

Comparative Effectiveness of Intravenous Immunoglobulin (IVIg) and Subcutaneous Immunoglobulin (SCIg) versus Historical Controls in Management of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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Type of Grant: Patient Centers Outcome Research Institute (PCORI) Comparative Effectiveness Grant

Submitted: 2019

Grant was: Not Funded

This was a grant we submitted to PCORI as a comparative effectiveness study comparing IVIg and SCIg for CIDP. It was reviewed but not funded. We believe there was and is merit in such a study and therefore are publishing our grant and the critiques for others to read. We may try to pursue this avenue again in the future, but if others are willing to try to get such a study funded they are welcome to see our work as it might be helpful. The proposed study would randomize 50 CIDP patients, in an open label prospective design, to IVIg or SCIg. The IVIg arm would receive a loading dose of 2g/kg followed by 1 gm/kg every three weeks for 24 weeks. The SCIg arm would receive 0.4 gm/kg weekly divided over three days per week for 24 weeks. The SCIg group would get no prior IV loading dose. So, we were asking both: are the treatments comparable, and do SC patients need a loading dose? The endpoint measure was the INCAT scale and we used the definition of improvement used in the pivotal ICE trial (1). In that trial the placebo group had a 22.4% response rate. We considered this a historical placebo control group. Therefore, the primary analysis was to determine the proportion of favorable outcomes that is bigger than or equal to 22.4%. We prespecified that a clinically relevant effects size would be 25% absolute difference in favorable outcome proportions. To achieve 80% power, we needed 25 subjects in each group. The study planned to leverage the Greater Plains

Collaborative (GPC) PCORnet which at the time included Allina Health, Indiana University, InterMountain Healthcare, Marshfield Clinic, Medical College of Wisconsin, University of Iowa Healthcare, University of Missouri, University of Nebraska Medical Center, University of Utah, University of Texas Health Science Center at San Antonio and University of Texas Southwestern Medical Center.

We are attaching the Research Plan and the PCORI Summary Statement/Critiques. The reviewers appreciated the question we were trying to address although they were not very impressed that we were willing to tackle the comparison of IVIg to SCIg. We clearly did not explain the issue well as one reviewer said we did not describe or give data on the number of patients that seek IV versus subcutaneous treatment. We did not explain well that currently all patients begin with IV and then some choose to be converted and that this trial was a head to head comparison of IVIg versus SCIg as initial treatments. One reviewer was critical that we did not have insurance companies as stakeholders. They were critical that our dissemination plan did not include venues outside of the neurology world. We had neurologists at all GPC sites do letters of support but one reviewer sited as a major weakness that they were identical template letters and did not include what they would have considered statements of interest or demonstrate a need to answer the clinical question. One reviewer stated that while we adhered to PCORI Methodology Standards, they were skeptical about our use of what we called "historical controls" from the ICE study. They were critical for not justifying the effect size of 25% we said we could demonstrate with 50 subjects and this is probably a reasonable criticism. As usual, they were skeptical due to all my administrative responsibilities whether I would have time to devote to this study! A frequent criticism when I submit grants, but on the other hand they always say my background is ideal to do studies like these.

As you can see, PCORI reviewers are tough. And the critiques are different from NIH critiques. There is always a lot of emphasis on whether we have patient engagement, have adequate stakeholders, and conform to PCORI methodology. We do not know if we will try again to do a CER like this. If any of you want to take it on, we hope our proposal and the critiques will be helpful.

Reference

1. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate- chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomized placebo-controlled trial. *Lancet Neurol* 2008; 7: 136-144.

RESEARCH STRATEGY

A. Specific Aims

Chronic Inflammatory Demyelinating Neuropathy (CIDP) is an acquired autoimmune neurological condition that affects about 4.7 per 100,000 people. Intravenous immunoglobulin (IVIg) has been approved for treatment of CIDP based on prior trials showing its efficacy¹⁵ and recently the PATH study compared relapse rates in patients given subcutaneous immunoglobulin (SCIg) versus placebo in patients who responded to IVIg previously and has shown SCIg to be more efficacious than placebo¹⁸. A meta-analysis of studies looking at SCIg vs IVIg in CIDP and Multifocal Motor Neuropathy (MMN) patients showed no difference in the motor strength outcomes in the two groups and efficacy of SCIg is similar to IVIg for CIDP and MMN and has significant safety profile of SCIg, similar to IVIg for CIDP and MMN²¹. In both these studies, patients were already in IVIg before converting to SCIg. However, there is no literature comparing the effectiveness of IVIg with SCIg in CIDP¹⁸. This study will help address the decision to use either SCIg or IVIg for CIDP. In other words, we will conduct two one-sample tests comparing SCIg vs historical control rate, and separately, IVIg vs historical control rate. This will allow us to assess how each treatment performs relative to control with a sample size of 25 patients in each of the two arms. Otherwise a two-arm (SCIg vs IVIg) comparison would require twice as many patients which would not be feasible for this rare disease.

Aim 1: Determine if IVIg or SCIg in CIDP management is more effective than historical control data

Aim 2: Determine which of the two treatments (IVIg or SCIg) has less side effects

B. Background

CIDP is an acquired neurological, demyelinating neuropathy with an assumed autoimmune mediated pathogenesis. The clinical course can be relapsing/remitting or chronic and progressive,^{1,2} the former being much more common in young adults. The prevalence of CIDP is estimated to be about 4.7 per 100,000 adults³ and about 0.5 per 100,000 children.^{2,4} In addition to the significant medical burden, it has a significant economic impact, with disease-related expenses and high costs related to the immune therapies used to treat this condition.⁵ The first line treatments presently being used include corticosteroids, intravenous immunoglobulins and plasmapheresis.⁶ Other immunosuppressive therapies including azathioprine, cyclophosphamide, cyclosporin, etanercept, mycophenolate, rituximab and tacrolimus are considered in patients who do not improve with corticosteroids or have frequent relapses with attempts at weaning the corticosteroids.⁷ Although case studies and small series report apparent benefit from each there is no consensus about whether they work and which is the best.⁸ Approximately two-thirds of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) need long-term intravenous immunoglobulin.^{7,9} Subcutaneous immunoglobulin (SCIg) recently has been shown to be an option for patients already responding to IVIg.¹⁰ The greatest evidence is in CIDP, otherwise when the decision to use immunoglobulin is considered SCIg is as effective as IVIg for CIDP. There is no data on this. SCIg does not require IV access and patients can self-administer the medication. Then overtime patients can continue to perform their activities of daily living during the treatments. This would lower the burden of the disease and the treatment. Both IVIg and SCIg avoid the complications of prednisone treatment

For this study, we are collaborating with the GBS|CIDP Foundation. The GBS|CIDP Foundation has agreed to allow access and data linkages to their CIDP patient registry, which is managed by the National Organization for Rare Diseases (NORD). By partnering with the GBS|CIDP Foundation and NORD, we will be able to recruit patients from the registry while also providing data and study results to both organizations through the KUMC REDCap database. We are also collaborating with NuFactor, a specialty infusion company. NuFactor has agreed to provide the infusion services to IVIg patients for this study as in-kind support. RMS Medical Products has agreed to collaborate on this study as well. RMS Medical Products is a leading developer and manufacturer of medical devices and supplies. They have agreed to provide

infusion equipment for SCIg patients in in-kind support. Making these important community contributions will bring future rapport between partners and patients with both nonprofit and industry partners. As a result of this relationship, both the GBS| CIDP International Foundation and external industry collaborators are eager to work with other projects stemming from PCORnet especially for immune-related neuropathy research as well as any other disease states that require infusion care.

GPC and PCORnet were new networks in 2013. We now: (1) contribute regularly to large pragmatic observational studies and respond quickly to national queries, (2) are testing PCORnet's capacity to characterize molecular testing and therapeutics, (3) have seen IRB reciprocity in the GPC blossom into SmartIRB nationally, (4) integrate patients and other stakeholders in our networks as collaborators, and (5) account for a third of enrolling ADAPTABLE sites and second by volume.

The University of Kansas Medical Center is the lead site for the Greater Plains Collaborative (GPC), a PCORNet network of 12 leading medical centers in 9 surrounding states. We plan to use each member of the GPC (Allina Health, Indiana University, InterMountain Healthcare, Marshfield Clinic Research Institute, Medical College of Wisconsin, University of Iowa Healthcare, University of Missouri, University of Nebraska Medical Center, University of Utah, University of Texas Health Science Center at San Antonio, University of Texas Southwestern Medical Center) as a site for this study.

The GPC network is committed to a shared vision of improving healthcare delivery through ongoing learning, adoption of evidence-based practices, and active research dissemination. The GPC builds on strong research programs at our sites, existing community engagement and informatics infrastructures and data warehouses developed through the NIH Clinical and Translational Science Award (CTSA) initiative at most of our sites, extensive expertise with commercial EHR systems and terminology standardization, and strong working relationships between investigators and healthcare system information technology departments. Our network brings together a diverse population of over 19 million patients across 1,300 miles covering 9 states with a combined area of 679,159 square miles.

GPC has streamlined data governance and technical processes to be highly responsive to PCORnet queries and share opportunities across our communities. Our bi-weekly Data Request Oversight Committee meetings provide a forum for peer discussion amongst data honest brokers, patients, and regulators; making streamlined data access an expectation that benefits PCORnet and our research communities. GPC sites have outstanding response times for menu driven and SAS queries (~5 and 10 days respectively).

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Greater Plains Collaborative CDRN Collaboration

Collaboration is critical to address many research questions in clinical and translational sciences. There has been extensive interest from CDRNs, PPRNs, community partners, academia in general, and private industry to collaborate with the Greater Plains Collaborative CDRN.

Collaboration Overview

Collaboration Activities include, but are not limited to, the following:

- Development and validation of computable phenotypes (algorithms to identify patients)
- Prep to Research activities such as obtaining counts for feasibility or sample size estimates
- Research on de-identified and limited electronic health record data
- Identification of patients across the Greater Plains Collaborative CDRN
- Contact of potential study subjects through phone, email, and other modalities

- Survey Research
- Observational research
- Pragmatic clinical research
- Hypothesis Generation
- Stakeholder Engagement (Patients/Families, Clinicians, Clinics, etc)
- Health Information Technology support for patient-facing studies
 - o Electronic survey
 - o Electronic payment
 - o Electronic decision support for trial delivery

GPC pursued several collaborations with the Multiple Sclerosis and DuchenneConnect Patient Powered Networks building upon established relationships between GPC clinicians and patient advocates.

C. Significance

IVIg is an approved treatment for several immunodeficiency syndromes¹¹⁻¹⁴ and more recently has been approved for the management of two other autoimmune neuromuscular disorders, chronic inflammatory demyelinating polyneuropathy (CIDP)¹⁵ and multifocal motor neuropathy.¹⁶ Intravenous immunoglobulin (IVIg), a pooled gammaglobulin product from several thousand blood donors, has a complex immunomodulatory mechanism of action. It is thought to involve pathogenic autoantibody production modulation and binding inhibition, pro-inflammatory cytokinesuppression, Fc receptor blockade, macrophage colony stimulating factor and monocyte chemotactant protein-1 increase, alteration in T cell function, decrease in circulating CD54 lymphocytes, and inhibition of cell transmigration into the muscle.¹⁷ More recently, investigators from the Rockefeller found that Fc core polysaccharide 2,6-sialylation mediates the anti-inflammatory properties of IVIg.¹⁸

IVIg is administered as an induction dose of 2 gm/kg over 2 to 5 days, followed by monthly maintenance doses of 0.4-2.0 gm/kg given every 2 to 4 weeks. While it is generally infused no faster than 150 to 200 cc/h, a recent report described infusion rates of up to 800 cc/h in 50 patients, which was reasonably well tolerated.⁹ Lee and colleagues treated two CIDP patients with subcutaneous infusion of immunoglobulins (SCIg) after IVIg therapy was shown to be effective.¹⁰ Application of SCIg was well tolerated and led to stabilization of the disease course.¹⁰

IgPro20 (Hizentra®) is a ready-to-use formulation of human Immunoglobulin with ≥98% purity for subcutaneous (SC) administration. It is approved in the United States of America (US), in the EU, in Switzerland, and in Canada under the brand name Hizentra® for SC application in primary immune deficiency (PID) syndromes, recently FDA approved in US for CIDP and is manufactured at CSL Behring's (CSLB's) facility in Berne, Switzerland. It is a 20% liquid formulation (200 mg/mL) of human normal immunoglobulin for subcutaneous use, administered SC weekly or biweekly (ie-using 2x the weekly dose). Bioavailability and pharmacokinetics of SCIg and intravenous Immunoglobulin (IVIg) differ in patients with primary immunodeficiencies. Based on area under the curve (AUC) of serum Immunoglobulin versus time and trough level ratios (TLRs) on SCIg/IVIg, the mean dose adjustments required for non-inferior AUCs with multiple different SCIg preparations were 142% (± 11, with no real difference between different preparations).¹⁹ However, there were wide variations between adjustments required by different subjects. Combined data from multiple studies allow estimation of the ratio of Immunoglobulin levels with different dose adjustments, and of the steady state serum levels with different SCIg doses. When switching a patient from IVIg to SCIg, individualizing the dosage based on measured serum Immunoglobulin levels and the clinical response is preferable to using mean pharmacokinetic parameters.¹⁹

Preparation and Planning for Authentic Patient and Stakeholder Engagement: Patients and physicians have shaped the research question from inception, and they strongly endorse the study's approach and intended outcomes. For the proposed intervention, patient partners (those with a lived experience) informed the project from original concept to

implementation plan to help the project be as successful as possible. Additionally, clinicians who provide care also contributed to the design and implementation plan.

