RESEARCH PROTOCOL

International CIDP Outcome Study (ICOS)

A prospective study on clinical and biological predictors of disease course and outcome in CIDP

Research protocol, version 04 d.d. 14-07-2015
‘International CIDP outcome study’

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## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

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<tr>
<td>A-CIDP</td>
<td>Acute onset Chronic Inflammatory Demyelinating Polyneuropathy</td>
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<tr>
<td>CIDP</td>
<td>Chronic Inflammatory Demyelinating Polyneuropathy</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
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<tr>
<td>EFNS/PNS</td>
<td>European Federation of Neurological Societies/Peripheral Nerve Society</td>
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<tr>
<td>EQ-5D</td>
<td>EuroQoL 5D Health Questionnaire</td>
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<td>GBS</td>
<td>Guillain-Barré Syndrome</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>IGOS</td>
<td>International GBS Outcome Study</td>
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<td>ICOS</td>
<td>International CIDP Outcome Study</td>
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<tr>
<td>INC</td>
<td>Inflammatory Neuropathy Consortium</td>
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<td>ISS</td>
<td>Inflammatory Neuropathy Cause And Treatment Sensory Sum Score</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<td>IVIg</td>
<td>Intravenous Immunoglobulins</td>
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<td>LSS</td>
<td>Lewis Sumner Syndrome</td>
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<td>METC</td>
<td>Medische Ethische Toetsings Commissie</td>
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<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>NCS</td>
<td>Nerve Conduction Studies</td>
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<tr>
<td>PI-NRS</td>
<td>Pain Intensity Numerical Rating Scale</td>
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<td>PNS</td>
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<td>R-FSS</td>
<td>Rasch-built Fatigue Severity Scale</td>
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<tr>
<td>R-mlISS</td>
<td>Rasch-modified ISS</td>
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<td>R-MRC</td>
<td>Rasch-built MRC sum score</td>
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<td>R-ODS</td>
<td>Rasch-built Overall Disability Scale</td>
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<tr>
<td>WMO</td>
<td>Medical Research Involving Human Subjects Act</td>
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<td>BMC study</td>
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SUMMARY

**Rationale:** CIDP is a heterogeneous disorder, as indicated by the variety in clinical and electrophysiological phenotypes, response to treatment and long-term outcome. At present, there are no standardized data collected from a substantial number of patients with CIDP to document this heterogeneity or to investigate the clinical and biological determinants of this heterogeneity.

**Objectives:** The objective of the International CIDP Outcome Study (ICOS) is to describe in detail the variation in clinical and electrophysiological subtypes, current practice of treatment, clinical course and outcome of CIDP. The second objective is to define the clinical and biological determinants and predictors of this variation in subtypes, disease activity, treatment response and outcome.

**Study design:** Multicenter, prospective, observational cohort study.

**Patients:** Patients fulfilling the EFNS/PNS criteria for the diagnosis CIDP, independent of age, disease severity or treatment. Both newly and previously diagnosed patients can be included.

**Methods:** ICOS is based on the format of the International Guillain-Barré syndrome Outcome Study (IGOS). In the ICOS data will be collected on: (1) the diagnosis, including data from investigations required for diagnosis, (2) data about demography, clinical history and clinical course, (3) previous and current treatments and clinical response to those treatments, (4) biomaterials, including serial follow-up serum samples, DNA and (if available from previous diagnostic procedures) cerebrospinal fluid. Data will be acquired via a web based data entry system and biosamples will be stored until use.

**Expected results and planning:** ICOS will start as a pilot in a limited number of neuromuscular centers in The Netherlands. After evaluation and improvement of the initial study protocol, the other centers in The Netherlands and from abroad will be invited to participate, this in collaboration with the existing research consortium of the IGOS and collaborating patient organizations. The ICOS will result in a unique collection of prospectively collected and highly standardized clinical data and a biobank from a large population of well-defined patients with CIDP. This data-/biobank will be used to optimize the diagnostic criteria for CIDP (subtypes), to identify biomarkers to monitor and predict disease activity and response to treatment, and to predict models for treatment response and outcome in individual patients. The ICOS will provide an infrastructure that enables international collaboration in the conduct of therapeutic and other studies in CIDP. The ICOS in part can also support national ongoing studies, including the DRIP trial, BMC study, IOC trial and HOPE study (see supplements 13-16).
1. INTRODUCTION AND RATIONALE

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy that can cause severe and persistent disability [1]. According to the guidelines developed by the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) (supplement 1), the diagnosis of CIDP is primarily based on the clinical presentation and the evidence of demyelination demonstrated with nerve conduction studies (NCS) [2]. Typical CIDP is characterized by a slowly progressive and symmetric weakness and sensory symptoms in arms and legs. In addition, CIDP is a remarkably heterogeneous disorder and patients may differ considerably from each other with respect to clinical presentation. Various atypical clinical phenotypes of CIDP have been described, including pure motor or sensory variants, predominantly distal and asymmetric forms [3-7]. Some patients may have an acute onset CIDP (A-CIDP) with a more rapidly progressive disease onset that may initially mimic the Guillain-Barré syndrome (GBS) [8]. The clinical diagnosis of CIDP can be confirmed by the presence of demyelinating features in peripheral nerves and/or nerve roots but patients may highly differ with respect to the type and extend of these demyelinating features [9]. The clinical and electrophysiological diversity may indicate the presence of distinct subtypes of CIDP, which may have in part a different pathogenesis. This heterogeneity of CIDP has led to the development of various sets of diagnostic criteria [2, 10-12], but controversy persists about their use in clinical practice and whether these sets of criteria are able to discriminate between these subtypes. More importantly, it is unclear whether NCS studies are sensitive enough to capture all patients with CIDP, as there are several reports of improvement after treatment in patients with the clinical picture of CIDP but not fulfilling the current electrophysiological criteria of the EFNS/PNS [13]. In particular, patients with pure sensory neuropathy often fail to meet these diagnostic criteria that focus entirely on the conduction of motor nerves [14, 15].

Corticosteroids, intravenous immunoglobulin (IVIg) and plasma exchange are proven effective treatments for CIDP. The therapeutic efficacy has been demonstrated for the short- and midterm periods in randomized controlled trials and has been substantiated in Cochrane reviews [16-18]. At present, the choice of first-line treatment is primarily led by preferences of patient and physician, as these treatments in general have a comparable effect. In clinical practice, however, some patients may respond to one specific treatment and not to others, although no clinical or biological predictors are available to predict the response. Regardless of the chosen treatment, CIDP has a highly variable disease course and clinical outcome. Some patients show a monophasic disease course with improvement and a stable condition already after a single course of IVIg, while others have a relapsing-remitting or a chronic progressive course requiring regular maintenance treatment. Larger
retrospective studies have indicated that maintenance treatment is required in 37 to 62% of cases [1, 19-23]. During maintenance treatment in clinical practice, the optimal dose and interval of the regimen is defined more or less by trial and error, since evidence-based strategies to optimize the treatment in specific patients have not been defined. Long-term treatment is further complicated by the highly variable disease course, lack of biomarkers to assess disease activity, and lack of evidence on sustained therapy. IVIg is often the preferred treatment for long-term use given the hazards of prolonged corticosteroid treatment. The EFNS/PNS guidelines recommend individualizing treatment regimens to a dose between 0.4 to 1.2 g/kg in intervals of 2 to 6 weeks [2]. In current practice there probably is an even greater variation in IVIg treatment regimens. Furthermore, there is increasing evidence of overtreatment in patients with maintenance IVIg treatment [24, 25]. These patients may receive far too high dosage of IVIg or at too short intervals. Others have achieved remission but are still using IVIg because withdrawal has not been attempted. Reducing overtreatment is important to prevent unnecessary adverse events, discomfort of regular infusion and high health care costs associated with IVIg treatment. On the other hand, progression of CIDP has been reported during maintenance treatment, which may imply that some patients with CIDP are undertreated.

