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FACILITATORS

Cover Image: "Hope Infusion" (left) and "Pills, Pills, Pills" (right) by Dylan Mortimer.

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REMINDER!

MUSCLE STUDY GROUP
23rd Annual Meeting
Stresa, Lake Maggiore, Italy
September 30 - October 2, 2022

Meeting Registration is live,
Sign up at https://musclestudygroup.org/events/2022-muscle-study-group-annual-scientific-meeting/

Current meeting draft agenda is also posted.

The MSG is offering meeting registration at a discount to sites with paid up dues

Members and non-members are all welcome to attend!

All MSG Hotel reservations made at Regina Palace are to be made through Liz Paulk

If you are interested in sponsoring the 2022 meeting, please contact Liz at epaulk@kumc.edu

MSG 2022 Planning Committee

Valeria Sansone, MD // Chair, NEMO Clinical Center
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University of Missouri
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What's In This Issue?

Letter from the Founding Facilitator for Volume 3, Issue 2

Richard J. Barohn, MD

The current RRNMF Neuromuscular Journal issue, volume 3/issue 2, marks the two-year anniversary of this new and innovative communication vehicle. We have come a long way. Thanks to all the facilitators (editors) and reviewers, and authors. This journey has been both educational and fun, and I am looking forward to the third year of this journal.

In this issue, in the "What's on Your Mind?" section, we have many articles of interest. One is a piece I wrote honoring Dr. Jane Cooke Wright during African American history month for my Executive Vice Chancellor message at the University of Missouri. Dr. Wright was an oncologist, and her father was also a distinguished cancer physician. They were a cancer-fighting team. She was a pioneer in using methotrexate for cancer, a drug we use in neuromuscular disease to this day. Dr. Josh Freeman provides his thoughts on being a physician specialist from a family practice doctor's perspective. I thought it would be a good piece for our ultraphysician specialist's neuromuscular group to read.

Another well-known and respected family physician, Donald Frey, has contributed a piece he wrote: an imaginary letter from the Chinese Communist Party to the People to the American people! Like Dr. Freeman, Dr. Frey is a retired physician who has a fascinating blog site called "A Family Doctor Looks at the World" (afamilydoctorlooksattheworld.com). Check this site out for Don's other blog pieces, and we may publish more in this journal.

Two other pieces in this section are very moving and personal. In the last issue, we heard from Marci Gibson, who has ALS and who I have known for nearly 30 years since she developed symptoms of the disease as a young adult. In this issue, her father, Harold, discusses the many frustrations the family has encountered in communication devices for Marci. Harold is an engineer, and over the last several decades, he has had to be very creative to develop a communication system that allows Marci to continue communicating with the world. To say we need more time, effort, and money to develop modern and more effective communication devices for those who lose the motor ability to speak is an understatement.

The other extraordinary piece in this section is by the artist Dylan Mortimer. I have known Dylan for about a decade. He has cystic fibrosis, and he has undergone two lung transplants. His medical odyssey inspires his art, and he explains this better than I can attempt to in his article.

The cover of this issue has two recent paintings by Dylan that I purchased from him (remember always to support the artist whose work you appreciate and enjoy). One is an IV bag full of stuff, and one is of many colorful pills. In the past, Dylan has also created vast works of art over 60 feet long that have been installed in buildings in Kansas and Missouri. One large piece of work is in the Health Education Building at KU Medical Center. We have inserted a few of these pictures at the end of this piece and the end of Dylan's.

In the "New Stuff" section, our colleague Dr. Mazen Dimachkie, with the support of CSL Behring, provides a wonderful discussion about subcutaneous immunoglobulin for CIDP. Also, in new stuff, Dr. Avdagic and colleagues at the University of Missouri focused on diagnosing and misdiagnosis of CIDP from a series of 20 patients.

In the "Clinic Stuff" section, the MIZZOU team, Molly Shipman, a medical student, and Dr. Govindarajan describes a lumbosacral Plexopathy due to an internal iliac artery aneurysm and reviews the literature. From the University of Kansas, Dr. Mai Yamakawa, a neurology resident, and Dr. Mamatha Pasnoor present a case of Vasculitis neuropathy and myelopathy. Drs. Abhiram Bhashyam and Salman Bahai (from Orthopedics at the Massachusetts General Hospital and Neurology at the University of Texas Southwestern Medical Center, respectively), discuss a very interesting case of a patient with transient shock symptoms while cycling under a power line- or biking induced kinetic electrical micro shocks-BIKE! Who knew? And the same Boston-Texas team used a case to illustrate the approach to evaluating an elevated creatine kinase and provide a nice algorithm diagram.

In the "Proposed Stuff" section, our large team is publishing a grant we wrote for PCORI that did not get funded. The grant is called BEAT CSPN and stands for Determining Best of Inferior Drug(s) Using an Adaptive Platform for Cryptogenic Sensory Polyneuropathy. This was an extension of our prior PAIN CONTROLs comparative effectiveness

research study (CER) of CSPN that compared nortriptyline, duloxetine, pregabalin, and mexiletine. In BEAT CSPN, we proposed a CER to randomize CSPN patients to six different drugs: gabapentin, topiramate, valproate, venlafaxine, levetiracetam, and lacosamide. We all thought it was a great idea. The study section did not. So, we are publishing the proposal and the critiques for others to learn from, and perhaps someone else will take this idea and run with it in the future.

Finally, in the "Other Stuff" we again are honored to have poems by Elizabeth (Betsy) Rowe PhD and Vernon (Bud) Rowe MD, who are poets inspired by their science and medical background.

Enjoy this jam-packed and exciting issue of the RRNMF Neuromuscular Journal. And once again, thanks to all who continue to make this unusual publication and communication platform possible.

Rick

Dylan Mortimer, left, and Dr. Richard J. Barohn pose with Mortimer's artwork titled "So Fresh, So Clean."

Jane Cooke Wright, MD: A pioneering cancer physician and researcher

Richard J. Barohn, MD

Following up Black History Month in February is Women's History Month in March. It is a fitting time to remember Jane Cooke Wright, MD, (1919-2013) a leader in the field of cancer therapeutics.

Dr. Wright was born in New York City and attended the prestigious Smith College in Massachusetts. She wanted to attend Harvard Medical School, but they were not accepting women into medical school at that time. Her father, Louis Wright, MD, was one of the early African American graduates of Harvard Medical School and became a prominent surgeon and cancer researcher in New York City. He was the first African American admitted to the American College of Surgeons.

Jane followed in his footsteps, and together, they would become a team in fighting cancer.

Dr. Jane Cooke Wright

She attended New York Medical College on a four-year scholarship and then was an intern and resident at Bellevue Hospital and Harlem Hospital. Harlem Hospital at the time was primarily used by affluent white individuals and her father had risen to the director of surgery and then the chair of the Medical Board. He established the Cancer Research Foundation to study chemotherapy with grants from the National Cancer Institute.

Jane joined her father, and they became a team in fighting cancer. Dr. Louis Wright died of a heart attack and Jane took over the work and directorship of the cancer program at Harlem Hospital at the age of 33. In the laboratory, she screened hundreds of drugs for their potential to kill human tumors. Using cells from cancer patients obtained at the time of surgery or biopsy, she developed tissue cultures of these cells and exposed the tumor cells to a variety of drugs. There were only about 20 anti-cancer drugs available at the time and she would try to predict which drug would be most effective in destroying that patient's tumor cells.

This was very much an early attempt at precision medicine targeted for an individual patient.

In 1951, she was a pioneer in establishing that methotrexate was effective in treating breast cancer, which led to accepting chemotherapy as a treatment for cancer. Methotrexate continues to be used to this day. Prior to that time, there was significant hesitancy toward chemotherapy, which was used as a last resort.

President Lyndon B. Johnson appointed Dr. Wright to the President's Commission on Heart Disease, Cancer and Stroke. In 1967, she returned to New York Medical College and became professor of surgery, the head of the cancer chemotherapy department and an associate dean, becoming the highest ranking African American woman at a nationally recognized medical institution and the first African American dean at a medical school. The accolades continued as she was the first woman to be elected the president of the New York Cancer Society. She was one of seven founding members — and the only woman — of the American Society of Clinical Oncology.

Dr. Wright mentored many students and scientists over her 40-year career. She published many research papers on cancer chemotherapy and led delegations of cancer researchers to Africa, China, Eastern Europe and the Soviet Union.

Dr. Wright shakes the hand of President Lyndon B. Johnson. (Image credit: Cancer History Project; Edith Mitchell, MD)

She married an attorney and they had two daughters, Jane, who became a psychiatrist, and Alison, became a clinical psychologist. She had her first daughter as a resident in 1948. She took a six-month leave for the birth of her first daughter and returned to complete her residency as the chief resident.

Alison said of her mother in a 2011 interview: "She never looked at things as obstacles. She looked at them as challenges and I think that she was a very ambitious person and I think that she never let anything stand in the way of her doing what she wanted to do."

Tuesday, March 8, was International Women's Day. The theme this year is #BreakTheBias, which seeks to create a gender equal world free of bias, stereotypes and discrimination. In learning more about Dr. Wright, I hope you have been able to see how she fought against — and achieved so much — in the face of inequity.

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Physician Specialists: What's in a Name?

Joshua Freeman, MD

I had a recent conversation with someone who said that they were looking for a gerontologist for their parents. Since they were talking about a physician, I noted that the correct term is "geriatrician", one who practices geriatrics; a gerontologist is someone who studies aging but is not a physician. Geriatrician is parallel to pediatrics/pediatrician or obstetrics/obstetrician.

But it is not at all obvious. Indeed, most medical specialties and their physician practitioners follow the "ology/ologist" model: anesthesiology, radiology, neurology, cardiology, and so on. Therefore, it made sense to think a physician caring for older adults might be a gerontologist. But it isn't.

There are other terms for physicians in other specialties, and I guess you have to know each one. Sort of parallel to geriatrics/gerontology might be psychiatry/psychology, but the physicians who practice psychiatry are a psychiatrist, and psychologists can also be clinical practitioners, if not physicians. Following this psychiatry/psychiatrist model, the specialty that used to be called physical medicine is now called physiatry, and physicians practicing it are physiatrists. The parallel to psychology might be physiology, but physiologists, though they can have MD degrees, are researchers in physical function, not clinicians.

And the physicians who practice orthopedics, which seems similar to geriatrics/pediatrics and obstetrics are called orthopedists, not orthopedicians. The same ending is used for genetics and ethics, geneticist and ethicist, and these can be either physicians or other professionals! The general physician for adults is called an internist, but practices internal medicine, not internics. Internal medicine subspecialists are almost all "ologists" (cardiologists, gastroenterologists, nephrologists, rheumatologists, etc.). And now some internists have become "hospitalists", based on taking care of only hospitalized patients, and we are also hearing not only the opposite, "ambulists", but subtypes of hospitalists based on when they work – "nocturnists" and even "weekendists"!

The specialty of family medicine is practiced by family physicians or family doctors; the old terms family practice and family practitioner are no longer used. Of course, there are family nurse practitioners, generalists in the field, compared with pediatric, psychiatric, and adult (not internal medicine) nurse practitioners. Those who do solely women's reproductive health may be called women's health or OB-Gyn nurse practitioners, but the nurses trained to deliver babies are nurse-midwives.

A lot of these names are from Greek and Latin, and sometimes both are used in ways that can be confusing to a regular person. Pediatrics comes from the Greek for child, while podiatrist (a foot doctor, a DPM, not an MD) comes from the same root as pedal, the Latin for foot. Indeed, in anatomy, while the larger bone in the lower leg, the tibia, has a tibial artery, tibial vein, and tibial nerve, the smaller, the fibula (from Latin) has a peroneal artery, vein, and nerve, from the Greek for the same bone!

I have observed that, while to a health professional, the difference between orthopedics (bones) and orthodontics (straightening teeth) is clear, it is also obvious why these names might be confusing to a regular person. Knowing this stuff as a health professional makes you part of the in-group; knowing it as anyone else means you spend too much time at the doctor's!

You really can't tell the players without a scorecard!

An Open Message to the People of the United States of America

Donald R. Frey, MD

In the infamous words of the cartoon character Pogo, "We have met the enemy, and he is us." While many Americans are angrily looking about for an enemy, The People's Republic of China has emerged as a significant challenge to the United States. But what is actually the greatest threat to American democracy? In this imaginary letter from the Chinese Communist Party to the American people, our country's greatest threat gets explicitly spelled out. This may upset folks. I hope it does.

Of course, this is all just tongue in cheek. Or maybe not...

Dear America,

Hello neighbors! Your old friends at the Chinese Communist Party here. We understand that some of you are a little worried about the things we've been doing lately. So we decided to take a few moments away from our 100th year Anniversary celebration (Woo Hoo!) to assure you that we're the last people on earth you need to be worrying about right now.

Yes, over the past several decades we've been transitioning dramatically. We switched our economic system from pure communism to a mixture of capitalism and state oversight. It was pretty obvious we needed to do that as soon as we saw communism collapse in the old Soviet Union. Oh, we still call ourselves communists. We're still authoritarian. You might even call us a dictatorship. But as an economy? That's different.

And the results speak for themselves, don't they? Our economic growth is outpacing yours, pandemic or no pandemic. We have more people in our middle class than you have in your entire country. They're all consumers, they're all working, they're all travelling, they're all spending money. But most of all, they're all growing our economy.

Your little trade war has really helped in this regard—thanks a lot for that. Sure, trade with your country has slowed. But because of all the uncertainty America has forced upon the rest of the world, more and more nations now see us as the trusted trade partner. While you were abandoning your allies and tearing up your treaties, we've been quietly sending a different message to the rest of the world: "See—you can't trust America. New election? New President? It all disappears. America can't be counted on the way it used to be."

There was a time when your word was good. It didn't matter who your president was, or what party was in power. The world always looked to America for leadership. They knew what you stood for. Democracy. Fairness. Justice. And a concern for the world as a whole.

That's all out the window now, isn't it? You may not know it, but every time you start blustering about "America First!" your allies realize they can't depend on you. And if they're vulnerable, they have to look out for themselves. And that means seeking other alliances wherever they can.

That's where we come in. If the rest of the world can't trust you, they still have to do business with us. Maybe not trust us. Maybe not even like us. But they know they have to strike deals with us to protect their own interests.

While you've been drawing inward and turning your back on the world, we've been expanding. Our Belt and Road Initiative will lock-in worldwide trade in a fashion you can't even imagine. Right now, we have more economic development going on in Africa than you've ever dreamed of. And Europe? We've just signed one of the biggest trade deals in history with the European Union.

Your decision to pull out of the Trans-Pacific Partnership Agreement, of course, was a big plus for us, too. Can't trust the U.S? Here we are!

The rest of the world sees this, even if you don't. Every economic study shows our economy blowing past yours before 2030. How will you compete with us then with no allies? Where will your former allies turn if they can't trust you, and you offer no leadership?

You know the answer. Us.

The idea of a single-party state doesn't sound nearly as bad to the rest of the world now as it did when you were in your heyday. If the U.S. is really the great example of democracy, that "shining city on the hill," then the rest of the world is getting pretty nervous about whatever it is that that's supposed to mean.

You claim to be all about free elections, yet months after a clear decision, 40% of your own people think your last election was rigged. You keep counting ballots, over and over, for no other reason than to subvert the very democracy you claim to hold so dear. You already know the result. You just don't care. Or maybe democracy just isn't that important to you anymore.

The world watched in horror as you stormed your own capitol and tried to overthrow your own government. Well, most of the world watched in horror. We didn't. We just sat back, laughed, and said thank you, America. Thank you very much.

The truth is, right now you are so utterly divided you couldn't begin to deal with an advisory. No, we don't mean militarily. We mean economically. Politically. You've nearly isolated yourselves completely, and you're too self-absorbed to even see what's happened. And you're apparently too clueless to understand the long-term ramifications.

Q-Anon, Proud Boys, 3%er's, Oath Keepers, Militias, you name it. The fact that so many of your people think these groups are making America great is music to our ears. It's the gift that keeps on giving.

We also really appreciate your disdain for anything that even sounds like science. Yes, we could be acting more quickly regarding climate change, but at least we recognize

that it's real. We don't run around calling it an American hoax.

But it's been the pandemic that's really brought out the best in your science-denial lunacy. We fumbled the opening days of the pandemic, we admit that. But once we confronted the truth, we acted boldly and with purpose. We shut down Wuhan province. Our scientists sequenced the COVID viral genome in less than 36 hours. Our factories manufactured N-95 masks at a rate of 100 million per day. We had vaccines available by last July. And we're now supplying them to over fifty countries around the world.

So much for that "Operation Warpspeed" of yours.

And yes, one party rule has its advantages. When we commit, we commit. No local governors whining about masks and lockdowns, or pushing quack-science. The result has been that we've come out of this pandemic faster and stronger than you.

Oh, yes, we know that about half of your country thinks either this virus is a hoax, or that it was intentionally caused by us (we suppose some people hold both opinions, which seems pretty dumb, but hey—you're America). You'll be happy to know that we have millions of people here who think the virus was smuggled into our country by your CIA. As your famous Senator Forrest Gump once said, "stupid is as stupid does." It seems to work that way in all countries.

There was a time when your Centers for Disease Control (CDC) would have stepped in to lead the world out of this whole thing, but those days are long gone, aren't they? But thanks for giving us a chance to replace you.

And what about science more fundamentally? While you've focused on cutting taxes, we've been plowing money into research facilities. We've landed a Rover on the dark side of the moon, something you haven't come close to doing. We've transmitted messages with quantum encryption over 2,000 kilometers, and now we're zeroing in on quantum supremacy. When that happens, your national data will be toast.

