to ensure study success.
- **[Moderate strength]** The primary investigator and two co-PIs have worked closely together on previous research regarding CSPN. The application clearly outlines the roles and responsibilities for each investigator within the leadership plan for this study. The organizational chart demonstrates how key members of various stakeholder groups will interact with each other.

Weaknesses:

- **[Minor weakness]** Although the application provides for the establishment of a Patient Advisory Council and a Stakeholder Advisory Council, these councils will interact only with the overall PI Barohn. Members of the PAC or SAC groups, including patient or caregiver representatives, are purposefully not integrated into the leadership. It will be the responsibility of the study engagement lead to bridge among the Councils and the CCC to maintain ongoing dialog.

Please provide your overall comments

Please provide your overall narrative here. The narrative should be written in paragraph form and provide a summary of strengths and weaknesses that drove the overall impact score.

The proposed study — Determining Best or Inferior Drug(s) Using an Adaptive Platform for Cryptogenic Sensory Polyneuropathy (BEAT CSPN) — has many major and moderate strengths and very few minor weaknesses which drive an overall high impact score. This application is a resubmission and appropriate changes to the original proposal have been made based on previous reviewer critiques. An experienced team of researchers, who were instrumental in defining cryptogenic sensory polyneuropathy (CSPN) and who worked together to conduct a prior PCORI-funded comparative effectiveness research study of drugs used to treat CSPN, propose a study to compare the effects of six medications (not included in the first study) in the treatment of CSPN. Based on study design, results from both studies may be statistically combined to provide important information regarding the treatment of CSPN. Results from this study will improve treatment decision making for clinicians, patients, and caregivers who currently do not have clear guidelines for the treatment of CSPN. Identifying the non-opioid treatments that are more effective (or less effective) in treating CSPN will improve patient outcomes and clinician confidence in treatment recommendations. Stakeholder engagement plans are robust, particularly planned engagement with neurologists and primary care physicians. The study is highly patient-centered with study outcomes chosen by people living with CSPN participating in focus groups who selected fatigue, sleep, pain interference, and self-reported impact of pain on daily life as secondary outcomes.

A moderate weakness of the study is the lack of clearly identified potential barriers to intervention adoption or strategies to address such barriers. A clear list of anticipated barriers and strategies to address those barriers would strengthen the proposal. Stakeholder and patient engagement could be improved by including the lead patient research partner on the Steering Committee to ensure that the study remains patient-centered from the feasibility phase through implementation and dissemination. In short, this proposal presents a thorough plan for an important study the results of which have the potential to significantly improve patient quality of life and treatment guidelines for patients experiencing peripheral neuropathy of no known cause.

Protection of Human Subjects (Scientist Reviewers):

Does the application have acceptable risks and/or adequate protections for human subjects?

Please provide comments related to human subjects protections, if any

Reviewer 4:

Criterion 1: Potential for the study to fill important gaps in evidence

Strengths:

- CSPN affects 20 million people in the US, and its most common symptom is pain. Identifying effective, non-narcotic treatments for pain is important to patients, their family members, and providers. (Major)
- The proposed study aims to determine which drugs out of nortriptyline, duloxetine, gabapentin, topiramate, levetiracetam, lacosamide and venlafaxine and topical lidocaine - are most effective for reducing pain and improving quality of life in patients with cryptogenic sensory polyneuropathy (CSPN). (Major)
- The study will include two medications (nortriptyline, duloxetine) that were found to be effective in prior trial. (Moderate)

- In response to comments in the previous submission, the study now includes a topical medication as one of the comparators. This provides a wide range of possible treatments. (Moderate)

Weaknesses:

- The drugs examined have been used by patients/practitioners for years with various degrees of success. Thus, it is unclear if one "best" drug can be identified, and there is no description by how much one would expect the most effective drug to be. One should consider that this trial only provides average effectiveness, and it could be that certain populations may benefit from one drug over another. The adaptive trial design may not enable the identification of the heterogeneous effects, because some drugs may be dropped early on. (Moderate)
- There is no description of the expected correlation between the short-term outcome (90 days effectiveness) and the long-term outcome of up to a year. Are patients usually staying on the same medication, do they switch over time, at what rates, and does the effectiveness of the medication wear off over time. In addition, it is unclear if the study is powered to estimate long-term effects. (Moderate)

Criterion 2: Potential for the study findings to be adopted into clinical practice and improve delivery of care

Strengths:

- The application identifies the following end-users: patients who can benefit from receiving a better intervention, clinicians who would be informed of the findings, and a patient advocacy group that can inform patients of possible treatments and their effectiveness. (Major)
- The proposal includes multiple medications that were selected from multiple recommended lines of treatments. (Major)
- The study could inform stakeholders of the effectiveness of non-narcotic pain medication for CSPN patients. (Major)

Weaknesses:

- It is unclear what is the expected level of effectiveness and adverse effects of the "best" medication. This is important in order to balance between effectiveness and possible adverse effects and long-term use. (Moderate)
- The description of the adoption strategies is relatively limited. One would expect that because of the prior expertise of the researchers in the area, the adoption strategy would be more fleshed out. Specifically, it is unclear what the possible barriers to adoption are and what this proposal would do to change that. (Moderate)