The subtype of CIDP may influence disease course and response to treatment. In several studies for example corticosteroids were less effective in patients with Lewis-Sumner syndrome and motor-dominant forms of CIDP [26, 27]. Furthermore, patients with a pure motor variant of CIDP may deteriorate after corticosteroids and in these patients the first-choice treatment is now IVIg [2, 28]. Electrophysiological features might also have a predictive value for treatment response. In one study decreased compound muscle action potential amplitude was more pronounced in IVIg unresponsive patients [29]. Other studies have suggested that a pure focal demyelination pattern with NCS is associated with a poor treatment response or even deterioration to corticosteroids [30, 31].

In general, there are no extensive and systematic prospective cohort studies on predictors of outcome for CIDP and validated prognostic models to predict outcome in individual patients with CIDP are not available. Moreover, very few studies have used the recently optimized outcome measures for CIDP, including Rasch-built outcome measures. In addition, in children with CIDP the determinants and predictors of clinical course and outcome are poorly defined. Pediatric patients may also differ from adult patients regarding clinical and biological characteristics and therefore may be a distinct population [32].

In conclusion, CIDP is a heterogeneous disorder with a highly variable clinical course and outcome. It is unclear which factors influence the CIDP subtypes and variability in treatment response and outcome. Due to this lack of information it is currently unknown what is the best treatment for each subtype of CIDP is, and how treatment should be monitored. Long-term
treatment of CIDP is particularly challenging due to the lack of biomarkers to monitor disease activity and effectiveness of treatment. Further research is required to (1) define the diagnostic clinical and electrophysiological boundaries of CIDP and its subtypes, and (2) the role of biomarkers (e.g. nerve ultrasound, blood characteristics) to support the diagnosis, monitor disease activity and predict response to treatment and outcome. Ideally, the choice of treatment should be based on a personalized profile including clinical, electrophysiological and biological characteristics that accurately predicts which treatment and which treatment regime will be most effective in a specific patient. To address these research questions, it is required to conduct a prospective study with standardized collection of clinical data, electrophysiological data and biomaterials from a large group of well-defined CIDP patients during a long follow-up period.
2. OBJECTIVES

The general objective of the ICOS is to describe the variation in clinical and electrophysiological characteristics of CIDP and to identify the clinical, electrophysiological and biological predictors of disease activity, treatment response and outcome in patients with CIDP.

More specifically, the ICOS has the following objectives:

1. Standardize the documentation of clinical characteristics, nerve conduction study protocols and disease course and to start collecting a data-/biobank of well-defined patients with CIDP.
2. Describe the variation in clinical and electrophysiological characteristics of CIDP to improve the current diagnostic criteria for CIDP and its subtypes.
3. Describe the current practice of treatment of CIDP.
4. Describe the short-term and long-term efficacy of treatment of CIDP in relation to the clinical and electrophysiological subtypes of CIDP.
5. Identify biomarkers that can be used to define the clinical and electrophysiological subtypes of CIDP and to monitor disease activity and predict therapeutic efficacy.
6. Develop prognostic models to predict the clinical course and outcome in individual patients with CIDP as a first step to personalize medicine.
7. Provide an infrastructure to collaborate in the conduct of new therapeutic and other studies in CIDP, including the ongoing DRIP trial, BMC study, IOC trial and HOPE study that have recently been initiated in The Netherlands.
3. STUDY DESIGN

The ICOS is a multicenter, prospective observational cohort study including patients diagnosed with CIDP based on the criteria of the EFNS/PNS. To minimize selection bias, all patients diagnosed with CIDP can participate, independent of age, disease duration, disease severity or if the patients receive treatment. At study entry, data will be collected about the diagnosis, including data obtained during the previous diagnostic work-up, and the clinical situation at the moment of inclusion. For patients diagnosed with CIDP in the past, additional questions will be asked about the prescribed treatment(s), response to those treatment(s) and the clinical course since the diagnosis. In addition, there is the opportunity to collect serum and DNA. Two schedules will be used for follow-up (Figure 1). Schedule A will be used in case of (a) newly diagnosed patients who require treatment or (b) previously diagnosed patients requiring a switch to another type of treatment, or (c) previously diagnosed patients stopping treatment. Schedule B is the default setting for all other cases. In patients treated with IVIg or plasma exchange, the study aims to plan the follow-up visits just before a new treatment course.

Figure 1. Collection of data and biomaterials in ICOS.

*More detailed description of the schedule options A and B see Methods: Study procedures (page 18-19). At (study) entry, data about diagnosis (including routine cerebrospinal fluid and electrophysiological examination if available from previous diagnostic procedures), clinical severity an course, and treatment will be obtained from all patients at entry. Follow up of schedule A and B will take place via the follow-up website form.
4. STUDY POPULATION

4.1 Population (base)
The aim of the ICOS is to investigate the full spectrum of patients with CIDP, independent of age, disease duration or severity of treatment. The ICOS is using the EFNS/PNS criteria for the diagnosis of CIDP (see supplement 1). All patients who fulfill the clinical criteria for typical or atypical CIDP and the electrophysiological criteria for possible, probable or definite CIDP are eligible for the study. Considering the variety in nerve conduction findings in CIDP, patients who fulfil the clinical criteria for CIDP and at least two supportive criteria (but not the electrophysiological criteria) are also eligible for ICOS. Patients with a pure sensory CIDP not meeting the EFNS/PNS criteria, are eligible if they fulfil the adjusted clinical criteria for the diagnosis and at least two supportive criteria defined in supplement 2. Both newly and previously diagnosed patient with CIDP can be included in ICOS. The diagnosis may be challenging in patients with a relapsing-remitting or chronic course who are already on maintenance treatment for a longer period. In all these cases, the clinical and diagnostic data will be reviewed to verify the diagnosis and cases not fulfilling the criteria will be excluded from the study.

4.2 Inclusion criteria
1. The ICOS is using the EFNS/PNS criteria for the diagnosis of CIDP. Three categories of patients are eligible for the ICOS:
   a) Subjects fulfilling the clinical criteria and the definite, probable or possible electrophysiological criteria defined in supplement 1.
   b) Subject fulfilling the clinical criteria and at least two supportive criteria defined in supplement 1.
   c) Subjects fulfilling the clinical criteria for pure sensory CIDP and at least two supportive criteria defined supplement 2 (if not fulfilling the electrophysiological criteria).
2. Being able and willing to conduct a follow-up of at least 2 years.
3. Informed consent.

There are no exclusion criteria.

4.3 Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:

not applicable
4.4 Sample size calculation

The general objective of the ICOS is to describe the variation in clinical and electrophysiological characteristics of CIDP and to identify the clinical, electrophysiological and biological predictors of disease activity, treatment response and outcome in patients with CIDP. To enable external validation of a predictive logistic regression model, the smallest outcome group should include at least 100 patients [33]. No or insufficient treatment response to corticosteroids, IVIg and/or plasma exchange is described in about 10-20% of patients, implicating that the total population of patients required is about 500-1000 patients. A change of diagnosis during follow-up is also estimated in 10% of newly diagnosed patients based on previous reports, especially in subjects who do not respond to treatment [34]. To provide a safety margin for patients lost to follow-up, change in diagnosis, testing of multiple panels of potential determinants and for possible influences of geographical or ethnic factors, we aim to include at least 1000 new CIDP patients.
5. TREATMENT OF SUBJECTS

not applicable

5.1 Investigational product/treatment

not applicable

5.2 Use of co-intervention (if applicable)

not applicable

5.3 Escape medication (if applicable)

not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

6.1 Name and description of investigational product(s)

6.2 Summary of findings from non-clinical studies

not applicable

6.3 Summary of findings from clinical studies

not applicable

6.4 Summary of known and potential risks and benefits

not applicable

6.5 Description and justification of route of administration and dosage

not applicable

6.6 Dosages, dosage modifications and method of administration

not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

not applicable

6.8 Drug accountability

not applicable
7. **NON-INVESTIGATIONAL PRODUCT**

*not applicable*

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

*not applicable*

7.3 Summary of findings from clinical studies

*not applicable*

7.4 Summary of known and potential risks and benefits

*not applicable*

7.5 Description and justification of route of administration and dosage

*not applicable*

7.6 Dosages, dosage modifications and method of administration

*not applicable*

7.7 Preparation and labelling of Non Investigational Medicinal Product

*not applicable*

7.8 Drug accountability

*not applicable*
8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint
The main study parameter is to describe the variation in clinical and electrophysiological characteristics of CIDP and to identify the clinical, electrophysiological and biological predictors of disease activity and treatment response in patients with CIDP. As primary outcome we will use the grip strength using a Martin-Vigorimeter or Jamar dynamometer and the inflammatory Rasch-Overall Disability Scale (R-ODS) a patient self-report linearly weighted scale that measures activity and social participation limitations. [39] This disability scale has been developed specifically for inflammatory neuropathies including CIDP, and was recently validated in a large group of patients.