Also, a big shout out for your anti-immigration policies. This helps ensure that our scientists who might otherwise have relocated to Caltech, MIT, and Harvard will be staying right here at home and making their discoveries at our facilities.

Oh, we admit we haven't always been the nicest guys. But you've given us plenty of cover. Sure, we've been brutal to the Uyghurs. But they're Muslims. And half the rightwing nut jobs in your country think that all Muslims are terrorists. So why should we be any different? We're just being careful, that's all.

And maybe we were a little rough on those Hong Kong protestors. But you know all about that, don't you? Those Black Lives Matter protestors, those Native Americans at Standing Rock? Sometimes you have to break a few bones to keep the peace, right? But regardless, at this point, no one else in the world thinks you have any moral authority to criticize us for what we do.

And your whole backing away from foreign aid (unless it involves selling fighter jets to Israel and Saudi Arabia) has really opened doors for us. We pitch in when you pull out. And it pays. Throughout the world, international media gives us great press while your coverage continues to slide. Don't your schools teach anything about The Marshall Plan anymore? Remember, that's how you once won the world, and set the stage for winning the cold war. But it's sure not happening now, is it?

Speaking of school, what the hell is going on with your educational system, anyway? Most of your parents are more concerned about what their kids *don't* learn in school, than what they actually *do* learn. Evolution, racial injustice, sexual identity, library books that seek to ask questions that parents don't like—banning all of these things is way more important than whether a kid can actually read or write, much less know anything about calculus. Oh, that, and whether or not they get to start on Friday night for the local football team.

So you have lousy schools for the majority of your kids, and fancy private schools for the privileged few. And then the powerful use their influence to get their kids into your so-called "Ivy League" colleges, where they'll be set for life. (Who was that guy that was your President's son-in-law—you know, Kushner—who magically got accepted at Harvard shortly after his father had donated over a two million dollars to the School? And you guys call us corrupt).

And just for the record, Chinese students' test scores, especially in Math and Science, continue to be some of the best in the world. Just one more example of how we're blowing you away.

This stuff you keep yelling at each other baffles us, too. Cancel culture, wokeness, critical race theory (whatever that is). My God (that's just an expression, we really don't believe in God), you'd think you were arguing over really important stuff like mask mandates, vaccines, evolution, the big bang, viral exposure, or whether the earth is flat. Don't get us started on powerful lights and injectable disinfectants to treat COVID. We have no idea what you're thinking, but whatever it is, please, please keep thinking it. You just grow weaker every day, and we grow stronger.

Oh, and please keep demonizing immigrants, too. Keep calling women and children who are just trying to escape a land of death and destruction "rapist and murders." Keep calling them caravans (a good way to dehumanize them, right?). Keep letting them die in the desert. The whole world remembers how you took in every Cuban who fled that country, but now slam the door in the face of people whose conditions are even more dire.

There's a name for that. It's called hypocrisy.

Most of all, keep physically attacking every Asian you can find. Videos of elderly Asian women being beaten on the streets of America make for great press around the world. Never mind that these people, whose ancestors happened to come from places like Japan, China, Korea, and Thailand,

are just as "American" as you. Never mind that many have family members who fought and died in the American military. That doesn't matter, does it? Just because their eyes are shaped differently, keep abusing them.

People look at these pictures in disbelief, then look at us. We just smile, shrug, and say, "well, I guess that's democracy for you."

Oh, we almost forgot. Your religion. Regardless of what "faith" you might claim, the whole world knows what you truly worship.

Your guns.

We admit, we shouldn't find it amusing how you keep killing each other off in your country, then excuse it by saying, "that's just the price we pay for our freedom." But really? You've had your sacred second amendment for 200 years, but you were never anything like this.

But now, for whatever reason, you have this absolute fetish for guns. Maybe they make you feel safer. Maybe they make you feel powerful. But one thing is certain—you're slowly killing yourselves off.

Vladimir Lenin supposedly said, "when it comes time to get rid of the capitalists, they'll sell us the rope to hang them with." Who knows if he really said it or not, but one thing is certain. If he were alive today, he'd say something else: "When it comes time to get rid of the Americans, don't worry about rope. Just make sure they have plenty of guns. They'll do the job themselves."

So keep believing that having a pile of guns "keeps you free" even though history doesn't support it. The Soviet Union fell. Apartheid South Africa fell. What were the decisive battles of those wars, where people's guns brought down the government?

You know the answer. There weren't any.

But never mind. Please keep hoarding guns and using them on one another. Keep passing laws that make it easier to carry them, display them, sell them, use them. Whatever. They won't do a bit of good in a cyber-attack (and we hope it never comes to that), but it'll sure make the job a lot easier for your attacker. Because there won't be nearly as many of you around.

We sometimes watch old American television. Some of it's actually pretty entertaining. One of our favorites was the old science fiction show called "The Twilight Zone." One episode speaks loud and clear to America today. It's called "The Monsters are Due on Maple Street." Fortunately, most Americans haven't seen it. And most probably wouldn't understand it anyway. So just forget we even mentioned it, OK?

We admit that we're not quite sure what to think about your new guy, Biden. He's pushing buy American and all of that stuff. Good luck with that. The way you people think, half of your country will buy even more of our goods just to spite him.

But we *are* worried that he'll start to reengage with the rest of the world. The last thing we want to see is America rebuilding its international partnerships. But we'll see. As we've said, we think America has decided that its own internal politics are the only thing that matters. So we predict you'll continue to drift off, further and further, into your own little world, regardless of which of your political parties is in charge. And we'll just grow stronger.

So that's where we see things, America. We're passing you up economically and commanding more and more of the spotlight on the world stage. Really, for us, Donald Trump could not have come along at a better time.

It's much like that old folk tale about the tortoise and the hare. While you, the speedy hare, have been snoozing and basking in your past glory, we, the tortoise, have been gradually plodding along and catching up. But in our story, there's a twist. Now the tortoise has sprouted wings and we are flying away from you faster and faster.

All things end, including empires. From the Moguls to the Khmer, from the Incas to the Aztecs, from the French to the British, there have always been nations who believed they were the strongest in the world. And maybe they were, for a while. But eventually even the British—the empire upon which the sun would never set—saw its light grow dim. It bowed to a new empire—America.

And now you are about to be eclipsed by us. Perhaps it was inevitable. But the 21st century will be remembered as the time that China became the dominant empire. How many centuries will we last? Who knows?

Or perhaps not. There might always be the chance, no matter how slim, that you will awaken and recognize that we're not the ones you have to fear, rather it's yourselves and your own ignorance and divisiveness. You might just reunite as a nation, reengage the rest of the world, promote your principles of democracy and justice, and once again become the dominant force in forming alliances throughout the globe.

Yes, perhaps you will. But we aren't holding our breath.

You see America, it's not us you need to be worried about. It's you. The rest of the world sees this very clearly. It's a shame you can't.

But what a gift it is to us!

Love and Kisses,

The Communist Party Central Committee of The People's Republic of China, Beijing

Communicating with ALS: A Caregiver's Perspective

Harold Gibson

Premise

One of the unfortunate consequences of ALS is the significant problem of communicating with the patient. When the disease progresses to the stage of tracheotomy for continuation of breathing, the ability to communicate verbally is gone and secondary measures need to be implemented.

Observations

The most primitive of these is the letter board. This device is a chart of letters and numbers arranged in rows and columns. The caregiver points to a column until the patient responds by eye movement, then points to items down the rows of the column until selection confirmed. This is terribly slow and tedious usually results in frustration of all parties. This is a last resort option.

Probably the most common technologies offered to ALS people are computer aided communication systems known as Augmentative and Alternative Communication (AAC) devices. These are normally laptop computers running the Windows operating system and the provider's proprietary software. An infrared (IR) camera is mounted on the bottom of the laptop and functions by means of a reflection from the eye(s) which simulate mouse movements on the screen. Embedded software then interprets these movements and allows writing text, which can then be spoken by the computer voice. This also allows controlling things such as TV, DVD, etc., running Windows applications, like browsers and email, and other functions set up for users.

AAC is a great idea in theory, but there are problems associated with this technology. The Windows operating system tends to become bloated with accumulating broken links and data debris and requires occasional tech intervention to keep things running efficiently. These devices are expensive and, for most people, will require some sort of financing, usually provided from a government program and usually with a significant waiting period prior to approval. Most systems are designed for children and/or intellectually challenged persons which results in usage limitations for those with ALS who are largely more mature and intelligent. The learning and adaptation curve is quite long so a large investment and time and effort is required by both users and caregivers who are not necessarily technologically savvy. This can lead to limited and ineffective use of these system. The screens, while fine for interior locations, are not useable in bright light conditions such as outdoors or in a vehicle since they are simply too dim to be seen during daylight hours.

Although there have been tremendous advancements in computers and cameras, the software available is basically unchanged in the 16 years of our usage. Providers of AAC devices have done very little development in their systems and appear to simply put the same software on the newer devices. Perhaps this is because there is no great financial reward for investing in advanced development. This is a relatively limited market and usage, for the most part, ends up being short lived.

Another issue is how to communicate at night when in bed and the AAC is not available. Alarms will go off on the ventilator if things are not within settings, but what if a pressure point develops on a shoulder or the neck starts aching or a mosquito lands on the nose? Caregivers do need sleep occasionally and, even with good scheduling, it's difficult to have eyes on twenty-four hours a day. We've kludged up an alarm using piezo electric disks placed on the forehead (where there is still small movement) and, although effective, this is not a failsafe system due to dead batteries and failed sensors.

Future Hopes

From the caregiver's viewpoint, what do we hope for the future? As stated above, it appears the major providers of AACs are simply repackaging their existing software into newer hardware technology. If there were an effort to rethink the software application, it's likely that more effective systems could result.

Elon Musk, of Tesla electric vehicle fame, is developing a "neuralink system" which involves implanting sensors in the brain. Others, primarily in universities, have been studying this or a form of it with a sensor cap to be worn on the head. To date none of these systems have seen use in the real world. Not really sure how to feel about this solution as of yet and it's apparently some time away

Military aircraft for a couple of decades have been using "heads up displays" (HUDs) where images are visible on the forward windscreen or helmet visors. These give aircraft status, environmental and weapons data to the pilot without having to look down at gauges. Certainly, this technology is mature enough to be adapted to assist disabled persons.

In some industrial processes, cameras are employed to inspect widgets as they pass by at high rates of speed. Such systems are able to process an image through computer algorithms (software) to determine if they are correct or should be rejected. Why shouldn't this type of imaging processing be available to non-communicating people? For example, if a patient is in bed with no AAC set up and

attention is needed, a camera or maybe even a cell phone could be set up to focus on the face. As the eyes open wider, or move left, right, up, down, or close, visual attributes change. These changes, through image processing, could be used to activate an alarm so that assistance would be at hand. Law enforcement and the military are using facial recognition even today, so this is not that big of a reach. With state of the art cell phone cameras and the ability to write apps for them, this should not be a pie in the sky application.

Conclusion

ALS is a very unfortunate disease for people afflicted with it and is traumatic for loved ones and friends. Trying to communicate with patients is frustrating, and sometimes even maddening, for all involved. It's discouraging that in an age of ever advancing information processing technology and software development methods that more progress has not been made in this area.

Reflections on My Double Lung Transplant

Dylan Mortimer

I was born with a respiratory disease called cystic fibrosis. It's a deadly degenerative disease that had a life expectancy of 17 when I was born. There was not a lot of hope in those days for someone like me. I turned to art as a way to imagine. Not to simply escape my fears, but to own them and be honest with them. I began drawing and painting from an early age, and though the work did not directly have to do with my health condition, it framed much of how I saw the world. As time went on I continued with art, majoring in Painting for a BFA at the Kansas City Art Institute and in Fine Arts for an MFA at the School of Visual Arts. My work at the time had to do with ideas of faith, prayer and spirituality. I got married and had kids, both miracles for a CF patient like me, but my health began to worsen and I began evaluation for a double lung transplant.

At this time I felt it dishonest not to bring my health into the visual conversation. I reconciled that my disease was not all of me, but it had been a significant part. I started making work directly in response to my journey, and my experience spanning between trauma and joy. The subject matter I began to use were symbols of immense difficulty for me: bronchial trees, scars, iv bags, cells, and a variety of biological and medical imagery. I was drawing these images on thick paper to cut out. I had been using glitter in the previous work, and this seemed to make perfect sense with this new imagery. Transforming the trauma and difficulty into glistening, glowing objects of inspiration and hope. I began to see the parallels of glitter with disease. It's dirty, gets everywhere, and people are afraid of it. Yet it transforms things. The stories of overcoming and victory are unlike anything. Glitter held the tension for me. Speaking to the unspeakable terror of living with a degenerative rare disease, yet offering hope in the midst of it.

So I adorned these objects and created collage paintings out of them. All bathed in glitter. And the glitter layered on top of itself in a baroque symphony of pain and joy. It was important to evoke that balance. Having a disease like this is terrible. Yet the triumph over it brings unspeakable joy. Much like the symbols I use. You wouldn't wish them in themselves on anyone: scars, cells, pills, medical equipment. But those very things save our lives. It is both/and. But the triumph of living amidst all these challenges far outweighs the physical and metaphysical challenges.

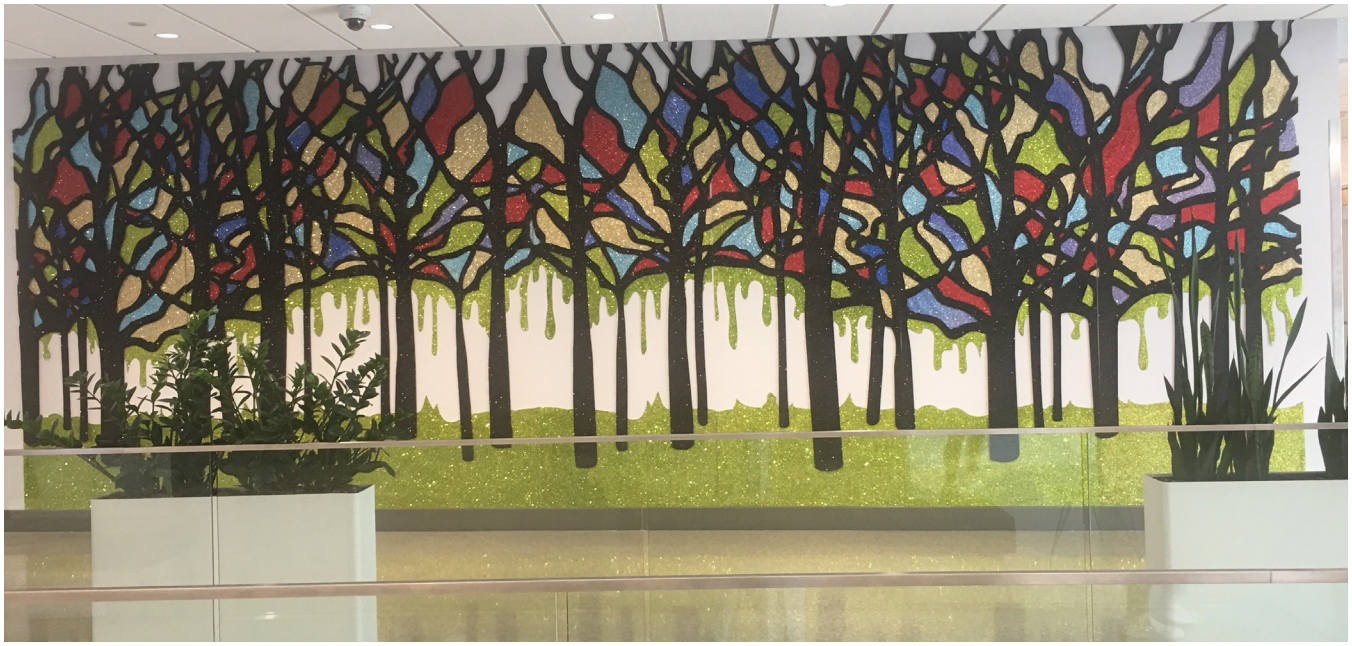
I went on to receive a double lung transplant in 2017. I felt the best I ever have in my life for about a year and a half. I began to make artwork about what healing feels like... imagining how to visualize breathing fully for the first time in my life. But then quickly I experienced rejection and was listed for a second double lung transplant. I received a second transplant in April 2019 at Columbia University in New York City. In the most unlikely of ways, I was matched when I had less than a 1% chance to find a donor.

"Assaultingly Beautiful" by Dylan Mortimer.

Receiving someone else's lungs is an experience beyond words. It draws me again to the tension. It is tragic that two people died, and I mourn their loss with every breath. Yet I live because of them, and honor them with every breath. I did not earn or deserve new lungs... they were a gift. No one "earns" breathing! We receive it as a gift—whether through birth or transplant. And with this gift we celebrate. The way I celebrate is through visual art. It is my way to share that which is genuinely too much for words. But I can imagine and tell the story this way. My glistening symphony is my attempt to transform all this difficulty and pain into a celebratory party. I hope my story helps others to keep up the fight to see life beyond what is thought possible.

I'm fortunate not only to be alive but to create in this way. I have installed work in public and private

collections nationally and globally. I love to transform hospital and clinic spaces especially. As a patient I walked by too many blank hospital walls, or walls with stock art or neutral environments. Where are people more in need of inspiration, hope, and a sense of dignity? I have personally found hospitals and clinics to be some of the more undignified places. The neutral atmosphere often feels cold and impersonal to someone struggling. We need hope in those spaces. I aim transform more spaces and have been very fortunate to be a part of that transformations in hospitals around the world. I aim to keep breathing, keep creating and sprinkling hope everywhere I can.



"The Congregation" by Dylan Mortimer.

"On My Mind" by Dylan Mortimer. Pictured with the artist, left, and Dr. Richard J. Barohn, right.

