Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTRoLS)

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Version 1.4

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A. Abstract:

Peripheral Neuropathy affects over 20 million Americans. Some neuropathies are secondary to readily identifiable causes, with diabetic sensory polyneuropathy being the most common cause in the United States. Once known causes are excluded, approximately 25 to 50% remain idiopathic and are referred to as cryptogenic sensory polyneuropathy (CSPN). This usually affects people over the age of 50.[1]Neuropathic pain is a presenting symptom in 70-80% of CSPN. According to a poll obtained by the Neuropathy Association, 87% of patients rated pain management as the most challenging in managing their neuropathy. Currently there have been no prospective trials performed in the large CSPN group.

The overall objective of this trial is to determine which pharmaceutical therapy is most effective and causes the fewest side effects in CSPN. To do this comparative effectiveness study, we will use an adaptive design model.

Specific Aim 1: Determine which drug is most effective in producing pain relief and improving quality of life in patients with CSPN. We will perform a prospective randomized comparative effectiveness adaptive design study in neuropathy patients with pain who do not have diabetes and for whom no other cause has been found. The four drugs we will use are nortriptyline, duloxetine, pregabalin and mexiletine.

Specific Aim 2: Determine which drug has the fewest and which has the most side effects. We will use the MedDRA adverse event coding system and the number of dropouts due to side effects.

B. Prevalence, Background:

Prevalence:

Cryptogenic Sensory Polyneuropathy (CSPN) is a common but under recognized and understudied condition that is debilitating due to pain [(1)]. It is estimated that ~20 million people in the United States have peripheral neuropathy (PN), with an annual cost to Medicare exceeding $3.5 billion [(2)].

Background:

Many peripheral neuropathies are secondary to identifiable causes, such as diabetes, alcohol abuse, medications. However, once known etiologies are excluded, at least 25% of neuropathies remain idiopathic [(3-4)]. We refer to these as CSPN [(1, 3-7)]. The onset is usually in the sixth and seventh decades of life. The mean age of patients in prior published series ranges from 51 to 63 years old.[1,6,12] Prior reports describing CSPN have used other terms such as idiopathic neuropathy or small fiber sensory peripheral neuropathy, but we prefer CSPN. The diagnostic criteria for CSPN have been established by Wolfe et al [(6)]. One recent study of peripheral neuropathy, which tested for impaired glucose tolerance and celiac disease in patients with abnormal skin biopsy findings, found 50% to be idiopathic[(8)]. Our retrospective review of databases from two North American (NA) and one South America (SA) tertiary neuropathy clinic showed that CSPN represented at least one-fourth of all referred PN patients and is the most common form of neuropathy evaluated at these sites (Table 1)[(7)].

Table 1. Total number of PN cases in six major categories [7]

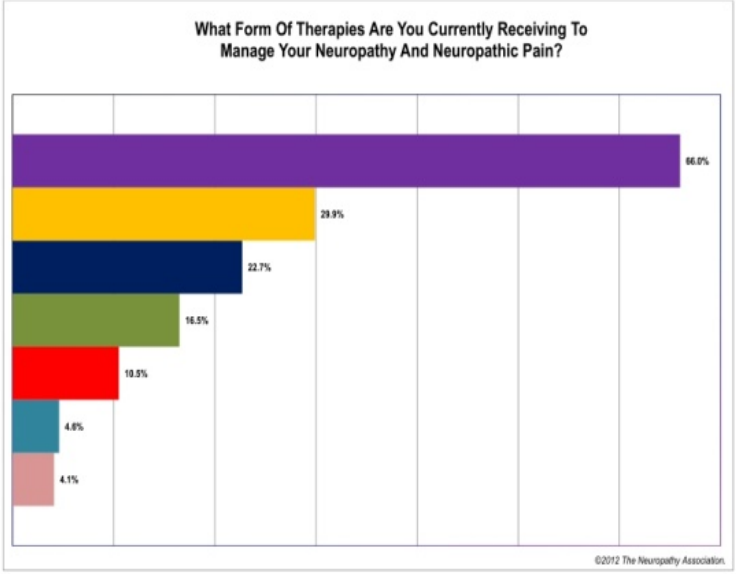
Major category	*NA # of pts (%)*	*SA # of pts (%)*
Total # of cases	1090	1034
Immune mediated	215 (19.7%)	191 (18%)
Diabetic	148 (13.5%)	236 (23%)
Hereditary/degenerative	292 (26.7%)	103 (10%)
Infection/inflammation	53 (4.8%)	141 (14%)
Syst./metab./toxic (Non-diabetic)	71 (6.5%)	124 (12%)
Cryptogenic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

In 2009, the National Chapter of the Neuropathy Association polled 1,000 members asking what form of neuropathy they had. Fifty-two percent described their neuropathy as idiopathic [9]—twice what the academic institutions found based on referrals—which might understate the actual frequency of idiopathic (cryptogenic) neuropathy. Regardless, 5 to 10 million people (25 to 50% of all neuropathies) in the US have CSPN. Clearly CSPN is a common, but under recognized and understudied condition.

CSPN is usually diagnosed on the basis of pain, 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 and geographic regions. The most common symptoms are pain (54% to 100% of patients), sensory loss (86%), and paresthesia (86% to 100%) [1, 5, 6, 10-13]. Lower extremity symptoms usually precede upper extremity symptoms [6, 10]. Approximately one-third to one-half of patients will have symptoms confined to their lower extremities [10, 13]. The average time for symptoms to spread to the upper extremities appears to be about 5 years [10]. Worsening of sensory symptoms with heat exposure, activity, or fatigue is commonly reported [13].

Genetic testing is not generally indicated in CSPN. However, recently a mutation in a gene for peripheral nerve sodium channel was discovered in 8 of 28 (29%) patients with CSPN [14]. While this finding has not been confirmed in a larger population, it is intriguing and may explain why some neuropathy patients with pain respond well to drugs that block sodium channel conductance in peripheral nerves.

As reported in the May 2012 National Neuropathy Association newsletter, out of 1,922 people polled, ~66% of those with neuropathy currently receive some form of treatment for their pain (Figure 1) [15] and ~87% view pain management as the most challenging aspect of their neuropathy (Figure 2) [15].



Neuropathic pain medications (e.g., pregabalin, gabapentin, duloxetine, amitriptyline, opioids)

I do not receive any treatments for pain relief

Complementary therapies (e.g., vitamin supplements, acupuncture, TENS unit)

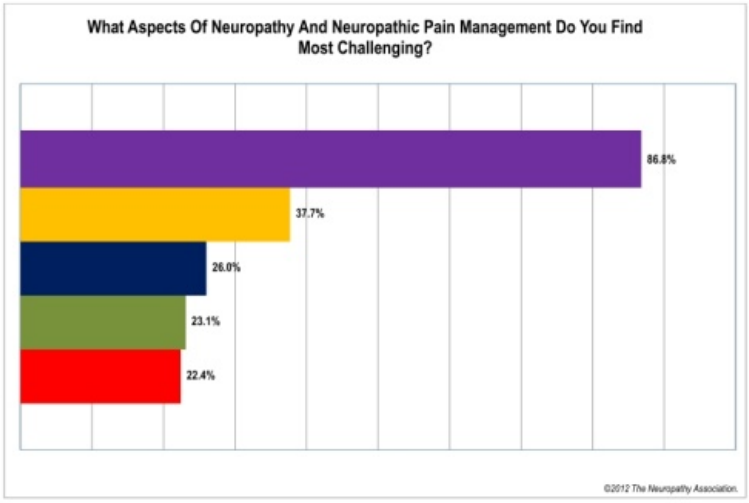
Topical medications (e.g., lidocaine patch, capsaicin)

Rehabilitative therapy (e.g., physical therapy, occupational therapy)

Intravenous immunoglobulin/IVIG, plasmapheresis

Interventional therapies (e.g., local anesthetic blocks, spinal neurostimulators, intrathecal pumps)

Figure 1: Forms of therapies currently receiving [15]



Controlling my sensory neuropathy symptoms (e.g., numbness, tingling, neuropathic pain, shooting pains, impaired balance, loss of sensations, hypersensitivity to sensations)

Controlling my motor neuropathy symptoms (e.g., weakness in the arms and legs, muscle wasting, lack of coordination)

Finding the right healthcare specialists to manage my pain

Understanding how my neuropathic pain is treated and managed

Controlling my autonomic neuropathy symptoms (e.g., dry skin to due to lack of sweating or excessive sweating; lightheadedness; urinary discomforts; gastrointestinal discomforts; and sexual dysfunction)

Figure 2: Most Challenging Aspects of Neuropathy and Pain Management [15]

We recently asked 38 of the 161 patients with CSPN who are in the neuromuscular division database at the University of Kansas Medical Center to rate their symptoms of pain, numbness, tingling, weakness, and poor balance from 1 to 5, with 1 being the most important and 5 being the least important. Approximately 63% rated pain as either the most or the 2nd most important symptom. In contrast, we surveyed patient with neuropathy due to Guillain–Barré syndrome and Chronic Inflammatory Demyelinating Polyneuropathy at a recent Guillain–Barré syndrome/Chronic Inflammatory Demyelinating Polyneuropathy support group meeting in Kansas City on June 29, 2013 and only 33% rated pain as most important. For those patients, weakness and loss of balance were rated as most important.