Criterion 3: Scientific merit (research design, analysis, and outcomes)

Strengths:

- The proposed application is a randomized trial that overall adheres to the PCORI Methodology Standards. (Major)
- The Data Coordinating Center (DCC) would be involved in the development of the trial protocol, which includes the overall study design and the statistical analysis plan. The DCC will be involved in planning the feasibility phase and will be responsible for overseeing the data collection, data quality, and study reporting. Lastly, the DCC is headed by a biostatistician who has experience with Bayesian adaptive designs and will perform the statistical analyses for the full trial. (moderate)
- The project timeline and milestones are reasonable and are supported by prior experience with a similar type of

study. (Moderate)

- The application is using Bayesian adaptive trial to reduce the number of required participants. (Moderate)
- There are plans for the DCC to develop and provide infrastructure for centralized statistical analysis, data sharing, data collection, management, quality, analysis, reporting, and dissemination. Members of the DCC have extensive experience and have published in the area of adaptive Bayesian designs.

Weaknesses:

- in the full study, there seems to be a disconnect between the primary outcome and the "utility" used to drop medications arms from the trial. The utility penalizes arms in which there are more dropouts. If the main goal is to identify the best effective medication, this should be the criteria to drop arms from the study. However, if the goal is to have a composite outcome, then this should be defined as the primary outcome as well. (Major)
- The power simulations for the full trial are not fully justified. If I am reading the charts correctly, the expectation is for at least a 15% absolute increase in efficacy and a 12% reduction in dropout rates. First, it is unclear what is the origin of these effect sizes. Second, these are pretty significant effects, and one would expect that if there is a real equipoise between the different medications the effect sizes would be smaller. Third, it is unclear what the lowest effect size expected is and can be detected at 80% power (commonly used standard). Lastly, the origins of the baseline effectiveness and quit rates are not justified. (Major)
- The prior distributions that would be used for the "best" medications found in the previous trial in the full trial seem to use all of the information from the previous trial. This is appropriate if one expects the exact same population in both trials. However, variation in the population may influence the results, and because this prior is strong it may result in biased estimates with a finite number of participants. The justification for the prior should be more explicit and possibly weakened. (moderate)
- There is a very limited description of the HTE analysis for the feasibility and full trial, and it is unclear if one can be validly obtained with the proposed Bayesian design. Specifically, there may not be enough participants on the different arms to observe such differences. (Major)
- It is unclear what is the expected proportion of people who would not agree to participate in the study. The study does not describe how results would be generalized to the population if this proportion is large, because it is expected that those that do not enroll are different from those that do. (Moderate)
- in the full trial, the duration of each patient's participation, 3-6 months, may be appropriate but is not clearly justified. The proposal should explain what factors were considered when deciding that 3-6 months are sufficient for meaningful assessment of the primary and secondary outcomes. (Minor)
- There is no missing data protocol for the full and feasibility trials. It is unclear what methods would be used to address it. (moderate)
- Time is an important factor when considering a relatively long-term trial. The analysis plan does not describe how time would be accounted for in the analysis. (moderate)
- Open label trials may introduce bias in the analysis, especially when examining PROs. (minor)
- In both the feasibility and full trial, the quit rate and possible adverse events are not part of the analysis of the secondary outcome. These are important when choosing between medications. (moderate)

Criterion 4: Investigator(s) and environment

Strengths:

- The Principal Investigators and collaborators are well qualified to conduct this study. Both PIs have participated in large clinical trials and have the clinical, informatics, and managerial expertise to implement this study. (Major)
- The co-PIs have complementary expertise. Dr. Barohn is a clinician with experience in translational research and Dr. Waitman is an informatician with experience in conducting trials and managing a data center. (Moderate)
- The research team has adequate experience in conducting large complex clinical trials and members of the team

have received PCORI grants in the past. (Moderate)

- The leadership, governance, and organizational structures are adequate for this proposal and the Leadership Plan clearly delineates the investigator roles. (Moderate)
- The institutional support and the facilities available for the researchers seems adequate for the proposed research. (Major)
- The experience and capabilities of the DCC and its leadership are appropriate to the proposed study. (Major)
- The DCC investigators are members of the Department of Biostatistics & Data Science at the University of Kansas Medical Center. They are experienced in conducting and analyzing Bayesian adaptive trials. The DCC members would ensure effective data collection, processing, analysis, and reporting for the proposed study. The DCC statisticians also serve on the Data Safety and Monitoring Board (DSMB) which can facilitate the work of the DSMB via periodic reports. (Moderate)

Weaknesses:

- The roles of the two post-doctorates are not clearly defined. It seems that they are included for training them in translational research. This does not seem to be the overall goal of the study. Because of the significant budget invested in these personnel, their roles should be aligned with the project goals. (Moderate)
- The roles of the two graduate research assistants are not clearly delineated. In addition, it is unclear what is their expertise. Because of the significant budget invested in these personnel, their roles should be clearly defined (Moderate)

Criterion 5: Patient-centeredness

Strengths:

- The medications that will be examined provide challenging choices for patients in terms of effectiveness and possible adverse effects. (Major)
- The proposal describes a focus group comprised of CSPN patients that were conducted to examine their views of medication effectiveness and tolerability. (Major)
- The secondary outcomes include some patient-reported outcomes that would be important to patients in deciding between different medications. (Minor)

Weaknesses:

- The proposal does not discuss the relationship between the short-term outcome vs. long-term outcomes. Specifically, how correlated are the short-term outcomes with long-term outcomes and compliance with medication regimen. (Moderate)
- The proposal did not assess whether patients will consider out-of-pocket costs when deciding between medications. (Minor)

Criterion 6: Patient and stakeholder engagement

Strengths:

- The engagement approach is appropriate to the study with reasonable involvement of patients, providers, and payers. In addition, there are current plans on how to ensure that all stakeholders are engaged. (Moderate)
- The inclusion of a payer/insurer stakeholder is important to adoption of trial results. This is because there may be some differences in out-of-pocket payments for the different medications. (Major)

- There is a clear description of the role of the advisory committee, its participants, and the time that it would convene. (Moderate)
- Several non-patient stakeholders provided letters of support. The Stakeholder Advisory Council currently includes Lindsay Colbert (Executive Director for The Foundation for Peripheral Neuropathy), Vinit Nair (Government Research and Consortiums at Humana.), Mary Kay O'Connor who is an entrepreneur in the health system space, and Jonathan Curtright who is the CEO of MU Health Care. (Moderate)

Weaknesses:

- It might have been useful to obtain support letters from international organizations so that the results will have broader appeal. (Minor)
- Engagement of caregivers is limited, and not fully described. Because caregivers may be influenced by possible adverse effects or ineffectiveness of medications it is important to consider their input as well. (Minor)

Please provide your overall comments

Please provide your overall narrative here. The narrative should be written in paragraph form and provide a summary of strengths and weaknesses that drove the overall impact score.

This application proposes a clinical trial to compare 6 non-narcotic medications to treat pain due to Cryptogenic Sensory Polyneuropathy (CSPN). The primary outcome of the trial is the reduction of pain due to CSPN on a Likert pain scale at 12 weeks. Secondary outcomes include sleep disturbances, fatigue, quality of life, and clinician's knowledge of CSPN and experience.

The main strengths of the application are 1) The trial would attempt to identify the best medication for reducing pain among CSPN patients by comparing currently prescribed non-narcotic medications. 2) The trial identifies and receives support from clinicians and patients. 3) The application adheres to PCORI methodology standards. 4) The research team includes clinical, data management, and clinical trial implementation expertise. 5) The application presents results from a focus group on the outcomes that are important to CSPN patients. 6) The application is using a Bayesian adaptive trial to reduce the number of required participants.

The main weaknesses of the application: 1) The primary outcome that is examined is a short-term outcome, and its relationship to long-term outcomes is unclear. 2) There is a limited description of the HTE analysis, and it is unclear if one can be validly obtained with the proposed Bayesian design. 3) The power calculations in the study are not justified, and the effects that were examined are relatively large (15%). It is not clear what are the minimal effect sizes that can still be observed in the trial with high power. 4) There is no missing data protocol. It is unclear what methods would be used to address it. 5) The quit rate and possible adverse events are not part of the analysis of the secondary outcome. 6) It is not clear if there is a process to handle the possibly large number of individuals that will not agree to participate. 7) The roles of the two postdocs and the two grad students are not clear. 8) the decision to remove arms from the trial is not aligned with the primary outcome.

In conclusion, this is a strong application using Bayesian adaptive design to compare 6 possible medications for CSPN. However, it is unclear that the sample sizes would be sufficient to identify small but significant effects, and the ability of the trial design to generate estimates of heterogeneous treatment effects is limited.

Protection of Human Subjects (Scientist Reviewers):

Does the application have acceptable risks and/or adequate protections for human subjects?

Yes

Please provide comments related to human subjects protections, if any

Reviewer 5:

Criterion 1: Potential for the study to fill important gaps in evidence

Strengths:

- How best to treat cryptogenic sensory polyneuropathy, a common and often debilitating problem, is a question important to patients, clinicians, health systems, payers, and policymakers. (Major)
- The application provides data from a poll obtained by the Neuropathy Association that 87% of patients with neuropathy rated pain management as their greatest challenge. (Major)

Weaknesses:

- Even if the study is successful, it is unclear whether its results will help clinicians or health system decision-makers. Primary care physicians are noted to be unfamiliar with the term cryptogenic sensory polyneuropathy, its diagnostic criteria, and management. Given their lack of knowledge about cryptogenic sensory polyneuropathy and the plan for primary care clinicians to both diagnose and treat cryptogenic sensory polyneuropathy, it is unclear that study findings will be generalizable to the broader community of primary care clinicians and health systems, as it is unclear that primary care clinicians are interested in or willing to assume this work which has traditionally been under the purview of neurologists. (Major)

Criterion 2: Potential for the study findings to be adopted into clinical practice and improve delivery of care

Strengths:

- The applicant has identified local and national stakeholders, including The Foundation for Peripheral Neuropathy and United Healthcare as end-users of study findings. (Moderate)
- The applicant has identified potential barriers to intervention adoption including under-recognition of cryptogenic sensory polyneuropathy in clinical care, lack of neurologists to care for patients with cryptogenic sensory polyneuropathy, and uncertainty about non-opioid treatments for pain relief. The application proposes strategies to address these barriers. (Moderate)
- The applicant has identified resources that would promote intervention adoption, including training primary care clinicians to diagnose and manage cryptogenic sensory polyneuropathy. (Minor)

Weaknesses:

- No national primary care organizations are involved in the proposed project (e.g., American Academy of Family Medicine, Society of General Internal Medicine), which is important because the application aims to improve primary care clinicians' ability to care for patients with cryptogenic sensory polyneuropathy given the shortage of neurologists to care for patients with this problem. Although two members of the study team are involved

with the North American Primary Care Research Group, there is no letter of support from that organization. (Moderate)

- It is unlikely that the findings of the proposed study will inform decision-making for the identified key stakeholders due to concerns about study feasibility. The scope of work required during the feasibility phase is overly ambitious. It is unclear that primary care clinicians will participate in the proposed project because they will be asked to diagnose and treat a condition with which they are currently described as being unfamiliar and which is typically cared for by neurologists. In addition, they will be asked to prescribe medication that is uncommonly used in primary care. It is further unclear that primary care clinicians will translate knowledge gains during training to their clinical practice of medicine because they may not feel comfortable caring independently for patients with cryptogenic sensory polyneuropathy after only a brief training period and hospitals/health systems may consider caring for this condition beyond their scope of practice. (Major)

Criterion 3: Scientific merit (research design, analysis, and outcomes)

Strengths:

- The overall study plan for both phases is justified and coherent. (Minor)

Weaknesses:

- The application was partially responsive to reviewers' prior critiques. Among concerns that were not addressed, there remains a plan for participants to fill the prescribed study medication as they would any other prescription. Because insurance plans may not cover the prescribed medication (e.g., many insurance plans do not cover 5% lidocaine patches for cryptogenic sensory polyneuropathy) some medications will be more difficult to evaluate than others or will only be evaluative among patients who can afford them. (Moderate)
- While the patient population is appropriate for the planned study, it is unclear whether the proposed setting (neurology and primary care clinics) is appropriate because it is unclear that primary care clinicians are interested and willing to participate. Only a very few primary care clinicians have been recruited to participate in the proposed project so far. If insufficient numbers of primary care clinicians are willing to participate, the proposed project will not be feasible. (Major)
- The plan to train primary care clinicians to care for patients with cryptogenic sensory polyneuropathy and participate in the proposed study is extensive including how to 1) diagnose cryptogenic sensory polyneuropathy; 2) perform a neurologic examination for neuropathy; 3) learn about all of the non-opioid treatments for the treatment of painful cryptogenic sensory polyneuropathy; 4) offer non-pharmacologic therapies including relaxation, meditation, biofeedback, and spinal cord stimulation; and 5) counsel patients about their prognosis. It is unclear whether this training can be achieved within the needed time frame and that busy primary care clinicians have the desire or enough time to accomplish it. (Moderate)
- Anti-epileptic medications such as levetiracetam and lacosamide are infrequently prescribed by primary care clinicians. No data are presented that primary care clinicians will be willing to prescribe these medications, even after receiving additional training about them. (Moderate)
- The application seems to use the terms primary care and family medicine interchangeably. As a result, it is unclear whether or not the proposed project will include primary care practices (family medicine and general internal medicine) or whether it includes family medicine practices alone. (Minor)
- No general internists or advanced practice providers have been recruited to participate in the proposed project. Educational content developed by family physicians may not translate to general internists or advanced practice providers who also provide primary care. (Minor)
- The scope of work planned for the feasibility phase is overly ambitious, especially determining the comparators, outcomes, and analyses; identifying and training to participate primary care clinicians; assessment of clinician willingness to prescribe a randomly assigned medication and the potential need for protocol adjustment should clinicians be unwilling to do this. The project timeline and milestones are unrealistic, largely due to the scope of

work that must be accomplished during the feasibility phase. (Major)

Criterion 4: Investigator(s) and environment

Strengths:

- The personnel responsible for managing the engagement activities have the appropriate experience, resources, and time commitment to carry out the proposed patient and stakeholder engagement. (Moderate)

Weaknesses:

- None noted.

Criterion 5: Patient-centeredness

Strengths:

- The application includes a thorough description of the outcomes that are important to patients (especially pain, pain interference, fatigue, and sleep disturbance) and these outcomes are included in the study plan. (Major)
- There is a plan to refine the proposed comparators during the feasibility phase, including determining patients' willingness to accept them. (Moderate)

Weaknesses:

- Although many of the comparators represent challenging choices that patients confront, lacosamide is not commonly used for the treatment of cryptogenic sensory polyneuropathy so is not a choice typically available to patients. In addition, because 4% topical lidocaine is well tolerated and available over-the-counter and because many insurance plans don't cover 5% topical lidocaine for the treatment of cryptogenic sensory polyneuropathy, many patients trial topical lidocaine early in their treatment journey and so do not desire a prescription for it later. (Moderate)
- There is a plan to refine the proposed comparators during the feasibility phase, including determining patients' willingness to accept them. However, there is no clear plan to determine clinicians' willingness to accept the proposed comparators. (Moderate)