Optimizing Chronic Inflammatory Demyelinating Polyneuropathy Care with Subcutaneous Immunoglobulin: The Polyneuropathy and Treatment with Hizentra Open-Label Extension (PATH OLE) Study and Beyond

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ABSTRACT

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a heterogeneous, acquired autoimmune neurological disorder affecting peripheral nerves. CIDP is characterized by progressive weakness, reduced or absent tendon reflexes and impaired sensory function in the lower and upper limbs. CIDP diagnosis is mainly based on clinical, laboratory and electrophysiologic criteria and there are currently no diagnostic or prognostic biomarkers. First-line treatment options include corticosteroids, intravenous immunoglobulin (IVIg) and plasma exchange (PLEX). While IVIg and corticosteroids are the most common therapies administered for CIDP, there are challenges associated with their use, including systemic adverse events (AEs), some of which can be serious. Studies have shown that subcutaneous immunoglobulin (SCIg) may be associated with improved quality of life, which is attributed partially to the patients' freedom to administer SCIg at home and at their convenience. While AEs with SCIg mostly consist of local site reactions, SCIg is associated with fewer systemic AEs compared with IVIg, and these are commonly mild, though severe reactions may rarely occur. A number of studies in the last decade have assessed SCIg in CIDP. One of these studies, the Polyneuropathy and Treatment with Hizentra® (PATH) study, was a global phase 3, double-blind, randomized, placebo-controlled trial that assessed the efficacy, safety, and tolerability of SCIg treatment in patients with CIDP. Based on the results of the PATH study, the US Food and Drug Administration (FDA) approved SCIg as a maintenance treatment for CIDP in 2018. This review summarizes and discusses the results of the PATH study and its open-label extension (OLE) study and provides an overview of the April 2021 update to the Hizentra® FDA-approved U.S. package insert based on findings from the PATH OLE. In addition, the review highlights key elements of the second revision of the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guideline for the diagnosis and treatment of CIDP. Finally, this review discusses the characteristics of patients with CIDP who may benefit from SCIg treatment.

Keywords: *Chronic inflammatory demyelinating polyneuropathy; Subcutaneous immunoglobulin; Immunoglobulin therapy; Maintenance therapy; Treatment guidelines.*

CIDP Pathophysiology

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disorder that typically presents with symmetric distal and proximal weakness of the leg and arm muscles that progresses over more than 8 weeks, abnormal sensation such as tingling or numbness (beginning in the toes and fingers), and reduction or loss of deep tendon reflexes (hypo or areflexia) (1, 2). Additionally, less prominent symptoms of CIDP include fatigue, ataxia and neuropathic pain (1-3). The diagnostic criteria for CIDP were recently published (4), and a more detailed description of CIDP and its variants will follow in section '*Updated 2021 European Academy of Neurology (EAN)/ Peripheral Nerve Society (PNS) guideline*'.

The pathophysiology of CIDP is incompletely understood and involves mobilization of cellular and humoral autoimmunity, although the relative contribution of each is not well elucidated (1). CIDP is believed to be driven by heterogeneous immune-mediated processes (1). Humoral factors are thought to play a major role in CIDP pathogenesis, as demonstrated in passive transfer experiments using sera and purified IgG from patients with CIDP (5). The role of humoral factors in CIDP is also supported by the beneficial effects observed with plasma exchange (PLEX) while T cell activation leading to macrophage-induced myelin degradation supports the contribution of cellular immunity (6).

CIDP Epidemiology

Due to its heterogeneous presentation, CIDP diagnosis relies on findings from multiple modalities. CIDP is more common in males and can occur at any age, but the onset is usually between 40 and 60 years with peak prevalence in the 8th decade (4, 7).

An estimated 20–21% of neuropathy cases at large academic centers are inflammatory neuropathies (8, 9). A 2019 systematic review of 11 CIDP studies that reported the incidence and prevalence of CIDP, showed substantial heterogeneity between studies, which may partly be explained by the use of different diagnostic criteria (10). CIDP prevalence increased with age, and most patients were male, but no evident geographical variation in the incidence or prevalence rates was observed (10). The

reported prevalence of CIDP varies greatly, from 0.67 to 10.3 per 100,000 (10). In Olmsted County, Minnesota, at the start of 2000, CIDP had a prevalence of 8.9 per 100,000 (11). Between 1982 and 2001, CIDP incidence was 1.6 per 100,000 per year (11). A meta-analysis published in 2019 estimating the prevalence and incidence of CIDP worldwide, provided a pooled crude incidence rate for CIDP of 0.33 per 100,000 person-years and a pooled crude prevalence of 2.81 per 100,000 persons (10).

Current Treatments for CIDP

First line pharmacological treatments target immune dysfunction and include primarily induction with intravenous immunoglobulin (IVIg) or corticosteroids (e.g., prednisone) (4). PLEX (also known as plasmapheresis) is logistically complicated and is therefore recommended when IVIg and corticosteroids are ineffective (4). Choices for first line maintenance therapy include IVIg, subcutaneous immunoglobulin (SCIg), corticosteroids and possibly chronic PLEX (4). Immunosuppressive and immunomodulatory agents such as azathioprine, cyclophosphamide, rituximab, and mycophenolate mofetil are employed as second line therapeutic agents with limited evidence and variable results (4). Challenges with IVIg, corticosteroids and PLEX include systemic adverse events (AEs), some of which can be serious (12). A detailed description of the challenges associated with the aforementioned treatments is provided in a recent review (13). Retrospective cohort studies have reported that the incidence of thromboembolic events ranges from 10.6% to 16.9% in IVIg-treated inflammatory neuropathy patients (14-16). IVIg infusions also require monitoring by a clinician and can last four or more hours over one or several days (17). Regular peripheral venous access can be difficult to maintain for chronic intravenous (IV) treatments. Additionally, IVIg can be challenging to schedule for patients who work or travel (18). IVIg and SCIg exhibit comparable efficacy (19), but SCIg offers improved tolerability and enhanced autonomy and more stable IgG levels compared with IVIg (20).

IVIg infusions lead to a high post-infusion peak in serum IgG concentration at the end of the infusion, followed by a rapid decrease 48 hours post-infusion, and a slower decrease in IgG concentration over the next 30 days (21). This decline in IgG concentration can result in disease fluctuations and a return of symptoms prior to the next scheduled dose, also referred to as 'wear-off effects', which can be a concern as patients approach trough IgG values. Patients reporting wear-off effects may be suitable for considering dosage escalation (17). Wear-off effects are not typically seen with frequent SCIg administration, which is associated with stable, 'steady-state' plasma IgG levels between doses (22). Indeed, pharmacokinetic studies have shown that higher steady-state serum IgG levels are achieved with SCIg compared with IVIg, and that SCIg infusion results in higher trough and lower peak serum IgG levels than with IVIg, and smaller fluctuations in serum IgG levels (23, 24).

In the past decade, several studies have been conducted to investigate SCIg in CIDP. A meta-analysis evaluating results from eight of these studies, comprising 88 patients with CIDP and 50 patients with multifocal motor neuropathy, found that the use of SCIg was associated with a significant 28% reduction in the relative risk of moderate and/or systemic AEs compared with IVIg (20). In addition, studies have demonstrated an enhanced quality of life in patients with chronic inflammatory neuropathies receiving SCIg compared with IVIg therapy (25, 26).

The Polyneuropathy and Treatment with Hizentra (PATH) study (27), and its open-label extension (OLE) (28) demonstrated that SCIg is efficacious in maintaining patients previously stabilized on IVIg, and that treatment with SCIg beyond 24 weeks is safe and efficacious (**Table 1**). Both trials have been the catalyst for changes in treatment practices for the management of CIDP and improvement of patient care (27-29).

Hizentra®, a Subcutaneous Immunoglobulin

Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid, is a ready-to-use, sterile 20% (0.2 g/mL) protein liquid preparation of polyvalent human immunoglobulin G (IgG) for subcutaneous (SC) administration. It is manufactured from large pools of human plasma through a combination of cold alcohol fractionation, octanoic acid fractionation, and anion exchange chromatography (29). In the U.S, Hizentra® is indicated for immunoglobulin replacement therapy in adult and pediatric patients with primary immunodeficiency (PID) (29-33), and for maintenance therapy in adults with CIDP to prevent relapse of neuromuscular disability and impairment (29).

As indicated in the US Prescribing Information (USPI), a limitation of use associated with SCIg treatment in CIDP is that Hizentra® maintenance therapy has been systematically studied for 6 months in the PATH study and for a further 12 months in the PATH OLE study (29). Maintenance therapy beyond these periods should be individualized according to the patient's response and need for continued therapy (29).

The safety profile of Hizentra® is similar to that of other SC IgG therapies in terms of the type, frequency, and treatment-relatedness of AEs (34, 35). Data from seven open-label, phase 3, prospective, multicenter studies of

Table 1. Summary of the PATH (27) and PATH OLE (28) studies

Study characteristic		PATH study	PATH open-label extension study
Study endpoints and key efficacy data	**Primary endpoint**	• Proportion of patients with a CIDP relapse or who were withdrawn for any other reason during 24 weeks of treatment o In the ITT set, 36 (63%) patients on placebo, 22 (39%) on 0.2 g/kg SCIg, and 19 (33%) on 0.4 g/kg SCIg had a relapse or were withdrawn from the study for other reasons (p=0.0007)	• Determine the long-term safety of SCIg (Hizentra®) in patients with CIDP o In all, 62 (76%) patients had AEs; most were mild (62%) or moderate (29%); 8 (10%) had severe AEs; 3 serious local reactions in 1 patient were causally related to SCIg with no related serious AEs; 7 (9%) patients had serious AEs none of which were causally related to SCIg
	Secondary endpoints	• Time to primary endpoint, INCAT score, I-RODS score, Grip strength (dominant hand), Grip strength (non-dominant hand), MRC sum score o The probability of reaching the primary endpoint was significantly lower in both SCIg groups compared with the placebo group (p=0.0005 [0.4 g/kg SCIg vs placebo] and p=0.007 [0.2 g/kg SCIg vs placebo]) o Changes from baseline: INCAT score, p<0.0001; I-RODS score, p=0.0002; Grip strength (dominant hand), p=0.02; Grip strength (non-dominant hand), p=0.003; MRC score, p=0.003	• Determine the long-term efficacy of SCIg (Hizentra®) in patients with CIDP o Overall relapse rates were 10% in the 0.4 g/kg group and 48% in the 0.2 g/kg group o Following dose reduction from 0.4 to 0.2 g/kg, 51% of patients relapsed, of whom 92% improved after re-initiation of the 0.4 g/kg dose o Two-thirds of patients (19/28) who completed the PATH study without relapse remained relapse-free on the low-dose following dose reduction in the extension study
Most frequently reported AEs		• Any AE: o 33 patients (58%) in the 0.2 g/kg SCIg group o 30 patients (52%) in the 0.4 g/kg SCIg group o 21 (37%) in the placebo group • General disorders and administration-site conditions: o 16 patients (28%) in the 0.2 g/kg SCIg group o 18 patients (31%) in the 0.4 g/kg SCIg group o 6 (11%) in the placebo group • Local reactions: o 11 patients (19%) in the 0.2 g/kg SCIg group o 17 patients (29%) in the 0.4 g/kg SCIg group o 4 (7%) in the placebo group	• Any AE: o 33 patients (45%) in the 0.2 g/kg SCIg group o 46 patients (64%) in the 0.4 g/kg SCIg group • General disorders and administration-site conditions: o 8 patients (11%) in the 0.2 g/kg SCIg group o 18 patients (25%) in the 0.4 g/kg SCIg group • Local reactions: o 7 patients (10%) in the 0.2 g/kg SCIg group o 13 patients (18%) in the 0.4 g/kg SCIg group
Patient preference		Preferred current treatment: • 61 (53%) of 115 patients who received SCIg o 30 (53%) in the 0.2 g/kg group o 31 (53%) in the 0.4 g/kg group • 22 (39%) of 57 patients who received placebo Preferred previous IVIg treatment: • 21 (18%) patients receiving SCIg • 10 (18%) and 11 (19%) and 14 (25%) patients receiving placebo	Preferred current treatment: • 61 (82%) of patients preferred their current SC treatment o 35 (90%) in the 0.2 g/kg group o 50 (83%) in the 0.4 g/kg group Preferred previous IVIg treatment: • 9 (12%) of patients preferred their previous IVIg treatment o 2 (5%) in the 0.2 g/kg group o 7 (12%) in the 0.4 g/kg group

Abbreviations: AE, adverse event; CIDP, chronic inflammatory demyelinating polyneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Neuropathy-Rasch-Built Overall Disability Scale; ITT, intention-to-treat; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; PATH, Polyneuropathy and Treatment with Hizentra; SC, subcutaneous; SCIg, subcutaneous immunoglobulin

the efficacy and safety of Hizentra®, conducted in Japan, Europe, and the U.S showed that Hizentra® is well tolerated; reported AEs were predominantly mild or moderate, and mostly consisted of local injection-site reactions (ISRs) (36).

Optimizing CIDP Care with SCIg: The PATH Study

The PATH study was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group 3-arm study that evaluated the efficacy and safety of two doses of Hizentra® (0.2 g/kg body weight or 0.4 g/kg body weight) versus placebo during a 24-week SC treatment period in patients with CIDP who had previously responded to IVIg treatment (**Table 1, Figure 1A**) (27).

Following screening, all eligible patients progressed through three study periods: an IgG dependency test period (lasting up to 12 weeks), a period of restabilization on IVIg (lasting up to 13 weeks), and a randomized SC treatment period (24 weeks of treatment with a final assessment at Week 25) (27). The IgG dependency test period was necessary to ensure that only patients who were still in need of IgG were randomly allocated (27). Only those patients who were established to be IgG dependent were enrolled in the IVIg restabilization period.

During the SC treatment period, a total of 172 patients were randomly allocated to three groups: 57 (33%) to the placebo group, 57 (33%) to the 0.2 g/kg SCIg group, and 58 (34%) to the 0.4 g/kg SCIg group (27). The primary outcome was the proportion of patients with a CIDP relapse or who were withdrawn for any other reason during the 24 weeks of treatment (27). A CIDP relapse was defined as a deterioration (i.e., increase) by at least 1 point in the adjusted (by excluding a 0 to 1 change in the arm score) Inflammatory Neuropathy Cause and Treatment (INCAT) disability score (range 0 [healthy] to 10 [unable to make any purposeful movements with arms and wheelchair-bound]) (37) at any SC treatment period visit compared with baseline (baseline scores were defined as the scores assessed at the end of the IVIg restabilization period) (27).

Secondary outcomes for the SC treatment period were time to the primary endpoint, INCAT score, mean grip strength for both hands separately, Medical Research Council sum score (range 0–80; including shoulder abduction, elbow flexion, wrist extension, index finger abduction, hip flexion, knee extension, foot dorsiflexion, and great toe dorsiflexion), and Inflammatory Neuropathy-Rasch-Built Overall Disability Scale (I-RODS; range 0 [most severe activity and social participation limitations] to 100 [no activity and social participation limitations]) (27).

The proportion of subjects experiencing a CIDP relapse or those who were withdrawn for any other reason (the primary endpoint) significantly favoured both SCIg groups as compared to the placebo group (p=0.007 [0.2 g/kg SCIg vs. placebo] and p=0.0005 [0.4 g/kg SCIg vs. placebo]) (27). In the intention-to-treat set, 36 (63%) patients on placebo, 22 (39%) patients on 0.2 g/kg SCIg, and 19 (33%) patients on 0.4 g/kg SCIg relapsed or were withdrawn from the study for other reasons (p=0.0007) (27). The absolute relapse risk reduction was 25% in the 0.2 g/kg SCIg group (p=0.007) and 30% in the 0.4 g/kg SCIg group (p=0.001) compared with placebo (27). The potential to prevent relapse with SCIg in PATH was overall similar to that documented for IVIg in previous studies, though there are no head-to-head comparisons (37). This randomized trial in patients with CIDP is the largest to date and the only to study two doses of SCIg in parallel (27). Based on the PATH study results, the FDA approved Hizentra® as a maintenance therapy for CIDP in March 2018 (29).