8.1.2 Secondary study parameters/endpoints (if applicable)
As secondary outcome measures to assess clinical improvement or relapse we will monitor changes in:
1. Muscle strength, using the (Rasch) MRC sum score. [36,37]
2. Fatigue, using the Rasch Fatigue severity scale. [40]
3. Sensory impairment, using the modified INCAT sensory score. [38]
4. Pain, using the Pain Intensity Numerical rating scale. [41]
5. Quality of life, using the EuroQol 5D Health Questionnaire. [42]

8.1.3 Other study parameters (if applicable)
Not applicable

8.2 Randomisation, blinding and treatment allocation
Not applicable

8.3 Study procedures
At (study) entry, from all patients data will be collected about diagnosis, clinical situation and treatment, in addition blood samples will be collected to obtain DNA and serum (Figure 1). Various recommended and predefined clinical outcome measures will be used to document the clinical situation at study entry and during follow-up visits (Figure 2). Patients will be followed according to two different follow-up schedules: A or B, depending on their disease and treatment status (Figure 1 and 2).
Follow-up schedule A

Schedule A is the intensified follow-up that is applied for specific situations. In schedule A, patients are seen at the following time points: 3 weeks (2-4 weeks), 6 weeks (4-8 weeks), 12 weeks (10-14 weeks) and at 26 weeks (24-28 weeks). As indicated the timing of these visits for ICOS is rather flexible in an attempt to match with the regular clinical control visits as much as possible and to minimize the extra workload for both the patients and clinicians as much as possible.

Follow-up schedule A applies to the following specific situations:

1. Newly diagnosed patients who start with a specific treatment for CIDP (mildly affected patients not receiving a specific treatment for CIDP will be in follow-up schedule B).
2. Previously diagnosed patients who have a major change in specific treatment because of either a clinical deterioration attributed to the CIDP or because of side-effects of the treatment. Examples of such a major change in treatment are a switching to another drug or starting an add-on treatment with another drug. (A change in the dosage or interval of the initial treatment itself is not considered to be a major change in treatment).
3. Previously diagnosed patients with a stable clinical condition in whom the maintenance treatment is withdrawn or stopped.

After schedule A has been completed after 26 weeks/6 months, patients will return to or continue with schedule B for further follow-up (Figure 1). Schedule A can be repeated if appropriate, for example after a second deterioration.

Follow-up schedule B

Schedule B is the default setting for all patients in ICOS, provided they do not fulfil the requirements for schedule A. Patients in schedule B have a stable clinical condition with or without treatment, or have only minor changes in the dosage or interval of the treatment. In all patients on follow-up schedule B receiving maintenance treatment for CIDP, the regular visits are to be planned preferably just before a new course of treatment in case of IVIg treatment or plasma exchange. In addition, all patients treated with IVIg or plasma exchange on follow-up schedule B, will be asked to fill in an additional set of validated clinical outcome questionnaires one week after the visits to record treatment-related fluctuations in the clinical course (Figure 2). All patients included in ICOS will be in follow-up for at least two years after study entry. There is no maximum follow-up period.
(1) Data about the diagnostics
All patients diagnosed with CIDP will have had a routine diagnostic work-up. In this work-up most treating neurologists will use the current diagnostic criteria from the EFNS/PNS and conduct routine nerve electrophysiology examination to demonstrate demyelination and confirm the diagnosis CIDP. Cerebrospinal fluid examination is not mandatory to confirm the diagnosis but most treating neurologist will perform a lumbar puncture to rule out other causes. ICOS aims to determine how the diagnosis CIDP is made in daily clinical practice. For all newly diagnosed patients included in ICOS, physicians will be requested to deliver the key diagnostic information, including the results of the electrophysiological examination, and if available, the result of the cerebrospinal fluid examination. A standardized nerve conduction study protocol with a predefined minimum set of nerve segments that needs to be examined, including arm nerves, will be recommended to participating centers (supplement 9), but the execution of this NCS protocol will not be mandatory to participate in the study. The NCS protocol includes details such as site of stimulation and location of active electrode. Electrophysiological study reports will be uploaded as PDF after being made anonymous and will be reviewed by the steering committee. Data from previous conducted electrophysiological studies will be collected, also after being made anonymous. Data regarding cerebrospinal fluid examination from newly diagnosed and patients known with CIDP can be filled in using the website forms. The collection of the diagnostic data is also required to confirm if a patient fulfills the diagnostic criteria for CIDP. The diagnostic data will be collected at study entry and is mandatory for all patients included in ICOS.

(2) Additional clinical data
At study entry, apart from the clinical data important to confirm the diagnosis, additional clinical data will be collected regarding patient history, co-morbidity, disease severity and clinical situation. Additional clinical assessments will be performed during follow-up according to the standard protocols of schedule A and B that specify the timing of the visits (Figure 2). The entry form will largely focus on clinical subtypes and clinical predictors of outcome at study entry, including baseline data (demography, history, family, current condition, age, sex and co-morbidity associated with CIDP). The data entry forms at entry and during follow-up visits of both schedules can be filled out at the website, and contain a set of clinical outcome scales (figure 2). ICOS will mainly use the clinical outcome measures recommended for research in CIDP by the PeriNomS group [33]. Baseline muscle strength and grip strength will be measured using the (Rasch)-MRC sum score and the hand-held Vigorimeter or the Jamar dynamometer. Used clinical outcome measures are the modified INCAT sensory sum score (m-ISS), Rasch-Overall Disability Scale (R-ODS), the Rasch-built Fatigue Severity Scale (R-FSS), the Pain-Intensity Numerical Rating Scale (PI-NRS) and EuroQol-5D Health
questionnaire [34-40]. The outcome scales can be filled in by the patients and are specified in supplements 3 to 8.

Figure 2. Clinical assessments in the core study of ICOS

12

<table>
<thead>
<tr>
<th>Time line</th>
<th>Entry</th>
<th>Schedule A*</th>
<th>Schedule B*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Website form</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R) MRC sum score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m-ISS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaires</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* More detailed description of the schedule options A and B see Methods: Study procedures (page 18-19).
1 Using a Martin Vigorimeter or Jamar dynamometer.
2 Questionnaires include: Rasch-built Overall Disability Score (R-ODS), Rasch-built Fatigue Severity Scale (R-FSS), Pain-Muscle strength will be measured by using the MRC sum score and the Rasch-MRC sum score. Intensity Numerical Rating Scale (PI-NRS) and EuroQol-5D Health Questionnaire. (Supplements 5-8) [39-42]. Stripes boxes indicate the same questionnaires, filled in by patients at home 1 week after start of treatment, only in patients treated with IVIg or plasma exchange to record treatment-related clinical fluctuations.

(3) Data about treatment data and response to treatment

Detailed information will be collected regarding the current treatment regimen, including the type of treatment (in case of IVIg also the brand of IVIg product), dosage and interval. During follow-up visits, the clinical response after treatment will be recorded. In addition, possible wearing-off signs during maintenance treatment with IVIg will be noted. Duration of treatment and details on withdrawal attempts in previously treated subjects will be documented at entry and during every visit from patients in schedule B. In addition, data will be collected regarding possible side-effects of treatment.