The decisional dilemma of choosing between intravenous and subcutaneous delivery presents a challenge for both physician and patient. For the physician, no clear evidence guides a recommendation of one administration route versus the other. Interviews with clinicians, however, revealed biases and assumptions about patient preference for one administration modality vs. the other. These assumptions informed the questions and discussion guide developed to conduct two patient focus groups – one with patients who self-administer Immunoglobulin and one with patients who receive Immunoglobulin therapy at an infusion center or via infusion with support from home health. Each focus group was conducted to encourage a profile of facilitators, barriers and factors operant in the process of selecting the “right” administration option.

We learned that for patients, a wide array of personal, social and cost-related factors are involved with each administration option. A focus group with patients currently receiving Immunoglobulin therapy through home health or by traveling to an infusion center revealed a rich set of personal and social issues that characterize their choice of care. Some focus group participants shared that receiving intravenous medication motivated them to maintain their daily routines of bathing, dressing and leaving their homes for care. Without the need to travel to an infusion center, focus group participants said they feared they would become house-bound or socially isolated. They noted that there is a social solidarity formed with other patients who receive IV care at their local infusion center, and this sustains their positive outlook. For at least one participant however, this value was diminished because all the patients at their site were receiving cancer treatment, so being able to relate in terms of the specific disease attributes of CIDP were absent. For some patients receiving IV care at home, their sense of self-empowerment as well as the care they receive from their families, neighbors and faith community provides them with a sense of support they found reassuring and meaningful. Being home allowed their friends, family and community volunteers to stop by and visit while infusion was occurring, prepare meals in their presence and offer social and emotional support during the process. Some of these participants reported that their community support was crucial by providing them with a planned calendar and system of offering support to enable them to remain in their homes, alone, but getting the care they need. By contrast, patients who self-administer subcutaneous Immunoglobulin report very high self-efficacy and independence that they assume they would lose if they depended on IV administration. The travel costs, time requirements, the dependency-on-others and the rigor of the IV administration process are onerous and perceived to interfere with quality of life. What patients who use subcutaneous Immunoglobulin report is that they feel free to manage their health entirely on their own; in fact they all highlight that they maintain a totally “normal” daily schedule, and that “people have no clue” that they have a medical condition requiring self-care. A few focus group participants likened their choice to someone who has diabetes or other disease requiring self-monitoring and being about to do so with “no one knowing”. Not surprisingly, all focus group participants were able to rationalize and support their choice while respecting that others with CIDP made their own personal selection based on their own, personal priorities. What all patients appreciated was that their physician could not use evidence-based research to quantify or adequately describe the advantages and disadvantages of each method (which they would prefer), leaving them instead to consider a variety of non-medical factors.

Engagement Plan: The engagement plan includes the following features to reflect engagement in planning the study, conducting the study and disseminating the study. Each feature also ensures that the four pillars of engagement principles are adhered to: reciprocity, co-learning, partnership and transparency/honesty/trust.

Engagement Feature 1: Patient-Centered Input for Design and Refinement of Research Question

As described above, focus groups of patients who receive Immunoglobulin via the two administration modalities of interest, informed: 1) the factors they most felt were relevant in the selection process and 2) patient reported outcomes of greatest interest. They also emphasized features of their care that were underappreciated by their clinician caregivers (i.e., social connectedness) that should be captured during the study.

Engagement Feature 2: Patient Advisory Council

To ensure that CIDP patients' and caregivers' voices continue to infuse the project, a Patient Advisory Council (PAC) composed of an equal number of subcutaneous and infusion delivered patients and/or their caregivers will collaborate with the research team throughout the conduct of the study and with disseminating findings to diverse audiences. The PAC will meet virtually using Zoom or GotoMeeting so that they may choose to visually be seen by the group (or remain connect via voice only) on a monthly basis. Dr. Kimminau will facilitate the PAC establishing norms and interaction expectations with each other as well as with researchers, statisticians, informaticians and study personnel. Dr. Kimminau will facilitate PAC discussions and she will elicit the PAC's preferred channel(s) for information, desired contact frequency with individuals on the research team and she will serve as a conduit to the project PI (at the direction of the PAC). The PAC may review items such as the informed consent document, project summaries, preliminary reports, statistical/graphical outputs etc. throughout the course of the study. The PAC will be involved extensively in discussion of recruitment and retention of participants in the study as well as guiding how to frame the results of the study to provide the greatest benefit to stakeholders. Our intent is to fully engage the PAC throughout the course of the trial and in every aspect of the study. We recognize that ongoing feedback is essential, and we will ask PAC members for feedback after each conference call and meeting using a group-developed and approved evaluation tool to make adjustments and remain responsive to their ideas of how to improve and perform better as a team.

Engagement Feature 3: Patient Voice Sessions with Investigators and Clinicians

We plan to use what was learned during the formative, development of the research question with patients to expand the opportunity for clinician learning. Asking patients to lead discussions and to share their journey and decision-making process will be illuminating for clinicians and their care teams. Patients using each administration modality have much to offer clinicians in terms of insights to their decision-making process and to the daily challenges they face. This engagement feature will showcase patients as the experts in the lived experience of CIDP in a way not often revealed in non-patient-centered, "traditional" research clinical trials. The addition of this engagement feature is unique and likely to be impactful well beyond the boundaries of this particular trial to the clinicians who offer medical care for this condition.

Engagement Feature 4: Transparency and Processes for Continuous Quality Improvement

When continuous quality improvement (CQI) is included by design, rapid cycles of modification or adjustment result in timely and transparent change. To maintain fidelity to reciprocity, co-learning, partnership and transparency/honesty/trust, the PAC and research team have and will continue to co-develop a set of shared objectives and activities related to the conduct of the study and the dissemination of results. The experience of working together to build and revise this plan using CQI principles will strengthen trust, encourage openness demonstrate the value placed on the partnership with stakeholders

D. Study Design or Approach

This study will be a randomized, open labelled prospective comparative effectiveness trial of IVIg vs SCIg. Fifty patients with either newly diagnosed CIDP (fulfilling the EFNS criteria) or patients who have persistent symptoms needing alternative therapy and/or other immunosuppressive therapies will be invited to enroll in this study. Patients will be randomly allocated to either the IVIg or SCIg arm with a 1:1 randomization. Patients in the IVIg arm will receive 2g/kg bolus treatment with infusions divided over 3 days, followed by 1g/kg every 3 weeks maintenance dose for total of 24 weeks. Patients in the SCIg arm will receive 0.4g/kg weekly infusions divided over 3 days per week for 24 weeks. The dose adjustments will be made based on patient tolerance. While patients receiving IVIg will be given a loading dose of 2g/kg, patients receiving SCIg will start at 0.4g/kg and will remain on that dose for the rest of the study.

- **Data Linkages:**

Our proposal will link GBS|CIDP Foundation Registry with KUMC's study specific REDCap database for consistent data quality, data linkage and recruitment methods to provide a platform for comparing the effectiveness of Intravenous Immunoglobulin (IVIg) vs. Subcutaneous Immunoglobulin (SCIg) in management of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). This proposal will develop an approach with Datavant or a similar linkage solution and its use of data linking to connect Registry with REDCap database.

This study will pursue a data linkage strategy utilizing Datavant or similar technology and hope to enroll subjects in the GBS|CIDP Foundation Registry and integrate Registry with REDCap database for data collection in a streamline fashion. We will also use PCORnet Common Data Model (CDM) at sites to identify and recruit patient and gather patient data using CDM.

The proposal will serve as prototype for linkage technology's ability to target data exchange and trials for specific clinical populations and also leverage pragmatic data collection as a byproduct of healthcare delivery in contract to staffing retention efforts and data abstraction for traditional registries.

The approach will allow us to integrate and analyze data from a variety of sources (e.g. EMR (CDM), Registry, REDCap) to develop a more complete model of health for people with CIDP and understand quality of life (e.g., diagnoses, conditions health outcomes) and environmental (e.g. service utilization, access to services) factors that influence health.

Our goal will be to work collaboratively with program officers and Registry staff/contractors to implement streamlined linkage methods that integrate GBS|CIDP Registry and REDCap database for increasing data richness for CIDP research community.

We will evaluate the applicability of Datavant or similar deidentified linkage software. However, primarily our focus is on utilizing Datavant (<https://datavant.com/>), which is recently selected by PCORnet for consistent data linkage across its national network. The proposal is to integrate Registry with REDCap database utilizing Datavant to support study population. We are estimating the costs to configure the GBS|CIDP Registry System with Datavant at \$40,000.

Datavant is used for data de-identification, patient token creation and token transformation to enable de-identified linking of disparate data sets. Datavant's DeID application transforms input data into de-identified and tokenized output data.

DeID application creates irreversible, site-specific tokens by involving Hashing and Encryption. Hashing makes tokens irreversible, securing from employee or business associate regulatory violations. Encryption makes tokens site-specific, protecting each site from a partner's security breach (Figure 1).

The Link application enables secure transfer of tokens within Datavant ecosystem (Figure 1).

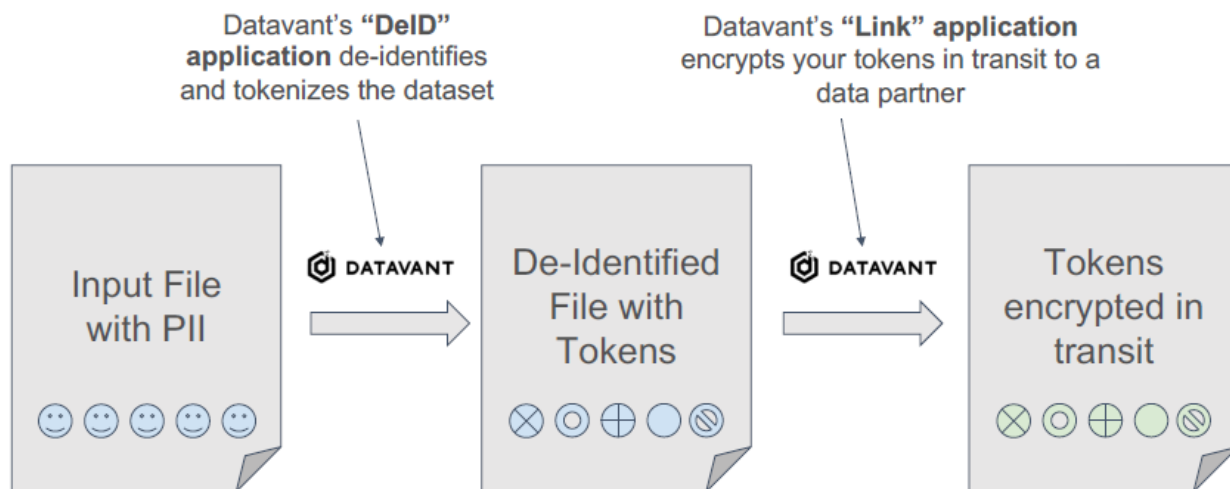


Figure 1. Datavant Applications: DeID and Link

If Datavant or a similar linkage solution is not applicable for this study, our strategy will be to follow ADAPTABLE’s use of a trial invitation identifier to link the de-identified pat_id identifiers used in the PCORnet CDM to the invited patient’s specific enrollment in CIDP Registry. In this scenario, the study team will generate random identifiers (trial_invite_code) centrally for each recruiting site who will track their relationship to the random identifiers used to uniquely identify patients in their site PCORnet CDM (e.g. pat_id). Sites then distribute these trial_invite_codes to the subject when they are approached for participating in CIDP Registry and the study. Upon enrollment, the subject will enter their trial_invite_code into the Registry directly. Upon enrollment, Registry will send back to the sites the trial_invite_codes of the patients who have enrolled and consented to share their Registry data. These codes and the definitions for this specific study are logged in the PCORNET_TRIAL table (Figure 2) with column definitions described in the CDM specifications (<https://pcorntest.org/pcorntest-common-data-model/>).