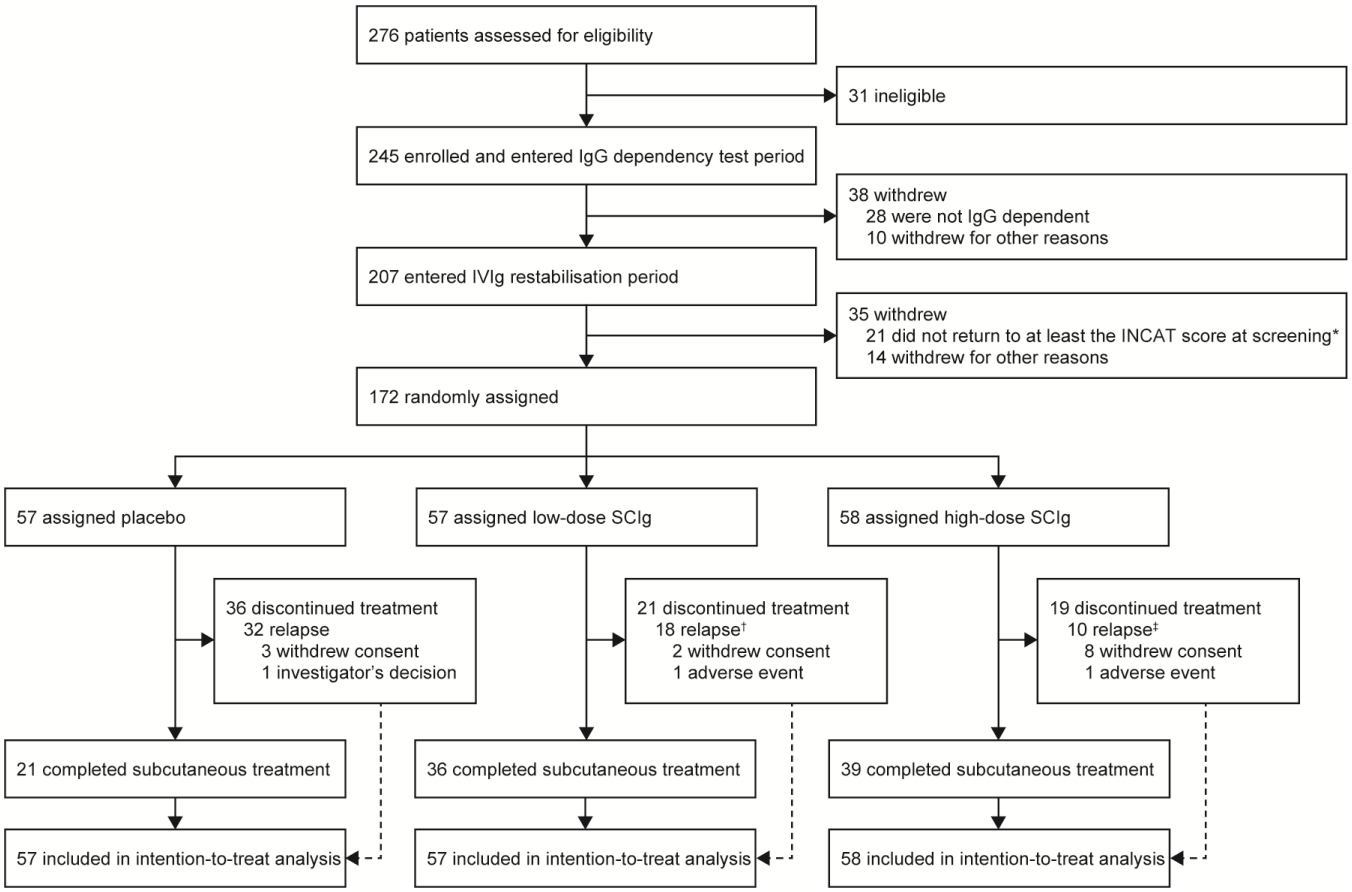
The findings from the PATH study have practical implications for the treatment of CIDP, demonstrating that patients on a standard regimen of IVIg can be safely transitioned to SCIg. The recently updated EAN/PNS treatment guideline recommend individualization of IgG dose, by using the same mean dose (1:1) per week when switching patients with CIDP from IVIg to SCIg. If the treatment effect is found to be insufficient, the guideline recommends that the dose be adjusted using reliable outcome measures (4). In line with the updated EAN/PNS treatment guideline, it is good practice to tailor SCIg doses in the range between 0.2–0.4 g/kg, based on patient intrinsic factors: previous IVIg dose and frequency, overall social situation and clinical response (4, 27, 29).

Optimizing CIDP Care with SCIg: The PATH Open-label Extension Study

This 48-week prospective open-label extension to the PATH study aimed to investigate the long-term safety and efficacy of weekly SC Hizentra® in CIDP (**Table 1, Figure 1B**) (28). In total, 82 patients were enrolled; 62 patients initially received 0.4 g/kg weekly, and 20 patients received 0.2 g/kg weekly. Clinically stable patients switched to 0.2 g/kg weekly after 24 weeks (28). After a protocol amendment, the low dose (0.2 g/kg weekly) was chosen as the initial dose. Patients remained on the 0.2 g/kg dose for 48 weeks unless relapse occurred, in which case the patients were given the option to switch to 0.4 g/kg. CIDP relapse was defined as a deterioration by at least 1 point in the total adjusted INCAT score (28).

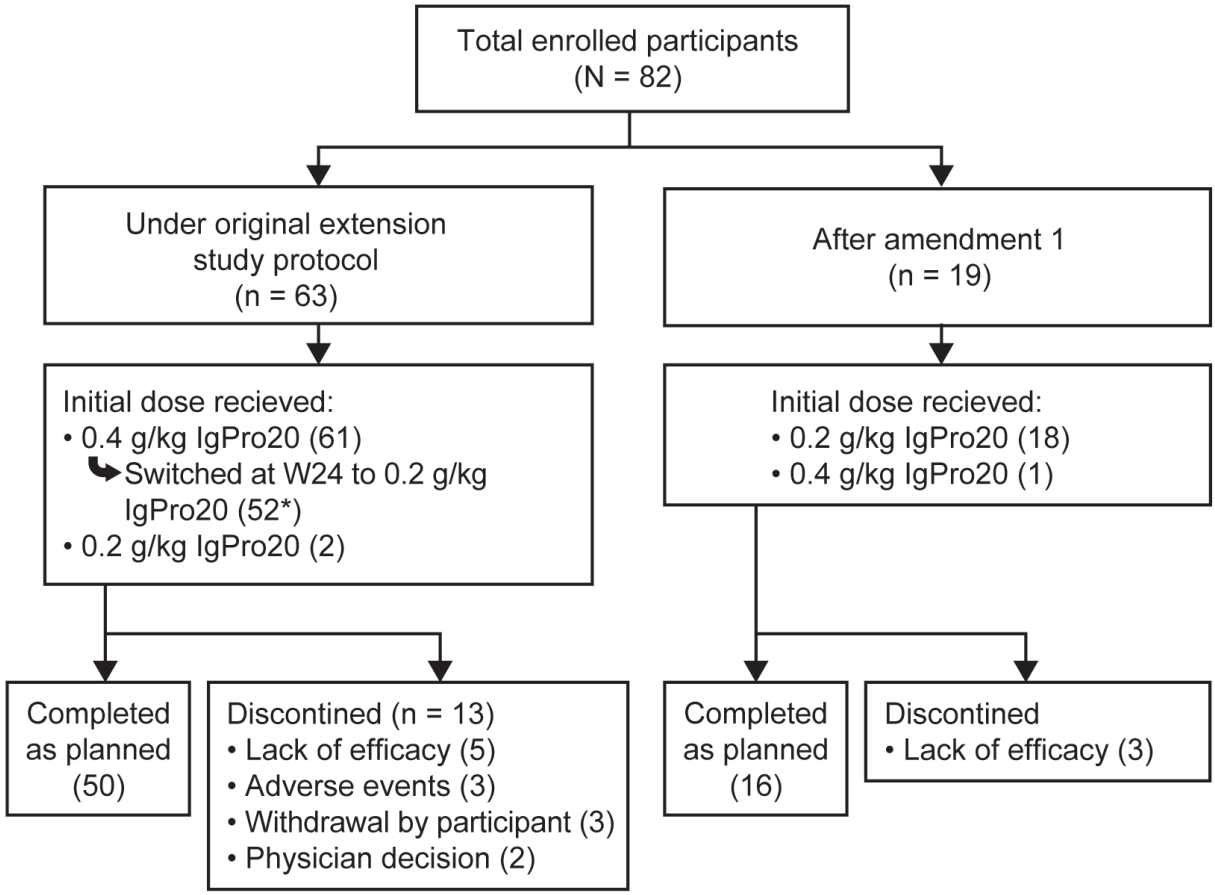
Of the 62 patients who initially received 0.4 g/kg SCIg, 52 switched to 0.2 g/kg SCIg after 24 weeks, of whom 26 (50%) relapsed (28). Overall relapse rates were 48% in patients treated with 0.2 g/kg SCIg, and 10% in patients

Figure 1. Trial design for PATH and PATH-OLE studies
A. PATH study design (Diagram taken from van Schaik IN et al. 2017 (27))



Abbreviations: INCAT, Inflammatory Neuropathy Cause and Treatment; PATH, Polyneuropathy and Treatment with Hizentra; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin
Footnotes: *An additional patient did not return to at least the INCAT score at screening, but was randomly allocated in error. †One patient relapsed at the end of study visit, but was not discontinued, so the total number of patients with a relapse in the low-dose group was 19. ‡One patient relapsed at the end of study visit, but discontinued the study because of an adverse event, so the total number of patients with a relapse in the high-dose group was 11.

B. PATH-OLE study design (Diagram taken from van Schaik IN et al. 2019 (28))



Abbreviations: PATH-OLE, Polyneuropathy and Treatment with Hizentra open-label extension
Footnotes: *Including one subject who relapsed twice on high dose but switched to low dose at week 24 and discontinued due to lack of efficacy.

treated with 0.4 g/kg SCIg (28). Of the 35 patients who relapsed on 0.2 g/kg SCIg, 31 (89%) improved within 4 weeks after re-initiation of 0.4 g/kg SCIg (28). Three of the 7 relapses (43%) occurring on 0.4 g/kg SCIg improved spontaneously without further intervention. Two-thirds of patients (19/28) who completed the PATH study without a relapse remained relapse-free after switching from 0.4 g/kg SCIg to 0.2 g/kg SCIg in the OLE (28). Overall, AEs were reported in 62 patients (76%), of which most were mild or moderate (28). Seven patients (9%) had 8 serious AEs (SAEs); none of these events were considered causally related to SCIg. Twelve severe AEs were reported in 8 patients (10%). All severe AEs resolved, except for a pre-existing vitamin D deficiency in 1 patient in the low-dose group, and 1 AE of infusion site swelling and 1 AE of infusion site erythema, which occurred in the same patient in the 0.4 g/kg SCIg group. Two patients were discontinued from the study as a result of AEs while on 0.2 g/kg SCIg and 1 patient while on 0.4 g/kg SCIg (28).

At study end, 82.4% of patients preferred their current SC treatment (28). In comparison, 12.2% of patients preferred IV treatment, whereas 5.4% had no preference on the route of administration. Most patients (71.6%) preferred SCIg treatment as the treatment was believed to offer more independence (28). The second most common reason (as reported by 40.5% of patients) for SC preference was spending less time receiving therapy (28). Other reasons for SCIg preference included "preferred frequency of administration", "my therapy works better" and "seem to feel fewer side effects", reported by 37.8%, 35.1% and 31.1% of patients, respectively (28).

The PATH OLE study demonstrated that SC treatment with Hizentra® provides prolonged benefit at both 0.2 g/kg and 0.4 g/kg weekly doses and suggested lower relapse rates on the higher dose (28). Importantly, a substantial proportion of patients can be switched from 0.4 to 0.2 g/kg weekly SCIg dose without further worsening, emphasizing that in clinical practice, dose reductions should be

considered in optimally treated and stable patients, and patients who relapse can be treated by increasing the dose of SCIg (28).

Updated Hizentra® U.S Food and Drug Administration (FDA) US Prescribing Information: April 2021

The previous FDA prescribing information for Hizentra® in the treatment of CIDP required that if patients worsened while receiving 0.2 g/kg body weight per week SCIg, then IVIg should be re-initiated. In April 2021 the prescribing information was updated to no longer require stabilization with IVIg if a patient worsens while on 0.2 g/kg weekly SCIg. The FDA-approved update now recommends that if CIDP symptoms worsen while receiving 0.2 g/kg SCIg, an increase to 0.4 g/kg per week should be considered (29).

The update to the USPI includes the results of the PATH OLE study, which demonstrated that after transitioning from IVIg to SCIg, both SCIg doses (0.2 g/kg or 0.4 g/kg) were effective in preventing CIDP relapse, with the 0.4 g/kg dose more likely to prevent relapse (27, 29). In cases where CIDP symptoms worsen on 0.4 g/kg, re-initiating therapy with IVIg, while discontinuing Hizentra®, should be considered. Additionally, it is important to monitor patients' clinical response and adjust duration of therapy based on the individual needs of the patient (29).

Updated 2021 European Academy of Neurology (EAN)/ Peripheral Nerve Society (PNS) guidelines

The 2010 consensus guideline on CIDP (38) has been revised, and the clinical criteria for defining CIDP into 'typical CIDP' and 'CIDP variants' have been refined in the updated 2021 EAN/PNS guidelines on the diagnosis and treatment of CIDP (4). A description of the clinical characteristics of typical CIDP and CIDP variants is provided in **Table 2.** The aim of the update was to optimize diagnostic accuracy and to improve patient outcomes. The updated guideline provides more clarity on the clinical definition, electrophysiologic criteria, implications of nodal and paranodal antibodies, and individualization of treatment for CIDP. Among the notable changes, the previous term 'atypical CIDP' is no longer used and has been replaced by 'CIDP variants'. SCIg was strongly recommended as maintenance treatment in IVIg-responsive patients with active disease. While anti-myelin associated glycoprotein (MAG) neuropathy was not previously considered as part of CIDP, autoimmune nodopathies and chronic immune sensory polyradiculopathy are no longer considered subtypes or variants of CIDP (4).

Diagnostic criteria

Specific electrodiagnostic and clinical criteria were described, which are used to support the clinical diagnosis of typical CIDP and CIDP variants (**Table 2**) (4).

A comparison of the 2010 and 2021 electrodiagnostic criteria for a CIDP diagnosis is provided in **Table 3**. The revised EAN/PNS guideline has updated the motor nerve conduction criteria in support of the clinical diagnosis of CIDP (4). The distal compound muscle action potential (CMAP) duration increase (measured as the interval between onset of the first negative peak and return to baseline of the last negative peak) for support of the clinical diagnosis of CIDP in the 2010 guidelines was defined as median ≥ 6.6 ms, ulnar ≥6.7 ms, peroneal ≥ 7.6 ms, and tibial ≥ 8.8 ms (38). In the 2021 guideline, for distal CMAP duration prolongation, separate criteria were defined for four different low frequency filter (LFF) settings of 2, 5, 10, and 20 Hz (4). These criteria have been summarized in **Table 4**.

In patients fulfilling the clinical criteria for typical CIDP but not the electrodiagnostic criteria, the diagnosis of possible typical CIDP may be made if there is objective improvement with IVIg, plasma exchange, or corticosteroids, and if at least one additional supportive criterion (imaging [ultrasound, documenting nerve swelling at the site of conduction block], cerebrospinal fluid [CSF], or nerve biopsy) is met (4).

Clinical presentations different from typical CIDP are now considered CIDP variants, and not 'atypical CIDP'. The EAN/PNS 2021 guideline defines five CIDP variants: distal CIDP, multifocal CIDP, focal CIDP, sensory CIDP, and motor CIDP; however, no biomarkers specific to each clinical subtype have been identified (4, 39). A detailed description of the electrodiagnostic criteria for typical CIDP and CIDP variants is provided in **Table 2**.

Differential diagnosis

Aside from a combination of clinical, electrodiagnostic and laboratory features, the diagnosis of CIDP relies on exclusion of other disorders that may mimic CIDP (4). Differential diagnoses include drug or toxin exposure, IgM monoclonal gammopathy, elevated titer of antibodies to MAG, as well as other causes for a demyelinating neuropathy such as POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) and osteosclerotic myeloma (4).

Autoimmune nodopathies

Antibodies against nodal and paranodal cell-adhesion molecules (contactin-1 [CNTN1], neurofascin-155

Table 2. Clinical characteristics and electrodiagnostic criteria for typical CIDP and CIDP variants (4)

Typical CIDP and CIDP variants	Clinical description	Electrodiagnostic criteria
Typical CIDP	• Characterized by Progressive symmetric proximal and distal muscle weakness, decreased or absent deep tendon reflexes and sensory loss • The clinical course is most commonly progressive over more than 8 weeks • In up to 13% of CIDP cases, the clinical onset is acute, but patients continue to deteriorate for more than 8 weeks after onset or relapse at least three times after initial improvement with therapy, also known as the relapsing-remitting form	• To confirm the clinical diagnosis of typical CIDP, at least two motor nerves must have abnormalities which fulfil the motor conduction criteria • If criteria are fulfilled in only one nerve, the diagnosis is possible typical CIDP • Sensory conduction abnormalities must be present in at least two nerves to confirm the clinical diagnosis of typical CIDP
Distal CIDP	• Weakness in distal CIDP predominantly affects distal legs with distal arm and leg sensory loss leading to ataxia of gait • Those with IgM monoclonal gammopathy and those with nodal/paranodal antibodies are excluded from the distal CIDP category	• Motor conduction criteria fulfilment is required in at least two upper limb nerves to confirm the clinical diagnosis of distal CIDP • The distal CMAP amplitude should be at least 1 mV • If the motor conduction criteria are fulfilled in only 1 arm nerve or only in 2 leg nerves, the diagnostic certainty is possible distal CIDP • Sensory conduction abnormalities must be present in at least two nerves
Multifocal CIDP	• Also known as Lewis-Sumner syndrome or MADSAM • Usually affects the upper limbs first; lower limbs may be involved, but this occurs later on in the disease course	• Motor conduction criteria fulfilment is required in at least two nerves in total in more than one limb to confirm the clinical diagnosis of multifocal CIDP • Sensory conduction abnormalities must be present in at least two nerves of the affected limbs for the diagnosis of multifocal CIDP
Focal CIDP	• Focal CIDP is rare and typically affects the brachial or lumbosacral plexus, but can also affect individual peripheral nerves	• Motor conduction criteria fulfilment is required in at least two nerves in one limb for the diagnosis of focal CIDP • Sensory conduction abnormalities must be present in at least two nerves of the affected limbs for the diagnosis of focal CIDP
Sensory CIDP	• Sensory CIDP is characterized by sensory symptoms and signs (gait ataxia, impaired vibration and position sense, and changes in cutaneous sensation) without motor involvement	• A sensory CIDP diagnosis must fulfil sensory conduction criteria while motor conduction must be normal in all of at least four nerves • Sensory CIDP is often a transient clinical stage that precedes the appearance of weakness in about 70% of patients. Therefore, the maximum diagnostic certainty is possible sensory CIDP
Motor CIDP	• Patients with motor CIDP present with relatively symmetric progressive proximal and distal weakness with normal sensation clinically and electrophysiologically	• Motor CIDP diagnosis must fulfil motor conduction criteria in at least two nerves and sensory conduction must be normal in all of at least four nerves

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; IgM, immunoglobulin M

Table 3. A comparison of the EAN/PNS 2021 (4) and EFNS/PNS 2010 (38) electrodiagnostic criteria for the diagnosis of CIDP

NCS Parameter	EAN/PNS 2021 Definite CIDP One out of 8 NCS parameters each in two nerves	EFNS/PNS 2010 Definite CIDP One out of 8 NCS parameters each in two nerves
NCV	≥30%	≥30%
F-wave	≥20% or 50%*	≥30 or 50%*
DML	≥50%**	≥50%**
F-wave‡	Absent † + **1**	Absent † + **1**
CB	≥30% † (not tibial)	≥50% †
CB‡	In 1 nerve † + **1** (not absent F)	In 1 nerve † + **1**
TD	>30% (except tibial 100%)	>30%
Distal CMAP duration‡	In ≥1 nerve + **1**	In ≥1 nerve + **1**

Abbreviations: CB, conduction block; CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; DML, distal motor latency; EFNS, European Federation of the Neurological Societies; EAN, European Academy of Neurology; LLN, lower limit of normal values; NCS, nerve conduction study; NCV, nerve conduction velocity; PNS, Peripheral Nerve Society; TD, temporal dispersion
Footnotes: *cut-off values depend on CMAP amplitude being < or ≥80% LLN.
** Excludes median nerve at the wrist.
† CMAP amplitude must be ≥20% LLN.
‡ This abnormal NCS parameter can be present in only 1 nerve but is associated with another NCS abnormality in a different nerve. It is referred to in the table as +1.