(4) Biosamples

At study entry, **blood** samples will be obtained from all adult patients included in ICOS to be able to collect both **serum** (24 ml) and **DNA** (4 ml) (Figure 1). During all follow-up visits in schedule A and B, **blood** samples will be obtained to collect **serum** (16 ml). The first serum sample in newly diagnosed
patients’ should be obtained preferably before the start of treatment. Blood samples collected during follow-up according to schedule A or B in patients receiving IVIg or plasma exchange will be obtained preferably before a new course. Blood samples will be used to identify genetic and serological biomarkers to monitor disease activity and treatment response. A standard operating procedure for blood sampling is provided (supplement 10). Cerebrospinal fluid samples can also be stored for future research projects on biomarkers in ICOS, but only if residual material is left from the routine diagnostic work-up. No cerebrospinal fluid samples will be obtained for the purpose of ICOS only. For the optimal collection and storage of cerebrospinal fluid samples for ICOS, we provided a protocol (supplement 11) [43]. For children with CIDP it is optional to collect biosamples.

8.4 Withdrawal of individual subjects
Subjects can leave the study at any time for any reason without any consequences if they wish to do so.

8.4.1 Specific criteria for withdrawal (if applicable)
Not applicable

8.5 Replacement of individual subjects after withdrawal
Not applicable

8.6 Follow-up of subjects withdrawn from treatment
Not applicable

8.7 Premature termination of the study
Not applicable
9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects’ health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:
- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients’ hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs (through the web portal ToetsingOnline) to the accredited METC that approved the protocol, via biannual line listings of the serious adverse reactions. SAEs that result in death or are life threatening will be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.
9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

*Not applicable*

9.3 Annual safety report

*Not applicable*

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

As this study is observational no safety issues are expected, and no DSMB will be asked to monitor the study.

10. STATISTICAL ANALYSIS

Multiple statistical tests will be used to identify response to treatment and survival. Next to descriptive statistics, we will calculate proportions, logistic regression and possible survival analysis. One of the study objectives is to find prognostic factors of treatment response and disease course in patients with CIDP. We would like to predict disease course before start of treatment and during treatment throughout the disease course. Outcome variables will include clinical, diagnostic and quality of life parameters. With the collection of clinical, electrophysiological and serological parameters at baseline and during follow-up, we will try to construct the simplest models for prediction of outcomes. The statistical approach from previous studies will be used [44-46]. The association between the putative prognostic factors and the outcome variable will be analyzed using univariable and multivariable logistic regression models. If two similar variables are equally associated with outcome, we will select the variable most easily obtainable in clinical practice. Model performance will be quantified with respect to discrimination (area under receiver operating characteristics curve). Calibration of predictions will be assessed graphically by plotting observed frequencies against predicted probabilities. The internal validity of the regression model will be assessed by bootstrapping techniques. This technique gives an impression of how “over-optimistic” the model is i.e., how much the performance of the model deteriorates when applied to a new group of similar patients. If possible, the models will be applied to a validation data set for external
validation. The multivariable regression coefficients will be used to develop practical prognostic models.

10.1 Primary study parameter(s)
In adult patients, the following data and biomaterials will be collected (see Figure 1):
1. Diagnostic data regarding key clinical features and results from routine diagnostic work-up, including electrophysiology, cerebrospinal fluid and other examinations if indicated.
2. Data about patient history, demography and current clinical situation defined by patients’ complaints, neurological deficits and various outcome measures.
3. Data about treatments in the past and at study entry and the clinical response to those treatments.
4. Collection of a blood sample to obtain DNA once and serial blood samples to obtain serum for future biomarker studies.
5. Collection of cerebrospinal fluid samples, but only if residual material is left from the diagnostic work-up that can be used for the current study. No cerebrospinal fluid samples will be obtained for the ICOS only.

In children, clinical assessments and sampling of biomaterials will be more limited depending on the age of the patient. An adapted version of the procedures during follow-up for children is provided (supplement 12).

10.2 Secondary study parameter(s)
Not applicable

10.3 Other study parameters
Not applicable

10.4 Interim analysis
Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement
The study will be conducted according to the principles of the Declaration of Helsinki (version Fortaleza Brasil, October 2013), and in accordance with the Medical Research Involving
Human Subjects Act (WMO) and other guidelines, regulations and Acts. Data management, monitoring and reporting of the study will be performed in accordance with the ICH GCP guidelines.

11.2 Recruitment and consent

When the selection criteria are fulfilled, the patient or, if necessary, the patient's representative will be asked for written informed consent, in accordance with the guidelines of the local medical ethics committee (METC). Information materials for patients and patient's relatives are attached separately. For children, the parents or legal guardian will be asked to sign the informed consent form. Provided informed consent procedures and privacy measures and safeguards are in accordance with the Dutch Personal Data Protection Act and the Medical Treatment Contract Act and the EU-Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

11.3 Objection by minors or incapacitated subjects (if applicable)

*Not applicable*

11.4 Benefits and risks assessment, group relatedness

*Not applicable*

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

*Not applicable.*
12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The study will be conducted according to the principles of the Declaration of Helsinki (version of 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. Data management, monitoring and reporting of the study will be performed in accordance with the ICH GCP guidelines. Technicians and data managers of the Erasmus Medical Center in Rotterdam will provide support for the central data management. Internet-based remote data capture will be used for entering, managing and validating data from the investigative sites. For ICOS a web based data entry system will be developed taking in account all safety measures and ICH-GCP regulation on privacy. When the study is finished, all essential documents (Case Record Forms, Informed Consent forms, patient files, radiological images and electrophysiological data) will be archived and stored for the next 15 years, in accordance to GCP guidelines.

Coding of and access to data

Patient’s data will be coded with a unique number. The study code does not include data that may be used for identification of the patient such as date of birth, initials or codes for hospital of admission. The key to this code is only known in the including hospital and with the treating neurologist. This code will also be used to store reports with electrophysiological data, serum, DNA, RNA, PBMC, cerebrospinal fluid and ultrasonography images. The health-inspection (Inspectie voor Gezondheidszorg – IGZ), the METC, and audits will have access to source documents.

Storage of biomaterials

All biosamples collected for ICOS will finally be transferred to the ICOS coordinating center for storage in the central ICOS biobank, which will be governed by the ICOS Steering Committee. Initially, in the pilot phase when the study is running only at Erasmus MC, AMC and UMCU, serum, DNA and cerebrospinal fluid samples will be collected at the individual sites. At the end of the pilot phase, all above mentioned samples of biomaterials will be transferred to the central ICOS biobank. All patient samples stored in the central ICOS biobank will only be used for research relevant for CIDP and after approval of the ICOS steering committee. As research on epidemiology, pathophysiology and changes in management requires large number of patients and samples, all samples will be stored for a period of 50 years.
12.2 Monitoring and Quality Assurance

Independent monitoring will be established to ensure that the study is conducted, recorded and reported in accordance with GCP guidelines. The risk classification of this study is considered as negligible. Therefore monitoring should be performed once a year per center. See for further details the monitoring plan.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The steering committee is responsible for all decisions regarding publication of data for scientific purposes. Financial sponsors of the study will have no role in the study design, data collection, data analysis and interpretation, or in preparation, review or approval of manuscript or other presentations.

Further regulations regarding the ownership and usage of the data and biosamples collected in ICOS will be defined in the ICOS Consortium Policy Agreement which will be established.
13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

*Not applicable*

13.2 Synthesis

Given the observational nature of the study wherein no alternations will be made to the treatment of patients, any remaining risks are considered to be minimal and part of the regular maintenance treatment.
14. REFERENCES


15. SUPPLEMENTS

SUPPLEMENT 1 – EFNS/PNS diagnostic criteria for CIDP

Three categories of patients are eligible for the ICOS:

a. Subjects fulfilling the clinical criteria and the definite, probable or possible electrophysiological criteria defined in Supplement 1.
b. Subject fulfilling the clinical criteria and at least two supportive criteria defined in Supplement 1.
c. Subjects fulfilling the clinical criteria for pure sensory CIDP and at least two supportive criteria defined in supplement 2 (if not fulfilling the electrophysiological criteria).

Clinical criteria:
Inclusion criteria
(a) Typical CIDP

• Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities.
• Developing over at least 2 months.
• Absent or reduced tendon reflexes in all extremities.

(b) Atypical CIDP
One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):

• Predominantly distal (distal acquired demyelinating symmetric, DADS) or
• Asymmetric (multifocal acquired demyelinating sensory motor neuropathy, MADSAM) or
• Lewis-Sumner syndrome or
• Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb) or
• Pure motor or
• Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron).

