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 CIPD 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.

<u>Engagement Plan:</u> 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 a 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 CIPD 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 does 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).

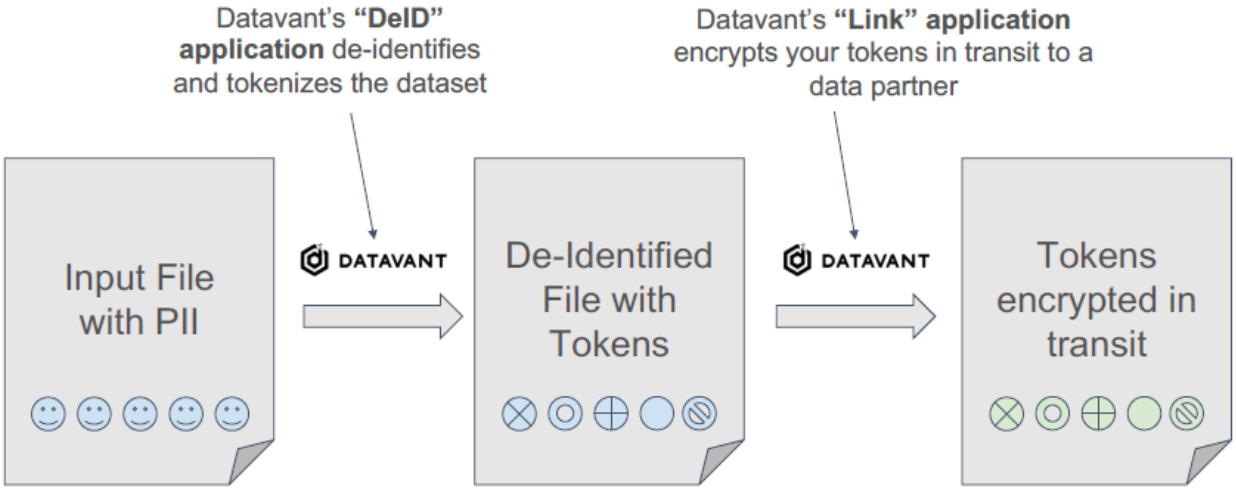

Figure 1. Datavant Applications: DeID and Link

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://pcornet.org/pcornet-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 does 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 Ch-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 us 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