- **Existing Resources:**

At the University of Kansas Medical Center (KUMC), we currently use the Streamlined, Multisite, Accelerated Resources for Trials Institutional Review Board (SMART IRB) for our multi-center studies. For sites that currently do not use this method, we establish a reliance agreement, so that their site will allow KUMC to be the IRB of Record. Within the Greater Plains Collaborative, our sites have established a ‘central’ contracting form. The PCORnet 2.0 infrastructure will be used to streamline administrative aspects of the trial, including centralization of institutional review board (IRB) functions and contracts, electronic consent and use of EHR data standardized into the CDM format.

- **Comparators:**

This is the first head to head study of IVIg vs SCIg. A previous CIDP study compared relapse rates in patients given SCIg versus placebo and showed SCIg to be more efficacious than placebo.¹⁸ One Italian study compared the SCIg costs with IVIg therapy in CIDP and found that SCIg may be cost saving in Italian CIDP patients.¹⁹ A meta-analysis of studies looking at SCIg vs IVIg in CIDP patients found no difference in the motor strength outcomes in the two groups, and that efficacy and safety profile of SCIg was similar to IVIg for CIDP.²⁰ However, there is very limited literature comparing the effectiveness of IVIg with SCIg in CIDP. This study will help address the decision to use either SCIg or IVIg for CIDP.

- **Outcomes:**

Subjects will be asked about the functionality of their upper and lower extremities using the Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, which will serve as the primary outcome. They will also undergo strength testing using the Medical Research Council (MRC) sum score, perform grip strength testing, and will be asked about their ability to perform everyday tasks using the Inflammatory Rasch-built Overall Disability Scale (I-RODS). Short forms for the PROMIS instruments for physical function (20 items) and upper extremity (7 items) measure signs and symptoms using general questions without a temporal reference. Short forms for the Patient Reported Outcomes Measurement Information System (PROMIS) instruments for fatigue (8 items) and dyspnea severity (10 items) measure signs and symptoms over the past 7 days. A 5-point scale is used for each instrument (though responses may vary within or among instruments), and a total score is generated for each instrument. Patient input during the project development phase revealed a substantial interest in patient-reported outcomes in self-efficacy. Both focus groups identified their high level of satisfaction with their selected administration mode because it supported their values in disease self-care management. As a result, the research team is including a secondary outcome of self-efficacy to be responsive to patient priority. We will use the validated PROMIS® self-efficacy instrument to collect baseline and post-study individual-level metrics to assess change.

Subjects will be interviewed at each visit about possible side effects of medications and CIDP-related symptoms. Patient safety will also be assessed by physical examinations and vital signs at clinic visits. At each visit, patients will be questioned about the development of any new symptoms including deep vein thrombosis assessments. If an unscheduled visit is deemed necessary, the patient will be asked to return for a clinic visit within 48 hours where the site investigator will evaluate the subjects and determine if intervention is necessary. At all scheduled/unscheduled clinic visits, the site investigator will complete a Treatment Failure Questionnaire if the patients meet any of the criteria for treatment failure.

- **Study Design:**

This study will be a randomized, open labelled prospective comparative effectiveness trial of IVIg vs SCIg. Fifty patients with either newly diagnosed CIDP (fulfilling the EFNS criteria) or patients who have persistent symptoms needing alternative therapy and/or other immunosuppressive therapies will be invited to enroll in this study. Patients will be randomly allocated to either the IVIg or SCIg arm with a 1:1 randomization. Patients in the IVIg arm will receive 2g/kg bolus treatment with infusions divided over 3 days, followed by 1g/kg every 3 weeks maintenance dose for total of 24 weeks. Patients in the SCIg arm will receive 0.4g/kg weekly infusions divided over 3 days per week for 24 weeks. The dose adjustments will be made based on patient tolerance. While patients receiving IVIg will be given a loading dose of 2g/kg, patients receiving SCIg will start at 0.4g/kg and will remain on that dose for the rest of the study.

- **Analytic Plan:**

The primary analysis will be a one group Chi-square test that proportion of favorable outcomes is bigger than or equal to 22.4%. This 22.4% was based on the placebo response in ICE15 trial. This test is done for both the IVIg group and the SCIg group. There are no pre-specified subgroup analyses.

As shown in the sample size and power section it is required to have 50 patients with endpoint data. If a patient withdraws from the study they will be replaced with a new patient to be randomized. Also specified are some secondary analyses. The IVIg and SCIg groups will be compared using a Chi-square test for investigating therapy differences. Additionally, all secondary measures will be investigated using multivariate analysis of variance. If omnibus test across the two groups is significant ($p < .05$) then the secondary analyses will be performed using two-sample t-tests for the measures Medical Research Council (MRC) sum score, perform grip strength testing, and Inflammatory Rasch-built Overall Disability Scale (I-RODS).

- **Study Population and Setting:**

Fifty patients newly diagnosed CIDP will be invited to participate in this study. Patient selection will be based on a diagnosis of CIDP and the following significant inclusion/exclusion criteria:

Inclusion Criteria:

- (1) CIDP diagnosed according to the EFNS/PNS criteria 2010;
- (2) Patient’s signs and symptoms should not be better explained by another disease process;
- (3) If taking prednisone or steroid equivalent, there must be no dose change for 2 weeks from baseline;
- (4) Patients can be on the following medications as long as there has been no change in dose 60 days prior to the baseline visit: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, or other immunosuppressive drugs;
- (5) INCAT score ≥ 2

Exclusion Criteria:

- (1) Prior treatment of IVIg or SCIg for any reason;
- (2) Presence of any other causes of polyneuropathy or multifocal motor neuropathy;
- (3) Other neurologic or orthopedic condition causing weakness;
- (4) Treatment with PLEX within the last 30 days from baseline or rituximab within the past 12 months;
- (5) Participation in another trial within the last 3 months;
- (6) Latent tuberculosis or active infection;
- (7) Previous or present use of IVIg or SCIg;
- (8) Previous or present Infection with hepatitis C and hepatitis B;
- (9) Evidence of renal insufficiency or liver disease;
- (10) Skin disease that would interfere with assessment of injection site reaction;
- (11) History of thrombotic episodes within the last year prior to enrollment;
- (12) History of IgA deficiency or evidence of IgA deficiency

Recruitment Plan for Prospective Studies

1. Estimated number of potentially eligible study participants (describe how you determined this number [e.g., EHR, claims data, clinic logs, administrative data, other])	125
2. Total number of study participants you expect to screen	65
3. Total number of study participants you expect to be eligible of those screened	55
4. Target sample size (use same number stated in milestones)	50
5. If applicable, total number of practices or centers that will enroll participants	12
6. Projected month first participant enrolled (month after project initiation)	June 2020
7. Projected month last participant enrolled (month after project initiation)	January 2022
8. Projected rate of enrollment (anticipated number enrolled per month of enrollment period)	2-3
9. Estimated percentage of participant dropout	10%

- **Sample Size and Power:**

The primary endpoint is favorable outcome at 6 months post randomization, where favorable outcome is defined according to the dichotomy of the INCAT as described above. A clinically relevant effect size of 25% absolute difference

in favorable outcome proportions is prespecified. In order to achieve 80% power with a two-sided type I error probability of 0.025, 25 subjects are required for both the SCIg and IVIg groups for a total of 50 subjects.

In an effort to sustain PCORnet collaboration and engagement, we have decided to invite sites that are members of the Greater Plains Collaborative to participate in this study. The University of Kansas Medical Center is the lead site for the Greater Plains Collaborative with the other sites being Allina Health, Indiana University, InterMountain Healthcare, Marshfield Clinic Research Institute, Medical College of Wisconsin, University of Iowa Healthcare, University of Missouri, University of Nebraska Medical Center, University of Utah, University of Texas Health Science Center at San Antonio, University of Texas Southwestern Medical Center.

These sites share a vision of improving healthcare delivery through active research dissemination. Each site has a strong research program, informatics infrastructures, and strong working relationships between investigators and healthcare system information technology departments.

Research Team and Environment

Richard Barohn, MD is a renowned clinical leader in neuromuscular disease. He is the PI on our CTSA and is Director of Frontiers, the University of Kansas Clinical and Translational Science Institute. In his CTSA role, he was a co-leader in a NIH supplement which recommended GCP training for all personnel involved in clinical trials and this has since become NIH policy. He is involved in many federally- and foundation-funded clinical research studies for rare neuromuscular diseases, such as amyotrophic lateral sclerosis, myasthenia gravis, inflammatory myopathies, and muscular dystrophies. He was the co-PI on the NeuroNEXT trial of rituximab for myasthenia gravis. He has had leadership positions in two NIH Rare Disease Consortia: CINCH and CReATe. He was the PI on three completed multicenter R01 grants: 1) mexiletine in non-dystrophic myotonia; 2) methotrexate in MG; 3) rasagiline in ALS. He is the PI or co-leader on two other multicenter R01 grants through the FDA OPD which we coordinate at KUMC (memantine for ALS and arimocloamol for IBM). He is the rare disease leader on our Greater Plains Consortium PCORNet CDRN, in which the rare disease we study is ALS. As stated above, he was PI on a recently completed PCORI comparative effectiveness study for drugs in painful neuropathy. He was made Vice Chancellor for Research of KU Medical Center and President of the Research Institute in 2014 and in those capacities as well as the Director of Frontiers, he has the authority to provide the resources and space at our institution needed to accomplish the aims we propose in this application.

Mamatha Pasnoor, MD is an Associate Professor in the Department of Neurology at the University of Kansas Medical Center (KUMC). She and Dr. Barohn will equally share leadership roles and will be able to act on each other's behalf for all study decisions. She co-Directs the peripheral neuropathy clinic at KUMC and works closely with the national Foundation for Peripheral Neuropathy. She is a leader in the diabetic neuropathy field and has been actively involved in collaborative studies in diabetic neuropathy. She is a coinvestigator for the University of UTAH and University of Kansas NIH funded diabetic neuropathy exercise intervention study (ADAPT study). Along as serving as co-Investigator in our ongoing multi-center ADAPT study, she is site PI on our current Topiramate study through NeuroNEXT. With Dr Barohn, she was the co-leader of the recently completed FDA-OPD RO1 funded methotrexate trial in Myasthenia gravis which was published in Journal of Neurology as the primary author. This was a 20-site study in which she played a similar role as she played in PCORI study by facilitating coordination among on the sites, so that study completion was accomplished on time.

Byron Gajewski, PhD, Professor in the Department of Biostatistics is a nationally recognized leader in the Bayesian adaptive design. He received his training in the Bayesian adaptive design from Scott M Berry PhD, who is an Adjunct Professor in the Department of Biostatistics at KUMC. Dr. Gajewski developed the statistical plan used in the PCORI-funded PAIN-CONTRoLS study.

Lemuel Russell (Russ) Waitman, PhD is the Director of Medical Informatics at the KUMC. Dr. Waitman is a national informatics leader and the director in the CTSA Informatics core at KUMC. He was responsible with the development of REDCap™ database that data from PAIN-CONTRoLS is entered. His department was responsible for the training of personnel at the sites. Medical Informatics would generate the reports presented at the DSMB meetings. They took part of the monthly study calls, DSMB and if needed the patient advisory groups.

Andrew Heim, BSc, Project Manager has been involved in neuromuscular research for over three years. He has served as project manager for approximately one year. During this time, he has project managed two other studies and helped submit many grant applications to various funding agencies.

Kim Kimminau PhD. Dr. Kimminau is Associate Director of Frontiers, the K CTSA supported institute. She is a leader in community-based research and a facilitator of patient focus groups to obtain patient perspective and advice on

research. She facilitated the patient focus groups for the original PAIN-CONTRoLS and she will continue to do so. In the first year, she will establish a patient/community committee to work with and advise the steering committee in the trial. One member of the patient/community committee will serve on the overall steering committee.