Exclusion criteria

• Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy.
• Hereditary demyelinating neuropathy.
• Prominent sphincter disturbance.
• Diagnosis of multifocal motor neuropathy.
• Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and nondiabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features.

Electrophysiological criteria:

Definite:
At least one of the following:

(a) Motor distal latency prolongation \( \geq 50\% \) above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or

(b) Reduction of motor conduction velocity \( \geq 30\% \) below LLN in two nerves, or

(c) Prolongation of F-wave latency \( \geq 30\% \) above ULN in two nerves (\( \geq 50\% \) if amplitude of distal negative peak CMAP \( < 80\% \) of LLN values), or

(d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes \( \geq 20\% \) of LLN + \( \geq 1 \) other demyelinating parameter in \( \geq 1 \) other nerve, or
(e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve, or

(f) Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or

(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms) + ≥1 other demyelinating parameter in ≥1 other nerve.

Probable:
- ≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve.

Possible:
- As in “definite” but in only one nerve.

CMAP = compound muscle action potential; ULN = upper limit of normal values; LLN = lower limit of normal values.

Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb’s point and the wrist is required for probable conduction block. Temperatures should be maintained to at least 33°C at the palm and 30°C at the external malleolus.

Supportive criteria:
1. Elevated CSF protein with leukocyte count <10/μl.
2. MRI abnormalities: gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses.
3. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes.
4. Sensory conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal).
5. Delayed somatosensory evoked potentials without central nervous system disease.
6. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis.

Reference
SUPPLEMENT 2 – Inclusion and exclusion criteria for pure sensory CIDP

These criteria apply only to subjects with the clinical picture of pure sensory CIDP who do not fulfill the definite, probable or possible EFNS/PNS electrodiagnostic criteria for CIDP. Subjects fulfilling the clinical criteria below and at least two of the supportive criteria can be included in ICOS as having pure sensory CIDP.

**Clinical criteria:**

**Inclusion criteria**
- Presence of a sensory polyneuropathy.
- Clinical progression of symptoms over more than 2 months.
- Presence of 1 or more of the following features atypical for CIAP: proprioceptive ataxia, generalized areflexia, young age at onset (≤55 years), upper limb onset or rapid upper limb involvement (involvement of the upper limbs during the first 6 months of symptoms) and cranial nerve involvement.

**Exclusion criteria**
- Presence of a motor deficit.
- *Borrelia burgdorferi* infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy.
- Hereditary demyelinating neuropathy.
- Prominent sphincter disturbance.
- Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and nondiabetic lumbosacral adipuloplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features.

**Supportive criteria:**

1. Elevated CSF protein with leukocyte count <10/μl.
2. MRI abnormalities: gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses.
3. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes.
4. Sensory conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal).
5. Delayed somatosensory evoked potentials without central nervous system disease.
6. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis.

References
### SUPPLEMENT 3 – MRC sum score and Rasch-built MRC sum score

#### MRC sum score

The MRC sum score is the sum of MRC scores of six muscle groups, including shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsiflexors on both sides. The scores range from 60 “normal” to 0 “quadriplegic” and has 6 categories.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visible contraction.</td>
</tr>
<tr>
<td>1</td>
<td>Visible contraction without movement of the limb.</td>
</tr>
<tr>
<td>2</td>
<td>Active movement of the limb, but not against gravity.</td>
</tr>
<tr>
<td>3</td>
<td>Active movement against gravity over (almost) the full range.</td>
</tr>
<tr>
<td>4</td>
<td>Active movement against gravity and resistance.</td>
</tr>
<tr>
<td>5</td>
<td>Normal strength.</td>
</tr>
</tbody>
</table>

#### Rasch-built MRC sum score

The Rasch-built MRC sum score consists of the same muscle groups as the MRC sum score, but the Rasch-built MRC score only has 4 categories, with the Rasch-built MRC sum scores ranging from 48 “normal” to 0 “quadriplegic”.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visible contraction.</td>
</tr>
<tr>
<td>1</td>
<td>Severe weakness (&gt;50% loss of strength).</td>
</tr>
<tr>
<td>2</td>
<td>Slight weakness (&lt;50% loss of strength).</td>
</tr>
<tr>
<td>3</td>
<td>Normal strength.</td>
</tr>
</tbody>
</table>

#### Reference

SUPPLEMENT 4 – Modified INCAT sensory Sum Score (mISS)

The mISS\(^1,2\) incorporated light touch and joint position sense and ranges from 0 “normal sensation” to 33 “most severe sensory deficit” and is composed of the summation of the following sensation qualities:

- Pinprick arm grade (range 0-4).
- Pinprick leg grade (range 0-4).
- Vibration arm grade (range 0-4).
- Vibration leg grade (range 0-4).
- Joint position arm grade (range 0-4).
- Joint position leg grade (range 0-4).
- Two-point discrimination grade (range 0-1).

<table>
<thead>
<tr>
<th>Sensation</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 0</td>
<td>1</td>
</tr>
<tr>
<td>Pinprick</td>
<td>Arms</td>
<td>at index finger</td>
</tr>
<tr>
<td></td>
<td>Legs</td>
<td>at hallux</td>
</tr>
<tr>
<td>Light touch</td>
<td>Arms</td>
<td>at index finger</td>
</tr>
<tr>
<td></td>
<td>Legs</td>
<td>at hallux</td>
</tr>
<tr>
<td>Vibration sense</td>
<td>Arms</td>
<td>at index finger</td>
</tr>
<tr>
<td></td>
<td>Legs</td>
<td>at hallux</td>
</tr>
<tr>
<td>Joint position</td>
<td>Arms</td>
<td>DIP joint index finger</td>
</tr>
<tr>
<td></td>
<td>Legs</td>
<td>DIP joint hallux</td>
</tr>
<tr>
<td>Two-point discrimination</td>
<td>Index finger</td>
<td>at index finger*</td>
</tr>
</tbody>
</table>

DIP=distal interphalangeal. * Normal values are provided in the following table.
Normative static and dynamic two-point discrimination values

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Static assessment</th>
<th>Dynamic assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>4.0</td>
<td>3.5</td>
</tr>
<tr>
<td>40-49</td>
<td>4.5</td>
<td>4.0</td>
</tr>
<tr>
<td>50-59</td>
<td>5.0</td>
<td>4.0</td>
</tr>
<tr>
<td>60-69</td>
<td>6.0</td>
<td>5.0</td>
</tr>
<tr>
<td>70-79</td>
<td>7.0</td>
<td>6.0</td>
</tr>
<tr>
<td>≥ 80</td>
<td>8.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Reference
SUPPLEMENT 5 – Rasch-built Overall Disability Scale (R-ODS)


- Als u ergens hulp bij nodig heeft of er een hulpmiddel voor gebruikt, vul dan in “met moeite uitvoerbaar”.