Criterion 6: Patient and stakeholder engagement

Strengths:

- The roles and contributions of all study collaborators in decision making are clear. (Major)
- The frequency and level of involvement of patients and non-clinician stakeholders is appropriate to support study goals. (Moderate)
- The proposed engagement approach is tailored to the study. (Moderate)

Weaknesses:

- General internists are lacking from the stakeholder team. This is important only if the applicant plans that the study will take place in the primary care setting (rather than exclusively in the family medicine setting). In order to ensure diverse perspectives throughout the research process, the study plan should include a larger number of practicing clinicians, ideally including those working at other institutions. This is important to ensure generalizability of study results, especially related to transitioning the care of cryptogenic sensory polyneuropathy to primary care clinicians. (Moderate)
- While the planned engagement activities are appropriate to assist in determining the acceptability of the comparators, randomization, and requirements of study conduct and participation for participants, there are inadequate engagement activities to determine the acceptability of the education activities, comparators, and requirements of study conduct and participation for primary care clinicians. (Major)
- The frequency and level of involvement of clinician stakeholders is insufficient to meet project goals. (Moderate)

Please provide your overall comments

Please provide your overall narrative here. The narrative should be written in paragraph form and provide a summary of strengths and weaknesses that drove the overall impact score.

The applicant proposes an open-label, pragmatic comparative effectiveness trial using an adaptive design of six different non-opiate medications for the treatment of cryptogenic sensory polyneuropathy in the neurology and primary care settings. How best to treat cryptogenic sensory polyneuropathy, a common and often debilitating problem, is a question important to patients, clinicians, health systems, payers, and policymakers. The applicant has identified and engaged local and national stakeholders. The application includes a thorough description of the outcomes important to patients and these outcomes are included in the study plan. The roles and contributions of all study collaborators in decision making are clear.

However, numerous moderate and major weaknesses dampen enthusiasm for the proposal. Given primary care clinicians' lack of knowledge about cryptogenic sensory polyneuropathy and the role that primary care clinicians play in the proposed project, inadequate data are presented that improving the diagnosis and treatment of cryptogenic sensory polyneuropathy among primary care clinicians is a priority for primary care clinicians and that they are willing to perform this work. Despite the goal to improve primary care clinicians' ability to care for patients with cryptogenic sensory polyneuropathy, no national primary care organizations are involved in the proposed project. Very few primary care clinicians have been recruited to participate in the proposed project, and all are family medicine physicians, most from a single institution. If insufficient numbers of primary care clinicians are unwilling to participate in the proposed project, it will not be feasible.

The plan to train primary care clinicians to care for patients with cryptogenic sensory polyneuropathy and participate in the proposed study is so extensive that it is unclear the training can be achieved within the needed time frame and that busy primary care clinicians have enough time to accomplish it. There is no clear plan to determine clinicians' willingness to accept the proposed comparators. No data are presented that primary care clinicians will be willing to prescribe anti-epileptic medications, even after receiving additional training about them. There is inadequate engagement of primary care clinicians to determine the acceptability of the education activities, comparators, and requirements of study conduct and participation to them.

The scope of work planned for the feasibility phase is overly ambitious. As a result, the project timeline and milestones are unrealistic. Overall, due to concerns about study feasibility primarily regarding the 1) ambitious scope of work required during the feasibility phase and 2) uncertainty that primary care clinicians will a) participate in the proposed project and b) ultimately translate any knowledge gains to their clinical practice of medicine, the impact of the proposed project is likely to be low.

Protection of Human Subjects (Scientist Reviewers):

Does the application have acceptable risks and/or adequate protections for human subjects?
Yes

Please provide comments related to human subjects protections, if any

Reviewer 6:

Criterion 1: Potential for the study to fill important gaps in evidence

Strengths:

- The proposal makes a compelling case that better care for CSPN is a worthy goal and that patients and physicians would benefit from having better information about which non-opioid medications are most effective and best tolerated. Treatment for CSPN is a pressing problem for patients and their providers, and the lack of information about treatment approaches is central to the problem. (Moderate)
- Results from the proposed study are likely to remain relevant for some time, at least until the field reaches a better understanding of both clinical efficacy and comparative effectiveness of the target medications and also their effectiveness in comparison to opioid medications and other treatment approaches. (Moderate)

Weaknesses:

- The proposal does not adequately establish that relative effectiveness and tolerability among non-opioid is the most critical question in order to advance CSPN care at this stage. It notes that each of the six target non-opioid medications is currently in use, but offers no substantiation of their clinical efficacy, no evidence that they work at least as well as opioids, and no evidence that they are superior to non-pharmaceutical approaches that are currently in use. Essentially, it proposes a comparative effectiveness study when basic clinical efficacy has not been established. Patients and physicians would still face a decision dilemma about how best to treat CSPN. (Major)
- The proposal does not show that it addresses a critical knowledge gap by citing guideline development efforts, systematic reviews, or other authoritative sources. (Minor)
- The scope and magnitude of the study are not well justified, given that the basic clinical efficacy of the medications studied would still not be established. (Moderate)
- The proposal includes a specific aim of improving CSPN care by primary care providers, but provides little justification that this is an established objective of primary care physicians, providers, and other important stakeholders, and does not offer substantial evidence of a related knowledge gap. Perhaps a knowledge gap is a barrier for primary care, but this is not established and other factors are not considered. (Major)