The goal of this research project is to find the best drug for the treatment of pain in patients with CSPN. While the pharmaceutical industry has focused attention on drugs for

treating diabetic sensory neuropathy (DSPN), and two drugs are now FDA approved, there have not been any prospective trials in CSPN. And, because there are no studies with CSPN patients, insurance carriers often reject authorizing prescriptions for some drugs for patients with CSPN. Additionally, while recommendations from diabetes associations and neurologists for treating DSPN [16-17] exist, no information is available to guide physicians and patients in treating CSPN. **Therefore, we propose conducting a comparative effectiveness prospective study using drugs commonly prescribed by physicians when caring for CSPN patients in order to identify the best therapy for CSPN.** Scientifically establishing a treatment for CSPN will substantially improve care and outcomes for these patients.

Most randomized, controlled pharmacologic studies in neuropathic pain have evaluated antidepressants and anticonvulsants. Prospective randomized controlled clinical trials in neuropathic pain using placebos share a number of challenges and shortcomings. The response to placebo is considerable, typically observed in one-third [18-19] and at times in more than one-half of patients [21]. Although statistically significant differences may be demonstrated between active treatment and placebo groups, the actual clinical benefit of a 1- or 2-point drop on an 11-point Likert-type scale for pain intensity is debatable. And, although they provide objective data, neurophysiologic outcome measurements have not been helpful [22].

Another consideration for U.S. clinicians is that labeled indications in the U.S. are limited to duloxetine and pregabalin for painful diabetic neuropathy; carbamazepine for trigeminal neuralgia; and gabapentin, pregabalin, lidocaine, and high-dose capsaicin patches for postherpetic neuralgia. Some countries permit more liberal indications that cover neuropathic pain in general, whereas others require labeling for only specific forms of painful neuropathy [20, 23]. In the United States this seems to vary based on the insurance carriers. Some carriers deny the use of a neuropathic pain drug if it is not one of the two FDA approved drugs for diabetic neuropathy patients.

For this study, we will use two drugs that are FDA approved for diabetic peripheral neuropathy (**pregabalin** and **duloxetine**) and two drugs (**mexiletine** and **nortriptyline**) that are often used in U.S. clinics to treat painful peripheral neuropathy. We will not use a placebo group in this comparative effectiveness study. Below we discuss these drugs; further rationale for choosing these is provided under Criterion 3.

Nortriptyline

Nortriptyline is a tricyclic antidepressant. Tricyclic antidepressants presumably exert their analgesic effect by modulating voltage-gated sodium channels and by inhibiting the reuptake of biogenic amines, norepinephrine and serotonin. They are the most extensively studied agents for neuropathic pain, especially in diabetic neuropathy [31-32]. Efficacy for the different tricyclics is roughly similar [33-34]. We selected nortriptyline because, in general, nortriptyline is preferred by our clinical experts as it has fewer side effects than the older drug, amitriptyline. The recommended daily dose for treatment for pain ranges from 75 mg to 200 mg. Tricyclics have been effective in relieving pain in both depressed and non-depressed patients, with an analgesic action independent of mood alteration and clinically evident as early as 1 to 2 weeks [35-36].

Duloxetine

Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI). Selective serotonin reuptake inhibitors (SSRIs and SNRIs) are most commonly used as antidepressants. In general, however, they have been less effective than tricyclic antidepressants in controlled studies of neuropathic pain [22, 33, 37]. The exception has been duloxetine which was released in the fall of 2004 as the first FDA-approved agent for treatment of diabetic peripheral neuropathic pain. Its analgesic effects are believed to be related to potentiation of descending pain inhibition by blocking serotonin and norepinephrine reuptake. Duloxetine has a higher, more balanced affinity at these transporter sites than do prior generations of antidepressants. In several diabetic neuropathy trials, delayed-release duloxetine at doses of 60 and 120 mg/day was more effective than placebo in reducing pain severity scores, with significant improvement seen as early as one week [38-39]. The target for improvement in these studies was a 50% reduction in pain. A lower 20 mg/day dose was not effective. Patients with major depression were excluded from studies. The 120 mg/day dose was no more effective than 60 mg/day and caused more side effects. Significant improvement in several secondary outcomes also was observed, including night pain severity, the SF-MPQ, and a brief inventory on the effects of pain on daily activities and mood.

The main adverse events were nausea, which tended to occur in the first week and last ~6 days, somnolence and dizziness. Approximately 15% of patients in the duloxetine arms (groups) dropped out due to adverse events. Contraindications include hypersensitivity, use of monoamine oxidase inhibitors, and uncontrolled narrow-angle glaucoma. No specific laboratory monitoring is needed, but duloxetine is not recommended in cases of severe renal or chronic hepatic insufficiency. While labeled at a dose of 60 mg/day, 20 and 30 mg capsules are available, titrating up from lower doses may be better tolerated from the standpoint of nausea.

Pregabalin

Pregabalin, an analog of GABA, is an anticonvulsant that has been shown to have analgesic, anticonvulsant, and anxiolytic activity, although via GABA-independent mechanisms. Similar to gabapentin, it binds potently to the $\alpha_2\delta$ subunit of voltage-activated calcium channels, reducing the release of several excitatory neurotransmitters. Unlike gabapentin, pregabalin exhibits linear pharmacokinetics across the standard dose range, and can be initiated at a therapeutic dose without a long titration. Pregabalin significantly reduced mean pain scores at a dose of 100 mg tid (3x/day) versus placebo in painful diabetic neuropathy [47]. The target for improvement was a 50% reduction in pain. No titration was used, and significant pain relief was observed by the end of the first week. Secondary efficacy variables also improved significantly, including the SF-MPQ, sleep outcomes, pain domains in the SF-36, tension-anxiety, total mood scores, and both patient and clinician-rated global impressions. Other studies in diabetic neuropathy have demonstrated efficacy versus placebo using fixed or flexible dosing regimens ranging from 150 to 600 mg/day [48-50], whereas 75 mg daily in one study [48] and 150 mg in another study [49] did not differ from placebo. As a result, increasing the dose to 300 mg/day or higher in partial or non-responders who tolerate the medication seems appropriate.

The main adverse events of pregabalin were dizziness (up to 39%), somnolence (up to 22%), infection (15%), and peripheral edema (up to 17%), a profile similar to gabapentin. The frequency of side effects increases with higher doses. Adverse events were mostly mild to moderate in severity, and overall this drug is well tolerated [47-48]. Infections were mainly of the upper respiratory variety. Eleven to 15 percent of pregabalin-treated patients discontinued taking it due to adverse events.

Pregabalin was released in the fall of 2005 with indications for both painful diabetic neuropathy and postherpetic neuralgia. It is a Schedule V medication in the US due to a low

frequency of euphoria, insomnia and headache with sudden discontinuation, and from responses on surveys of non-dependent sedative or hypnotic users.