<table>
<thead>
<tr>
<th>ACTIVITEITEN</th>
<th>Moeilijkheid bij het uitvoeren van deze activiteiten</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Kunt u:</strong></td>
<td></td>
</tr>
<tr>
<td>1 Sokken en iets oppakken</td>
<td></td>
</tr>
<tr>
<td>2 Langdurig staan, bijv. enkele uren</td>
<td></td>
</tr>
<tr>
<td>3 Eén trap oplopen</td>
<td></td>
</tr>
<tr>
<td>4 Rennen</td>
<td></td>
</tr>
<tr>
<td>5 Buiten lopen: tot maximaal één km</td>
<td></td>
</tr>
<tr>
<td>6 Lopen met omzeilen van obstakels</td>
<td></td>
</tr>
<tr>
<td>7 Dansen</td>
<td></td>
</tr>
<tr>
<td>8 Met het openbaar vervoer reizen</td>
<td></td>
</tr>
<tr>
<td>9 Een slot dichtdraaien</td>
<td></td>
</tr>
<tr>
<td>10 Een zwaar voorwerp dragen en neerzetten</td>
<td></td>
</tr>
<tr>
<td>11 Een stoel verschuiven</td>
<td></td>
</tr>
<tr>
<td>12 Een voorwerp (bijvoorbeeld een bal) vangen</td>
<td></td>
</tr>
<tr>
<td>13 Uw bovenlijf wassen</td>
<td></td>
</tr>
<tr>
<td>14 Uw onderlijf wassen</td>
<td></td>
</tr>
<tr>
<td>15 Een douche nemen</td>
<td></td>
</tr>
<tr>
<td>16 Uw tanden poetsen</td>
<td></td>
</tr>
<tr>
<td>17 Naar toilet gaan/op toilet zitten</td>
<td></td>
</tr>
<tr>
<td>18 Uw bovenlijf aankleden</td>
<td></td>
</tr>
<tr>
<td>19 Eten</td>
<td></td>
</tr>
<tr>
<td>20 Afwassen</td>
<td></td>
</tr>
<tr>
<td>21 Een boterham klaarmaken</td>
<td></td>
</tr>
<tr>
<td>22 Boodschappen doen</td>
<td></td>
</tr>
<tr>
<td>23 Naar de huisarts gaan</td>
<td></td>
</tr>
<tr>
<td>24 Een boek/krant lezen</td>
<td></td>
</tr>
</tbody>
</table>

Reference
SUPPLEMENT 6 - Rasch-built Fatigue Severity Scale (R-FSS)

Deze vragenlijst gaat over vermoeidheidsklachten die bij CIDP kunnen voorkomen. Met behulp van deze gegevens kan worden gekeken in hoeverre vermoeidheid invloed heeft op uw dagelijks functioneren. Hoe hoger de score die u kiest; hoe meer u het eens bent met de stelling. Hoe lager de score, hoe minder u het eens bent met de stelling.

<table>
<thead>
<tr>
<th></th>
<th>Volledig oneens</th>
<th>Volledig eens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lichamelijke inspanning leidt tot vermoeidheid.</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>2. Ik ben snel vermoeid.</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>3. Moeheid/vermoeidheid belemmert me in mijn lichamelijk functioneren.</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>4. Moeheid/vermoeidheid leidt voor mij vaak tot problemen.</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>5. Moeheid/vermoeidheid verhindert langdurige lichamelijke inspanning.</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>6. Moeheid/vermoeidheid beïnvloedt de uitvoering van bepaalde taken en verplichtingen.</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>7. Moeheid/vermoeidheid beïnvloedt mijn werk, gezinsleven of sociale activiteiten.</td>
<td>0 1 2 3</td>
<td></td>
</tr>
</tbody>
</table>

Reference
SUPPLEMENT 7 – Pain-Intensity Numerical Rating Scale (PI-NRS)

Met deze schaal willen we uw pijnintensiteit meten. Wij verzoeken u met een cijfer aan te geven hoe hevig uw pijn gemiddeld was de afgelopen week. De score ‘0’ is geen pijn, score ‘10’ de ergste pijn die u ooit heeft ervaren. Kies het cijfer dat het beste de ernst van uw pijn aangeeft.

<table>
<thead>
<tr>
<th>Geen pijn</th>
<th>Ergste pijn ooit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

**Reference**
SUPPLEMENT 8 – EuroQol EQ-5D Health Questionnaire

Netherlands (Dutch) v.2 © 2010 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

Zet bij ieder onderwerp een kruisje in het hokje dat het best past bij uw gezondheid **VANDAAG**.

**MOBILITEIT**

<table>
<thead>
<tr>
<th>Ik heb geen problemen met lopen</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ik heb een beetje problemen met lopen</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb matige problemen met lopen</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb ernstige problemen met lopen</td>
<td>☐</td>
</tr>
<tr>
<td>Ik ben niet in staat om te lopen</td>
<td>☐</td>
</tr>
</tbody>
</table>

**ZELFZORG**

<table>
<thead>
<tr>
<th>Ik heb geen problemen met mijzelf wassen of aankleden</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ik heb een beetje problemen met mijzelf wassen of aankleden</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb matige problemen met mijzelf wassen of aankleden</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb ernstige problemen met mijzelf wassen of aankleden</td>
<td>☐</td>
</tr>
<tr>
<td>Ik ben niet in staat mijzelf te wassen of aan te kleden</td>
<td>☐</td>
</tr>
</tbody>
</table>

**DAGELIJKSE ACTIVITEITEN**

*(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

<table>
<thead>
<tr>
<th>Ik heb geen problemen met mijn dagelijkse activiteiten</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ik heb een beetje problemen met mijn dagelijkse activiteiten</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb matige problemen met mijn dagelijkse activiteiten</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb ernstige problemen met mijn dagelijkse activiteiten</td>
<td>☐</td>
</tr>
<tr>
<td>Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren</td>
<td>☐</td>
</tr>
</tbody>
</table>

**PIJN/ONGEMAK**

<table>
<thead>
<tr>
<th>Ik heb geen pijn of ongemak</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ik heb een beetje pijn of ongemak</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb matige pijn of ongemak</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb ernstige pijn of ongemak</td>
<td>☐</td>
</tr>
<tr>
<td>Ik heb extreme pijn of ongemak</td>
<td>☐</td>
</tr>
</tbody>
</table>

**ANGST/SOMBERHEID**

<table>
<thead>
<tr>
<th>Ik ben niet angstig of somber</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ik ben een beetje angstig of somber</td>
<td>☐</td>
</tr>
<tr>
<td>Ik ben matig angstig of somber</td>
<td>☐</td>
</tr>
<tr>
<td>Ik ben erg angstig of somber</td>
<td>☐</td>
</tr>
<tr>
<td>Ik ben extreem angstig of somber</td>
<td>☐</td>
</tr>
</tbody>
</table>
• We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
• Deze meetschaal loop van ‘0’ tot ‘100’.
  ‘100’ staat voor de beste gezondheid die u zich kunt voorstellen,
  ‘0’ staat voor de slechtste gezondheid die u zich kunt voorstellen.
• Markeer met een X op de meetschaal om aan te geven hoe uw
  gezondheid VANDAAG is.
• Noteer het getal waarbij u de X heeft geplaatst in onderstaand vakje.

UW GEZONDHEID VANDAAG = ☐
SUPPLEMENT 9 – Nerve conduction study protocol

The nerve conduction study protocol is based on the EFNS/PNS guidelines (see supplement 1). This nerve conduction study protocol is recommended but not mandatory to fulfill the electrophysiological EFNS/PNC criteria and the ICOS inclusion criteria.

Methods
Warming up of upper and lower limbs to a skin temperature of at least 32 °C at the palm and at the external malleolus. Record temperature just before starting examination. It is recommended to use the negative peak to quantify the compound muscle action potential (CMAP). Definitions and cut off values of demyelinating features can be found in supplement 1. Focus on arm nerves if the time slot is limited.

Required materials
Surface or cup electrodes (motor nerves); surface, cup or clamp electrodes (sensory nerves).

Motor nerve conduction study
Motor nerve examination:
(1) Both median nerves:
   - Recording site: abductor pollicis brevis muscle\(^1\) (m.APB)
   - Stimulation sites:
     ▪ Wrist
     ▪ Elbow
     ▪ Axilla (Erb’s point is recommended)

(2) Both ulnar nerves:
   - Recording sites: abductor digiti minimi muscle\(^2\) (m. ADM)
   - Stimulation sites:
     ▪ Wrist
     ▪ Below and above elbow\(^2\)
     ▪ Axilla\(^2\) (Erb’s point is recommended)

(3) Both peroneal nerves:
   - Recording sites: m. extensor digitorum brevis (m. EHB)\(^3\) (Optional extra recording of m. tibialis anterior)
   - Stimulation sites:
     ▪ Ankle
     ▪ Below and above head of fibula\(^4\)

(4) Both tibial nerves:
   - Recording site: m. abductor hallucis brevis\(^5\)
   - Stimulation site:
     ▪ Ankle
     ▪ Popliteal fossa

\(^1\) Distance from electrode to stimulation site at wrist 6 cm.
\(^2\) Minimal distance between stimulation sites is 8 cm.
\(^3\) Distance from electrode (m. EHB) to stimulation site at ankle 8 cm.
\(^4\) Minimal distance between stimulation sites (below and above fibula head) is 8 cm.
\(^5\) Distance from electrode to stimulation site at ankle 10 cm.
Parameters recorded:
(1) Distal latency in milliseconds (DML in ms).
(2) Nerve conduction velocity in metres per second (NCV in m/s).
(3) Terminal latency index (TLI), ratio between distal and proximal conduction velocity.
(4) Compound motor action potential in millivolts (CMAP in mV).
(5) F-Wave.