Table 4. Summary of distal CMAP duration prolongation criteria for the clinical diagnosis of CIDP, according to the revised EAN/PNS guideline (4)

LFF setting (Hz)	Distal CMAP duration (ms)			
	Median nerve	Ulnar nerve	Peroneal nerve	Tibial nerve
2	> 8.4	> 9.6	> 8.8	> 9.2
5	> 8.0	> 8.6	> 8.5	> 8.3
10	> 7.8	> 8.5	> 8.3	> 8.2
20	> 7.4	> 7.8	> 8.1	> 8.0

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; EAN, European Academy of Neurology; LFF, low frequency filters; PNS, Peripheral Nerve Society

[NF155], contactin-associated protein 1 [Caspr1], and neurofascin isoforms NF140/186) have been detected in a small subset of patients fulfilling 2010 EFNS/PNS criteria for CIDP. More recent studies reported a higher frequency of autoantibodies against these proteins (up to 12% of patients diagnosed with CIDP) (4, 39). The presence of autoantibodies against the nodal-paranodal cell-adhesion molecules (CNTN1, NF155, Caspr1, and NF140/186) is now associated with conditions known as 'autoimmune nodopathies', which were previously regarded as CIDP variants (4). A study conducted by Querol and colleagues reported that antibodies against yet-to-be-identified antigens are detectable in a larger proportion of patients with CIDP (39). In IgG immunocytochemistry experiments, 24.6% of patients showed reactivity against dorsal root ganglion neurons, 12.3% showed reactivity

against Schwann cells, and 5.3% showed reactivity against motor neurons (39).

The updated EAN/PNS guideline now considers autoimmune nodopathies a separate entity from CIDP, because they lack classical hallmarks of CIDP, including overt inflammation and macrophage-mediated demyelination, and are poorly responsive or refractory to IVIg (4). The updated guideline also suggests considering testing for nodal and paranodal antibodies in all patients with clinical suspicion of CIDP, to rule out autoimmune nodopathies (4).

Antibodies against CNTN1 are associated with acute or subacute disease onset and motor or ataxic features (4). Antibodies against NF155 were detected in patients diagnosed with CIDP who were younger at onset and had a subacute or chronic disease course, distal weakness, ataxia and tremor (4). Evidence suggests paranodal NF155 and CNTN1 are the most consistent and clinically relevant targets and demonstrate a pathogenic role in immune neuropathies (40, 41). Antibodies against Caspr1 are linked to an acute/subacute neuropathy frequently associated with ataxia, neuropathic pain and cranial nerve involvement (4).

Treatment of CIDP

The updated EAN/PNS guideline strongly recommends first line treatment with IVIg, corticosteroids or PLEX (4). Although there is only very low certainty evidence, the guideline advises for the use of second line therapy with azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, and rituximab (4). Second line therapies are to be employed after failure of proven effective first line therapy or as add-on medication to reduce dosage or optimize therapeutic response of first line therapies (4).

The new guideline recommends the use of SCIg for maintenance treatment in CIDP, but either IVIg or SCIg can be used for maintenance treatment (4). During follow-up, dosage should be adjusted according to individual treatment response. Data suggest that there is insufficient evidence that 0.4 g/kg weekly is more efficacious than 0.2 g/kg weekly for maintenance treatment, but the PATH OLE reported lower relapse rates in patients receiving the 0.4 g/kg dose (4, 28). Limited available evidence indicates that patients with CIDP might in some cases require higher mean doses of SCIg compared with their previous IVIg dose. Additionally, the updated guideline recommended weakly against using SCIg for induction treatment in CIDP due to lack of evidence, as currently there has been only one small cross-over trial involving 20 patients, which reported earlier maximal improvement in motor performance following IVIg treatment, as compared with SCIg treatment (42).

The guideline revision recommended that the same mean dose (1:1) per week is a reasonable starting point, when patients with CIDP switch from IVIg to SCIg (4). If the treatment is insufficient, the dose should be adjusted based on reliable outcome measures. If the dose is high (>20–30 g/infusion), an option is to split doses, increase frequency of infusions or use multiple injection sites for SC infusions (4). Patient personal preference should be considered when making decisions regarding the use of SCIg or IVIg (4). Advantages associated with the use SCIg include autonomy and convenience of self-administration at home, avoiding IV cannulation, and possibly reduced frequency of systemic AEs (18, 20, 26). Additionally, with IVIg objective end-of-dose low IgG serum concentrations before the next IVIg infusion may occur (4). If this happens, the guideline recommends minimising this effect by increasing the IVIg dose or shortening the infusion interval (4). Disadvantages associated with the use of SCIg include local side effects (infusion site swelling and pain) and the need for more frequent infusions (4).

Beyond the EAN/PNS 2021 guidance – when should clinicians consider conversion from IVIg to SCIg

It is this author's opinion that other patients with CIDP could also be considered as candidates for conversion from IVIg to SCIg. A recently published review by Goyal et al provides detailed guidance for clinicians including when to consider SCIg, and when to initiate the transition from IVIg to SCIg (43). Patients who are likely to benefit from a switch to SCIg are those with venous access problems and those who have been previously affected by IVIg-related adverse effects, in particular headaches and nausea (44).

SCIg administration is associated with stable serum IgG levels (45). SCIg treatment can be self-administered at home, allowing for more flexibility, convenience and autonomy (18). Logistically, SCIg is less complicated than IVIg, and does not require hospital visits (34). During the coronavirus disease 2019 (COVID-19) pandemic, a switch from IVIg to SCIg in stable patients with CIDP has the potential to reduce nursing resource utilization, which are already stretched to the limit. Self-administration at home was encouraged during the COVID-19 pandemic, as it allowed patients to continue their treatment outside hospitals and minimized the risk of SARS-CoV-2 infection (46). Fewer hospital resources and reduced nursing capacity also contributed to patients switching from IVIg to SCIg. A study conducted in Canada demonstrated that a transition from IVIg to less labor-intensive SCIg had the potential to alleviate nurse shortages and decrease overall health care costs (47).

Conclusion

This review discussed recent advancements in treatment strategies in CIDP and the updated EAN/PNS CIDP guideline (4, 29). Through a discussion of the PATH studies, the updates to the Hizentra® FDA prescribing information of April 2021, and the 2nd revision of the EAN/PNS guideline for the diagnosis and treatment of CIDP, this review explored the evolution and role of SCIg in optimizing CIDP care and management (4, 27-29).

The PATH and PATH open-label extension studies provide evidence for the efficacy of SCIg as a maintenance therapy in CIDP (27, 28). Results from these studies were included in an update to the U.S prescribing information for Hizentra® in April 2021 (29).

The 2021 EAN/PNS guideline outlined a comprehensive approach to the management of CIDP (4). The revised guideline provided an updated clinical definition and supportive electrophysiologic criteria for the diagnosis of CIDP (4). Autoimmune nodopathies were listed as a separate entity from CIDP; their diagnosis has been associated with the presence of nodal and paranodal antibodies (4). Recommendations for individualized treatment and the use of SCIg were also included in the revised guideline (4).

CIDP is a clinically heterogeneous disease with complex pathophysiology and diagnosis, and relatively few treatment options. Despite these challenges, significant advancements have been made to understand the pathogenesis, simplify the diagnosis and provide better treatment for patients. Results from the PATH studies demonstrated that SCIg provided patients with an alternative to IVIg, offering improved tolerability as well as convenience and independence (27, 28). Ongoing and future clinical trials may provide further insights into treatment strategies for CIDP.

Competing interests

Dr. Dimachkie serves or recently served as a consultant for Amazentis, ArgenX, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoR1, Janssen, Kezar, Momenta, NuFactor, Octapharma, RaPharma/UCB, Roivant Sciences Inc, RMS Medical, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Third Rock and UCB Biopharma.

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Factors Influencing the Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy

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ABSTRACT

BACKGROUND: Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a neurological disorder that leads to demyelination of peripheral nerves presenting with an array of symptoms. Symptoms of CIDP include but are not limited to loss of sensation, loss of reflexes, tingling and pain, and weakness. European Federation Neurological Society (EFNS) has developed guidelines for the diagnosis of this disorder. The objective of this study is to look at the relationship between the EFNS diagnostic criteria and whether patients that have the diagnosis of CIDP met this criteria. Data collection was completed on the patients diagnosed with CIDP and then the patients that were diagnosed but did not meet the criteria were analyzed to see what common outliers exist that led to the diagnosis.

RESULTS: A total of 20 patients (13 males and 7 females) were included in the study. Eighty-three percent of patients that were correctly diagnosed using the EFNS/PNS guidelines displayed hyporeflexia at the time of their diagnosis. A large majority of the patients (83%) correctly diagnosed using the EFNS/PNS guidelines displayed distal weakness at the time of their diagnosis. At the time of their diagnosis, EMG showed that majority of those who did not meet the EFNS/PNS criteria had no nerves that displayed increased latency. Fifty-eight percent of those who did meet the criteria outlined by the EFNS/PNS guidelines had two or more nerves that presented with increased latency. Testing the velocity of patients displayed that all of the patients that did not meet the EFNS/PNS criteria did not present with nerves that had diminished velocity.

CONCLUSION: CIDP misdiagnosis continues to be an issue leading to mismanagement of these patients. This study showed a preference of the clinical component for diagnosis of CIDP even if electrophysiological criteria was not met.

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common chronic immune-mediated disorder of the peripheral nervous system.[1] CIDP incidence rate is 0.33 per 100,000 people/year, whereas the prevalence rate is 2.81 per 100,000 people.[2] CIDP is an immune mediated disorder where many autoantibodies (NF155, NF186, CNTN1, etc) have been identified yet the mechanism and etiopathology of this disease is still not fully understood.[1] CIDP is classified into typical and atypical subtypes. The key to differentiate between the two is that typical CIDP presents as symmetric and distal weakness and sensory dysfunction of all extremities, whereas atypical may have varying presentations.[3] Accurate diagnosis of CIDP remains a challenge due to the range of clinical symptoms and presentations that the disorder can have.[5] Thus, there have been several diagnostic criteria developed including American Academy of Neurology (AAN), Inflammatory Neuropathy Cause And Treatment (INCAT), and European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS).[4] These criteria focus on clinical, electrophysiological, and supportive criteria when diagnosing the condition. The clinical criteria aspect assesses for distal weakness and sensory dysfunction of extremities. The various criteria present primarily differ in the electrophysiological criteria proposed. The most utilized diagnostic criteria is the EFNS/PNS diagnostic criteria. The EFNS/PNS electrophysiological criteria requires only 1 of its 7 criteria to be met, conveying the impression of being less conservative than other guidelines. The correct diagnosis of a CIDP is vital for administration of appropriate treatment. The objective of this study is to look at the relationship between the EFNS diagnostic criteria and whether patients that have the diagnosis of CIDP clinically meet this criterion.

Methods

This study is a retrospective chart review of patients that underwent care from a university-based hospital for their diagnosis of CIDP. A total of 20 patients diagnosed with CIDP were included in the study. Variables including but not limited to age, gender, race, history of diabetes, alcohol use, deep tendon reflexes, presence of proximal or distal weakness, sensory deficits, and EMG data were collected.

Data collected was analyzed to identify whether they meet the European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) criteria for diagnosis of CIDP. The patients were then categorized in one of the two groups – those who met the EFNS criteria (definite, probable, or possible) and those patients that did

not meet the criteria but were still diagnosed as patients with CIDP. Patient demographics and pain scores in form of descriptive statistical variables were analyzed, and mean, standard deviation, ranges, and percentages were calculated. All statistical analyses were done using SPSS v22 software (IBM, Armonk, NY).

Results

Demographics

A total of 20 patients (13 males and 7 females) were included in the study. The average age of the participants was 59 years old for the true positives and 61.63 for the false positives. For this study, the ethnicity for the patient population consisted mostly of Caucasians in the patients that met criteria (100%) and patients that did not meet criteria (75%). The analysis and breakdown of the patient demographic is displayed in Table 1.

Table 1. Demographics of the patients who were diagnosed with CIDP including the patients who correctly met the guidelines of the EFNS/PNS criteria and those who did not meet the criteria.

	True Positives	False Positives
Average Age	59.00 +/- 14.92	61.63 +/- 10.39
Gender (M/F)	(10/2)	(3/5)
Race (White/AA/Hisp)	(12/0)	(6/1/1)
Diabetes	4	2

Clinical Factors

Clinical variables of the patients are presented in Table 2 and Table 3. Almost all the patients that were correctly diagnosed using the EFNS/PNS guidelines displayed hyporeflexia at the time of their diagnosis. When assessing reflexes, 10 of 12 participants that met criteria (83%) had hyporeflexia present whereas 4 of 8 participants that did not meet criteria (50%) had hyporeflexia. A large majority of the patients correctly diagnosed using the EFNS/PNS guidelines displayed distal weakness at the time of their diagnosis. Motor and sensory abnormalities were present in all patients including 10 patients that met criteria with distal weakness (83%), 6 patients that met criteria with proximal weakness (50%), and 12 patients that met criteria with sensory deficits (100%).

Table 2. Results from the patient reflex assessment at the time of the patient's diagnosis. Almost all the patients that were correctly diagnosed using the EFNS/PNS guidelines displayed hyporeflexia at the time of their diagnosis.

Reflexes	True Positives	False Positives
Hyporeflexia	10	4
Normal reflexes	2	2
Hyperreflexia	0	1
Unknown	0	1

Table 3. Clinical symptoms that the patients displayed at the time of their diagnosis with CIDP. A large majority of the patients correctly diagnosed using the EFNS/PNS guidelines displayed distal weakness at the time of their diagnosis. All of the true positives also displayed sensory deficits.

Clinical Symptoms	True Positives	False Positives
Distal weakness (No weakness/ weakness)	(2/10)	(4/4)
Proximal weakness (No weakness/weakness)	(6/6)	(6/2)
Sensory deficits (No deficits/ deficits)	(0/12)	(2/6)

Electromyography

Electromyography was conducted on each patient. Subjects were stratified into groups with 0, 1, or 2+ nerves with abnormal latency or velocity. These groups are presented in Table 4 and Table 5. Results of the latency that was observed in patients at the time of their diagnosis showed that those who did not meet the EFNS/PNS criterion mostly had no nerves that displayed increased latency. The majority of those who did meet the criteria outlined by the EFNS/PNS guidelines had two or more nerves that presented with increased latency. In this study, 63.6% of patients that met criteria had increased latency of 2 more nerves, whereas 25% of these patients had diminished velocity. None of the patients, that did not meet criteria, in this study had 2 or more nerves with abnormal latency or velocity.

Table 4. Results of the latency that was observed in patients at the time of their diagnosis showed that those who did not meet the EFNS/PNS criterion mostly had no nerves that displayed increased latency. The majority of those who did meet the criteria outlined by the EFNS/PNS guidelines had two or more nerves that presented with increased latency.

		Number of Patients
True Positive	2 or more nerves with increased Latency	7
	1 nerve with increased Latency	3
	No nerves with increased Latency	2
False Positive	2 or more nerves with increased Latency	0
	1 nerve with increased Latency	1
	No nerves with increased Latency	7

Table 5. Velocity displayed in the patients at the time of their diagnosis with CIDP. Testing the velocity of patients demonstrated that all of the patients who did not meet the EFNS/PNS criteria did not present with nerves that had diminished velocity.

		Number of Patients
True Positive	2 or more nerves with diminished Velocity	3
	1 nerve with diminished Velocity	5
	No nerves with diminished Velocity	4
False Positive	2 or more nerves with diminished Velocity	0
	1 nerve with diminished Velocity	0
	No nerves with diminished Velocity	8

Discussion

CIDP has a spectrum of phenotypic presentations where different autoimmune mechanisms have been discovered that lead to similar clinical features. CIDP continues to be diagnosed clinically, and without a gold standard, it continues to make proper evaluation and diagnosis difficult.