Mexiletine

Trials of **mexiletine**, a class IB antiarrhythmic agent and oral analogue of lidocaine, have generated conflicting data in studies involving patients who are diabetic [55-57], alcoholic [58], or have HIV-related neuropathy [59-60]. In a crossover study of diabetic painful neuropathy in which mexiletine was titrated up to a daily dose of 10 mg/kg, the pain score and clinical symptom scale showed significant improvement ($p< 0.02$ and $p<0.01$, respectively) compared to placebo [56]. A larger study involving 126 diabetics also suggested improvement in sleep disturbance and nocturnal pain at 675 mg/day [55]. In contrast, others [57] failed to differentiate between mexiletine and placebo using two different pain scales, although a subanalysis suggested stabbing or burning pain, heat sensations, and formication improved. Clinical trials with HIV-related neuropathy patients have failed to demonstrate any benefit for mexiletine at doses up to 600 mg/day [59-60].

We have considerable experience with mexiletine in multicenter trials of patients with muscle stiffness [61]. Since the drug works at the sodium channel, we are intrigued with the possibility of using mexiletine in CSPN based on the recent publication that up to a third of CSPN patients may have a sodium channel mutation [14]. The starting dose is 150 mg/day, with titration up to 600 mg/day divided into two or three doses per day. The half-life of mexiletine is 10 to 12 hours. Main side effects include nausea, vomiting, dizziness, tremor, nervousness, headache, and liver function abnormalities. Mexiletine is contraindicated in patients with second- or third-degree atrioventricular blockade or cardiogenic shock [62].

Past Experience at University of Kansas Medical Center

We performed a retrospective chart review of 143 patients who were started on pregabalin or duloxetine, primarily for painful neuropathy, during a 10-month period at the University of Kansas Medical Center [63]. Ninety-two patients tried only one of these two medications, while both medications were used at different time periods in 51 of the 143 patients. Follow-up was available for 87 of the 91 patients who took pregabalin and 89 of the 103 patients who took duloxetine. We found more patients with neuropathic pain reported an improvement with pregabalin (49%) than with duloxetine (41%), but duloxetine had a higher frequency (38%) of side effects compared to pregabalin (30%). However, these differences between pregabalin and duloxetine were not statistically significant, suggesting that both pregabalin and duloxetine may be effective for neuropathic pain secondary to diabetes or cryptogenic sensory peripheral neuropathy (Table 2) and are worthy of further investigation.

TABLE 2. Comparison of efficacy and side effects in 143 neuropathic pain patients using pregabalin and duloxetine

	Pregabalin		Duloxetine		
	Number[a]	Percentage	Number[a]	Percentage	*p*
Number of patients	91	63.6	103	72	
Dose (in mg)	217 ± 128	(range: 50Ð600)	59 ± 14	(range: 30Ð120)	
Follow-up available	87	97	89	86	.03
Efficacy					
No improvement	36/69	52.2	46/78	59.0	.47
Minimally improved	10/69	14.5	16/78	20.5	.35
Much improved	23/69	33.3	16/78	20.5	.09
Side effects	22/74	30.0	32/85	37.6	.29
Medication continued	25/76	32.9	24/89	27.0	.61
Medication stopped due to lack of efficacy	25/51	49.0	32/65	49.2	.58
Medication stopped due to side effects	12/51	23.5	16/65	24.6	.81
Medication stopped due to a combination of lack of efficacy and side effects	8/51	15.7	12/65	18.5	.51
Medication stopped due to financial reasons	6/51	11 .8	3/65	4.6	.22

[a] Due to the unavailability follow-up data for all patients, the denominator is the number in that group for whom follow-up data were available. Also, recall that 51 patients took both Pregabalin and Duloxetine, although at different times, so the N's do not add up to 143.

Measures to Assess Outcomes

A variety of outcome measures have been used in neuropathic pain studies. Visual analogue scales and 10-point and 11-point numeric rating scales such as the Likert-type scale (0=no pain, 10=worst possible pain) are conventional primary outcome measures. Patients record their pain levels in daily diaries, and mean values (averages) over a specified interval are compared to baseline values. Although these instruments provide reliable and valid measurements of pain intensity and unpleasantness, they do not address other aspects of the neuropathic pain experience [(25)]. As a result, a variety of quality-of-life and daily activity measures have been introduced, especially in more recent trials [(26)].

Recently the NIH published a Toolbox to measure pain in research. They recommend using an eight item pain interference measure from their Patient Reported Outcome Measurement Information System (PROMIS) that has undergone validation testing in pain studies [(27-30)]. The patient is asked to score each from 1 to 5, where 1=not at all, 2=a little bit, 3=somewhat, 4=quite a bit, and 5= very much. In this study, at all study visits, we will use this 6 item pain interference scale, a Likert-type pain experience scale, the SF12, and the 8 item scales for fatigue and sleep disturbance from the NIH Toolbox . The latter two measures were added to our design after meeting with our Patient Advisory Group and hearing from them that

sleep disturbance and fatigue were very important to them with respect to their pain. All measures are in the Appendix.

C. Study Design

If a patient agrees to participate in the study, they will be randomized to one of the 4 drug options. They cannot be currently taking one of the study medications or similar class of medication and they must have a Likert type pain score of 4 or higher. They will then be written a prescription for the drug at the study dose. The drug is not provided by the study; the cost of the drug will be the responsibility of the patient or their insurance provider. Target drug daily doses are nortriptyline 75 mg; duloxetine 60 mg; pregabalin 300 mg; mexiletine 600 mg. Doses will be escalated weekly during the first month until the target doses are achieved (all by 4 weeks).

Doses will be escalated by the following schedule:

- Nortriptyline: 25 mg at bedtime for 1 week, then 50 mg at bedtime for 1 week, then 75 mg at bedtime
- Duloxetine: 20 mg for 1 week, then 40 mg for 1 week, then 60 mg daily
- Pregabalin: 100 mg at bedtime for 1 week, then 100 mg 2 times a day for 1 week, then 100 mg 3 times a day for the remainder of the study
- Mexiletine: 200 mg at bedtime for 1 week, then 200 mg 2 times a day for 1 week, then 200 mg 3 times a day for the remainder of the study

If suggested medications are not available in the dosage outlined in this protocol, then an alternate dosing schedule may be utilized providing that patients achieve the target daily drug dosage at week 3 of the study.

The length of the study for each patient is 3 months. After this point, they can stay on the medication of their choice.

If the patient cannot tolerate the maximum dose, then (at the discretion of the physician) they may be titrated down to the previously tolerable dose. Patients who are currently taking narcotics for pain control are eligible to participate in this study if they meet all other inclusion criteria.

a. Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Age 30 or older.
2. Diagnosis of cryptogenic sensory polyneuropathy.
3. Likert Pain Score of greater than or equal to 4.
4. Must not currently be on nortriptyline, duloxetine, pregabalin or mexiletine or similar class of medication for at least 7 days from baseline study visit.

Exclusion Criteria:

1. Any medical condition or current medication (Appendix G) that would prevent them from taking either nortriptyline, duloxetine, pregabalin or mexiletine.

2. Unable to give consent.
3. Unable or not willing to comply with the study.
4. Other causes for polyneuropathy.

b. Study Procedures:

Prescreening: Subjects must be identified with having CSPN prior to the baseline visit into the study.

Screening/Baseline Visit: (Screening/baseline period may take up to 14 days if patients need to titrate down off of medication)

1. Subjects will be asked to read and sign the consent form.
2. Medical history
3. List of concomitant medication
4. Likert pain scale
5. NIH Pain Interference Scale
6. NIH Fatigue Interference Scale
7. NIH Sleep Disturbance Scale
8. A three month prescription will be given to the subject at this visit.
9. SF-12

Month 1 and 2:

1. Visits will be completed via phone unless a clinical visit is requested by the subject or the physician.
2. Likert pain scale
3. NIH Pain Interference Scale
4. NIH Fatigue Interference Scale
5. NIH Sleep Disturbance Scale
6. Concomitant medication
7. Adverse events
8. SF-12

Month 3: (titration down of the medication is not required)

1. In-person clinical visit is required for the final month 3 visit (no phone option).
2. Adverse events
3. Likert pain scale
4. NIH Pain Interference Scale
5. NIH Fatigue Interference Scale
6. NIH Sleep Disturbance Scale
7. Concomitant medication
8. Subjects can either can go off medication or be prescribed medication they were on (titration down is not necessary)
9. SF-12
10. 28 day post call.
    1. There will be a call by the study coordinator to close out any adverse events left open at the end of the study.