Sensory nerve conduction study
Sensory nerve examination:
(1) One median nerve:
   - Recording site: index finger\(^1\)
   - Stimulation sites:
     - Wrist
     - Elbow
(2) One ulnar nerve:
   - Recording site: index finger\(^1\)
   - Stimulation sites:
     - Wrist
     - Elbow
(3) One sural nerve:
   - Recording site: posterior the external malleolus\(^3\)
   - Stimulation site:
     - Posterior-lateral calf

\(^1\) Distance from electrode to stimulation site at wrist 14 cm.
\(^2\) Distance from electrode to stimulation site at wrist 12 cm.
\(^3\) Distance to stimulation site 15 cm.

*Radial nerves are optional in case of median neuropathy from carpal tunnel syndrome or ulnar neuropathy from compression across the elbow. Stimulation over radius, recording over the radial sensory nerve as it runs over the extensor tendons to the thumb (3 cm apart). Distance between stimulation site and recording site 10 cm.

Parameters recorded:
(1) Latency in milliseconds (ms).
(2) Duration of SNAP in milliseconds (ms).
(3) Amplitude of SNAP in microvolts (µV).
(4) Conduction velocity in meters per second (m/s).

Reference
SUPPLEMENT 10 – Protocol for blood sampling

Standardized collection and analysis of blood samples forms an integral part of the biomarker development and prognostication components of ICOS. Blood samples will be used to obtain DNA and serum to identify genetic and serological markers for disease course and outcome. Serum will be used to determine preceding infections, autoantibodies, identifying biomarkers, immune effector molecules and nerve degradation products.

Protocol for collecting serum:

- Serum is derived from clotted blood and will be obtained at every visit when patients are neurologically examined. For all patients with proven diagnoses of CIDP this is at entry and every 6 months after entry (following schedule B). In case of newly diagnosed patients or patients who show a relapse or have a change in treatment, blood will be obtained at entry and at 3, 6, 12 and 26 weeks (following schedule A). Then they will further follow schedule B.
- Obtain clotted blood; 3 tubes of 8 ml at study entry and 2 tubes of 8 ml at other visits.
- Label sample with a sticker indicating: (1) the patient study code, (2) the date and time of blood collection.
- Send these tubes immediately to the coordinating center (or to the country coordinator when the study is in the international stage) (at room temperature, preferably <24 hours for arrival).
- On arrival, the coordinating center (or country coordinator) will centrifuge the sample at 2000 g for 10 minutes (at room temperature) to obtain serum.
- Serum samples will be stored at –20°C as aliquots of 0.5-2 ml in vials with a screw cap (eg. T341-6TPR, Simport or equivalent).
- Collect more samples this way from other time points or patients for a period of maximum 6 months.
- Send this collection once every 6 months on dry ice to an expertise center.
- At the expertise center, the serum samples will be stored at –80°C until use.

Protocol for collecting DNA:

- DNA sample should be obtained within the first month of the entry in to the study.
- Obtain 4-5 ml of EDTA blood in a plastic (not glass) tube.
- Label sample with sticker indicating: (1) the patient study code, (2) the date and time of blood collection.
- Send this blood samples immediately to the country coordinator or to the DNA expertise center directly (at room temperature, preferably <24 hours for arrival).
- At arrival, the country coordinator will store the sample at –20°C (this can only be done safely with plastic tubes).
- Collect more samples this way from other patients for a period of maximum 6 months. Send this collection once every 6 months on dry ice to an expertise center for DNA extraction.
- At the expertise center for genetic studies the DNA will be extracted according to a standard, validated and quality controlled method and stored in a single vial (Eppendorf) at –20°C until use.
SUPPLEMENT 11 – Protocol for cerebrospinal fluid sampling

Standardized collection and analysis of cerebrospinal fluid (CSF) samples forms an integral part of the biomarker development and prognostication components of ICOS. CSF samples will be used for advanced serological and proteomics studies to identify markers for disease course and outcome. CSF will be used to determine autoantibodies, immune effector molecules and nerve myelin and axonal degradation products. Protease activity in CSF may significantly affect these studies; therefore standardized collection and storage of CSF is ideally required, as far as is practicable.

If patients do not undergo diagnostic lumbar puncture, or if no CSF sample is available or if CSF cannot be obtained according to the following protocol, they can still be included in ICOS. Please do not send CSF samples that are not acquired according to this strict protocol, since these suboptimal samples may influence the research.

CSF sampling:
• Collect an additional amount of 2 ml during diagnostic lumbar puncture in a separate collection tube (aim is no traumatic puncture so free of visible blood).
• To pellet any cells, centrifuge the tube with CSF sample within 2 hours maximum following collection at 400 g for 10 minutes (at room temperature).
• To remove the cells, transfer the supernatant of the centrifuged CSF sample to another tube (leaving the cell pellet in the first tube) (eg. T341-6TPR, Simport or equivalent).
• Label this second tube (1) a patient code, (2) a date and time of CSF collection, and (3) mark as CSF.
• Transport this sample at room temperature to the country coordinator or to the expertise centers directly (preferably <24 hours for arrival).
• Store the CSF samples at -80°C and collect more samples this way for a period of maximum 6 months.
• Transport this collection once every 6 months on dry ice to an expertise center.
• In the expertise center, the CSF samples will be stored at −80°C until use.

If possible from all patients included in ICOS data will be collected about the diagnostic CSF sample, irrespective if a CSF sample is obtained for the above mentioned CSF proteomics study. At the ICOS website questions will be asked if CSF was examined for diagnostics and what were the results of the diagnostic tests (concentration of protein, erythrocytes and leukocytes). Also this diagnostic information potentially can be very useful for prognostic studies.

Reference
SUPPLEMENT 12 – Protocol for CIDP in children

Children can be included in ICOS using an adapted version of the study protocol. Children are defined as people ≤ 17 years at diagnosis and separated in three age categories: preschool children (age < 6 years), school children (≥6 and <12 years) and adolescents (≥12 and ≤17 years). Informed consent will be obtained from the parents/legal guardians (and children) following the local medical ethical regulations. Patients ≥ 18 years can be included in regular ICOS protocol, although in some countries up to a certain age consent may be required from their parents/legal guardians.

Clinical assessments

<table>
<thead>
<tr>
<th>Age categories</th>
<th>Preschool children</th>
<th>School children</th>
<th>Older children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 6 years</td>
<td>≥6 and &lt;12 years</td>
<td>≥12 and ≤17 years</td>
</tr>
<tr>
<td>Forms E, A, B</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(R)-MRC score</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grip strength</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>R-ODS</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>mISS</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>R-FSS</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PI-NRS</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Diagnostic electrophysiology
Most children will have an electrophysiology examination during routine diagnostic work-up for CIDP. There is an option to register the electrophysiological raw data of this examination. No extra electrophysiology examination will be performed for research only.

Blood sampling
Most children will have a blood sampling during the diagnostic work-up for CIDP. If blood samples are obtained for diagnostic procedures there is an option to collect an extra amount of clotted blood (to obtain serum) and EDTA blood (to obtain DNA) for research (supplement 10). Blood sampling will take place at same frequency, as in adults provided blood can be drawn from the intravenous access just before IVlg treatment. The minimal amount of blood for research in children is 1 ml. The collection of blood samples in children for ICOS is not mandatory.

Cerebrospinal fluid (CSF) sampling
Most children will have a spinal tap to obtain CSF for diagnostic work-up for CIDP. There is an option to store CSF samples for future research projects on biomarkers in ICOS, but only if residual material is left from the routine diagnostic work-up. No CSF samples will be obtained for the purpose of ICOS only. For the optimal collection and storage of CSF samples for ICOS, we provided a protocol (supplement 11).
SUPPLEMENT 13 – DRIP trial (coordinated by Erasmus Medical Center, Rotterdam)

Every known CIDP patient fulfilling the inclusion criteria listed below can be included in the DRIP trial.