The Neuromuscular Research team at the University of Kansas Medical Center is housed at the Fairway North Building which is in close proximity to the Clinical Research Center and neuromuscular clinic. The team is composed of 7 physicians that specialize in neuromuscular practice, 4 project managers, 7 research coordinators, 2 administrative assistants, 2 clinical evaluators, and 1 budget analyst. Each staff member has a dedicated space, a computer that is linked to a secure network server, phone and access to a copier that can fax and scan. With Dr. Barohn serving as PI, the other 6 neuromuscular physicians will serve as sub-I's for this study. KUMC will also dedicate one project manager and one research coordinator to this project.

Neuromuscular clinic is held primarily on Tuesday's and Thursday's, but patient's with CIDP may be seen any weekday. Annually, approximately 10 new CIDP patients are seen at KUMC. The clinics are staffed with research assistants/coordinators that approach every patient regarding available research opportunities. The research assistants/coordinators screen all of the charts before the clinic visits to determine if the patients are eligible for any of the ongoing clinical trials. This will be the practice for this study.

Two companies, NuFactor and RMS Medical Products have agreed to donate services via in-kind support. NuFactor will donate infusion services to patients randomized to the IVIg arm. RMS Medical Products has agreed to donate supplies to patients randomized to the SCIg arm. The total amount of services being provided total \$1,150,625.

Since 1995, NuFactor has been providing the specialty products and care that infusion patients deserve, to help solve the acute problems of availability, affordability and safety in chronic care. NuFactor provides nationwide patient customized home infusion services.

RMS Medical Products is a fully integrated medical device company (eg. Research & Commercialization) that focuses on home and specialty infusion solutions, emphasizing responsive problem-solving for our customers, and careful consideration for the patient experience. We are dedicated to providing safe, effective, and cost-conscious drug delivery solutions to global healthcare markets.

The GBS/CIDP Foundation International is working for a future when no one with Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and related syndromes such as multifocal motor neuropathy (MMN) suffers alone and that everyone has access to the right diagnosis and the right treatment, right away.

Since the Orphan Drug Act, NORD has served as the hub of the rare disease community, leading efforts to connect patients and patient organizations with other stakeholders and driving progress for all. Since 1989, NORD has administered a Research Program through which we provide grants that have resulted in numerous published advances and at least two FDA-approved therapies. NORD is also working with rare disease organizations to launch disease-specific registries to support research.

The University of Kansas Medical Center is the lead site for the Greater Plains Collaborative (GPC), a PCORNet network of 12 leading medical centers in 9 surrounding states. We plan to use each member of the GPC (Allina Health, Indiana University, InterMountain Healthcare, Marshfield Clinic Research Institute, Medical College of Wisconsin, University of Iowa Healthcare, University of Missouri, University of Nebraska Medical Center, University of Utah, University of Texas Health Science Center at San Antonio, University of Texas Southwestern Medical Center) as a site for this study.

DISSEMINATION AND IMPLEMENTATION POTENTIAL

Describe the potential for disseminating and implementing the results of this research in other settings.

A. Describe how you will make study results available to study participants after you complete your analyses.

1. The study will be registered with ClinicalTrials.gov after notice of award and prior to enrolling participants. Registration data elements submitted to ClinicalTrials.gov will include descriptive information, recruitment information, location and contract information, and administrative data. Results information will be submitted to ClinicalTrials.gov no later than 12 months after the primary completion date. Results information data elements to be submitted to ClinicalTrials.gov include participate flow, demographic and baseline characteristics, outcomes and statistical analysis, adverse events, the protocol and statistical analysis plan, and administrative information.
2. The informed consent documents for the clinical trial will include a specific statement relation to posting of the clinical trial information at ClinicalTrials.gov.
3. The University of Kansas Medical Center Research Institute, Inc. (KUMCRI) has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements. The office of Clinical Research Administration (CRA) manages and executes the regulatory elements for clinical trials at KUMCRI. After notice of award, a CRA compliance office will be notified and will confirm the submission meets all requirements for registration in ClinicalTrials.gov, and that proper data elements are include dint he initial registration. After initial registration, the compliance officer will monitor and confirm study updates are posted in ClinicalTrials.gov with the required timeline.
4. In addition to posting on clinicaltrials.gov, results will be presented to participants and their family members via a webinar which will be posted online.
5. We will announce the study in the GBS|CIDP Foundation newsletters and we will use our broad patient and community engagement network to organize a webinar to present the results to the broader community of people with CIDP and their family members.
6. We will use our associations with patient advocacy groups, to ensure the results are widely distributed to physicians who treat patients with CIDP.
7. In addition, we will ensure our clinical trial methodology outcomes are also widely distributed.
8. We will use the PCORnet and Greater Plains Consortium to disseminate this data and will present at national and international meetings. Data on clinical trial results as well as process improvement will be prepared for publication in scientific communications.

B. Describe possible barriers to disseminating and implementing the results of this research in other settings.

1. Not all patients may have access to clinicaltrials.gov.
2. After receiving their diagnosis, patients sometimes choose to not be followed in a GBS|CIDP Foundation Center of Excellence.
3. Not all patients have access to CIDP clinicians. Therefore, these clinicians may not understand the latest CIDP research.

PROTECTION OF HUMAN SUBJECTS

Describe the protection of human subjects involved in your research.

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

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

I. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

Chronic Inflammatory Demyelinating Polyneuropathy is a characterized by the occurrence of symmetrical weakness in both proximal and distal muscles that progressively increases for more than two months. The condition is associated with impaired sensation, absent or diminished tendon reflexes, an elevated cerebrospinal fluid protein level, demyelinating nerve-conduction studies, and signs of demyelination in nerve-biopsy specimens. The course can be relapsing or chronic and progressive, the former being much more common in young adults. CIDP has an estimated prevalence of 0.5 per 100,000 children and 1 to 2 per 100,000 adults.

We will include all CIDP patients more than 18 years of age who meet the EFNS/PNS diagnosis criteria, have an INCAT score ≥ 2 , have been stable on concomitant medications according to protocol, and have symptoms that are not explained better by another disease process. We are using these criteria so that all patients enrolled and randomized to therapy will be able to obtain standard of care approval. Recruitment will be done through site specific clinics, using and Electronic Health Records to identify potential subjects and facilitate electronic screening, contact, and enrollment with the site clinical teams, and through the data linkage with the GBS|CIDP Foundation patient registry.

Randomization will be a 1:1 ratio using the REDCap database system managed by the KUMC Research Informatics team. The dose and frequency of immunoglobulin therapy will be administered per standard of care treatment.

Collaborating sites will be responsible for recruiting and enrolling patients for this study. Data from all sites will be obtained by study staff and will be managed and protected using the REDCap database system.

b. Sources of Materials

The research material that is being collected in this study mostly coincides with other CIDP research studies and standard of care procedures. We will utilize as many SOC procedures as possible during the course of this study. If a site doesn't normally collect the INCAT, I-RODS, or MRC score during clinic, then this element will be collected by research staff. Some samples of SOC items include forced vital capacity, physical exam, vital signs and safety labs. Items including consenting, obtaining medical history, demographics, adverse events, and concomitant medications will be collected by research staff during their visits.

Data will be collected by local study staff only. No private health information will be collected by the study. Patients will be deidentified and assigned a study number. Patient information will be stored at local site research facilities where it is only accessible to study staff. Electronic data will be collected, managed, and protected via the REDCap EDC system. Study staff at local sites will have access to their patient data only. The project manager and statistician will have access

to all study data for monitoring, compliance, and statistical analysis purposes. By collected mostly standard of care data and aligning research visits with clinic visits, it is our hope that this will prevent missing data from occurring.

c. Potential Risks

Most patients tolerate IVIg therapy well. Mild and moderate side effects of intravenous IG (IVIg) are headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension. Headaches and their more severe form, migraines, tend to be one of the more common side effects.

For SCIg patients, the most common side effects include headaches and local irritation (redness, swelling, itching, blanching) at the needle site. Some reactions, especially for patients new to SCIg therapy, are expected, and most decrease with time once the body becomes accustomed to the therapy.

Serious side effects are rare, and most can be reduced by screening the patient for factors predisposing them to complications. Serious side effects can include acute renal failure, thrombosis, Stevens-Johnson syndrome, serum sickness, aseptic meningitis and anaphylaxis. The most severe form of IG-related headache comes from aseptic meningitis, and in fact, patients with a history of migraines appear to be more susceptible to aseptic meningitis.

There may be unforeseen financial risks due to cost of immunoglobulin therapy. These medications will be billed to the participants insurance, but the infusion costs will be donated in-kind. Participants can withdraw from the study at any time if the financial risks become intolerable. We have budgeted \$600 for the duration of the study to offset insurance copays. We do not anticipate any psychological, legal, or social risks.

Since we are studying the only two FDA-approved medications for ALS, the only options for alternate treatment are investigational medications or no treatment at all.

II. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Patients will be recruited through each local site's clinic and through the GBS|CIDP Foundation registry. Patients that meet the entry criteria will be approached about participating in this study. We will also deploy computable phenotypes against data repositories and electronic health records to identify potential subjects.

Informed consent will be sought and done by local study staff that are delegated to do so. Consenting will take place in a private room. Subjects will be given sufficient time to make a decision and ask any questions regarding the study to the study staff. All study procedures, a background of CIDP, why the study is being done, any financial/legal details, voluntary participation, and protection of private health information will be explained to the subject. HIPAA laws will be included in the main consent form. Documentation of consent will be done per each local site standard operating procedures.

We will not enroll children in this study and therefore will not need an assent form.

b. Protections Against Risk

Both medications being studied have a potential to cause physical risks, but these risks are minimal. For this study we propose real-time safety monitoring which will be AE reporting monthly. Safety will be monitored by our investigators and coordinators, by KUMC compliance office, and by our DSMB.

We do not plan to enroll any patients that fall in the 'vulnerable populations' category.

All adverse effects will be graded, reported, and handled by the local site PI. Local site PI's will be responsible for using best clinical judgement when addressing adverse effects and patient safety. Data and safety results will be will be monitored by both principal investigators, the medical monitor, and the data and safety monitoring board. The DSMB will meet quarterly to discuss. During the study the ongoing monitoring of data quality and subject safety will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. An independent DSMB will be established and is responsible for periodic review of the data related to Adverse Events throughout the trial. The DSMB will consider study data including information on all Serious Adverse Events, other Adverse Events, laboratory test results, recruitment and retention, data completeness and data quality. The DSMB will act independently to review ongoing data.

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

Patients will receive minimal benefit from participating in this study. By being placed on an FDA approved medication, the research conduct will parallel standard of care treatment. It is our hope that subject payment will benefit patients to help offset some costs that might be associated with medication co-pay. By participating in this research project, participants will help future CIDP patients make an informed decision on medication use and administration. While there is minimal benefit to this research project, there is also minimal risk. The potential side effects of both drugs are known and the drugs have been proven to be safe. Bleeding/bruising may occur during blood draws, but this procedure is typically done as part of standard of care as well. We hope to assist in any financial risk by providing patient stipends.

IV. Importance of the Knowledge to be Gained

When patients are diagnosed with CIDP, they face the tough decision of what medications they should take. Immunoglobulin therapy has proven to be effective therapy for most patients diagnosed with CIDP. When the patient and clinician agree to use immunoglobulin therapy, the patient is faced with the choice of receiving the medication either intravenously or subcutaneously. There are several factors patients must consider when making this decision, such as cost and convenience. What has yet to be studied, however, is the effectiveness of the two administrations for patients that are newly diagnosed. By doing this study, we hope to gain knowledge on the effect of both administrations after a 6 month time period and disseminate the information to clinicians and patients alike.

Estimated Final Racial/Ethnic and Gender Enrollment Table

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native	1	0	1
Asian	1	1	2
Black/African American	4	4	8
Hawaiian/Pacific Islander	0	1	1
White	18	17	35
Multirace	1	2	3
Ethnicity	Male (N)	Female (N)	Total (N)
Hispanic (Latino/Latina)	3	5	8
Non-Hispanic	20	22	42

CONSORTIUM CONTRACTUAL ARRANGEMENTS

For detailed instructions, refer to the Application Guidelines for this PFA. Do not exceed 10 pages.