Choice of Study Design

We chose the Bayesian Adaptive Design with efficiency in mind. Using adaptive randomization (being able to change how we assign patients to the drugs during the study based on information gained during the study) not only allows for substantially smaller sample sizes, but also provides better conclusions about what treatments are the most effective because 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 [64]. We conducted extensive trial simulations comparing different designs measuring the resources (time and number of patients required) and the ability to draw important conclusions about relative efficacy of the four drugs (i.e., which is better) and selected the proposed design as the most effective and efficient.

Choice of Outcomes

Patients will complete a Likert-type scale for pain, the PROMIS 6 item pain interference scale, the SF-12, and the PROMIS fatigue and sleep disturbance scales. The first endpoint, or outcome, is a patient responder-defined measure of efficacy (i.e., if the patient reports a pain score at the end of 12 weeks that is 50% or greater from what they reported when they started the study, then it is efficacious for that patient). The second endpoint is the percentage of patients who discontinue treatment. Our secondary endpoints, SF-12, pain interference, fatigue, and sleep disturbance, also will be longitudinally modeled (see content after Table 5.)

D. Analytic Methods

Overview

The primary aim of this study is to determine which drug is most effective and most tolerable in producing pain relief. We will perform a prospective randomized comparative effectiveness adaptive design study with those who do not have diabetes and in whom no other cause for neuropathy has been found. We have an agreement from 40 sites to participate in the study and four drugs will be tested. In this design we will perform several interim analyses (interims) while controlling the overall Type I error rate.

The following sections focus on specific details of this design and detail how we determined power, sample size, and duration of this trial. Throughout we add information to help those less familiar with our design and analyses better understand what we did and plan to do with this study.

Bayesian Adaptive Design

Patients will be randomized to one of four treatment arms (groups) with a maximum number of patients n_{max}= 400. Using a Bayesian Adaptive Design, at each interim analysis a decision will be made to either continue enrolling patients or to stop the trial for success. If patient enrollment continues, the randomization structure (i.e., how we randomize patients to each drug) will also be updated. Two endpoints are used to drive the adaptive randomization and stopping criteria. The first endpoint is the percentage of patients who report a 50% or greater decrease on the Likert-type pain scale after 12 weeks. The second endpoint is the percentage of patients that discontinue treatment. After 80 patients are enrolled (see definition of “enrolled” in the consent form section towards the end of this protocol) and equally randomized to the four arms, we begin adapting the randomization. Then, after we have endpoint data on 100 patients, the data will be analyzed (a first interim analysis) and an updated randomization schedule will be used. Specifically, the arm, or drug, that looks to be the best

will get more participants allocated to it in this subsequent randomization. A new adaptive randomization schedule will be updated and an interim analysis will occur every 13 weeks after the first interim analysis, using up to date outcome data, until the trial is stopped (i.e. for early success). Early success stopping criteria will be if the probability of the maximum arm (i.e., the best drug), measured by a combined utility of the pain and treatment discontinuation endpoints, is larger than 0.925. While this will halt new patient enrollment, we will confirm this finding with a subsequent analysis and evaluation after all data from all enrolled patients are obtained as some will still be actively in the study when the early stopping criterion is identified. Also determined is which of the arms are losers, and is defined as an arm that has a probability of being maximum as less than 0.01. This will be a useful result in cases where a best arm could not be identified. If a loser or two is identified then the drug(s) would not be recommended for use in clinical practice.

A summary of the overall general design is as follows.

- Begin a new adaptive randomization schedule once 20 patients have been enrolled on each treatment.
- Stop for success if the probability a treatment is best, defined as pr(t_i is best) > .925, for some treatment.
- Perform an interim analysis after 100 patients have 12 week data and every 13 weeks thereafter.
- For interim analyses, all data are used on all enrolled patients with at least 4 weeks of data.
- For the final analysis: (1) a treatment is <u>best</u> if pr(t_i is best) > .925 or (2) a treatment is <u>loser</u> if pr(t_i is best) < .01.

<u>Combining Endpoints</u>

We are combining the two endpoints using a utility function framework, which has been discussed from a Bayesian adaptive design point of view [65]. The following describes how we built our utility function. Suppose Drug B has better efficacy than Drug A, but Drug A has a lower quit rate due to tolerability than Drug B. What would the "quit rates" and "efficacies" have to be in order for Drug A to be clinically the same as Drug B? An elicitation tool that looks at various comparisons (seven of them) was created [66] that asked three of the clinical experts on this proposal (i.e. Barohn, Dimachkie, and Pasnoor) to provide the point of equivalency (Table 3).

Table 3. This table was presented to clinical experts and they were asked to fill in the underlined values, which are filled-in here but were blank when given to the experts.

	Drug A			Drug B	
Scenario	%Efficacy	%Quit		%Efficacy	%Quit
#1	30%	15%	Equals	40%	**<u>30%</u>**
#2	30%	5%	Equals	**<u>40%</u>**	10%
#3	50%	20%	Equals	40%	**<u>15%</u>**
#4	50%	30%	Equals	**<u>40%</u>**	20%
#5	30%	15%	Equals	**<u>50%</u>**	30%
#6	20%	2%	Equals	**<u>50%</u>**	10%
#7	25%	15%	Equals	50%	**<u>35%</u>**

We then plotted the points from Table 3 that were considered "equal" and then plotted lines of constant utility. This resulted in identifying that 4 points of efficacy = 3 points of quit rate. This utility function was acceptable to the clinical team. Specifically, the utility function is U(*E*,*Q*)= *.75E*+1-*Q*.

Combining patient ratings of efficacy with data on the percentage of patients who stop taking the drug to which they were assigned provides us with an important single measure of which drug is 'best.'

Virtual Participant Response

For the purposes of this investigation we looked at several virtual (or "pretend") responses to determine the power, sample size and time (duration) needed for our study. We created several scenarios for both efficacy and quit rates using five patterns for efficacy and three patterns for quit rates (Table 4). These were then combined into several possible combinations (e.g., one combination would be a 'best' and '2nd best' drug for efficacy and a 'no differences' for quit rate, another might be 'no differences' for efficacy and 'no differences' for quit rate, etc.).

Table 4. Virtual response patterns for each endpoint.

	1	2	3	4	
		Efficacy			
No Difference	0.30	0.30	0.30	0.30	all drugs are equally efficacious
Best and 2nd Best	0.30	0.40	0.50	0.30	one drug is best, one is 2nd best
All Different	0.40	0.45	0.50	0.30	all have different efficacy
One Strong Best	0.30	0.30	0.50	0.30	one drug is much better
One Modest Best	0.30	0.30	0.40	0.30	one drug is modestly better
		Quit			
No Difference	0.20	0.20	0.20	0.20	all drugs have same quit rates
Positive Relation	0.30	0.25	0.15	0.30	Most efficacious drug has lowest quit rate
Negative Relation	0.20	0.40	0.60	0.20	Most efficacious drug has highest quit rate

NOTE: "Positive" relation refers to both efficacy and quit percentages being good; "Negative" relation refers to either good efficacy and high quit percentages or low efficacy and low quit percentages.

Accrual (patient enrollment) Patterns

Accrual patterns are important to Bayesian adaptive designs and refer to how rapidly each site enrolls patients in the trial. We assume that the distribution of the accrual patterns follows a Poisson distribution with a mean, or average, number of patients accrued per week. The accrual patterns depend on two factors: (1) the number of sites actively enrolling patients in the trial, and (2) how fast the sites can enroll, which we assume is a constant for each. We expect after a ramp-up of around 8 weeks of enrolling patients, using information from the participating 40 site investigators, we should accrue an average of 4.2 patients/week. Determining this is important for identifying how long the trial will last.