The EFNS/PNS criteria that was investigated in this study has been found to most sensitive compared to AAN criteria.[3] "Possible" electrophysiological CIDP as outlined by EFNS/PNS criteria still has a poor specificity of 69.2%.[3]

This study looked at 20 patients diagnosed with CIDP and found that 40% of those patients failed to meet the EFNS/PNS criteria. These findings are supported by other studies such as the one conducted by Allen and company.[6] Allen and company completed a retrospective study of 59 patients diagnosed with CIDP. The study found that 47% of those patients failed to meet the minimal CIDP diagnostic criteria by EFNS/PNS criteria.[6]

The data above looks at the EMGs conducted in the patients diagnosed with CIDP. When comparing patients that met criteria to those that did not, it appears that the EMG data is not resulting in improper diagnosis of the disorder. On the other hand, clinical symptoms such as reflexes and sensory deficits have shown to be increased in both groups. These results show the presentation of these clinical symptoms may be leading to the misdiagnosis of CIDP when the patient is not meeting all of the clinical and electrophysiologic criteria as outlined by the EFNS/PNS guidelines. Patients who showed no diminished velocity also did not meet the criteria outlined by the EFNS/PNS guidelines. These patients additionally had little to no nerves that displayed increased latency. These factors assessed have revealed potential components that led to the misdiagnosis of CIDP.

Conclusion

The guidelines outlined in the EFNS/PNS criteria were developed to provide set criteria to be used for correct diagnosis of CIDP. Since there are several guidelines used to diagnose CIDP throughout the world the specificity of the diagnosis is not consistent. The EFNS/PNS guidelines requires the patient to meet certain electrodiagnostic criteria as well as clinical criteria leading to a more concise diagnosis of the neurological symptoms. CIDP misdiagnosis continues to be an issue leading to mismanagement of these patients. This study identified potential components that led to the misdiagnosis of CIDP. Further evaluation and investigation into the misdiagnosis of CIDP is required due to the limitation of sample size. Another limitation of this study is that this was a prospective chart review where only the data documented was available.

Declarations

Ethical Approval and Consent to Participate

This study is a retrospective chart review of patients that underwent care from a university-based hospital for their diagnosis of CIDP. The study was approved by MU Human Subjects Research Protections Program and Institutional Review Board of MU School of Medicine and the need to collect informed consent was waived by the institutional review board named above. The study was performed in accordance with the MU Human Subjects Research Protections Program Institutional Review Board of MU School of Medicine Guidelines and procedures. The need to collect informed consent was waived by the institutional review board named above. Data was de-identified upon extraction and stored on a hospital encrypted server, that leads to minimal risk to research subjects. There was no direct patient contact for this study.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. **Competing interests:** The authors declare that they have no competing interests.

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Authors' contributions: AA conducted the study and wrote the manuscript.

TM aided with data analysis, editing, and reviewing the manuscript.

KS researched other literature related to our topic and aided in editing.

RG is the PI for this study and supervised all data collection and analysis and reviewed manuscript.

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Lumbosacral Plexopathy Secondary to Internal Iliac Artery Aneurysm: Case report and review of literature

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Introduction

Iliac artery aneurysms are usually asymptomatic and can manifest symptoms only when there is compression, erosion, or trauma present. Compression most commonly occurs in three areas: ureters, colon, and lumbosacral plexus [1]. In patients with a documented iliac artery aneurysm, approximately 10-15% present with neurological symptoms [2]. There are currently limited reports on the manifestations of iliac artery aneurysms. Previous reports have described buttock pain, mono-paresis, cramps, pain, and weakness of dorsiflexion [3, 4, 5, 6, 7].

We report an internal iliac artery aneurysm causing lumbosacral plexopathy that developed post hernia repair surgery presenting with right lower limb weakness and numbness.

Case Report

An 83-year-old male was admitted for an incarcerated left inguinal hernia repaired surgically. The patient's past medical history is complicated with a history of coronary artery disease, status post coronary artery bypass surgery, atrial fibrillation on coumadin, mitral valve prolapse, status post mitral valve replacement, hypertension, and hyperlipidemia. Three days post-operation, the patient noticed he had weakness in his right lower limb. The weakness was gradual in onset and progressed with associated numbness and tingling in the right lower limb. The patient noticed more weakness proximally and had difficulty lifting his right lower limb off the bed. The patient had an additional complaint of urinary retention. On exam, he displayed hyporeflexia with reflexes being 1/4 except for the right knee and right ankle, which were 0/4. The plantar responses were mute bilaterally. Motor examination showed an MRC strength grade of 3/5 with knee flexion and extension, 3/5 with hip flexion, 4/5 with ankle dorsiflexion and plantarflexion, 4/5 distally in the right lower limb, and 5/5 in the left lower limb.

The sensory exam showed reduced sensation to temperature and light touch on the right lower limb compared to the left lower limb. Multiple imaging studies were performed. MRI of the cervicaland thoracic spine with and without contrast and diffusion-weighted imaging showed chronic degenerative changes, but no spinal cord infarctions were present. MRI of the brain with and without contrast showed chronic microvascular changes and generalized cortical atrophy. MRI of pelvis without contrast showed a right internal iliac artery aneurysm measuring 10.6 cm in craniocaudal dimension and 6.5 x 6 cm in transverse dimension (Images 1A & 1B) exerting mass effect on the right lumbosacral trunk L3, L4, L5, and S1 nerve roots (Images 2A & 2B, arrows).

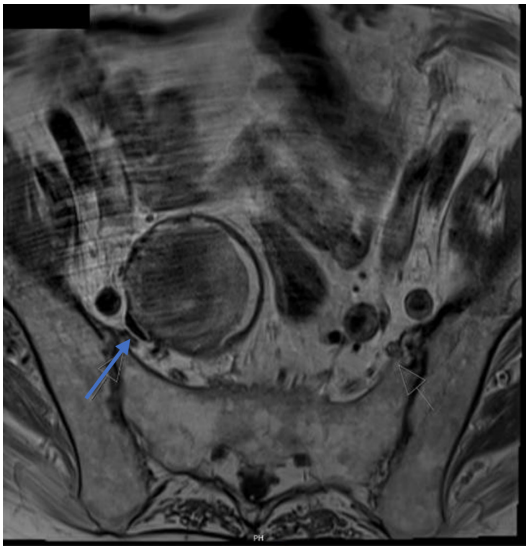

Figure 1A: T1 Axial MRI Pelvis without contrast. MRI of pelvis without contrast showed right internal iliac artery aneurysm measuring 10.6 cm craniocaudal dimension and 6.5 x 6cm transverse dimension (arrow).

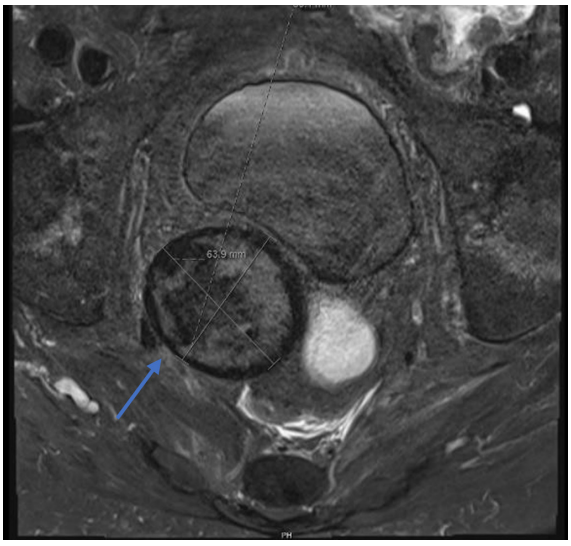

Figure 1B: T1 Axial STIR. MRI of pelvis without contrast showed right internal iliacartery aneurysm measuring 10.6 cm craniocaudal dimension and 6.5 x 6cm transverse dimension(arrow).

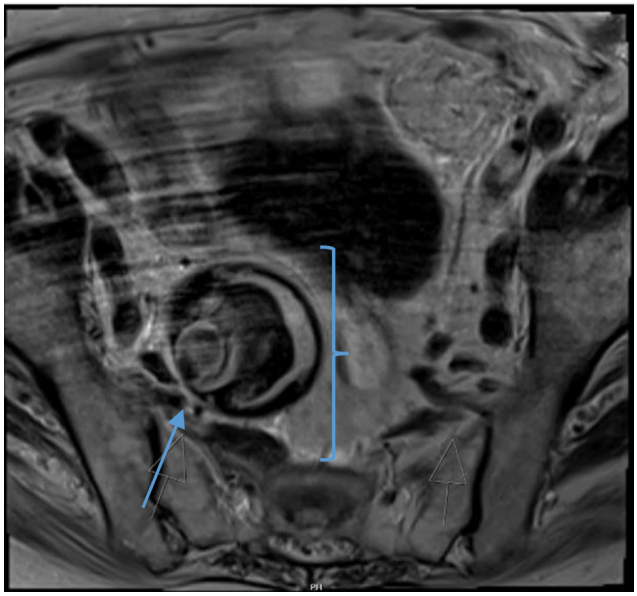

Figure 2A: MRI Pelvis T2 Axial. Image showed aneurysm (arrow) exerting masseffect (bracket) on the right lumbosacral trunk L3, L4, L5, and S1 nerve.

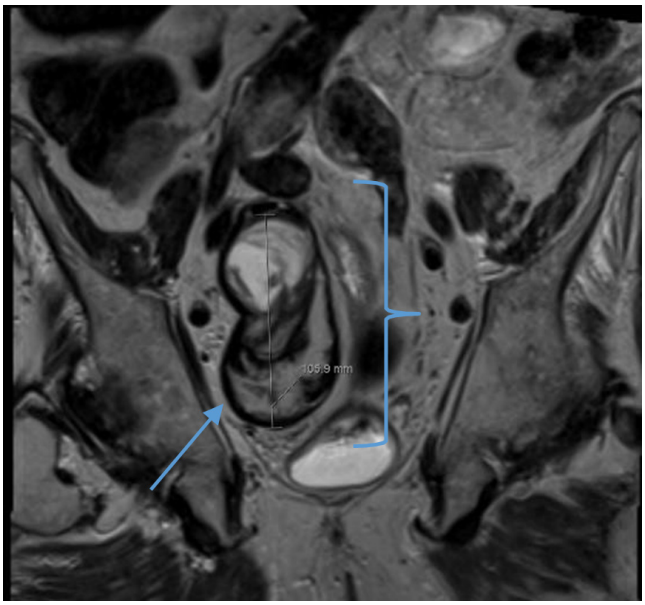

Figure 2B: MRI PelvisT2 Coronal. Image showed aneurysm (arrow) exerting masseffect (bracket) on the right lumbosacral trunk L3, L4, L5, and S1 nerve.

Discussion

Iliac artery aneurysms are seen predominately in white men over the age of 60 with a history of smoking, hypertension, and atherosclerotic disease [1, 9], as seen in the patient presented above.

Our patient presented with lower limb weakness and numbness, which started three days post-operatively, thus excluding traction injury. In addition, while the patient had numbness, there were no significant pain issues that ruled out any ischemic processes. The weakness affected multiple myotomes and dermatomes, thus raising the possibility of lumbosacral plexopathy.

Previously reported cases showed different presentations with iliac artery aneurysms. Mohan et al. reported a patient presenting with the inability to bear weight on the right leg, radiating pain to the right buttock, loss of ankle reflex, and a right foot drop [3]. Feinberg et al. reported a patient with only pain, cramps, and weakness in the left lower extremity [4]. Iodice et al. reported a patient presenting with progressive numbness and weakened foot dorsiflexion [5, 6, 7]. The average size of an iliac artery aneurysm in men is 1.2 +/- 0.2cm and in women is 1.0 +/- 0.2cm[8]. When aneurysms become 5cm – 7cm large, the risk of rupture is very high, and mortality is increased. Our patient had an aneurysm greater than 7cm and had not ruptured. No symptoms of an aneurysm appeared until post-operative, and we suspect this is coincidental.

Our case is unique in that our patient had more proximal weakness than distal weakness compared to previously reported cases. While urinary retention raised concern for cauda equina syndrome, a lumbar spine MRI ruled it out. We suspect urinary retention was due to compression of the bladder by the iliac artery aneurysm.

Patients with unexplained lower extremity weakness, numbness, and iliac artery aneurysm compressing the lumbosacral plexus should be considered. Further imaging of the pelvis should look for compressive etiologies of the plexus.

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Case of Vasculitic Neuropathy and Myelopathy

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Introduction

Eosinophilic granulomatous polyangiitis (EGPA) is a rare form of antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. Vasculitic peripheral neuropathy could be the sole or the first and most prominent manifestation of systemic vasculitis. Here, we present a case with cervical spondylotic myelopathy and vasculitic neuropathy which was initially misdiagnosed as statin-induced myopathy and later diagnosed as EGPA following nerve biopsy.

Case

A 61-year-old female with coronary artery disease status post coronary artery bypass surgery 3 years ago presented with a 4-month history of numbness with severe burning pain that started in the toes and ascended up the legs and then into the hands. She also had proximal and distal weakness worse in the arms, headaches, myalgia, and arthralgia. The onset coincided with the initiation of amlodipine for hypertension; she presented to an outside hospital 1 month later due to persistent symptoms, where she was diagnosed with statin-induced myopathy, and both amlodipine and atorvastatin (that she had been taking for 3 years) were stopped at that time. Her headaches resolved, however her numbness, pain, and weakness progressed. She noted 20-pound weight loss in the initial month. She also reported odynophagia and Raynaud's phenomenon. Interestingly, she had similar symptoms when she took amlodipine in the past that spontaneously resolved after discontinuation of the drug. Social history and family history were non-contributory.

Review of outside records revealed that her highest creatine kinase (CK) was 55 U/L. Physical exam showed normal vital signs, no rashes, intact cranial nerves, symmetric proximal and distal weakness (medical research council (MRC) scales: shoulder abduction 4, elbow flexion 4, elbow extension 5, wrist extension 5, wrist flexion 5, finger flexion 5, finger extension 4+, finger abduction 4, thumb abduction 5, hip flexion 4-, knee extension 5, knee flexion 4, ankle dorsiflexion 4, plantar flexion 4+, eversion 4+, and inversion 4+, toe flexion 4, toe extension 3), diminished sensation to pinprick up to ankles, decreased proprioceptive and vibratory sense at the interphalangeal joint of the great toes bilaterally (timed vibratory sense: 12 and 9 seconds). Tone was normal. Deep tendon reflexes were prominent in upper extremities, 3 at brachioradialis and biceps with finger flexions, 3 at triceps, 2 at patella, 1 at ankle bilaterally; plantar responses were flexor, and Hoffman's sign was mildly positive bilaterally. Jaw jerk was absent. Coordination and gait were intact.

Initial admission labs showed anemia, thrombocytosis, leukocytosis with elevated nucleated cells, monocytosis ($0.87x10^3$/mL), and eosinophilia ($1.63x10^3$/mL); elevated C-reactive protein (16.45 mg/dL) and sedimentation rate (68 mm/hr); CK was below 5 U/L and aldolase 42 U/L. MRI of the cervical spine revealed multilevel cervical spondylosis most pronounced at C6-C7 with severe central spinal stenosis with a signal change in the spinal cord, as well as multilevel neural foraminal stenosis bilaterally. She was evaluated by orthopedic surgery and deemed not a surgical candidate as it was felt not to be the primary driver of her pain and weakness. MRI thoracic and lumbar spine, and vitamin B12 were normal. Serum immunofixation revealed IgG k paraproteinemia and elevated IgG (1,672 mg/dL) and IgE (368 IU/mL). PET-CT scan of the whole body showed diffuse nonspecific marrow and splenic hypermetabolism, and mildly hypermetabolic lymph nodes. Anti-HMG-CoA reductase (HMGCR) antibody was negative. Due to concern for autoimmune neuropathy including systemic vasculitis, cryoglobulinemia, and Sjögren's syndrome, as well as hematologic malignancy causing paraproteinemia, Rheumatology and Hematology were consulted; extensive workup revealed positive rheumatoid factor (97 IU/mL), P-ANCA (320 titer), and myeloperoxidase antibody (MPO-ANCA) (1.3 AI), anti-SS-A 52 kD antibody IgG (105 U). Negative results included cryoglobulin, vascular endothelial growth factor, anti- SS-A and SS-B antibodies, and lip and bone marrow biopsies. Nerve conduction study showed moderate, primarily axonal, sural-sparing, distal motor neuropathy or neuronopathy; mild, non-irritative myopathy; and right demyelinating median neuropathy with axonal loss (**Table 1**).

Table 1. Nerve conduction study.