Describe the proposed research projects that subcontracted organizations will perform. Explain the strengths that these partners bring to the overall project to ensure successful submission of contract deliverables in accordance with the milestone schedule.

REFERENCES CITED

For detailed instructions, refer to the Application Guidelines for this PFA. Do not exceed 10 pages.

Follow scholarly citation practice and list the source material cited in your Research Plan. PCORI suggests using American Medical Association citation style, but other citation styles are acceptable.

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APPENDIX

INCAT Disability Scale Score

ARM SCALE

Does the patient have any symptoms in their hands or arms, e.g., tingling, numbness, pain or weakness?

Yes No (If no, please go to 'legs section')

Is the patient affected in their ability to: (mark one option:)

	Not affected	Affected but not prevented	Prevented
doing all zips and buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
washing or brushing hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
using a knife and fork together?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
handling small coins?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

ARM GRADE

Work out the score from the answers to the questions using the scoring criteria.

- 0 = No upper limb problems
- 1 = Minor symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zippers *and* buttons, washing or brushing hair, using knife and fork together, handling small coins
- 2 = Disability, in one or both arms, affecting but not preventing any of functions listed above
- 3 = Disability, in 1 arm or both arms, preventing 1 or 2 of functions listed above
- 4 = Disability, in 1 arm or both arms, preventing 3 or all of functions listed above, but some purposeful movements still possible
- 5 = Inability to use either arm for any purposeful movement

Score =

LEG SCALE

(mark one option on each line:)

	Yes	No	Not applicable
Is the walking of the patient affected?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
How do they mobilise outdoors?			
without aid (independently)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
with one stick or crutch or holding someone's arm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
with two sticks or crutches or one stick or crutch holding onto someone's arm or frame	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
with a wheelchair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If they use a wheelchair, can they stand and walk a few steps with the help of one person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

LEG GRADE

Work out the score from the answers to the questions using the scoring criteria

- 0 = Walking not affected
- 1 = Walking affected, but walks independently outdoors
- 2 = Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors
- 3 = Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors
- 4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps
- 5 = Restricted to wheelchair, unable to stand and walk a few steps with help

Score =

Final INCAT Disability Scale Score =
Arm grade + Leg grade

Estimated time: 5-8 minutes

MEDICAL RESEARCH COUNCIL (MRC) SUM SCORE

MRC grading

	Left side of the body	Right side of the body
Movement^a		
Shoulder abduction		
Elbow flexion		
Wrist extension		
First dorsal interossei		
Hip flexion		
Knee extension		
Ankle dorsiflexion		
Extensor hallucis longus		

Total for each body side		
Total		
MRC grades:	Description:	
0	no movement, no contraction	
1	visible contraction without movement	
2	movement, but only with gravity eliminated	
3	movement against gravity	
4	movement against resistance, but weaker than normal	
5	normal strength	

The MRC sum score ranges from 0 (paralysis) to 80 (normal strength).

Inflammatory Rasch-built Overall Disability Scale (I-RODS)

Are you able to		Mark the best option with "x"		
Task	Not possible to perform	Possible, but with some difficulty	Possible, without any difficulty	
	[0]	[1]	[2]	
1. read a newspaper/book?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2. eat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3. brush your teeth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4. wash upper body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
5. sit on a toilet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6. make a sandwich?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
7. dress upper body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
8. wash lower body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
9. move a chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
10. turn a key in a lock?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
11. go to the general practitioner?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
12. take a shower?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
13. do the dishes?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

14. do the shopping?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. catch an object (e.g., ball)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. bend and pick up an object?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. walk one flight of stairs?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. travel by public transportation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. walk and avoid obstacles?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. walk outdoor < 1 km?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. carry and put down a heavy object?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. dance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. stand for hours?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. run?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

General Self-Efficacy

Please respond to each item by marking one box per row.

For the next set of questions, please read each sentence and rate your level of confidence in managing various situations, problems, and events.

Rate your level of confidence.		I am not at all confident	I am a little confident	I am somewhat confident	I am quite confident	I am very confident
GSE11_C	I can manage to solve difficult problems if I try hard enough.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE12_C	If someone opposes me, I can find the means and ways to get what I want.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE13_C	It is easy for me to stick to my aims and accomplish my goals.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE14_C	I am confident that I could deal efficiently with unexpected events.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE15_C	Thanks to my talents and skills, I know how to handle unexpected situations.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE16_C	I can solve most problems if I try hard enough.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE17_C	I stay calm when facing difficulties because I can handle them.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE18_C	When I have a problem, I can find several ways to solve it.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE19_C	If I am in trouble, I can think of a solution.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
GSE20_C	I can handle whatever comes my way.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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

Principal Investigator: Richard Barohn

Organization: University of Kansas Medical Center Research Institute, Inc.

Project Title: Comparative effectiveness of IVIg and SCIG vs Historical Control Data in management of CIDP

PCORI Funding Announcement: Partnerships to Conduct Research within PCORnet (PaCR)

Review Cycle: Off-Cycle 19C1

Request ID: 17149

NOTE: PCORI's Merit Review process includes written online critique and in-person discussion phases. All applications go through the online written critique phase, but only a subset continue to the in-person discussion phase. If an application does not progress to in-person discussion, the Summary Statement includes only the written online critiques. If an application progresses to in-person discussion, the summary statement includes in-person panel discussion notes; final average overall score; written online critiques; and, in some cases, application quartile, to help applicants understand how they did relative to other discussed applications.

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

Reviewer 1:

Strengths:

- The application by Barohn et al addresses a rare but potentially severely disabling acquired autoimmune neurological condition called Chronic Inflammatory Demyelinating Neuropathy (CIDP) that affects about 4.7 per 100,000 people. The authors describe the clinical burden of CIDP well and describe the limitations of the current management options too. Intravenous immunoglobulin (IVIg) is an approved treatment of CIDP and a recent small trial suggests the effectiveness of subcutaneously administered Ig (SCIG) in CIDP patients compared to those treated with placebo (MAJOR).
- The researchers identify a gap in the field where there is a lack of data comparing effectiveness of IVIg with SCIG in CIDP (MAJOR).
- This study proposes to determine if IVIg or SCIG is more effective in CIDP management compared to historical control group data from prior CIDP trials. The study will also compare the safety profile of the two treatments. The primary endpoint is improvement in Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. This will be the first study that will compare IVIg vs SCIG (MINOR).

Weaknesses:

- Weaknesses noted under scientific merit cast doubt on the likelihood that this study would address the evidence gap identified (MAJOR).

Reviewer 2:

Strengths:

- The study would allow a better understanding of the effectiveness of intravenous administration of immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) in the Chronic Inflammatory Demyelinating Neuropathy (CIDP) population.
- The researchers clearly identify the information gap between the efficacy of delivery methods of IVIg vs SCIg.
- The proposal explains the clinical burden on patients with CIDP and how this work might shift the time and financial burden of this chronic disease.

Weaknesses:

- MINOR WEAKNESS: The evidence gap should be further explained since the safety and efficacy of immunoglobulin therapy for CIDP has already been demonstrated.
- MINOR WEAKNESS: This research would be adding evidence to the decision-making process for patients and clinicians as to delivery methods but the focus group information provided already defines that process for most patients (convenience, cost, socialization, etc).

Reviewer 3:

Strengths:

- The clinical burden of Chronic Inflammatory Demyelinating Neuropathy (CIDP) is well explained. (moderate)
- Both intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg) have been found to be effective treatments in meta-analysis, but there is no literature comparing the effectiveness of IVIg with SCIg in CIDP. (moderate)

Weaknesses:

- This study proposes to conduct two one-sample tests, each separately comparing SCIg or IVIg to historical control. Such an experimental design is unlikely to address the evidence gap in the comparative effectiveness of IVIg vs SCIg. (major)

Reviewer 4:

Strengths:

- major strength – there are no other studies that have compared these two therapies in this patient population
- major strength – the two therapies being studied are the only options for these patients (besides no treatment)
- minor strength - the proposed randomized control trial (RCT) can empirically conclude which treatment is better for these patients

Weaknesses:

- none noted

Reviewer 5:

Strengths:

- Chronic Inflammatory Demyelinating Neuropathy (CIDP) is a rare condition that affects 4.7 per 100,000 people; there are clear diagnostic criteria, mature patient advocacy groups, active programs of research and patient registries.
- Immunoglobulin therapy has proven to be effective therapy for most patients diagnosed with CIDP but there is no evidence on the comparative effectiveness of intravenous versus subcutaneous administration.
- A randomized design and evaluation of the effectiveness of each route of administration, subcutaneous immunoglobulin therapy (SCIg) versus IV immunoglobulin therapy (IVIg), could inform patient and physician decision-making.
- The study is targeting newly diagnosed patients.

Weaknesses:

- There is no description or preliminary data to understand the relative number of patients that seek IV versus subcutaneous treatment. (Major weakness)
- There is no discussion of physician attitudes or reasons for prescribing IV versus subcutaneous treatment. (Major weakness)
- No conceptual model of choices for treatment is presented. Important criteria (cost, convenience, and efficacy) are mentioned, with the latter (efficacy) being the focus of this proposal. However, the cost and convenience factors of the two therapies are not well-described and there are no plans to collect patient perceptions and satisfaction of the different Ig approaches. (Moderate weakness)
- There is no discussion about potential bias in the selection or eligibility of patients for different treatments. (The application does mention variability in insurance coverage for Immunoglobulin therapy and mentions that travel and costs are barriers for IVIg and possibly study participation, but there is not mention of how this would impact the study sample and generalizability of results.) (Moderate weakness)

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

Reviewer 1:

Strengths:

- The application describes well the local and national stakeholders, including patients, caregivers, clinicians, and pharmaceutical companies about demand for this study comparing IVIG vs SCIG for CIDP and describes their input for the need for such studies as well (MAJOR).
- The application describes well the plans to disseminate study findings beyond publication in peer-reviewed journals and at national conferences (MAJOR).

Weaknesses:

- While the application describes the current decision-making process for CIDP management and how various stakeholders participate in that, the most significant factor in clinical practice for access to drugs is the insurance companies, and they will be important stakeholders in this drug choice decision-making. This barrier to adoption should

be acknowledged and addressed (MAJOR).

- The small sample size of the study and the comparison to the historical controls seems like a challenging enough problem that even with positive results, some doubts about the study's ability to inform decision-making could be raised (MAJOR).

Reviewer 2:

Strengths:

- The dissemination plan includes coordinating efforts through the GBS/CIDP Foundation to reach patients and their families, as well as clinicians. There is discussion of the clinician and patient decisional dilemma when prescribing treatment methods because there is no evidence-based research to support IVIg over SCIg or vice versa.
- Clinicians will be the primary end-user of this research study's results and there is an outreach plan noted on how to get this information to them for dissemination to their individual patients.
- The patient focus groups held led to better understanding of the patient administration preferences and showed strengths for both IVIg and SCIg; this study may give greater insight to those personal preference reasons.

Weaknesses:

- MINOR WEAKNESS: The proposal does not address any opportunities for publishing the results to the professional community for wider dissemination of results outside the CIDP network and Greater Plains Collaborative (GPC) members.