Statistical Model

Of necessity the following is fairly technical, but it is needed to allow for appropriate statistical review and because it is the statistical model that will evaluate final determination of which drug is "best". This is referred to as the arm of maximum utility (i.e., the drug with the

best combination of patient reported efficacy and percentage of patients who quit taking the drug.) For this study the two endpoints are respectively S_{EjT} for efficacy and S_{QjT} for quitting. The number who did not quit and were not efficacious is Sn_{EjT}. These are modeled as a multinomial distribution ($S_{QjT}, S_{EjT}, Sn_{EjT}$)~*MultNomial*($\theta^q_j, \theta^e_j, \theta^{ne}_j$). In addition, we provide "weakly informative" priors, ($\theta^q_j, \theta^e_j, \theta^{ne}_j$)~ *MultNomial(1/3,1/3,1/3))*. Using the endpoint data and the prior probabilities, we then use Markov Chain Monte Carlo computations to obtain the Bayesian posterior distributions of $\left\{\theta^e_j \mid S_{EjT}\right\}$ and $\left\{\theta^q_j \mid S_{QjT}\right\}$ respectively for each endpoint (i.e., efficacy and quitting.)

The utility function previously discussed is used for determining whether we have met our stopping criterion. Specifically, the rule is we will stop the trial if the probability of an arm (i.e., a drug) having maximum utility is greater than 0.925. This may first be determined after enrolling 100 of the 400 potential patients. The utility function is $U_{jT} = .75\left\{\theta^e_j \mid S_{EjT}\right\} + 1 - \left\{\theta^q_j \mid S_{QjT}\right\}$ and the arm (or drug) having the maximum utility is $U_{\max,T} = \max\left(U_{1T}, U_{2T}, U_{3T}, U_{4T}, U_{5T}\right)$. The stopping rule is mathematically $P(U_{max,T})$>.925). If a maximum utility arm (drug) is not identified after completed data on 100 patients, this procedure and accrual will continue until a maximum arm is identified or we reach 400 enrolled patients. At the end of the trial we will also decide that an arm is a "loser" if there is a very unlikely chance that it is the best, $P(U_{max,T})$<.01).

Adaptive Randomization: Allocation

After the stopping rule is evaluated the next round of patients are randomized using a formula that takes advantage of the information gained from our analyses up to that point. Using this formula, each arm (or drug) is allocated for the next patients to be enrolled in the j^{th} arm proportional to $V^*_j = \sqrt{\frac{\Pr\left(U_{jT} = U_{\max,T}\right) Var\left(U_{jT}\right)}{n_{jT}+1}}$. This type of allocation tends to have more desirable properties then simply using $\Pr\left(U_{jT} = U_{\max,T}\right)$. Using this approach will allow us to assign more patients to the most promising arm or drug, and fewer patients to the least promising drug.

Longitudinal Model

This model predicts patients 12 week data from data at early time points (4 and 8 weeks). Estimate transition probabilities from outcome at early time point to final outcome. The number of transitions to final outcome given early outcome is distributed as multinomial with the following parameters. If a patient quits treatment early, we transition the patient to quit at 12 weeks. Let p21, p22, and p32 be conditional on a patient showing early efficacy, the respective final probabilities of quit, efficacy, and not efficacy. For these we use a Dirichlet prior on transition probabilities, (p21,p22,p32)~Dirichlet(1,7,2). Similarly for a patient that shows no efficacy early, the final prior probabilities are (p31,p32,p33)~Dirichlet(1,2,7). These are fairly diffuse, each having a prior sample size equivalent to ten patients.

We estimate transition probabilities separately for each treatment group and for 4 and 8 week early time points. Here is the algorithm for the longitudinal model. Calculate the posterior probability each treatment is best by:

1. Sample posterior transition probabilities from longitudinal model
2. Impute 12 week data values for patients with at least 4 week values given sampled transition probabilities

3. Sample values from the posterior distribution under each treatment given imputed 12 week data
4. Given each vector calculate the utility under each treatment
5. Report the treatment with the max utility
6. Repeat 1-5 and summarize posterior probability that each treatment is best as the proportion of times it had the max utility.

Here is the longitudinal scenario based on elicitations from the clinical team, which resulted in transition probabilities for evaluating the trial's operating characteristics. To simulate the early outcomes, one first simulates the final outcomes from a multinomial distribution. Then the early outcomes are also multinomial simulations conditional on these final outcomes. Specifically, if the final outcome is a quit, then the probabilities of early quit, efficacy, non-efficacy is 0.80, 0.10, and 0.10 respectively. If the final is effective then we have 0, .67, and .33 respectively. If not effective then is 0, .33, and .67.

Simulation Algorithm

The following steps summarize the algorithm (or rule) used to determine power, sample size, and duration of the trial. These are all necessary elements for establishing that the trial is of sufficient size and length to yield valid results. For this algorithm we used the "virtual patient responses" parameters (or simulated data) previously discussed. **Step 0:** Set the index for simulation iteration to be b=0. **Step 1:** Set b=b+1. **Step 2:** Simulate the initial observed data. **Step 3:** estimate posterior parameters via simulation and calculate the stopping rule and the possible next allocation. **Step 4:** repeat steps 2 and 3 after collecting four more weeks of data. **Step 5:** evaluate all of the data after collecting all of the endpoints. **Step 6:** go to step 1 unless b=1000, then stop. Initially we used this algorithm in a software package called FACTS™ (Fixed and Adaptive Clinical Trials Simulator) [65]. FACTS™ is very powerful and can handle a wide variety of models for exploring the operating characteristics of Bayesian clinical trials designs. It was developed by S. Berry, who co-authored the PCORI methods guidelines and wrote the Bayesian adaptive design portion of those guidelines. Dr. Berry is a consultant on this application and the University of Kansas Medical Center is the first academic institution with license to use FACTS™. We then programmed the algorithm in the software R[66] to handle the multinomial case for the simulation and adapted it for use during the actual trial.

Power, Sample Size, and Trial Duration

We performed several trial simulations based on the various combinations of efficacy (5 types) and quit (3 types) endpoints that were shown in Table 4. We varied the maximal accrual into the study after several weeks and, as previously identified, found 4.2 patients/week to be very close to the optimal combination of sample size and trial duration [66]. 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 400 patients) (see Table 5). While some of these combinations are very unlikely to occur, we include all possible combinations in Table 5, ordered from most to least power. We highlight four scenarios, here.

First we want to highlight the unlikely scenario that serves as our null hypothesis **(scenario #1 in Table 6)**. In this scenario there are no differences in efficacy or in quit rates among the drugs. Therefore, the extent to which this scenario is "successful" actually reflects our Type I error rate. For this scenario, we estimated (identified) that 5.5% of the simulated trials had early success, .6% late success. Thus this trial scenario produced an appropriate expected Type I error (α~.05). The sample size of this scenario on average was 393 patients. The average length of the trials under this scenario was 108 weeks. **Second (scenario #2 in**

Table 6), if there is a best drug and second best drug in terms of efficacy and quit rates, we estimated (identified) that 78% of the simulated trials had early success, 2% had late success, and 20% had incomplete results. This trial scenario had 80% power and the sample size of this trial scenario was on average 298. The average length of this trial scenario was 78 weeks. **Third (scenario #3 in Table 6),** if there is one strong best drug in terms of efficacy and quit rates, we estimated (identified) that 92% of the simulated trials had early success, 2% late success, and only 6% had incomplete results. Thus this simulation had 94% power. The average sample size of this trial scenario was 266. The average length of these simulated trials was 68 weeks. Close to half of the sample size, 108, was on the best treatment. **Fourth (scenario #4 in Table 6), a very unlikely case, is** if there is one strong best drug in terms of efficacy and but quit rates that are higher for the drug with high efficacy, we estimated (identified) that 10% of the simulated trials had early success, 2% late success, and 88% had incomplete results. Thus this simulation had 12% power. The average sample size of this trial scenario was 387. The average length of these simulated trials was 107 weeks. However, this trial does a decent job correctly identifying treatment 2 as the loser (65%).

Table 5. Simulation scenarios.