Sensory nerve conduction study

Nerve / Sites	Onset Lat	Peak Lat	NP Amp	PP Amp	Segments	Distance	Velocity
	ms	ms	µV	µV		mm	m/s
R Median - Digit II (Antidromic)							
Wrist	NR	NR	NR	NR	Wrist - Dig II	130	NR
R Ulnar - Digit V (Antidromic)							
Wrist	2.71	3.44	12.2	30.6	Wrist - Dig V	110	41
R Radial - Anatomical snuff box (Forearm)							
Forearm	1.88	2.40	22.2	23.7	Forearm - Wrist	100	53
R Sural - Ankle (Calf)							
Calf	3.18	3.85	2.4	8.6	Calf - Ankle	140	44

Motor nerve conduction study

Nerve / Sites	Muscle	Latency	Amplitude	Segments	Distance	Velocity	Temp.
		ms	mV		mm	m/s	ºC
R Median - APB							
Wrist	APB	5.16	1.4	Wrist - APB	70		32
Elbow	APB	10.10	1.2	Elbow - Wrist	193	39	32
R Ulnar - ADM							
Wrist	ADM	2.97	6.0	Wrist - ADM	70		31.9
B.Elbow	ADM	5.99	5.6	B.Elbow - Wrist	158	52	31.9
A.Elbow	ADM	7.71	5.4	A.Elbow - B.Elbow	100	58	31.9
R Peroneal - EDB							
Ankle	EDB	3.70	0.8	Ankle - EDB	80		29.4
Fib head	EDB	10.36	0.5	Fib head - Ankle	275	41	28
Pop fossa	EDB	12.55	0.6	Pop fossa - Fib head	100	46	28
R Tibial - AH							
Ankle	AH	3.80	2.2	Ankle - AH	80		
Pop fossa	AH	10.36	1.4	Pop fossa - Ankle	325	50	
R Peroneal - Tib Ant							
Fib Head	Tib Ant	3.54	1.8	Fib Head - Tib Ant			25.9
Pop fossa	Tib Ant	5.83	1.7	Pop fossa - Fib Head	100	44	25.9

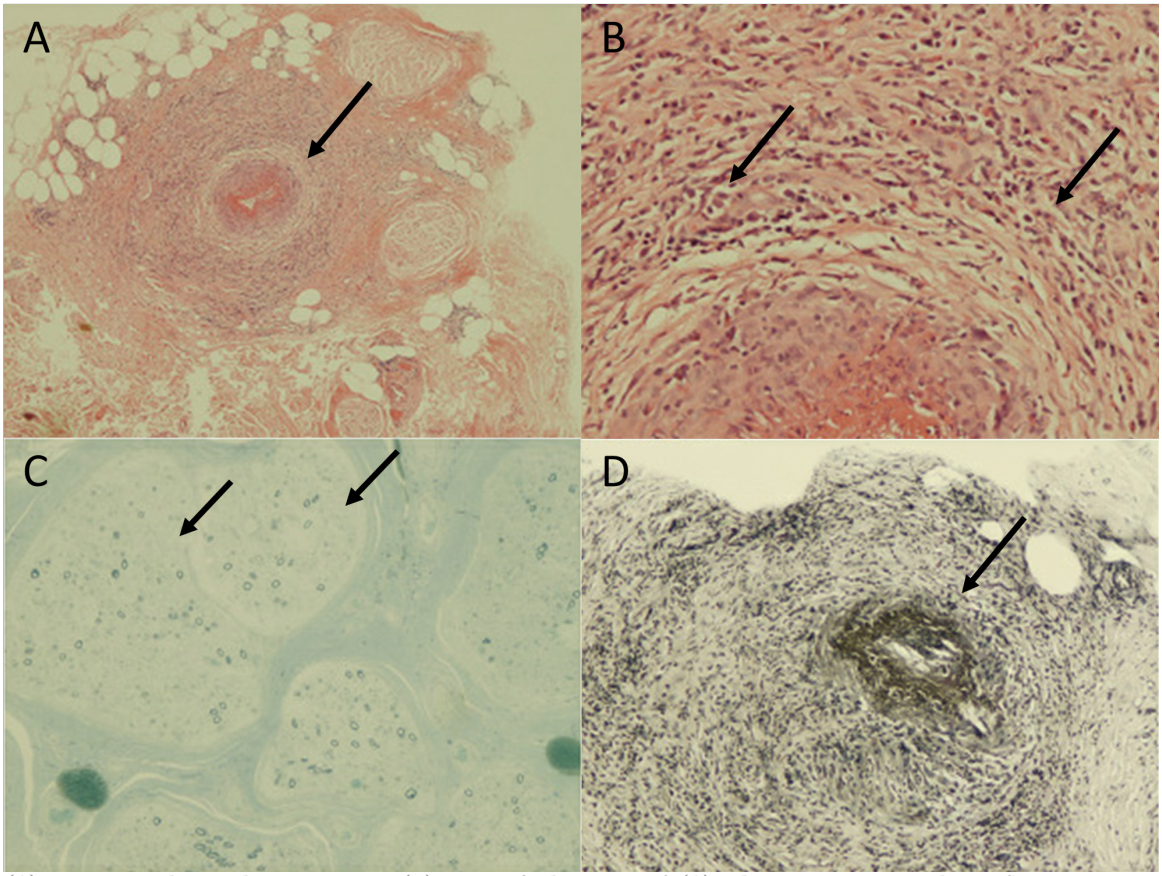
MRI of lower extremities showed heterogenous increased short T1 inversion recovery (STIR) signal intensity involving multiple muscles. She proceeded with muscle and nerve biopsies. Muscle biopsy from the left vastus lateralis showed nonspecific type 2 fiber atrophy and epimysial perivascular inflammation. Sural nerve biopsy showed vasculitis consistent with eosinophilic granulomatosis with polyangiitis and axonal neuropathy.

She was diagnosed with EGPA on the basis of nerve biopsy findings shown in **Figure 1**. Intravenous methylprednisolone was initiated resulting in spontaneous symptom resolution. Patient is currently undergoing protracted oral prednisone taper without signs of recurrence.

Discussion

We report a case of cervical spondylotic myelopathy and vasculitic neuropathy from EGPA preceded by amlodipine use, initially misdiagnosed as statin-induced myopathy despite absence of elevation in CK. Symmetric proximal weakness with myalgia and hyperreflexia in arms and preserved reflexes in Achilles tendon that did not go along with neuropathy likely led to confusion between myopathy and neuropathy. However, statin induced myalgia, myopathy, or necrotizing myositis are unlikely to present without hyperCKemia[1]. Negative anti-HMGCR antibody also supported against statin-induced myopathy. Neuromuscular exam favored neuropathic weakness than myopathic weakness in presence of distal weakness

Figure 1. Sural Nerve Biopsy.



(A) Hematoxylin and eosin stain, (B) magnified image of (A), showing perivascular inflammation in epineural vessels containing eosinophils (arrows). (C) Toluidine blue semithin EM stain showed severe loss of large myelinated axons (arrows). (D) Verhoeff EVG stain showed loss of internal elastic lamina in the epineural arteries (arrow).

and paresthesia; vasculitic neuropathy could present as symmetric length-dependent polyneuropathy and not limited to mononeuritis multiplex[2]. Mild proximal weakness and preserved reflexes were likely due to concurrent severe cervical spondylotic myelopathy. Workup at our institution showed elevated aldolase, positive anti-SS-A 52 kD antibody, heterogenous STIR hyperintensity in lower extremities involving multiple muscle groups, non-irritative myopathy on needle electromyography, and nonspecific findings on muscle biopsy; all suggested nonspecific muscle involvement. We believe that all those nonspecific muscle findings were likely from disuse or ischemia in the muscles, not from inflammatory myositis or necrotizing myositis in the absence of hyperCKemia, especially with the fact that muscle involvement in EGPA is exceedingly rare with only 8 cases reported to date, ranging from eosinophilic myositis to necrotizing eosinophilic vasculitis[3].

EGPA is an ANCA-associated vasculitis defined as eosinophil-rich with necrotizing granulomatous inflammation often involving the respiratory tract, necrotizing vasculitis predominantly affecting small to medium vessels, and associations with asthma and eosinophilia[4]. The incidence is estimated as 10.7 to 14 in 1,000,000, with median age of symptom onset at 40 years. P-ANCA and MPO-ANCA are seen in 40% of vasculitic type associated with myalgia, migrating polyarthralgia, weight loss, mononeuritis multiplex, and renal involvement either as crescentic or necrotizing glomerulonephritis. ANCA negative EGPA is associated with hypereosinophilic syndrome with myocarditis[5]. Peripheral neuropathy is commonly seen up to 80% of cases; central nervous system involvement is reported at a lower frequency, leading to ischemia and hemorrhage, granulomatous lesions, and hypertrophic pachymeningitis. Prognosis is favorable with 5-year survival of 90%; recurrence could occur in 20 to 30 % of all cases[6]. Poor prognostic factors include elevated serum creatinine (>1.58 mg/dL), proteinuria (> 1 g/day), severe gastrointestinal tract involvement, cardiomyopathy, and central nervous system involvement[7,8]. In the absence of poor prognostic factors, initial induction treatment consists of either oral or intravenous corticosteroids with

protracted taper; in the presence of poor prognostic factors, cyclophosphamide has been traditionally added[9]. In recurrent cases, methotrexate (10 to 25 mg per week), cyclosporin A (1.5 to 2.5 mg/kg per day), and azathioprine (2 mg/kg per day) have been used; in refractory cases, plasma exchange, intravenous immunoglobulin, interferon-alpha, tumor necrosis factor inhibitors, rituximab, mepolizumab, and omalizumab have been reported in literature[5, 9].

It is interesting that the initiation of amlodipine coincided with the symptom onset in our patient. Drug-induced vasculitis has been reported with agents such as antibiotics, anti-thyroid drugs, and anti-tumor necrosis factor-α agents[10]. Traditionally, drug-induced vasculitis involves skin and subcutaneous tissue, occasionally lung and kidney, and multi-organ involvement is rare. The specificity of ANCA antibodies is also helpful to discriminate drug-induced vasculitis from idiopathic ANCA-associated vasculitis. In drug-induced vasculitis, ANCA tends to be multi-specific with MPO-ANCA being most common but HLE-ANCA, lactoferrin-ANCA could be seen concurrently, although these ANCA are not available for routine testing at the University of Kansas Medical Center. In idiopathic ANCA-associated vasculitis, ANCA usually has only one target as in EGPA and MPO-ANCA[11]. Vasculitis would resolve after cessation of the causative agent in most cases. There has been only one case report that initiation of amlodipine preceded leukoclastic vasculitis of the skin, but no report was found with EGPA[12]. Collectively, we believe that the timing of amlodipine initiation at symptom onset was a coincidence rather than a plausible causative agent of drug-induced vasculitis.

Acknowledgement

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BIKE Syndrome: Biking Induced Kinetic Electroshock Syndrome

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Introduction

Patients with transient symptoms pose diagnostic dilemmas and may even be misdiagnosed with Functional Neurologic Disorder or somatization. We present a case of a patient with transient neuromuscular symptoms while cycling under a powerline. While this phenomenon is not reported in the clinical neurological or musculoskeletal literature, several online forums related to cycling describe bicyclists experiencing a similar sensation. To further investigate, we searched for all instances of microshocks occurring in cyclists using the following search term in Google: "electrical" AND ("bicycle" or "cycle") AND ("microshock" or "shock"). Between 2006-2021, we identified 51 unique reports across 18 blog forums of cyclists describing microshocks in their groin or upper extremity while traversing under high voltage power lines (**Table 1**). In 11 of 18 forums, at least one of the posts described friends or family members characterizing the experiences as "impossible" or "hallucinations." After an initial posting, additional shared experiences of microshock by other cyclists were offered in 12 forums. Seven forums speculated about short- and long-term health effects, while 13 forums specifically inquired about the etiology of the symptoms. Based on this review, electrical microshocks while cycling under high voltage powerlines may be more common than suspected *a priori* and are likely to be dismissed by close contacts or healthcare workers. These events commonly generate questions about health effects and potential causes for symptoms. Such questions are likely to be better addressed by healthcare providers or peer-reviewed literature as compared to unverified blog postings by anonymous authors.[1] This is the primary reason why we present this case.

Clinical Case

A 33-year-old man with migraines presented for evaluation of intermittent burning, "electric" radiating perineal and groin pain while road cycling over the last 6 months. The pain was unrelated to the duration or intensity of the ride. He denied radicular pain in the arms or legs, or neck or low back pain. He denied paresthesias in his feet, weakness, sexual dysfunction, and bowel/bladder dysfunction. Notably, he reported that the sensation occurred only when he was fully seated while riding his bike under a specific powerline. On focused exam of his right lower extremity, he had full range of motion in his hips, knees, and ankles. He denied tenderness to palpation over his greater trochanter, ischial tuberosity, and coccyx. His neurologic exam was normal; specifically, he had normal large and small fiber sensation in his legs and groin, reflexes were normal and symmetric throughout, and he had no weakness. Provocative testing for hip pathology was performed: (1) his log roll test was negative, (2) he denied sacroiliac, groin, or posterior hip pain with passive hip flexion, abduction, and external rotation (FABER test), and (3) he denied hip pain with passive hip flexion, adduction, and internal rotation (FADIR test). Given the presentation, reassurance was provided, and no further testing was ordered including nerve conduction studies/electromyogram (NCS/EMG), hip x-ray, lumbosacral spine MRI, or laboratory studies for neuropathy. The key to this patient's diagnosis is the finding of transient 'electric' pain specifically while cycling under a powerline in a seated position. We described this as a new clinical phenomenon, Biking Induced Kinetic Electroshock (BIKE) syndrome.

Discussion

In this clinical scenario, we present a previously unreported clinical phenomenon related to biking and local power grid lines, which we describe as a Biking Induced Kinetic Electroshock (BIKE) syndrome. The key to the correct diagnosis and management is an understanding of the clinical story, physical exam, and electromagnetic physics.

For this reason, it is critical to systematically work through differential diagnoses for anterior hip and groin pain along neurologic peripheral and musculoskeletal axes.

The history and physical make a diagnosis along the neurologic peripheral axis unlikely, including lumbosacral radiculopathy, focal mononeuropathy (e.g. ilioinguinal, genitofemoral, pudendal, perineal nerves), and generalized large or small fiber neuropathy. Musculoskeletal causes for hip pain, including femoroacetabular impingement, labral tear, greater trochanteric bursitis, and piriformis syndrome are also unlikely given normal hip range of motion and negative physical exam findings. Cycling is associated with non-traumatic injuries, typically handlebar palsy (ulnar neuropathy at the wrist), carpal tunnel syndrome

Table 1: Results of search for all instances of microshocks occurring in cyclists using the Google search terms: "electrical" AND ("bicycle" or "cycle") AND ("microshock" or "shock")

Blog/Forum Title	Year	Number of Patients	Symptoms Dismissed as "Impossible/ Hallucination/etc."	Additional Shared Experiences Provided	Inquiry about Health-related Effects	Inquiry about Etiology
Bike Forums	2006	6	No	Yes	No	Yes
MTBR	2009	11	Yes	Yes	Yes	Yes
BC Hydro	2010	1	No	No	Yes	Yes
Roadbike Review	2011	9	Yes	Yes	Yes	Yes
Physics-StackExchange	2012	1	Yes	No	Yes	Yes
Veritas	2012	1	Yes	No	No	Yes
DailyMail	2014	1	Yes	No	Yes	No
Singletrack	2014	3	Yes	Yes	No	No
ThumperTalk	2016	2	Yes	Yes	No	Yes
Reddit/Shocked	2017	2	Yes	Yes	No	Yes
Reddit/Bicycle	2017	2	Yes	Yes	No	Yes
CycleChat	2017	2	Yes	Yes	No	Yes
Bike Forums	2019	2	No	Yes	No	Yes
EMTB Forums	2019	1	No	No	No	No
The Cabin	2020	2	Yes	Yes	No	No
Adventure Rider	2020	3	No	Yes	Yes	Yes
NBC_Ark	2020	1	No	Yes	No	Yes
BayNews	2021	1	No	No	Yes	No

(median neuropathy at the wrist), sciatic neuropathy, dorsal pudendal neuropathy, ischial tuberosity pain, and orthopedic injuries related to overuse, poor biomechanics, or compression from incorrect rider-cycle fit. However, in this case, while a compressive neuropathy could be possible from poor bicycle fit that resolved after the compression was relieved, the association with the power line suggests an alternate pathology related to electromagnetic stimulation.

To provide evidence for such phenomenon, we asked the rider to cycle with a different bicycle, which then led to the same sensation. A different rider rode both bicycles in question as well as a third unrelated bicycle across the electric field and received the same shock. Lastly, a third rider tried all three bicycles and did not receive a shock. The difference between the riders was that the rider who did not receive a shock had smaller diameter thighs that did not contact the saddle rails. With a multimeter, we measured 1.2 mA at the saddle rails when moving the bicycle through the field at 3.5 mph. Thus, a current is present on the bicycle through the field at a level that is physiologically detectable and explained by contact with the saddle rails.

High-voltage direct current lines are increasingly the technology of choice for transport of large amounts of energy over long distances. These lines produce static electric fields that may interact with people during activities of daily living.[2,3] In addition, humans are able to perceive electric fields and ion currents, especially as intensity increases.[3,4] As a result, government regulatory bodies typically create guidelines for exposure of the public to electric and magnetic fields during construction of high voltage powerlines.[5] Microshocks are a type of indirect effect that are covered within these regulations. Indirect effects occur when an electric field induces charges on the surface of a conducting object. These charges then either interact with the electric field, or are transferred to another object.[5] Microshocks are a transfer of charge that occurs when a charged person who is well insulated from the ground touches a conductive grounded object, or when a grounded person touches a charged object that is well insulated from the ground.[6] In practice, microshocks can feel like "static shock" and are typically only relevant with high-voltage (>275 kV) overhead powerlines.

Applying this knowledge to the case of our patient and cycling, when a cyclist is riding under a powerline, if he is electrically isolated from the bicycle (e.g. holding rubber handlebar grips or wearing insulating gloves) a differential charge can build up between the rider and the bicycle. While the full physics is complicated, this scenario

can be simplified by thinking of the patient as one end of a capacitor. In this setting, the difference in charge (current) that would be expected to be discharged is most simply expressed as: $i = C\frac{dV}{dt} = \left(\frac{\varepsilon A}{d}\right) * \frac{dV}{dt}$, where i = current, C = capacitance, $\frac{dV}{dt}$ = instantaneous rate of voltage change over time, ε = material permissivity, A = parallel plate area, and d = distance between plates. Using this equation, we can see the possibility for a microshock if conducting surfaces of the rider and bicycle touch, thereby resulting in an equalization of potentials across the gap between the rider and bicycle. This microshock typically occurs on a small area of skin resulting in tingling or pain.[5] The most common places for this to occur are the fingers as they brush against the brake level or on the inside of the upper thigh as it comes close to the top of the seat pillar below the saddle or to the saddle rails during a pedal revolution. Factors that can alter the likelihood of electrical current perception or occurrence of a microshock include bike/rider size, gender, traveling velocity, distance from powerline, and meteorological conditions.[4]

Microshocks are not known to have long-term health effects or cause discernable skin damage.[5] A recent systematic review found that while humans and animals are able to perceive the presence of static electric fields, such as those generated from power lines, at high voltage levels, minimal adverse biological effects have been observed.[2]

Based on the diagnosis of BIKE syndrome, the patient was counseled to either avoid the specific route, maintain electrical contact with the metal part of the bicycle (e.g. handlebar, saddle rails) at all times, or insulate completely from the bicycle (e.g. change the seat or wear more insulating shorts). He opted to avoid the route, which relieved the issue. Given the very brief transient nature without deficits on exam, we relayed his good prognosis to him. No further testing was ordered.