Reviewer 3:

Strengths:

- Evaluating the comparative effectiveness of IVIg vs SCIg can support decision-making by physicians and patients in choosing the appropriate treatment. Interviews with clinicians and patient focus groups have shown the need of such a study. (moderate)
- This study establishes a partnership among academic (Kansas University Medical Center), non-profit (GBS|CIDP Foundation) and industry (NuFactor and RMS Medical Products) partners. The streamlined governance and technical processes can help others reproduce the research findings. (moderate)
- Besides journals and conferences, study results will be disseminated through GBS|CIDP Foundation newsletters as well as PCORnet and Greater Plains Consortium (GPC). Possible barriers to dissemination and implementation have been well discussed. (moderate)

Weaknesses:

- None noted

Reviewer 4:

Strengths:

- major strength – because both therapies are standard of care, it will be seamless for patients and clinicians to

modify treatment based on results

- minor strength - investigators indicate that both patients and clinicians are interested in knowing which treatment is better; as such, these groups will be targeted for dissemination of results

Weaknesses:

- minor weakness – items 6 and 7 in the dissemination plan are vague and do not describe how they will “ensure” distribution of results; clinicaltrials.gov is a federal regulation for all clinical trials and is not a novel way of disseminating results (described in items 1, 2, and 3 of dissemination plan); likewise, item 8 in the dissemination plan is also not novel (academic presentation/publication); only item 5 (CIPD newsletters and participant webinar) provides sufficient detail and is customized for this study
- minor weakness – proposal does not address solutions to the potential barriers they identify in dissemination
- minor weakness – this is a very rare disease so the impact of study results is limited in scope

Reviewer 5:

Strengths:

- The clinical problem is clearly stated and well justified. (Moderate strength)
- The patient-motivation for this question is well described. (Major strength)
- Comparative efficacy and side effect profiles for the two administration strategies for Ig is unknown and justify a comparative effectiveness study. (Moderate strength)
- Applicants are aware that cost and convenience (and perhaps other factors) currently drive the decisions between IVIg versus SCIg. (Moderate strength)

Weaknesses:

- No indication on Letters of Support (LOS) from physicians or patients that they are aware of or motivated by the question. The LOS are all template/identical letters that indicate agreement to participate, but do not include statements of interest or need to answer this clinical question. (Major weakness)
- No evidence or description that physicians are looking for the answer to this CER question, or what their information needs are. (However, the patient-motivation for this question is well described as noted above). (Minor weakness)
- The proposal does not clearly identify who will make the decision (i.e., the decision-maker) or use (i.e., the end-user) the study findings (not the intervention) that this study produces, such as local and national stakeholders. (Minor weakness)
- The proposal does not describe a plan for how to disseminate study findings beyond publication in peer-reviewed journals and at national conferences. (Minor weakness)

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

Reviewer 1:

Strengths:

- The applicants describe a clear conceptual framework for the study and describe the background literature that informs the design, key variables, and relationship between interventions and outcomes being tested (MAJOR).
- The randomized study design is appropriate for this proposal (MAJOR).

- Primary outcome of the study includes functionality of the subjects upper and lower extremities using the Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, and strength testing using the Medical Research Council (MRC) sum score, grip strength testing, and the Inflammatory Rasch-built Overall Disability Scale (I-RODS) will be used for secondary outcomes. These outcome measures in addition to the other outcomes are well justified, validated and appropriate for the population (MAJOR).
- For this study, data linkages will be performed with a patient registry of the GBS|CIDP Foundation, which is managed by the National Organization for Rare Diseases (NORD). This study will pursue a data linkage strategy utilizing Datavant or similar technology to enroll subjects in the GBS/CIDP Foundation Registry and integrate registry with REDCap database for data collection. The proposal describes that they will use the PCORnet Common Data Model (CDM) at sites to identify and recruit patients and gather patient data using the CDM. The application describes that data linkages will be done using Datavant (which is selected by PCORnet for consistent data linkage across its network) (MAJOR).
- Linkages between the required data sources to facilitate the conduct of the proposed study and the proposed data linkage work will contribute to PCORnet methodologies (MAJOR).
- The study design section of the proposed project describes the opportunity to utilize and enhance aspects of the PCORnet 2.0 infrastructure and it appears to adhere to PCORnet 2.0 governance. The application describes well the use of PCORnet infrastructure resources including the Coordinating Center, having streamlined IRBs, contracting, engagement and consenting processes and standardized data resources training (MAJOR).
- The project timeline could be realistic assuming the partner sites are able to recruit the subjects in time. Milestones are described well in the proposal. The study will need multiple sites to recruit from, hence the strategy for recruiting participants appears feasible (MINOR).

Weaknesses:

- While the Research Plan describes methods that demonstrate adherence to the PCORI Methodology Standards, the comparison of the study subjects to the historical controls (from prior studies) seems somewhat less feasible and/or valid, and raises doubts about study results informing decision-making. The study proposes 50 patients with newly diagnosed CIDP to be randomized to either IVIG or SCIG. From clinical experience, heterogeneity seen in the CIDP population may limit finding the comparable historical controls (from the prior CIDP trials) and hence risk compromising the study results or completion. Applicants should provide some additional data supporting the feasibility of subject enrollment with control arms selection to make the proposal more convincing (MAJOR).
- Study design/sample size: Although the applicants justify the sample size and effect size, these aspects might need additional review by a statistician (MINOR).
- The applicants propose in the study design/analytical plan that if a patient withdraws from the study they will be replaced with a new patient to be randomized. This plan may impact the study completion time (MINOR).

Reviewer 2:

Strengths:

- The researchers will use the PCORnet Common Data Model in their queries and database linkage. This is one of the few points where PCORnet resources are incorporated into the proposal.
- The proposal notes that the Smart IRB model will be used for this research. While this is an NIH developed process, it is endorsed by PCORnet to maximize resources and consistency of IRB processes across institutions.

Weaknesses:

- MODERATE WEAKNESS: The total patient enrollment number is 50, 25 for each method of delivery. This small sample size can be quickly influenced by patients dropping out of the study before its completion.
- MODERATE WEAKNESS: The use of PCORnet resources in this proposal appear to be limited and mentioned just briefly. Further explanation of how the coordinating center resources would be used would correct this weakness.
- MODERATE WEAKNESS: The data linkage of REDCap and the Registry with electronic health records (EHRs) and

other patient records is not adequately explained in the proposal.

Reviewer 3:

Strengths:

- The recruitment plan is reasonable. A dropout rate of 10% is assumed. (minor)
- The conceptual frame work is clear. The selection of interventions and outcomes are supported by background literature. (moderate)
- PCORnet 2.0 infrastructure and governance such as streamlined IRBs will be utilized. (moderate)
- The two comparators (IVIg and SCIg) are currently used in clinical practice. The primary outcome based on the Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score is reasonable. (moderate)

Weaknesses:

- The study population is unclear. In “Study Design” (Page 8, Research Plan), it is stated that either newly diagnosed CIDP patients or patients who have persistent symptoms will be enrolled. In “Study Population and Setting” (Page 9, Research Plan), however, only newly diagnosed CIDP patients will be enrolled. (major)
- The knowledge gap lies in the comparison between IVIg and SCIg. The proposed separate comparisons with historical control are unlikely to address the knowledge gap. (moderate)
- The dosage for SCIg of 0.4 g/kg in the clinical trial is not justified. This single dosage is concerning because on page 3 (of the Research Plan) it states that “when switching a patient from IVIg to SCIg, individualizing the dosage based on measured serum immunoglobulin levels and clinical response is preferable.” (major)
- The plan for data linkage lacks detail. It is also unclear what data elements will be contributed from the CIDP registry and what from the KUMC database. Hence the benefit or necessity of data linkage is unexplained. (moderate)
- Justification for the effect size of 25% absolute difference is not provided. Sample size justification is for a separate comparison with historical controls, not for the comparison between IVIg and SCIg. Furthermore, it is unclear what the historical control is or how it is selected. No description or citation was provided. In sample size justification, the baseline rate in the historical control is not presented. (moderate)

Reviewer 4:

Strengths:

- major strength – study compares two standard treatments for CIDP in randomized fashion with CER tenets
- minor strength – study leverages PCORnet and CIDP to identify a very rare patient cohort that could not otherwise be studied at a single institution

Weaknesses:

- major weakness – there is no detailed plan for study visits and assessments; this is an RCT of two therapeutic interventions which leverages standard of care, but it is impossible to determine if study procedures overlap with standard clinical visits, labs, examinations, etc. because the investigators have not included a study grid, patient timeline, or any details about what data is being collected in conjunction with the study
- major weakness – the specific aims section describes a control group integral to the study design; said control group is not mentioned in proposal again, therefore there is no information on how that cohort will be identified/defined/etc.

- major weakness – investigators acknowledge that they have not begun to think about how to perform the data linkage necessary to connect the CIDP registry with their study database; the proposal includes a best guess for the possible cost of using Datavant, but investigators explain that linkage may be pursued with a different product
- moderate weakness – the proposal indicates that only about half of the full pool of CIDP patients in PCORnet and CIDP registry combined will qualify for their study and they expect that all but 5 of them will consent; this rate of consent is highly ambitious and, given the small numbers in this patient cohort of newly diagnosed or refractory CIDP, it is concerning that the study will not meet its enrollment goal for statistical significance
- minor weakness – inclusion/exclusion criteria do not include considerations for patients under 18 or pregnant women but human subjects protections section indicate that those populations will be excluded
- minor weakness – it is unclear how PCORnet will be leveraged for data other than to identify patients

Reviewer 5:

Strengths:

- Randomization is a positive feature of this proposed study and can mitigate the effects of bias and confounding factors. (Major strength)
- Focus on newly diagnosed patients can reduce potential of patients experiencing both treatments or other treatments. (Major strength)
- Each of the comparators (IVIg and SCIg arms) are clearly justified and well defined. (Moderate strength)
- CIDP diagnosis is classified with published EFNS/PNS criteria (2010). (Major strength)
- This study will pursue a data linkage strategy (Datavant or similar) to integrate data from the GBS|CIDP Foundation Registry with data from PCORnet sites using a REDCap database. (Major strength)
- The proposal mentions the use of PCORnet and PCRF infrastructure resources (e.g., Coordinating Center, streamlined IRBs, etc.) (Major strength)
- The proposal does specify that the PCORnet Common Data Model (CDM) will be used across all sites to identify and recruit patient and gather patient data using the CDM. (Major strength)
- The Greater Plains Collaborative (GPC) is a member of PCORnet and has engaged in many data queries. (Major strength)

Weaknesses:

- The duration of treatment (6 months) is noted but the study plan does not clearly state when and how many measurements will occur. The proposed methods for ascertainment of outcomes and schedule of visits is not mentioned. (Major weakness)
- Aim 1 is to compare each treatment arm (IV versus subcutaneous Ig) to “historical control data” yet this is not defined anywhere in the proposal. It is not clear whether important assessment scales are collected historically. It is likely that the historical data is baseline visit data, but that it not clearly stated. (Major weakness)
- The data collection (use) and data analysis for Aim 1 (determine if IVIg or SCIg is more effective than historical control data) is not clearly defined. For example, what the definition of ‘more effective’ is and why the comparator is historical data rather than baseline data. Also, how far back it will be reasonable to look for historical data is not clear. (Major weakness)
- Similarly, the data collection or analysis for Aim 2 (determine which of the two treatments has less side effects) are not specifically addressed. (Major weakness)
- Aim 2 (the collection and analysis of side effects for each administration (IVIg versus SCIg)) could be better ascertained with an observational study on a larger sample. (Major weakness)
- The application does not include any description of the GBS/CIDP patient registry, including number of registrants, type of data, or connection of GBS/CIDP registry to PCORnet/GPC study sites. (Major weakness)

- A sample size of 50 is referenced, but no discussion of how these patients will be identified (specifically) and approximately how many patients will be identified at each site. (Major weakness)
- No preliminary data to support the estimates for sample size. (Major weakness)
- Since IVIg and SCIg are standard of care, and previous treatment is an exclusion criterion, the study team will have to recruit incident cases. There is no detailed information provided on the number of prevalent or incident cases at each site. The timeline indicates 2-3 patients will be enrolled per month for the duration of this study, but there is no way to know if this is realistic number. (Major weakness)
- Inclusion criteria are subjective (“patient’s signs and symptoms should not be better explained by another disease process”) and complicated (“If taking prednisone or steroid equivalent, there must be no dose change for 2 weeks from baseline”; ... other medications should have...“no change in dose 60 days prior to the baseline visit.”) The application does not describe how these subjective and complex criteria will be operationalized for screening. (Moderate weakness)
- Application should include a specification for which inclusion data elements are expected to be in the electronic medical record (EMR) and how they are coded. (Major weakness)
- Patients are randomized, but there is a risk that patients can differentially participate in one arm versus another (based on costs or other barriers). There is no plan to assess or address the risk of this. (Minor weakness)
- There is no discussion of the validity of the scales or appropriateness of the selected outcomes for the study. (Major weakness)
- The application does not provide justification or supporting references that the outcome measures are validated and appropriate for the population. In particular, there have been concerns about the INCAT scale (e.g., methodological quality of validation studies; failure to properly capture activity limitations due to proximal arm weakness or fatigue; heavy individual item weighting; and poor sensitivity for detection of clinically important change). (Major weakness)
- The application does not describe how adverse events (AEs) will be collected and coded. Nor does it describe how the number and type of AEs will be compared between treatment arms for Aim 2. (Moderate weakness)
- Sample sizes and power estimates are not well justified and the anticipated effect size is not adequately described or justified. (Major weakness)
- It is difficult to evaluate the feasibility of this study as there is no preliminary data or justification for recruitment goals. Also, there is little description of strategies for recruiting participants. Participant attrition rates are not provided. (Moderate weakness)
- The application does not sufficiently describe data linkages using the PCORnet 2.0 Common Data Linkage Method between the required data sources (i.e., EHR/EMR data, newly collected research data, and external patient registry data) to facilitate the conduct of the proposed study. Specifically, the application does not address which data elements will be used from each source. (Minor weakness)
- There are inconsistencies in the proposal and support letters from the National Organization for Rare Disorders (NORD) and patient advocacy groups on how patients will be recruited for this study, i.e., whether they are recruited from sites or from the patient registry. (Major weakness)
- The application does not state which sites will utilize SMART IRB. (Moderate weakness)

Criterion 4: Investigator(s) and environment

Reviewer 1:

Strengths:

- Dr. Richard Barohn, a professor of Neurology at the University of Kansas, is the contact PI and serves as the Vice Chancellor of Research at KUMC and the University of Kansas Clinical and Translational Science Institute, and hence is capable to manage the overall administrative and fiscal management of the project. In this role, he is well positioned to coordinate activities related to the study and ensure all participating sites leverage all available resources for implementation of the study. He has served as PI and co-PI on several multi-center NIH and PCORI grants. Dr. Mamatha Pasnoor will co-lead the development and implementation of this study (with Dr. Barohn) and seems well qualified to do so. Dr. Waitman, as the Director of the Center for Medical Informatics and Enterprise Analytics University of Kansas

Medical Center, has expertise in biomedical informatics, electronic health records, clinical research informatics, and developing reusable research data infrastructure for driving pragmatics comparative effectiveness research and is well suited to advancing Dr. Barohn's proposal (MAJOR).