		Treatment			
		1	2	3	4
Scenario 1	Pr(Quit)	0.2	0.2	0.2	0.2
Eff: No Difference	Pr(Efficacy)	0.3	0.3	0.3	0.3
Quit: No Difference	Utility	1.025	1.025	1.025	1.025
Scenario 2	Pr(Quit)	0.3	0.25	0.15	0.3
Eff: Best and 2nd Best	Pr(Efficacy)	0.3	0.4	0.5	0.3
Quit: Positive	Utility	0.925	1.050	1.225	0.925
Scenario 3	Pr(Quit)	0.3	0.25	0.15	0.3
Eff: One Strong Best	Pr(Efficacy)	0.3	0.3	0.5	0.3
Quit: Positive	Utility	0.925	0.975	1.225	0.925
Scenario 4	Pr(Quit)	0.2	0.4	0.4	0.2
Eff: One Strong Best	Pr(Efficacy)	0.3	0.3	0.5	0.3
Quit: Negative	Utility	1.025	0.825	0.975	1.025

Table 6. Simulated Trial Operating Characteristics.

				Mean Patients				
Scenario	Prob. Success	Prob. Early Success	Mean Trial Weeks	Total	T1	T2	T3	T4
1 (No Difference)	0.061	0.055	108	393	99	99	97	99
2 (Best & 2nd Best+)	0.798	0.777	78	298	51	80	116	52
3 (One Strong Best+)	0.939	0.923	68	266	51	58	105	51
4 (One Strong Best-)	0.115	0.103	107	387	108	62	107	109

	Prob. Drug Wins		Prob. Drug	

Scenario	Pr(Treatj Best)>.925 T1	T2	T3	T4	Loses Pr(Treatj Best<.01) T1	T2	T3	T4
1 (No Difference)	0.015	0.015	0.014	0.017	0.075	0.064	0.088	0.068
2 (Best & 2nd Best+)	0.000	0.001	0.797	0.000	0.744	0.238	0.000	0.736
3 (One Strong Best+)	0.000	0.000	0.939	0.000	0.661	0.461	0.000	0.682
4 (One Strong Best-)	0.053	0.000	0.011	0.051	0.030	0.647	0.104	0.034

NOTE: For Quit, "positive" means quit percentages are low and "negative" means quit percentages are high

Secondary Endpoints

The previous discussion focused on our primary endpoints, efficacy and quite rates. The temporal patterns of our secondary endpoints, SF-12, pain interference, fatigue, and sleep disturbance, will be longitudinally modeled using a two-level (time, patient) hierarchical linear modeling approach to evaluate these variables within each arm across time [67].

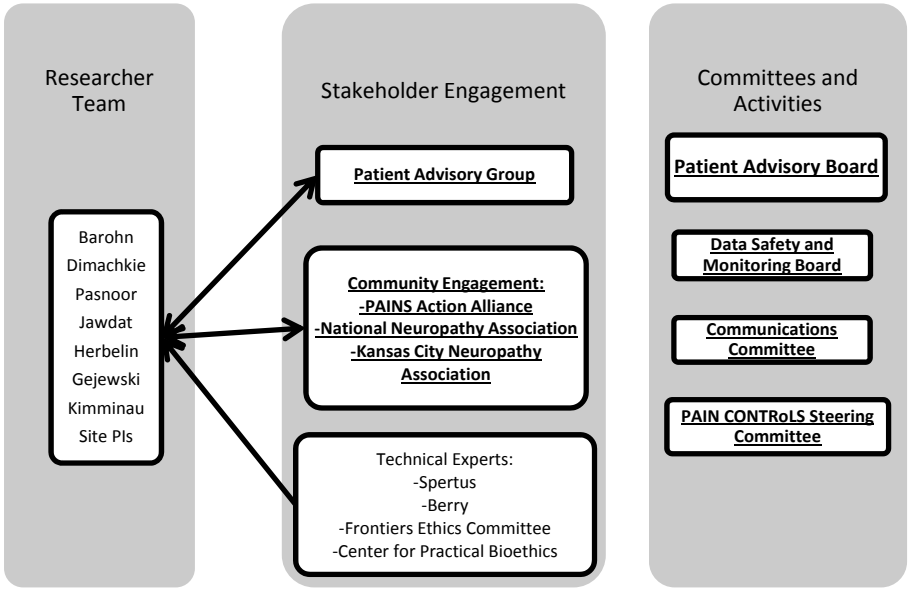
Missing data:

Our primary statistical inference of the intervention measures (efficacy and medication quit rates) will label all patients with missing VAS data to be imputed as a failure. Therefore our study has valid type I error rates and has nominal confidence interval coverage properties as detailed in the proposal. A patient that is enrolled and randomized (note: after signing the consent form) into the study will either continue to take the randomly assigned pain medication (quit=0) or discontinue (quit=1). Among the patients that continue the pain medication, and have follow-up VAS outcomes, that patient will either drop their VAS pain score by ½ or better (efficacy=1) or they will not (efficacy=0). Among the patients that discontinue treatment of assigned pain medication, or having missing VAS values, they will automatically be recorded as non-efficacious (efficacy=0). Patients that are lost from the study will be considered to have discontinued treatment (quit=1, efficacy =0). The rule above implies that missing data will result in an imputed failure (and hence there are no missing primary outcomes). The primary inference in our study automatically addresses MD-3 of the PCORI Methodology Standards. Note: our secondary statistical inference of the intervention measure of reported VAS changes will be conducted using Bayesian mixed-effect model repeated measures (MMRM) where missing data will be addressed using multiple imputation.

E. Stakeholders

The key stakeholders for the PAIN-CONTRoLS project are patients with Cryptogenic Sensory Polyneuropathy (CSPN), their families who cope with loved ones struggling with pain on a daily basis, providers who treat these patients, scientists involved in this study, patients' local and national associations (the local and national chapters of the Neuropathy Association), and ethicists working in healthcare in general and pain management in particular. We already have engaged a number of critical stakeholders—including in discussions of study design, for feedback on measures to be used, and for support for recruitment and completion of the proposed study. Indeed, the decision to propose this study and how it will proceed are a direct result of working with patients and tracking their symptoms. Our patients made it very clear that a rigorous comparative effectiveness study is desperately needed. The organizational

framework we present in Figure 3 visually demonstrates our commitment to inform our research with patient, caregiver, and consumer input at every level. Bold/underlined text in Figure 3 indicates that activity or membership includes patients and other stakeholders (see Engagement



Activities text below for details.)

Figure 3. Organizational Structure for Stakeholder Engagement

Engagement Activities: Researcher and Technical Expert Collaboration

Our engagement activities began over a year ago. We had an initial brainstorming meeting with approximately 30 researchers and staff at the *Personalized Medicine and Outcomes Center* within the NIH CTSA supported *Frontiers: Heartland Institute for Clinical and Translational Research* program in May 2012. We presented our initial concept of a comparative effectiveness study for painful neuropathy and received outstanding feedback. They advised that we should develop the study so that it most closely resembles real world activity and decision-making between physicians and patients in the management of neuropathy pain. This influenced us a great deal in deciding on the design to r[Safety Committee]ts to drugs that are currently given routinely, but for which there have been no systematic studies for use in CSPN. We also were mindful to design the study to dispense these drugs as they would be advised by their doctor—for example, one or two or three times a day, and not try to create a common time or strict number of pills dispensed for each drug. Dr. Barohn heard Scott Berry, PhD, talk about adaptive design models for clinical trials at a CTSA meeting in the spring of 2012, and this led to Dr. Berry joining the study development team as a consultant.

The **Data and Safety Monitoring Board** (DSMB) will be chaired by Dr. Anthony Amato, Professor of Neurology at Harvard Medical School. Other members of the DSMB will be Zarife

Sahenk, MD at Ohio State University, a peripheral nerve specialist; Elliott Frohman MD, a multiple sclerosis and clinical trials expert at UT Southwestern Medical Center in Dallas; Kim Kimminau, PhD, co-director of our CTSA's *Community Partnership for Health* program, Ms. Tockarshewsky; and Leslie McClure PhD, a biostatistician from a non-participating academic institution. The DSMB will meet via phone 3-4 times a year to review the status of the study and to make decisions about study continuation. After each meeting, they will prepare a letter that will be disseminated to all members of the PAIN-CONTRoLS Steering Committee and to each participating site. By including all members of the Steering Committee, we ensure that information will be available to our patient Committee members and if appropriate will be included in Newsletter and other communications.