In summary, transient neurologic symptoms can present diagnostic dilemmas and a clear history with associated symptoms and context can reveal the diagnosis without costly tests. This case demonstrates an unusual phenomenon of electrical microshocks from nearby powerlines while cycling leading to transient neurologic symptoms, i.e. a BIKE (Biking Induced Kinectic Electroshock) syndrome.

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Creatinine Kinase: A test done from muscle memory or clinical reasoning?

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Introduction

Creatinine kinase (CK) is a common lab ordered by generalists and specialists that is often misinterpreted. Given its prevalent use, we highlight a case that outlines pitfalls of the test. The case is of a gentleman who is referred to a neuromuscular clinic for weakness and an elevated CK. However, during the COVID-19 pandemic, this was initially a video visit, which then serves to highlight the challenges of video visits. In this report, we primarily aim to highlight an algorithm to evaluate CK in the presence of weakness. Secondary objectives include reviewing common pitfalls of CK testing, especially with the rising trend of video visits.

Practically, total CK enzyme activity (IU/L) is measured with a photometric assay utilizing the enzymatic rate method to calculate the rate of phosphate transfer from phosphocreatine to adenosine diphosphate per minute. Tissue isoform assays fractionate total CK using antibodies to CK-MM (skeletal muscle), CK-MB (cardiac muscle), or CK-BB (brain). Male sex, black race, younger age, and exercise are the most common reasons for normal physiologic increases in CK, possibly due to differences in muscle or total body mass and the permeability of the sarcolemma to CK.[1-3] Exercise causes transient increases in CK over 24-48 hours, followed by return to baseline over 7+ days.

Pathologic CK elevation is associated with myopathies or muscle injury, but can also occur in neurogenic disorders due to impaired muscle membrane integrity secondary to muscle degeneration from axonal loss.[4-6] Other causes of CK elevation include race, medication use, systemic disorders (e.g. acute renal failure, malignancy, viral illness), and endocrine abnormalities.[4, 5, 7] Of these, statin-induced CK elevation is most commonly observed.[3]

In clinical settings, assay manufacturers provide a CK reference range assuming a gaussian distribution (0-180 IU/L). This results in high false-positive rates as population CK distribution is skewed toward higher values.[5] For this reason, recent practice guidelines recommend using a upper limit of normal (ULN) threshold at the 97.5th percentile rather than manufacturer-quoted ULN (**Table 2**).[2,4,7,8] Using these guidelines, the prevalence of incidentally elevated CK in asymptomatic patients is 5.3%, with persistent unexplained elevation in 1.3%.[9] CK elevation can vary based on sex. In a cohort of musculoskeletal patients with elevated CK 29% were female (F) and 44% were male (M). Sensitivity using the 97.5th percentile versus manufacturer's guidelines was 29%(F)/60%(M) versus 50%(F)/80%(M) and sensitivity was 80%(F)/80%(M) versus 70%(F)/67%(M), respectively.[4] When using a cutoff of 1.5xULN instead of the 97.5th percentile, sensitivity for diagnosing myopathy decreased by 37%. CK > 1000 IU/L had a high likelihood for myopathy (11.0).[6,7] Thus, increasing the ULN improves specificity and decreases the false positive rate when evaluating CK elevation.[1,6,7] The cost of total CK to Medicare is $6.51. Total CK with isoenzymes is $13.39.

Case

A 72-year-old man with peripheral neuropathy and lumbosacral polyradiculopathy presented for a video visit with gradually progressive voice hoarseness, weakness, and an elevated CK over the past two years. Three years prior to his visit, he began having difficulty climbing stairs, making a closed fist, and standing from a seated position due to knee buckling. His symptoms progressed to include a right foot drop, right greater than left leg weakness with quadriceps atrophy, and left greater than right hand weakness with volar forearm atrophy, all evident on video examination. He denied dyspnea, pain, cramps, fasciculations, and fluctuations. Laboratory results are shown in **Table 1**. Previous magnetic resonance imaging of the spine showed multilevel cervical and lumbar degenerative changes without spinal cord signal changes.

Table 1. Patient's Laboratory Values

Laboratory Test	Patient's Values	Reference Value or Range
Creatine kinase (IU/L)	498	0-180
Thyroid stimulating hormone (mIU/L)	1.6	0.5-5
Vitamin B12 (pg/mL)	565	190-950
Vitamin D (ng/mL)	normal	20-40
Erythrocyte sedimentation rate (mm/h)	9	0-15 mmol/h
Serum protein electropheresis with immunofixation	Normal	N/A

Table 2: Upper limit of normal (IU/L; 97.5th percentile) for CK based on the current literature; *1.5 x 97.5th percentile of Brewster et al

	Manufacturer[4]	Brewster[8]	Kyriakides/EFNS*[7]	George[2]
Male	174			
Black		801	1201	1001
Non-black		336	504	
White				382
Hispanic				572
Asian				520
Female	140			
Black		414	621	487
Non-black		217	325	
White				295
Hispanic				279
Asian				194

This visit occurred early during the COVID-19 pandemic where in-person visits were very limited. While an in-person examination was clearly the most appropriate next step, other options were discussed with the patient including obtaining electrophysiologic and laboratory studies first. We jointly elected to have an in-person visit first, which clarified his diagnosis.

Discussion

An elevated CK in an elderly man with bulbar symptoms and chronic progressive, asymmetric distal arm and proximal leg weakness suggests a neuromuscular disorder, specifically inclusion body myositis (IBM); however, his pace of progression was too fast for such a diagnosis. An in-person physical exam is the best next step to narrow the broad differential associated with an elevated CK and weakness, especially since CK is not specific to primary myopathic processes.

The algorithm to evaluate CK (**Figure 1**) first branches based on the presence of weakness. The pattern of weakness can establish risk factors for physiologic or toxic etiologies and help localize pathology along the motor unit. Myopathies typically present with symmetric, proximal weakness, with some exceptions (e.g. IBM and facioscapulohumeral dystrophy). Non-myopathic neurogenic etiologies should also be considered. Fluctuating or fatigable weakness points toward a neuromuscular junction disorder, whereas cramps, fasciculations, sensory symptoms, or weakness in the distribution of specific nerves suggest a neurogenic etiology (e.g. peripheral neuropathy, radiculopathy, plexopathy, or motor neuron disease (MND)). EMG is a tool for localization within the peripheral nervous system. Tests to identify the specific cause of CK elevation include antibody testing, muscle biopsy, and/or genetic testing.

The patient's exam revealed lower motor neuron signs: diffuse fasciculations in the arms/abdomen/legs, reduced reflexes, and asymmetric extremity weakness. He had upper motor neuron (UMN) signs: increased muscle tone in the legs with the presence of the Babinski sign. He had spastic-flaccid dysarthria. By the Awaji Criteria, the patient had clinically probable ALS. To confirm, EMG was performed showing widespread active denervation changes, including in the thoracic paraspinal muscles, with additional reinnervation changes in the cervical and lumbosacral regions. Given the diagnosis of ALS, CK was not checked again. In one series of 30 patients with ALS, CK was elevated in 43% of patients with a CK range of 5-423 U/L. CK level was higher in limb onset rather than bulbar onset ALS, but did not significantly differ based on disease duration or severity[11]. He was treated symptomatically.

In subsequent visits, the patient's strength worsened, and he developed an upper motor neuron sign in the cervical region (positive Hoffman's sign in the right hand), confirming the diagnosis of ALS. He passed away 4 years after symptom onset. The case highlights that the work-up for an elevated CK begins with the history to identify potential risk factors and the exam to characterize strength. CK evaluation has several pitfalls, most important being that the ULN is physiologically higher than the manufacturer-provided reference limits, and varies by age, sex, race, and activity-level. Importantly, elevated CK, with or without weakness, has a broad differential diagnosis, including several non-myopathic causes such as neurogenic etiologies. Lastly, as video visits become more common, significant challenges

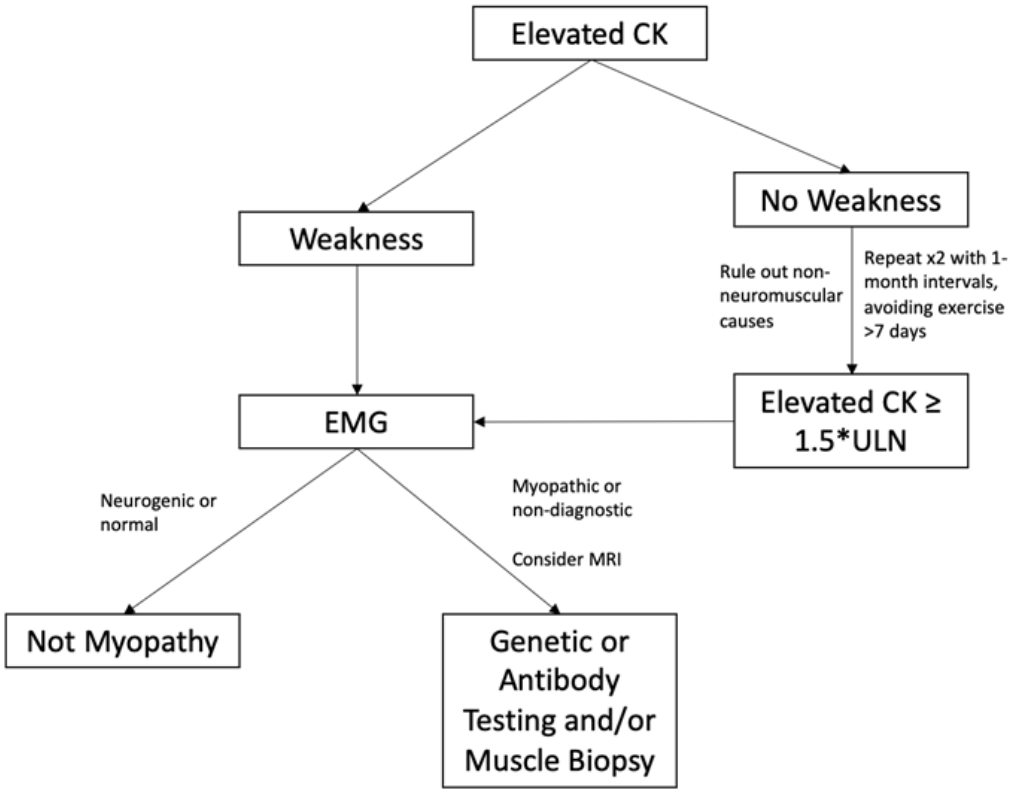

Figure 1: Approach to evaluating an elevated CK.

are increasingly encountered by neuromuscular specialists. While gross motor function and laboratory/imaging results can be reviewed, it is challenging to objectively assess sensation, muscle strength, and function without an in-person physical exam. While we navigate clinical practice through virtual platforms, we are once again reminded that our physical exam is indispensable.

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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

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.

Table 2. First-, second- and third-line therapeutic options for CSPN
(blue shaded medications were included in PAIN CONTROLS study); bold/CAP &yellow shaded medications included for this study)

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**

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 (Welbutrin)	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**
Zonismide (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,

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**europathy – **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

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.

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.

Table 3. BEAT CSPN (Initial Planned) Outcomes

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 Theory[36-38] 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 strategy[39] 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.

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 matric 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 1.5-2hours.

   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 unknow 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

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 daily[57] 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 (Keppra)*

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 study[59] 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

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 expands 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**

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-CONTRoLS[17] as utility = ¾*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 rational 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 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]

PAIN-CONTRoLS: Platform Trial

Done (n=402)				**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.

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

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 $\Pr(U_j = U_{max}) = \Pr(U_j > U_A; U_j > U_B; \ldots ; U_j > U_G)$ 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 jth arm would is 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 jth 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(Quit) is proportion of participants who quit; Pr(Efficacy) is proportion of participants efficacious; Utility=3/4*Pr(Effiacy)+(1-Pr(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

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

		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 (α=.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

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.

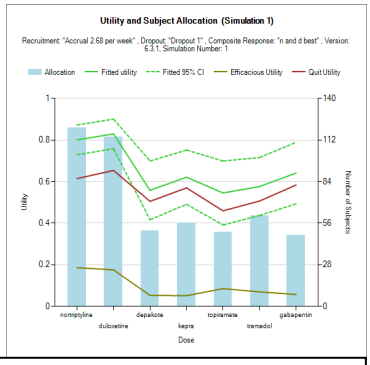

Figure 1. Simulation using PAIN CONTROLS

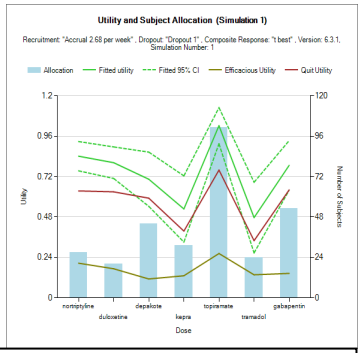

Figure 2. Simulation using

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.

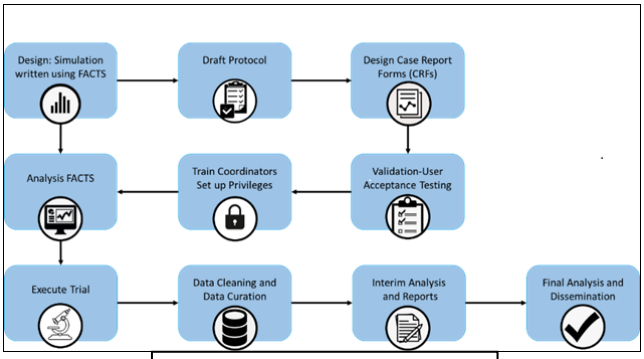

Figure 3. Data Coordinating Center

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,

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 Medical 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

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.

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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 addressed 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

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7. Projected month last participant is expected to be enrolled (month after project initiation)	Nove 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 al[81] 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.

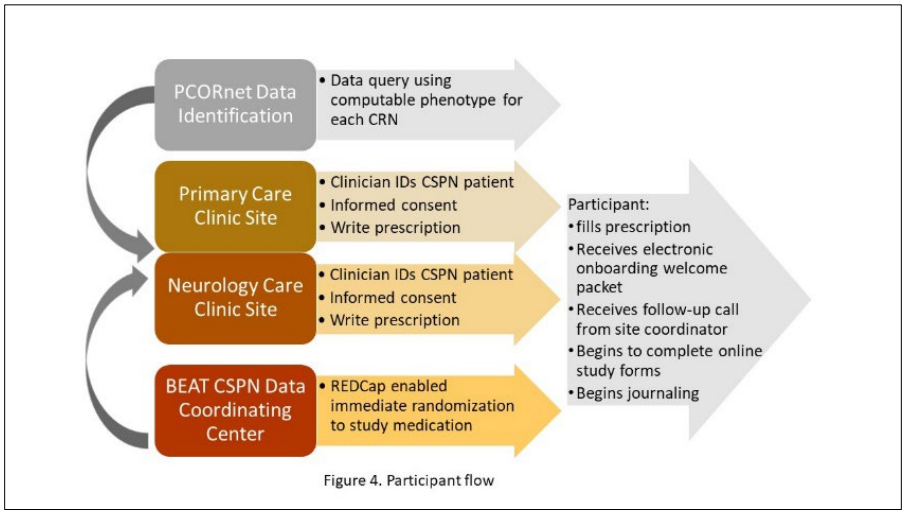

Figure 4. Participant flow

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

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)

Table 9. Major Feasibility Phase Activities to Be Accomplished

Research element	Which tasks will require significant development or effort in the feasibility phase?
1. Comparators	• 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	• 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	• Review/finalize 12-week duration and follow-up intervals post-3-month active study period
4. Setting(s)	• 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	• 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	• Develop and use computable phenotype • Refine estimates of effect size, likely enrollment, attrition, etc.
7. Study design and methods	• 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	• 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	• 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	• 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	• 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	• Finalize, and solicit additional stakeholder input for protocol • Test acceptability of protocol across key stakeholder groups
13. Various others as appropriate	• 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

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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 Baysian 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 venlafexine 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 heterogenous 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 evaluable 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 regiments, 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.

Kitt Peak Observatory

Elizabeth Snow Rowe

A mountaintop of telescopes in the desert
hovering above an ancient ocean floor.
The four meter sparkles in the sun.
We walk past signs that say
"Quiet please, day sleepers".
Astronomers sleep by day
and collect their stars by night.

The best part for me was searching space.
The best part for you was my breath
on your hand as you held it to my face
to shield my eyes from the blazing sun.

Published in *Sailing Downwind* by Elizabeth Snow Rowe,
And in *The Whirlybird Anthology of Kansas City Writers*.

Youth

Vernon Rowe, MD

She glided into
the office, lavender,
brilliant, springtime,
blonde. Her eyes
clear, hopeful
in the face of fear.

The only things betraying
her seventy-two years
were a few wrinkles
and a minimal tremor,
and we can fix those.