- The Department of Neurology at KUMC, with 7 neuromuscular specialists who focus on neuromuscular clinic and CIDP patients seems well equipped to conduct this study. Annually, approximately 10 new CIDP patients are diagnosed at KUMC. The clinics are staffed with research assistants/coordinators that approach every patient regarding available research opportunities (MAJOR).
- Other Centers participating in the study will include the University of Nebraska Medical Center Neuromuscular Clinic/Nebraska Medicine Neuromuscular clinic, Medical College of Wisconsin, University of Missouri, University of Texas Health Science Center at San Antonio and University of Utah (MAJOR).
- There are no concerns with the PIs, collaborators, and other researchers to conduct the proposed activities. There appears to be sufficient clinical and statistical expertise for the proposal. The investigators and co-investigators have demonstrated experience conducting projects of a similar size, scope, and complexity. The investigators have complementary and integrated expertise (MAJOR).
- The leadership, governance, and organizational structures appear appropriate for the project. In this Dual-PI study, the Leadership Plan adequately describes and justifies the PI roles and areas of responsibility (MAJOR).
- The application describes adequate availability of and access to facilities and resources (including patient populations, samples, and collaborative arrangements) to carry out the proposed research. Overall, the institutional support is appropriate for the proposed research (MAJOR).

Weaknesses:

- With so many administrative responsibilities, it is unclear how much effort Dr. Barohn may be able to put in the study execution. The project coordinator likely needs more effort than as proposed (MINOR).

Reviewer 2:

Strengths:

- The research team's credentials include experience with CIDP as well as large scale research projects.
- The investigator has ample experience with successful funding and completion of research grants/awards.
- The research team's home institutions have indicated their support of this work.

Weaknesses:

- MINOR WEAKNESS: GPC and the CIDP registry numbers of people living with this disease is not specified and understanding access to this population would be beneficial. For example, knowing whether the participating research sites are at clinics with specific expertise in the disease that draw patients with CIDP.
- MINOR WEAKNESS: The recruitment plan estimates identifying 125 potential participants but does not explain how the estimated patients are identified (EHRs, clinic notes, claims data).

Reviewer 3:

Strengths:

- The PI is and other team members are very experienced researchers with complementary expertise. The research team includes an experienced biostatistician to support analysis and study design. (moderate)
- The leadership plan is well developed with clearly defined roles and responsibilities for the dual-PIs. (minor)
- The level of effort for each team member is appropriate to accomplish the proposed work. (moderate)
- Institutional support and facility are appropriate. (moderate)

Weaknesses:

- None noted

Reviewer 4:

Strengths:

- major strength – study investigators are at the lead site for the Greater Plains Collaborative (GPC)
- major strength – study investigators have appropriate clinical expertise

Weaknesses:

- moderate weakness – while investigators do have brief letters of support from each collaborating institution/organization mentioned in the study plan, the section on contractual arrangements is entirely blank; this prompts concern that participation and/or budgetary considerations are not finalized and/or could fall through with critical collaborators after award
- moderate weakness - the explanation given about why Barohn and Pasnoor need to share PI oversight is lacking (other than because one PI may not be available for all necessary meetings/interactions); more thought needs to go into how to appropriately develop this partnership and/or if dual-PI is truly needed for this study
- minor weakness – number of sites in recruitment plan is different than the number of sites identified in the performance sites section, likewise budget justification and actual budget are disparate when it comes to number of sites and when/how they will be reimbursed for potential participation (perhaps this is because investigators did not procure letters of support from all institutional members of GPC)
- minor weakness – in performance sites section, the body of content for Medical College of Wisconsin actually describes Utah
- minor weakness – because IRB approval has not been awarded, reliance agreements have not been started, and Data Safety Monitoring Board (DSMB) and Patient Advisory Council (PAC) have not been assembled, it is unlikely that much (if any) enrollment will happen in the first year of award
- minor weakness - combined effort of support staff (key personnel other than PI/dual-PI) totals 1.5 full-time positions; given the large scope of the proposed study, investigators should consider having at least one full-time position for project continuity (such as the current project manager who is only listed with 40% effort) in order to push the study forward and facilitate greater likelihood of success

Reviewer 5:

Strengths:

- The investigative team have strong research background in neurology and CIDP in particular. Dr. Mamatha Pasnoor has recent experience as PI of 20-site trial. (Major strength)
- The Leadership Plan provides adequate description and justification of PI roles and responsibilities. (Moderate strength)
- A statistician and informaticist (L.R. Waitman) are included on the study team and are well suited to advise the statistical and informatics issues – particularly collection of data across PCORnet/GPC sites. (Major strength)
- Dr. Kimminau is a leader in community-based research and a facilitator of patient focus groups to obtain patient perspective and advice on research. She will support the Patient Advisory Council (PAC) and patient-lead development of study dissemination. (Major strength)
- Support of NuFactor and RMS Medical Products enhances the feasibility of the study, and addresses the stated

aims of the PFA. (Moderate strength)

Weaknesses:

- Although the PIs have experience supporting multi-site studies, the application does not address any procedures or approaches or logistics of coordinating 12 sites. (Moderate weakness)
- The application states that patients will be recruited from 12 clinical sites in the GPC, but neither the application nor the letters of support provide an estimate of the number of potentially eligible patients at each site. (Major weakness)

Criterion 5: Patient-centeredness

Reviewer 1:

Strengths:

- The study as proposed focuses on improving patient-centered outcomes for CIDP and employs a patient-centered research design. The application describes well the outcomes important to patients (effectiveness, safety, convenience of administration), and these outcomes are included in the study plan (MAJOR).
- The application describes the significance of closing the evidence gap to patients and other stakeholders (MINOR).
- The interventions (IVIg and SCIG) are available to patients now, and seem to be the best options for comparison since patients and their healthcare providers would choose them for managing CIDP (MINOR).

Weaknesses:

- The historical control arm aspect of the study as described in Criterion 3 makes the study somewhat less robust (MAJOR).

Reviewer 2:

Strengths:

- The research team clearly took the time to listen to people with CIDP and incorporate their questions of efficiency of resources into this proposal.
- The research question of IVIg vs SCIG delivery methods efficacy is identified as a key concern to both patients and clinicians.

Weaknesses:

- MINOR WEAKNESS: The patient focus groups showed each method of administration has its benefits, dependent on personal preference. These patient-reported outcomes (PROs) are not captured in the study design.
- MAJOR WEAKNESS: The mention of financial resources to support patients in this project are contradictory. The proposal states there will be financial support for the patients to assist with the burden of participation in the trial but also lists the burden of the financial costs are a potential risk to patients and a reason they might withdraw early (page 15, Research Plan). Then the proposal goes on to say that subject pay and stipends (page 16, Research Plan) will offset costs. The budget does not reflect these payments and this area is murky, at best, and is confusing.
- MAJOR WEAKNESS: PROs are captured through the self-efficacy PROMIS survey as a secondary outcome. Looking for meaningful outcomes in this study should include PROs in a more prominent manner.

Reviewer 3:

Strengths:

- The primary outcome, INCAT Disability Score, is important to patients. Other patient-reported outcomes (PROs) such as self-efficacy will be measured using the PROMIS instruments. (moderate)
- Closing the evidence gap regarding the comparative effectiveness of IVIg vs SCIg has the potential to support decision-making by patients and physicians and improve the quality of care. (moderate)
- The two comparators, IVIg and SCIg, are available to patients now and evaluating their relative benefit and harm is critically needed to address the decisional dilemma. (moderate)

Weaknesses:

- None noted

Reviewer 4:

Strengths:

- major strength – the study team clearly took time and effort to engage meaningfully with patients and caregivers prior to this application to seek their input and opinions on the grant (focus groups)
- major strength – a secondary aim of the study was added (with associated tool) based entirely on feedback from patients about what was important to them (self-efficacy)

Weaknesses:

- minor weakness – given that patients expressed great satisfaction and advocated strongly for their preferences with both therapies, there will clearly be a group of patients who will become markedly dissatisfied if one of the two study treatments stops being offered as a therapy to this patient group (i.e., if IVIG is found to have equal therapeutic benefit but is more expensive to administer, insurance may no longer cover that therapy and therefore those patients who appreciated the social benefits of going to infusion clinic will lose satisfaction)

Reviewer 5:

Strengths:

- Two prior focus groups with patients were conducted to understand the experiences and reasons for choosing different treatments. (Major Strength)
- Patient Advisory Committee (PAC) can provide a mechanism to engage patients and integrate their perspectives in the study conduct and dissemination of results. (Major strength)
- Patients are modestly compensated for phone calls; travel to meetings is compensated but no honorarium. (Minor strength)
- NORD and GBS/CIPD advocacy organizations are participating as study as advisors. (Major strength)

Weaknesses:

- It would be helpful to know when and where the patient focus groups were conducted, and how many patients participated and how they were selected. (Minor weakness)
- There is no LOS from affected patients. (Minor weakness)
- The LOS from the NORD and GBS/CIPD advocacy organizations do not convey genuine interest in the question or participating in the study as advisors. (Minor weakness)
- There is no estimate of the burden of these assessments on patients. For example, there is no description of how long the assessments will take, whether they'll be administered electronically or by an interviewer, or whether there are special administration issues or concerns for certain groups (e.g., low SES, low literacy). There is also no discussion of patients' thoughts on the relevance and understandability of the assessment items. (Moderate weakness)

Criterion 6: Patient and stakeholder engagement

Reviewer 1:

Strengths:

- The application provides a well-justified description of the research team incorporating stakeholder involvement that includes patients, caregivers, clinicians, policymakers and other healthcare system stakeholders. This strengthens the study for successful conduct and completion (MAJOR).
- The study has received support from the PCORnet 2.0 Steering Committee (MAJOR).
- The application shows evidence of active engagement among scientists, patients, and other stakeholders throughout the research process such as during formulating questions, identifying outcomes, monitoring the study, disseminating plan and result implementation. The active engagement and support of the stakeholders make the study highly relevant. The frequency and level of patient and stakeholder involvement appears sufficient to support the study goals except as described in the weakness section (MAJOR).
- The application demonstrates the potential for future partnerships/collaboration with the co-funder (MINOR).
- The proposed Engagement Plan appears appropriate and tailored to the study, except as described in weaknesses (MINOR).
- The roles and the decision-making authority of all study partners are clearly described. The organizational structure and resources are appropriate to engage patients and stakeholders throughout the project (MAJOR).

Weaknesses:

- One of the key stakeholders in this research question are the insurance companies/payers. Their primary interest is in cost savings and hence the application should address their concerns more clearly (MAJOR).