While we will have this official Data and Safety Monitoring Board (DSMB), we also will have a physician safety monitor, Jeffrey Statland, MD, who will chair a **Safety Committee** to discuss issues regarding side effects and adverse events in real time as they happen. This is standard for clinical trials. Our Safety Committee will have at least one patient with CSPN as a member, and at least one physician who is not associated with the study. Together they will assess side effects as they occur and make determinations regarding particular patient safety issues. They will provide this information to the study PI and Co PIs and the official DSMB.

The last committee we have previously referred to but did not detail is the PAIN-CONTRoLS **Steering Committee.** The Steering Committee is made up of the following: at least one representative from the Patient Advisory Board, Richard J. Barohn MD, PI, Mazen Dimachkie MD, Aziz Shaibani MD, Vera Bril MD, Jaya Trivedi MD, Gil Wolfe MD, Omar Jawdat MD, Andrea Nicol MD, Byron Gajewski PhD, statistician, Linda Ward from *the Center for Practical Bioethics*, and Kim Kimminau PhD, representing the community engagement function for Frontiers (CTSA grant at KUMC). Because we actively involved patients in developing the PAIN-CONTRoLS project, several have already agreed to serve on the Steering Committee. The Steering Committee will oversee additional development of the protocol and execution of the study. They will approve the final protocol before it is distributed to each site, and will be kept up to date on reports from the Data and Safety Monitoring Board. They also may ask the DSMB to convene for review of safety issues at any time.

The Steering Committee will review all manuscripts and presentations prepared about the PAIN-CONTRoLS project and using data from this project. The patient member of the Steering Committee will be charged with ensuring these are shared with the full Patient Advisory Board. The Steering Committee also will ensure that each site investigator maintains contact with their local chapter of the Neuropathy Association (if one exists near their site) and visits or sends a representative to the local chapter meetings several times a year.

We are committed to conduct this project in the most transparent way possible, seeking meaningful communication with and participation by all of our stakeholders. In particular, patients and other stakeholders have been fully integrated into the planning and the design of this project and all will be actively involved in the conduct of this study and the dissemination of findings from this study. Patients and other stakeholders sit on every committee, and a patient will co-chair the important Communications Committee.

KUMC intends to utilize a "remote or virtual" monitoring plan for this trial. The goal with remote monitoring is to help site investigators and research staff with the prevention or mitigation of important and likely risks to data quality, protection of human subjects and trial integrity.

The remote monitor will ask for copies of signed consent forms and other source documents to verify legal informed consent, subject eligibility and outcome measures entered into the database. We will try to request remote monitoring 2-3 subjects per site at random. Completion and accuracy of subject eligibility, the Likert Pain Scale, the NIH Pain Interference

Scale, the NIH Fatigue Interference Scale, NIH Sleep Disturbance Scale, SF-12 and adverse event reporting will also be verified during remote monitoring.

Each site will be asked to send protected documents containing individually identifiable personal and/or health information through KUMC's secure portal called Secure File Transfer Network.

The project managers will monitor the database and to confirm that all data has been entered on a weekly basis. They will report to Richard J. Barohn, MD if they identify a site that is unable to enter data in a timely manner.

Protection of Human Subjects

The University of Kansas Medical Center will serve as Internal Review Board (IRB) of record for this study for all sites. Each site must obtain approval from their IRB as well as from the IRB of record (KUMC) before enrollment at their site can begin. This process will be followed carefully by the Research Institute Clinical Research Administration office at KUMC (JoAnn Miller, BA, CCRP) to ensure that all sites comply.

Patients will need to be consented prior to participation in the study. All sites will need to document their consenting processes and the original signed and dated consent forms will be kept at each site. Each patient will be given a copy of their consent forms.

Each subject will sign two consent forms. The main consent form will explain the study, outline study visits and procedures and identify the risks that will be the same in each group. After all study procedures are performed and the subject is randomized, the subjects will then sign a drug specific supplemental consent form. This consent form will list the risks unique to the drug the subject is randomized.

Each main consent form will contain the following information found from the National Institutes of Health (NIH) website (www.grants.nih.gov/grants/funding/phs398/phs398.doc). The components of the consent form must contain the following information (copied from the above website):

I. Risks to Human Subjects

a. ***Human Subjects Involvement, Characteristics, and Design***

- Describe and justify the proposed involvement of human subjects in the work outlined in the Research Strategy section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.
- Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects' protection, describe and justify the selection of an intervention's dose, frequency and administration.

- List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

b. ***Sources of Materials***

- Describe the research material obtained from living individuals in the form of specimens, records, or data.
- Describe any data that will be collected from human subjects for the project(s) described in the application.
- Indicate who will have access to individually identifiable private information about human subjects.
- Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

c. ***Potential Risks***

- Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

II. Adequacy of Protection against Risks

a. ***Recruitment and Informed Consent***

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. ***Protections against Risk 9***

- Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:
    - Additional Protections for Pregnant Women, Human Fetuses and Neonates: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb
    - Additional Protections for Prisoners: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc
    - OHRP Subpart C Guidance: http://www.hhs.gov/ohrp/policy/index.html#prisoners
    - Additional Protections for Children: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd
    - OHRP Subpart D Guidance: http://www.hhs.gov/ohrp/policy/index.html#children

- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of the clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

III. Potential Benefits of the Proposed Research to Human Subjects and Others

- Discuss the potential benefits of the research to research participants and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

IV. Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologics) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

All sites will be trained to address potential susceptibility to therapeutic misconception by making sure that the participants understand the research, its purpose and their role, have been counseled about it, and know that additional support may be available for them should they withdraw from the study through alternative support from the Pain Action Alliance to Implement a National Strategy (PAINS) project and advocacy groups that may offer bio-psychosocial alternatives to pharmaceutical interventions that have failed them. (Note, the Pain Action Alliance to Implement a National Strategy (PAINS) project is different from this research study we call PAIN-CONTRoLS).

Children will not be entered into the study. Most of the study medications offered in this study is safe for pregnant females. Due to the short duration of the study (12 weeks) we are going to ask all females of childbearing potential use birth control. There will not be a caregiver form, so only patients that can comprehend the consent form will be enrolled.

F. **References:**

1. Pasnoor M, Dimachkie MM, Barohn RJ. Cryptogenic sensory polyneuropathy. Neurol Clin N. Amer, 2013; 31:463-76.
2. www.neuropathy.org website March 2013.
3. Barohn RJ. Approach to peripheral neuropathy and neuronopathy. *Semin in Neurology* 1998;18:7-18.
4. Barohn RJ, Amato AA. Pattern recognition approach to neuropathy and neuronopathy. Neurol Clin N Amer, 2013; 31: 343-61.
5. Wolfe GI, Barohn RJ. Cryptogenic sensory and sensorimotor polyneuropathies. Semin Neurology 1998;18:105-111.
6. Wolfe GI, Baker NS, Amato AA, Jackson CE, Nations SP, Saperstein DS, Cha CC, Bryan WW, and Barohn RJ. Chronic cryptogenic sensory polyneuropathies: clinical and laboratory characteristics. *Arch Neurol* 1999; 56:540-547.
7. **Pasnoor M, Nascimento O, Trivedi J, Wolfe GI, Nations S, Herbelin L, Freitas , Quintanilha G, Khan S, Dimachkie M, Barohn RJ.** North America and South America (NA-SA) Neuropathy Project. International Journal of Neuroscience 2013; 123:563-7.
8. Jann S, Beretta S, Bramerio M, Defanti CA. Prospective follow-up study of chronic polyneuropathy of undetermined cause. Muscle Nerve 2001;24(9):1197-201
9. www.neuropathy.org/site/DocServer/Issue_33_May_09 website March 2013.
10. Corvisier NVallat JMHugon JLubeau MDumas. Les neuropathies de cause indéterminée. Rev Neurol (Paris). 1987;143279- 283
11. England JD, Gronseth GS, Franklin G, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology 2009b;72(2):177-84.
12. 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 1994b;57(12):1525-7.
13. Lindh J, Tondel M, Osterberg A, Vrethem M. Cryptogenic polyneuropathy: clinical and neurophysiological findings. J Peripher Nerv Syst 2005;10(1):31-7.
14. Faber CG, Hoeijmakers JG, Ahn HS, Cheng X, Han C, Choi JS, Estacion M, Lauria G, Vanhoutte EK, Gerrits MM, Dib-Hajj S, Drenth JP, Waxman SG, Merkies IS Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol. 2012 Jan;71(1):26-39. doi: 10.1002/ana.22485. Epub 2011 Jun 22.
15. http://www.neuropathy.org/site/. Newsletter. The Neuropathy Association. May 14, 2012.
16. Bril V, England J, Franklin GM, Cohen J, Del Toto D, Feldman E, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy. Neurology. 2011 May 17;76(20):1758-65.
17. Boulton AJ, Vinik Al, Arezzo JC, et. Al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005;28:956-962.
18. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. JAMA 1998;280:1831-1836.
19. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998;50:1842-1846.
20. Trivedi JR, Silvestri NJ, Wolfe GI. Treatment of painful neuropathy. Neurol Clin N Amer, 2013 (in press).

21. Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin: a multicenter, double-blind, vehicle-controlled study. Arch Intern Med 1991a;151:2225-2229.
22. Sindrup SH, Gram LF, BrØsen K, EshØj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990a;42:135-144.
23. Chong MS, Bajwa ZH. Diagnosis and treatment of neuropathic pain. J Pain Symptom Manage 2003;25:S4-S11.
24. Cook KF, Dunn W, Griffith JW, Morrison MT, Tanquary J, etc. Pain assessment using the NIH toolbox. Neurology 2013;80 (Suppl 3):S49-53.
25. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. Neurology 1997;48:332-338.
26. Ware Jr JE, Snow KK, Kosinski M, Gandek B. SF-36 item short form health survey (SF-36). I. Conceptiual framework and item selection. Med Care 1992;30:473-483.
27. Amtmann D, Cook KF, Jensen MP, et al. Development of a PROMIS item bank to measure pain interference. Pain 2010;150:173-182.
28. Cella D, Riley W. Stone A, et al. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health coutcome item banks: 2005-2008. J. Clin Epidemiol 2010;63:1179-1194.
29. http://www.nihpromis.org. March 2013.
30. https://www.assessmentcenter.net. March 2013.
31. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. Neurology 1995;45 (suppl 9):S17-S25.
32. Calissi PT, Jaber LA. Peripheral diabetic neuropathy: current concepts of treatment. Ann Pharmacother 1995;29:769-777.
33. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250-1256.
34. Sindrup SH, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. Neurology 2000;55:915-920.
35. Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 1987;37:589-596.
36. McQuay HJ, Tramèr M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain 1996;68:217-227.
37. Sindrup SH, Gram LF, Skjold T, Grodum E, BrØsen K, Beck-Neilsen H. Clomipramine *vs* desipramine *vs* placebo in the treatment of diabetic neuropathy symptoms: a double-blind cross-over study. Br J Clin Pharmac 1990b;30:683-691.
38. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 2005;116:109-118.
39. Raskin J, Pritchett YL, Wang F, et al. A double-blind randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Medicine 2005;6:346-356.
40. Kuzniecky R, Ho S, Pan J, et al. Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults. Neurology 2002;58:368-372.
41. Petroff OAC, Rothman DL, Behar KL, Lamoureux D, Mattson RH. The effect of gabapentin on brain gamm-aminobutyric acid in patients with epilepsy. Ann Neurol 1996;39:95-99.
42. Taylor CP, Gee NS, Su T-Z, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res 1998;29:231-246.

43. Pandey CK, Bose N, Garg G, et al. Gabapentin for the treatment of pain in Guillain-Barré syndrome: a double-blinded, placebo-controlled, crossover study. Anesth Analg 2002;95:1719-1723.
44. Pandey CK, Raza M, Tripathi M, Navkar DV, Kumar A, Singh UK. The comparative evaluation of gabapentin and carbamazepine for pain management in Guillain-Barré syndrome patients in the intensive care unit. Anesth Analg 2005;101:220-225.
45. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. Clin Ther 2003;25:81-104.
46. Gorson K, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry 1999;66:251-252.
47. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110:628-638.
48. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004;63:2104-2110.
49. Richter RW, Portenoy R, Sharma U, Lamoreaux L, Brockbander H, Knapp LE. Relief of diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 2005;6:253-260.
50. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005;115:254-263.
51. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an "atypical" opioid analgesic. J Pharmacol Exp Ther 1992;260:275-285.
52. Richter W, Barth H, Flohe L, Giertz H. Clinical investigation on the development of dependence during oral therapy with tramadol. Arzniem-Forsch/Drug Res 1985;35:1742-1744.
53. Sindrup SH, Andersen G, Madsen C, Brøsen K, Smith T, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. Pain 1999b;83:85-90.
54. Harati Y, Gooch C, Swenson M, et al. Maintenance of long-term effectiveness of tramadol in treatment of the pain in diabetic neuropathy. J Diabetes Complic 2000;14:65-70.
55. Oskarsson P, Ljunggren J-G, Lins P-E, Mexiletine Study Group. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. Diabetes Care 1997;20:1594-1597.
56. Dejgård A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. Lancet 1988;1:9-11.
57. Stracke H, Meyer UE, Schumacher HE, Federlin K. Mexiletine in the treatment of diabetic neuropathy. Diabetes Care 1992;15:1550-1555.
58. Nishiyama K, Sakuta M. Mexiletine for painful alcoholic neuropathy. Intern Med 1995;34:577-579.
59. Kieburtz K, Simpson D, Yiannoutsos C, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. Neurology 1998;51:1682-1688.
60. Kemper CA, Kent G, Burton S, Deresinski SC. Mexiletine for HIV-infected patients with painful peripheral neuropathy: a double-blind, placebo-controlled, crossover treatment trial. J Acquir Immune Defic Syndr Hum Retrovirol 1998;19:367-372.
61. Statland JM, Bundy BN, Wang Y, Rayan DR, Trivedi JR, Sansone VA, Salajegheh MK, Venance SL, Ciafaloni E, Matthews E, Meola G, Herbelin L, Griggs RC, Barohn RJ, Hanna MG, and the Consortium for Clinica Investigation of Neurologic Channelopathies.

Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. JAMA 2012;308:1357-1365.
62. Wolfe GI, Hotz SE, Barohn RJ. Treatment of painful peripheral neuropathy. J Clin Neuromusc Dis 2002;4:50-59.
63. Manoj Mittal, Mamatha Pasnoor, Reddiah B. Mummaneni, Saud Khan, April McVey, David Saperstein, Laura Herbelin, Larry Ridings, Yunxia Wang, Mazen M. Dimachkie,and Richard J. Barohn. Retrospective Chart Review of Duloxetine and Pregabalin in the Treatment of Painful Neuropathy International Journal of Neuroscience, 121, 521–527, 2011.
64. Berry, SM, Carlin, BP, Lee, JJ, & Muller, P (2011), *Bayesian Adaptive Methods for Clinical Trials*, CRC Press, New York.
65. Berry, SM, Spinelli, W, Littman, GS, Liang, JZ, Fardipour, P, Berry, DA, Lewis RL, and Krams, M (2010),"A Bayesian dose-finding trial with adaptive dose expansion to flexibly assess efficacy and safety of an investigational drug," *Clinical Trials*, 7, 121-135.
66. Gajewski, BJ, Berry, SM, Pasnoor, M, Dimachkie, M, Herbelin, L, & Barohn, R (in preparation).Building Efficient Comparative Effectiveness Trials through Adaptive Designs, Utility Functions, and Accrual Rate Optimization: Finding the Sweet Spot. Presented at the 2013 Joint Statistical Meetings on 08/08/2013 in Montreal, QC.
67. Raudenbush SW, Bryk AS (2002), *Hierarchical Linear Models: Applications and Data Analysis Methods*, 2nd ed. Newbury Park, CA: Sage Publications.
68. http://en.wikipedia.org/wiki/demographic. March 2013.

APPENDIX

Appendix A: Likert Numeric Pain Rating Scale
Appendix B: Adverse Event
Appendix C: SF-12 Patient Questionnaire
Appendix D: NIH Pain Interference Scale- Short Form 8a
Appendix E: NIH Fatigue Scale- Short Form 8a
Appendix F: NIH Sleep Disturbance Scale- Short Form 8a
Appendix G: Exclusionary Medication List