Inclusion criteria
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1) Diagnosis of CIDP or acute-onset CIDP made by a consultant neurologist, fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) clinical diagnostic criteria.
2) Age ≥ 18 years.
3) Significant improvement following the first use of IVIg, defined as a decrease of ≥ 1 grade on the modified Rankin disability scale.
4) To indicate that the patient is still IVIg dependent and has active CIDP, he/she must have shown an objective deterioration (decrease in muscle strength measured with the Martin Vigorimeter and/or MRC sum score) following reduction of IVIg dose at some time during the 6 months before randomisation.
5) Ongoing intermittent treatment with 10% liquid IVIg (Kiovig) for at least 3 months. The dose must have been not changed within the 8 weeks prior to the study.
6) EMG findings compatible with CIDP showing peripheral nerve demyelination at least once during their illness. These findings should preferentially fulfil the electro diagnostic criteria proposed by the European Inflammatory Neuropathy Cause and Treatment group (INCAT)36 or EFNS/PNS.
7) Signed informed consent by the patient.

Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:
1) Known IgA deficiency or known allergic reaction to IVIg.
2) Hand grip strength measured by the Martin Vigorimeter ≥ the median value (kPa) for an age and sex matched healthy control.
3) Maintenance dose < 15 gram of IVIg every infusion or an infusion interval < 14 days.
4) Known hereditary neuropathy or severe concomitant diseases such as HIV infection, Lyme disease, chronic active hepatitis, congestive heart failure, systemic lupus erythematosus, drug or toxin induced neuropathy, vasculitis, and malignancies.
5) Multifocal motor neuropathy (MMN), fulfilling the EFNS/PNS criteria.
6) IgM paraprotein with anti-myelin-associated glycoprotein (MAG) antibodies.
7) Atypical CIDP with pure sensory or persistent unifocal impairment or significant central nervous system involvement.
8) Participation in a controlled trial of an investigational medicinal product within the past 12 weeks.
9) Severe known abnormalities in liver, kidney function or serum glucose level.
10) Treatment with > 20 milligrams of prednisone a day.
11) Treatment with other immunosuppressive drugs (e.g. methotrexate, azathioprine, prednisone) if the dosage has been changed within 8 weeks prior to start of the study.

In case of an eligible patient, please contact:
Krista Kuitwaard, trial coördinator
CIDP.studies@erasmusmc.nl
010-7043831

Prof. Dr. P.A. van Doorn, trial coordinator
p.a.vandoorn@erasmusmc.nl
010-7033780
SUPPLEMENT 14 – BMC study (coordinated by Academic Medical Center, Amsterdam)

Patients can only be included in Academic Medical Center Amsterdam, Erasmus Medical Center Rotterdam, UMC Utrecht and Academic Hospital Maastricht.

Inclusion criteria
(1) (a) Newly diagnosed untreated patients who fulfill the clinical and electrophysiological EFNS/PNS criteria for CIDP OR
(b) Patients diagnosed with CIDP according to the clinical and electrophysiological EFNS/PNS criteria for CIDP with maintenance IVIg treatment (> 6 months of treatment) OR
(c) Patients diagnosed with CIDP according to the clinical and electrophysiological EFNS/PNS criteria for CIDP with a stable clinical condition without treatment in the last 12 months.
(2) Adult males or females (18 year or more).

Exclusion criteria
(1) Lack of informed consent of the subject.

In case of an eligible patient, please contact:
Filip Eftimov, trial coordinator
f.eftimov@amc.uva.nl
020-5669111, sein 59462, 06-26658740

OR

Max Adrichem, PhD student
m.e.adrichem@amc.uva.nl
020-5664610, 06-53767429
### Chronologic overview per visit

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months*</th>
<th>Extra visit A: Relapse after IVIg withdrawal**</th>
<th>Extra visit B: Wearing-off symptoms In between IVIg infusions***</th>
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<tbody>
<tr>
<td>Clinical data</td>
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<td>Grip strength</td>
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</tr>
<tr>
<td>Reflexes</td>
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</table>

* Outpatient visit at 6 months only applies for group 1 and 2.

** Extra visit A in case of a relapse after IVIg withdrawal, also in case of deterioration after initial improvement after an IVIg loading dose.

*** Extra visit B (Group 1 en 2): in case of objectiviable wearing-off symptoms during IVIg maintenance treatment. Objective wearing-off symptoms are decrease in muscle strength/grip strength, decrease of the ability to walk, increase in the INCAT-SS score or decrease of the tendon reflexes. Visit takes place within 7 days prior to the infusion.
Patients can only be included in Academic Medical Center Amsterdam, Erasmus Medical Center Rotterdam, UMC Utrecht and Academic Hospital Maastricht.

**Inclusion criteria**
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1) Probable or definite CIDP according to the EFNS/PNS criteria 20103.
2) Stable disease for 6 months (e.g. no progression of disease in last 6 months).
3) IVIg treatment for at least 6 months.
4) IVIg infusion interval of 2 to 6 weeks.
5) Age > 18 years.

**Exclusion criteria**
A potential subject who meets any of the following criteria will be excluded from participation in this study:
1) Deterioration after IVIg withdrawal in the last 12 months.
2) Changes in IVIg treatment dose/interval in last 6 months.
3) Change of additional CIDP treatment, if any, in the last 3 months (e.g. corticosteroids or immunosuppressive treatment).
4) A prolonged period (> 6 weeks) of disability increase following an earlier IVIg withdrawal attempt.
5) History of respiratory failure related to CIDP.
6) Legally incompetent.
7) Lack of written informed consent.

**In case of an eligible patient, please contact:**
Max Adrichem, PhD student IOC trial
m.e.adrichem@amc.uva.nl 020-5664610, 06-53767429
OR
Filip Eftimov, trial coordinator
f.eftimov@amc.uva.nl 020-5669111, sein 59462, 06-26658740
### Chronologic overview

<table>
<thead>
<tr>
<th>Vital parameters</th>
<th>Follow-up (24 weeks)</th>
<th>Unplanned visit</th>
<th>(Premature) End visit</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>wk 3* (tel)</td>
<td>wk 6 (visit)</td>
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<tr>
<td>Care use</td>
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</tr>
</tbody>
</table>

* The first telephonic appointment will take place 3 weeks after the first study medication was administered.

tel = telephonic appointment, visit = outpatient visit.
SUPPLEMENT 16 – HOPE study (coordinated by UMC Utrecht)

Newly diagnosed and known patients can be included in St. Elisabeth hospital (Tilburg), Erasmus Medical Center (Rotterdam), UMC Utrecht (Utrecht), Academic Medical Center (Amsterdam) and UMC St. Radboud (Nijmegen).

Inclusion criteria
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1) Fulfilling EFNS/PNS criteria for CIDP or criteria for pure sensory CIDP as mentioned above.
2) Newly diagnosed CIDP patient or know CIDP patient on treatment >1j.
3) Age 18-80 years.

Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:
1) Physically unable to undergo electro diagnostic or HRUS of the peripheral nervous system (e.g. cast, recent pelvic fracture or prosthetic operation, extensive reconstructive surgery on the extremities).
2) Prior history of other polyneuropathy (e.g. related to DM, intoxications, deficiencies).

In case of an eligible patient, please contact:
1) St. Elisabeth hospital Tilburg:
   Prof. Dr. L.H. Visser, trial coordinator. Drs. J. Telleman, PhD student HOPE study
   l.visser@elisabeth.nl     j.telleman@elisabeth.nl
   Tel: 013-5392552     Tel: 013-5392552

2) UMC Utrecht:
   Drs. H.S. Goedee, trial coordinator. Prof. Dr. L.H. van den Berg.
   h.s.goedee@umcutrecht.nl    l.h.vandenberg@umcutrecht.nl
   Tel: 088-7558860, sein 74098, 06-28860484. Tel: 088-7558860