Reviewer 2:

Strengths:

- The proposal clearly outlines multiple ways the team intends to engage patients, using advisory panels, focus groups and Patient Voice Sessions with clinicians.
- The use of Patient Voice Sessions with investigators and clinicians is a novel way to infuse the patient experience into the understanding of the research results. It would be helpful to know how often these sessions might be convened during this project.

Weaknesses:

- MAJOR WEAKNESS: There is not a clear understanding of how the research team will use the resources available through PCORnet 2.0 and the coordinating center. The sole mention of PCORnet 2.0 infrastructure (page 7, Research Plan) consists of one sentence and does not elaborate on how those resources might be used or

strengthened through this project.

- MAJOR WEAKNESS: This may be merely a clerical error but the external vendors supporting this project are providing in-kind services. RMS Medical Products is listed as a partner and as providing infusion equipment to the SCIg arm of the study. SCIg is delivered subcutaneously and not intravenously. What RMS is providing for this research needs to be explained further.

Reviewer 3:

Strengths:

- Input from patient focus groups (about patient-reported outcomes of interest and factors relevant in the decision process) have been incorporated into the study design. (moderate)

Weaknesses:

- The engagement plan lacks detail. It is unclear how many patients will be involved in the Patient Advisory Council (PAC). For the patient voice sessions with investigators and clinicians, it is unclear how often the sessions will be held or how they will be organized. (moderate)
- The roles and decision-making authority of study partners are not explained. (moderate)
- There is no formal engagement plan with stakeholders other than patients (clinicians, insurance, policy makers, etc). (moderate)
- With the under-developed engagement plan, the potential for this study to foster future collaboration is limited. (moderate)

Reviewer 4:

Strengths:

- major strength – partnerships with the GBS/CIDP Foundation and National Organization for Rare Disorders (NORD) demonstrate excellent insight into working with appropriate stakeholders to increase study success
- major strength – in-kind support from industry sponsors (NuFactor and RMS Medical) is appropriately responsive to this funding mechanism and supplies necessary study resources
- major strength – engagement plan is detailed and describes equal/reciprocal partnerships with patients well
- minor strength – study team indicates that industry sponsors may be interested in pursuing partnerships for other diseases requiring infusion therapies

Weaknesses:

- minor weakness – given that the electronic linkage between the study team and CIDP registry has not been explored/designed yet, it is unclear if this partnership will lead to sustained collaboration
- minor weakness - it is unclear how, other than financially, the stakeholder partners (industry sponsors) will participate in the overall execution of the study (and/or contribute intellectually)

Reviewer 5:

Strengths:

- Patient Advisory Committee (PAC) provides a good mechanism for patient involvement. (Moderate strength)
- The compensation for patients to generate video “stories” of their experience can be informative for clinical decisions. (Minor strength)
- Dr. Kimminau has excellent experience soliciting patient input in research. (Major strength)
- The roles and the decision-making authority of all study partners is sufficiently described. (Moderate strength)
- The project does have the potential for future research collaboration with the co-funders. (Moderate strength)

Weaknesses:

- It is not clear what services or data the NORD and GSB/CIDP Foundation will provide. They have a large amount budgeted for “operations” with no clearly defined tasks. (Major weakness)
- Although it is clear that patients (or at least data from focus groups of patients) motivated this proposal, the application does not show evidence of active engagement among scientists, patients, and other stakeholders throughout the research process (e.g., formulating questions, identifying outcomes, monitoring the study, disseminating, implementing). A missed opportunity is the engagement of patients in the development of assessments and data collection. (Moderate weakness)
- There is no inclusion of patients on the study team. Although a PAC is mentioned, no one is named for that role. (Minor weakness)
- Dr. Kimminau is listed as stakeholder/partner in part of the application, but it appears from her affiliation that she is not truly a patient stakeholder herself. (Moderate weakness)

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

Reviewer 1: Yes

No concerns.

Reviewer 2: No

The statement “Participants can withdraw from the study at any time if the financial risks become intolerable” is difficult to understand in the context of being a PCOR study and one which will have a small population to recruit from. Listing financial hardship as a protection item without also having clearly defined plans to assist with this hardship is not acceptable from the patient reviewer perspective.

Note: Page 15 has the following statement which leaves much confusion and might be a cut and paste error from a different application - “Since we are studying the only two FDA-approved medications for ALS, the only options for alternate treatment are investigational medications or no treatment at all.”

Reviewer 3: Yes

Reviewer 4:

The proposal indicates a budget of \$600 to contribute to co-pays to assist those who incur a financial burden (unsure if this is per patient or total for study); equity of patient enrollment is a consideration given that not all patients may be able to pay out-of-pocket costs to participate if their insurance fails to pay because they are participating in research.

Reviewer 5: Yes

This is a randomized comparative effectiveness study of 2 FDA approved standard of care administration approaches to Ig therapy. The investigators state that the study is low risk. They include a DSMB but propose that the DSMB meet 3 times per year. This seems excessive and this reviewer wonders if perhaps this language was borrowed from a previous application. In any case, the criteria and selection process for DSMB members is not clear, nor is their charge or scope of work. There is no discussion of how adverse events and other data will be collected and reported to the DSMB.

Overall Comments:

Reviewer 1:

The application by Barohn et al addresses a rare but potentially severely disabling acquired autoimmune neurological condition, CIDP and proposes to conduct a randomized controlled study with a sample size of 50 newly diagnosed CIDP patients to determine if IVIG or SCIG is more effective in CIDP management compared to historical control. The study will also compare the safety profile of the two treatments. While the study has several strengths that include: a good research idea, well-chosen primary and secondary outcomes, good data linkage strategies and using PCORnet CDM at sites to identify and recruit patients, a very strong investigator team and environment, strong stakeholders engagement and their interest in this study, several concerns as summarized below should be addressed by the applicants to make this an even stronger application.

The comparison of the two Ig groups (IVIG or SCIG) to the historical control group data from prior CIDP trial seems somewhat concerning as heterogeneity in the CIDP populations and finding the right control from the prior CIDP trials could be challenging and may compromise the study results or completion. Another important aspect of this study that deserves some discussion by the applicants is the impact on the health care costs with the two forms of IVIG since cost savings are important for payers as well as the patients. In summary, there is moderate likelihood of the project to have a significant impact on practice and/or healthcare delivery in the field of CIDP.

Reviewer 2:

This application looks to compare the effectiveness of delivery methods of immunoglobulin treatments for people affected by Chronic Inflammatory Demyelinating Neuropathy (CIDP). CIDP is a rare disease with a small population in the US, making research on the disease a challenge. The proposal will use historical data gathered from a variety of sources as the control and then compare patient response to either intravenous administration of immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) to the control. They are not proposing to do a head-to-head comparison of IVIg vs SCIg, but the study looks to develop a better understanding of treatment effectiveness of one method over the other. The researchers have identified two aims for this study, the first being to see if either IVIg or SCIg is superior to the historical control data and the second to determine which treatment has less side effects.

The burden of care for people with CIDP receiving IVIg includes travel, infusion clinic costs, and additional time for treatment. Using SCIg would free the person from having to do their treatment in an infusion clinic setting, and presumes it would lessen then burden on the patient. Of note, in focus groups some patients identified being in a clinic setting with other people receiving infusions has benefits to socialization and a positive side toward motivating people to go outside their personal boundaries.

The study calls for a total of 50 people, split between the IVIg and SCIg treatments. The patients will be treatment naïve and identified through patient registries as well as PCORnet and CRNs. The patient population with CIDP is relatively small, and finding 50 treatment naïve patients within the Great Plains Collaborative (GPC) in the proposed time frame may present a problem.

The study includes sites from the GPC, a PCORnet clinical data research network (CDRN) comprised of 12 medical centers in 9 different states. The researchers have gained experience with large data research, capture of electronic health records, and patient-centered research through their connection with GPC.

There are two commercial partners for this research, demonstrating the interest and ability to bring in outside revenue for sustainability. The partners support infusion equipment and injection supplies. There is a question as to what in-kind services these partners will provide and needs to be further explained in the proposal or given more detail in the budget.

The common practice of taking prior proposals and adapting them to a current PFA to maximize resources for an institution is acceptable and understandable, but leaving key details from other applications that do not apply to the current PFA is sloppy. In particular, the mention of the lack of ALS drugs (page 15, Research Plan) is a glaring example. The confusion in other sections of this proposal may also be an result of this process and care should be taken in future applications to ensure only relevant material is included.

This proposal has several unanswered points, including how it might benefit the work of PCORnet and strengthen PCORnet processes. The capacity for data linkage with REDCap to other CRNs through the use of the PCORnet Common Data Model should be elaborated on further to demonstrate this project would test PCORnet's readiness to support research.

Reviewer 3:

This study proposes a randomized trial to assess the comparative effectiveness of IVIg vs SCIg in CIDP patients. Addressing this evidence gap has the potential to support decision-making by clinicians and patients and improve quality of care. The PI and other team members are highly qualified and experienced with adequate institutional support. There are several major concerns about this project. It proposes to conduct two one-sample tests, each separately comparing SCIg or IVIg to historical control. This setup is not very helpful in clarifying the comparative effectiveness of IVIg vs SCIg. The description of the study population is inconsistent within the proposal. It is concerning that a single dosage will be used for SCIg, although individualized dosage has been recommended in clinical practice. The purpose or the process of data linkage between the CIDP registry and KUMC database is not well explained. No description or citation was provided for the historical control. In the sample size justification, the assumption of "25% absolute difference" is not justified. The baseline rate in the historical control is not presented. The engagement plan lacks detail, especially for engagement with non-patient stakeholders. Overall, this study has many serious weaknesses and is unlikely to have significant impact on clinical practice/health delivery.

Reviewer 4:

This randomized control trial of IVIG versus SCIG for treatment of new or refractory CIDP certainly addresses a gap in the current literature. Study investigators are embedded in the hub of PCORnet's Greater Plains Collaborative (GPC) and have established connections with stakeholders highly engaged with these patients (NORD and GBS/CIDP Foundation). Responsive to this PFA, the study team has partnered with industry to acquire necessary supplies for this study. Patient-centeredness is high; there was thoughtful engagement with patients prior to developing the application, a secondary aim was added as a result of patient interest, and the investigators provide great detail into how they will partner with patients for successful engagement.

This application loses its merit primarily due to the lack of detail regarding the design of the study. Beyond a single paragraph describing medication and dose, there is no detail about study visits, timelines, labs, etc. and other pertinent study data; there is also no definition or description of how the study team plans to compile the control cohort and

data. Another critical consideration is the lack of support from all GPC sites, as well as a lack of legal contracts with any collaborators outside the Kansas team. This leads to concerns about how ready the study team truly is to execute the project if funded and/or if the study team indeed has everything secured to be successful. The application also falls short in responsiveness to the PFA related to the use of PCORnet resources and infrastructure, given that they have done no planning for data linkages between the GBS/CIDP Foundation Registry and PCORnet, and have included no detail in their proposal about how they will capitalize on the use of PCORnet data other than to identify patients for possible participation.

Reviewer 5:

The proposed study will compare the impact of intravenous (IV) versus subcutaneous (SC) administration of Immunoglobulin therapy for Chronic Inflammatory Demyelinating Neuropathy (CIDP), a rare condition. Immunoglobulin therapy has been shown to be effective in treating CIDP but the comparative efficacy of IV and SC administration is unknown. Because there are costs and burdens associated with IV treatment, the effectiveness results can inform treatment decisions for patients. The investigators are expert neurologists and experienced researchers in CIDP and have a long track record of engagement in PCORnet and leadership in the PCORnet Greater Plains Consortium.

Despite the importance of the clinical question and experience of the investigators and their research team, this application does not provide clear description or justification of the study size, data collection, and data analysis approaches. The proposed study includes a randomized design for 50 patients, 25 for IVIg and 25 for SCIg. Each arm will be compared with historical data (not defined in the proposal). Sample size considerations are used to justify this approach over direct comparison of the 2 arms. However, the sample size and clinical effect size criteria are not discussed. Further, the data sources and specific variables of interest are not clearly defined and it is not clear how this study will leverage PCORnet data resources. Two patient advocacy groups are included on the project as advisors to support the use of a registry for recruiting patients and providing data to the study, but there is not a description of the registry participants or data elements. There are several examples of conflicting information in the application, particularly around how study subjects will be identified and recruited, and how the safety aspects of this study will be managed. The feasibility of the study and relevance of the results to inform real-world treatment decisions in CIDP cannot be assessed because the application provides no preliminary data on the number of patients at each site, their features, and current treatment patterns.