Criterion 2: Potential for the study findings to be adopted into clinical practice and improve delivery of care

Strengths:

- The proposal identifies a modest set of stakeholders who would be interested in applying the study findings. (Minor)
- Results from the proposed study would likely inform decision making by many individual patients and

neurologists. (Moderate)

- The proposal does identify some factors that might promote adoption, especially engagement of primary care physicians and establishing partnerships between neurologists and PCPs. (Minor)

Weaknesses:

- Results from the proposed study are not likely to change CSPN diagnosis and treatment by primary care providers, payors, or other stakeholders, particularly because questions about basic clinical efficacy would remain unresolved. (Moderate)
- The proposal provides little in the way of demonstrating that the proposed role of primary care in CSPN care would be adopted, nor identifying barriers or facilitators. (Moderate)
- The application does little in the way of identifying specific barriers to adoption or to strategies to address barriers. This is surprising given that the PI has completed a very similar previous study and should be quite familiar with barriers to the adoption of findings from that study. If there are no barriers it would be great to establish that and claim success; if there are barriers they should be noted and realistic strategies noted that could address them. (Moderate)
- The implementation study that addresses Specific Aim 4 is too small and too narrow to meaningfully affect CSPN treatment in primary care. The implementation component seems mostly oriented toward supporting the primary care practices that participate in the proposed research than in laying the meaningful groundwork for broad practice change in CSPN care or chronic pain care. Numerous attempts have been made previously to expand treatment of chronic pain conditions in primary care. These have met with limited success, suggesting that broad practice change is not likely to result from a modest implementation study associated focused on a single chronic pain condition. (Moderate)

Criterion 3: Scientific merit (research design, analysis, and outcomes)

Strengths:

- The overall study design – a Bayesian adaptive trial – is well-justified, appropriate, and relatively novel. This is a distinct strength of the proposal. (Major)
- The primary outcome, whether it is pain control effectiveness or "utility," is appropriate and justified. (Minor)
- Planned participation of the DCC in the final design and analysis seems reasonable. (Minor)
- The proposed data quality monitoring procedures are strong and are described in great detail. (Moderate)
- Some potential obstacles are identified and contingency plans addressed. (Minor)
- Enrollment estimates seem reasonable, although their justification would be stronger if better supported by data from the PI's previous CSPN study. (Minor)

Weaknesses:

- The proposal is not explicitly anchored on any conceptual framework. It asserts "the fundamental premise that effective treatment for... CSPN depends on expanding comparative effectiveness research." The importance of CER may be true but is not a substitute for a conceptual framework. (Minor)
- The research plan does not include a full set of rigorous methods that adhere to the PCORI methodology standards. Lack of specificity and rigor exists in the study population, the outcomes, the analysis plan, the power calculations, and at least one sub-study. Specifics are in separate comments. (Major)
- The study population is not adequately defined. The proposal references a "computable phenotype" that has not yet been developed. The proposal would be stronger if this had been addressed during proposal development, with data presented about the performance of the algorithm. Also, the proposal indicates a desire to enroll treatment-naïve patients – offered as a justification for including primary care clinics as study sites –

but does not identify the basis for this, does not establish treatment-naivete as an inclusion criterion, and does not specify subgroup analysis to show differential treatment effects between naïve and non-naïve patients. (Moderate)

- The justification for the inclusion of primary care clinics is far from strong. The proposal does make a good case that it would be beneficial to provide primary care clinicians tools for managing CSPN and other peripheral neuropathies. But that desire does not address the ability of primary care physicians to handle all the knowledge and skills necessary to participate in the trial, including (from p. 17): CSPN diagnosis, differentiating small- vs. large-fiber neuropathy, and knowledge of "non-opioid drugs plus all other treatment modalities for pain beyond those being compared" (p. 17). The proposal offers no substantiation that participating PCPs would be able to meet these expectations, which far exceed what would be needed for PCPs to treat CSPN once a treatment algorithm has been established. (Major)
- The proposal is inconsistent in designating primary and secondary outcomes. In some instances, the primary outcome is identified as pain control effectiveness 90 days after enrollment; in other instances, the primary outcome is identified as "utility," a function of both effectiveness and quit rates. In at least one instance, an adverse event rate is identified as the subject of analysis, but the adverse event rate is not listed as a primary or secondary outcome. Table 3, which shows proposed study outcomes, identifies the specific outcome measure for the pharmacogenomic study as "conduct genomic analysis," which is clearly not an outcome. The outcome measures must be clearly defined and the use of each must be clearly and consistently defined. (Major)
- The comparators are not sufficiently justified. The drugs to be studied are shown in Table 2 and their pharmacology is reviewed in the text, but no information is provided about the current frequency of use or about efficacy (demonstrated or expected) in the study population. Thus the proposal does not substantiate that the comparator arms are efficacious and in widespread use. Further, Table 2 shows several other medications currently used for the treatment of CSPN that are not included in the proposed study, with no specified rationale for why some were included and others not. (Major)
- The analytic plan is minimal (1 paragraph, see sec. E), well short of PCORI methodology standards in terms of substance and specificity. (Major)
- Planned HTE analysis is thin. Most importantly, it does not specify assessing HTE by fundamental clinical characteristics such as treatment history and concurrent use of opioid or non-pharmacologic therapies. Instead, it specifies only simplistic HTE by demographic characteristics. (Moderate)
- The proposal provides no real power calculations and no anticipated effect sizes. The hypothetical "scenarios" shown in Table 5 are unrealistic, in that the best medications have both the highest effectiveness and the lowest quit rates. A different but equally feasible outcome is that the drug with the highest effectiveness will have other-than-lowest quit rates. (Major)
- The implementation study (Specific Aim 4) is relatively narrow and small, with methods that are not presented in significant detail. (Minor)
- The autonomy and independence of the DCC are not strongly justified, particularly both in the same institution and with interlocking reporting relationships. The proposal contains minor indications that the DCC and CCC will not be autonomous, such as: "[the PI] and other clinician co-investigators, engagement leader, and lead statistician ... will direct the CCC" (p. 16). (Minor)
- The accountability of the DSMB is not clear. The proposal indicates that the DCC will provide reports to the DSMB but does not indicate who will convene or lead the DSMB. The DSMB is not shown at all on the organizational chart (Figure 5). (Moderate)
- Several feasibility phase activities indicated in Table 9 (Summary Feasibility Phase Activities) would best be completed in the course of proposal development (e.g. assess clinician acceptance of comparators, refine pharmacogenomics data and analytic plan, determine primary, secondary, and exploratory analyses to finalize Statistical Analysis Plan, determine power, etc.). Table 9 also designates as a feasibility phase activity "identify 'winner' and 'loser' medications for pain control effectiveness," which is properly the focus of the full-scale trial. (Moderate)
- Overall, the current proposal combines without rational distinct functions – establishing comparative effectiveness and comparative adverse events, developing treatment algorithms, and practice implementation – that are typically addressed sequentially, for good reason. In particular, the proposal includes in its scope the development of treatment algorithms and EHR clinical decision support tools, activities that would be more

appropriately tackled in a separate project after clinical efficacy and comparative effectiveness (if any) have been determined and after an authoritative group has developed clinical guidelines based on both the proposed research and other relevant evidence. (Major)

Criterion 4: Investigator(s) and environment

Strengths:

- The investigators and collaborators are well qualified and experienced in all key areas. (Moderate)
- The investigative team has experience leading studies of comparable size, scope, and complexity. (Major)
- The personnel who will manage the engagement activities have relevant experience and have reasonable resources and time commitments. (Moderate)
- The application demonstrates adequate availability of facilities and resources. (Moderate)
- The application demonstrates institutional support from key institutions. (Minor)
- The DCC and DCC leadership have appropriate experience and capabilities. Their previous experience with managing Bayesian adaptive randomization and analyzing results are solid strengths. (Major)
- The application cites established DCC policies and practices that will contribute to maintaining data quality, privacy, and security. Practices described in the application - such as "dress rehearsals" and lessons learned sessions - are a plus. (Moderate)

Weaknesses:

- The proposal is ambiguous regarding whether or not it includes a dual PI structure. The research plan describes Dr. Waitman as a "co-PI" rather than a "dual PI" (p. 9), which has a different meaning for PCORI proposals. It nowhere identifies Dr. Waitman, the DCC lead, as a dual PI. The organizational structure chart (Figure 5) identifies Dr. Barohn as "Lead, Contact, and Overall PI." The proposal needs to be unambiguous and consistent in defining the leadership roles and structure and should provide justification if a dual PI structure is not intended. (Moderate)
- The proposal is inconsistent regarding the leadership of the DCC. For example, p. 16 states both "Dr. Waitman will lead the DCC" and "Dr. Gajewski is the PI of the BEAT-CSPAN DCC." Perhaps there is some fine distinction here or unintentional representation, but clarification is needed. (Minor)

Criterion 5: Patient-centeredness

Strengths:

- The proposal provides a solid rationale and previous evidence of their importance to patients for the primary outcome (pain control) and several secondary outcomes (including sleep, fatigue, and pain interference). The research team has very strong previous experience with these outcomes. (Major)
- The proposal provides strong substantiation that CSPN patients face challenging choices about treatment for their condition, that they would prefer non-opioid medications, and that the non-opioid medications included in the study are among the alternatives for patients and their providers to consider. (Major)
- The team's successful previous experience with an earlier PCORI-funded trial of oral medications for CSPN suggests that patients and clinicians accept the comparator arms and randomization to the medication arm. It would have been good to cite data from that earlier trial as evidence of willingness to accept the comparators. (Moderate)

Weaknesses:

- The proposal states, in identifying the patient-centered problem to be addressed: "Of grave concern is use of opioids," but does not include opioid use as an outcome and the protocol (specifically disallowing narcotic tapering for enrolled patients) prevents any assessment of opioid use reduction as an outcome. (Minor)
- The proposal gives little attention to the reality that some of the medications to be studied have side effects that some patients dislike sufficiently that they decline use. The proposal provides an extensive review of the pharmacology of medications to be studied but provides little or no information about their tolerability to CSPN patients. (Minor)
- The comparators to be studied do not represent the full range of choices patients confront. In addition to oral medications, patients also face choices to use topical medications, neurostimulators, exercise, and perhaps dietary or behavioral regimens, or none of the above. No data are provided regarding patient preferences for oral medication or other treatment modalities, alone or in combination with medications. (Moderate)

Criterion 6: Patient and stakeholder engagement

Strengths:

- The proposed engagement approach is generally appropriate and builds on engagement the investigators have used in previous studies. The proposal provides examples of stakeholder contributions that have been incorporated into the current proposal. (Moderate)
- The identified stakeholder groups are generally representative of the groups most likely to be impacted by the study question - patients and their clinicians - and engagement in each category is already underway. (Moderate)
- The planned engagement activities are adequate for determining the acceptability of the study to patients. (Moderate)
- The roles and expected contributions of all collaborators are clear and appropriate. (Moderate)

Weaknesses:

- Patient preferences are typically a significant driver in deciding on treatment for chronic pain, including patients' preferences for/against opioid medications, for/against non-opioid oral medications, and for/against non-pharmacologic therapies. The patient engagement should assure that patient advisory council includes patients with a full range of typical preferences. (Minor)
- Plans are light for meaningful engagement of groups representing primary care clinicians, beyond intended research partners, given that education and support for primary care clinicians is a Specific Aim of the proposal. The proposal provides little or no indication of engagement from primary care professional associations or from the primary care leaders of major health systems. (Minor)

Please provide your overall comments

Please provide your overall narrative here. The narrative should be written in paragraph form and provide a summary of strengths and weaknesses that drove the overall impact score.

The proposed study would assess optimal non-opioid medication for the treatment of cryptogenic sensory peripheral neuropathy (CSPN). This is important because there are many CSPN patients, the condition causes substantial morbidity and disability, and CSPN-specific evidence regarding optimal medication is currently lacking. The study would build on a previous PCORI-funded comparative effectiveness trial of four non-narcotic medications. It includes an admirable specific

aim of enabling primary care physicians to treat CSPN.

The core of the proposal is a multi-arm comparative effectiveness trial, with justified Bayesian adaptive randomization to maximize the chances of identifying one or more superior medications among those tested. The research team has strong expertise and experience, including their completed PCORI-funded trial.

Despite some strengths, the proposal has several major weaknesses, including: The comparator arms are not well justified, with the medications' basic clinical efficacy for treatment of CSPN not established, no clear rationale for the inclusion of some medications and not others, and no inclusion of non-pharmacologic treatment modalities that are currently part of patients' and clinicians' decision dilemma. Reduced opioid use is identified as a "grave concern" for patients but is specifically excluded as a study outcome. The analysis plan is minimal, well short of what could be reasonably expected for a study of this scope and magnitude. No real power calculations or anticipated effect sizes are provided. The proposal defers to the feasibility phase several activities that would have been better addressed during proposal development, such as the development of the "computable phenotype" that will be used to identify eligible patients, and is overly ambitious in including implementation support for embedding in primary care practices a treatment algorithm that does not yet exist. The proposal gives little attention to significant barriers that must be expected if primary care physicians are to treat CSPN. The CCC and DCC are both in the same institution, without an adequate explanation of how independence and autonomy would be maintained.

The proposal is a resubmission. The resubmission fixes a very serious problem in the initial submission – by dropping tramadol, which reviewers expected to yield to quicker pain relief than other study medications together with side effects over time, potentially resulting in problems with results interpretation and Bayesian randomization – and increases representation of selected primary care clinicians as study partners, but it falls short in leaving several major concerns unaddressed.

Successful completion of the study would extend previous comparative effectiveness research on non-opioid medication for CSPN, narrowing the choice set in patients' and clinicians' decision dilemma. However, a significant decision dilemma would remain for patients and their clinicians, in the form of medications and non-pharmacologic treatment options that are outside the scope of the study. The aim of making CSPN readily treated in primary care is admirable, but the study, even if it results in a new treatment algorithm, is unlikely to produce much change in primary care practice regarding treatment of CSPN because many implementation factors would remain unaddressed.

Protection of Human Subjects (Scientist Reviewers):

Does the application have acceptable risks and/or adequate protections for human subjects?

Yes

Please provide comments related to human subjects protections, if any

- The proposal minimizes the potential for medications tested to cause adverse events or other harms. It states, "Each medication being studied have a potential to cause physical risk, but these risks are small," but provides no quantitative information or further justification. Risk of adverse events from medications prescribed per study protocol constitutes a potential risk to human subjects, and as such should be meaningfully assessed and managed.
- The study protocol specifically bars opioid tapering during the first 90 days of study enrollment, when primary and several secondary outcomes would be measured. Barring narcotic tapering that might otherwise occur should be treated as a potential risk to human subjects, and as such should be assessed and managed.