**RESEARCH PROTOCOL**

**Inflammatory Neuropathy Consortium Base (INCbase)**

A prospective international CIDP registry

Research protocol

**Inflammatory Neuropathy Consortium Base**

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**PROTOCOL SIGNATURE SHEET**

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**LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

|  |  |
| --- | --- |
| **CDAS****CIDP****DNA****EAN/PNS****EQ-5D****GCP****GSES****HADS****INC****INCAT****INCbase****I-RODS****IVIg****mISS****MRC****NCS****PGIC****PI-NRS****R-FSS** | **CIDP disease activity status** **Chronic Inflammatory Demyelinating Polyneuropathy** **Deoxyribonucleic acid****European Academy of Neurology/Peripheral Nerve Society****EuroQoL 5D Health Questionnaire** **Good Clinical Practice****General Self Efficacy Scale****Hospital Anxiety and Depression Scale****Inflammatory Neuropathy Consortium****Inflammatory Neuropathy Cause And Treatment****Inflammatory Neuropathy Consortium Base****Inflammatory Rasch-Overall Disability Scale** **Intravenous Immunoglobulins** **Inflammatory Neuropathy Cause And Treatment Sensory Sum Score** **Medical Research Council****Nerve Conduction Studies****Patient Global Impression of Change****Pain intensity-numeric rating scale****Rasch-built Fatigue Severity Scale** |

# SUMMARY

**Rationale:** CIDP is a heterogeneous disorder with wide variability in clinical and electrophysiological phenotypes, response to treatment and long-term outcome. Standardized systematic data collection from large numbers of patients with suspected CIDP is needed to better define the clinical, laboratory and electrophysiologic boundaries of CIDP and to investigate the biological determinants of the disease.

**Objectives:**

The primary objective of the Inflammatory Neuropathy Consortium Base (INCbase) is to develop a prognostic model for treatment response. Other questions that will be explored include but are not limited to: 1) to discover clinical, electrophysiological and biological biomarkers for diagnosis, disease activity and prognosis, 2) to describe variation in clinical and electrophysiological characteristics of CIDP to define the spectrum and boundaries of CIDP, 3) to describe short and long-term outcomes at impairment, disability and quality of life levels of (subgroups of) CIDP patients, 4) to discover clinical, electrophysiological and biological determinants of treatment response and long-term outcomes, 5) to describe physician and patient perspectives on and satisfaction with different treatments that may be used for CIDP, including plasma-exchange and subcutaneous immunoglobulin and 6) to deepen knowledge on CIDP pathophysiology, including investigating immunological pathways underlying CIDP.

**Study design:** An international prospective observational study using a web-based modular registry.

**Patients:** Patients with the clinical suspicion of the diagnosis CIDP, independent of age, disease severity or treatment. Both newly and previously diagnosed patients can be included.

**Methods:** At enrollment baseline data will include demographics, clinical history, diagnostic data, treatment history, and focused clinical outcome measures. Follow-up visits will be scheduled according to disease phase and treatment. Newly diagnosed patients or patients starting new treatments will have more frequent follow visits in the beginning whereas for stable patients, follow-up visits will be planned every 6 months for a minimum of two years. Unscheduled study visits will be allowed for patients with active disease to capture relapse, treatment changes, and treatment response. At all follow-up visits, data will be collected that includes focused outcome measures and treatment.

 Individual centers will have the option to collect baseline and serial follow-up biomaterials including serum, peripheral blood monocytes (PMBC), DNA/RNA, cerebrospinal fluid and nerve/skin biopsy material. Collection of biomaterials is not mandatory for patient participation.

 Data will be acquired by the study site investigator and entered directly into a custom-made web-based data entry system. Biomaterials will be stored locally. Participating centers can export and use their own data. Collaborative studies using composite data from the Registry will be approved by the Steering Committee (SC) and will be based on an opt-out principle.

 To develop a prognostic model, treatment response will be defined based on changes in disability. Multivariate modelling will be used to identify predictors and construct a model that will be externally validated in a separate population.

**Main endpoint:** prediction model to predict treatment response after start of treatment

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** Participation in this study has negligible risk because the only intervention done is venapuncture to obtain blood. In principal, study visits will be planned to coincide with standard clinical visits to decrease the burden for participants. There is no direct benefit for participants. We expect to develop a prediction model that will provideguidance on the choice and duration of treatment in patients with CIDP**.** INCbase will result in collection of prospective and standardized clinical and biologic data from a large and diverse world-wide population of patients with suspected CIDP. The findings obtained from studies conducted using the INCbase infrastructure will deepen our understanding of the clinical, laboratory, and biological boundaries of CIDP. This data will provide a critical foundation to optimize CIDP diagnostic criteria, support the identification of diagnostic, disease activity and treatment response biomarkers, and explore treatment response in individual patients. INCbase will also provide an infrastructure that strengthens international collaboration, which in turn will be invaluable for conducting interventional studies in CIDP. This study can only be done in this population to capture the full diversity of human CIDP.

# INTRODUCTION AND RATIONALE

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare immune-mediated neuropathy that can cause severe and permanent disability.1 Although the condition is typically characterized by progressive or relapsing motor and sensory symptoms, it is now well understood that CIDP is a heterogeneous disease with wide variability in the clinical phenotype, pathophysiology, and prognosis. This realization has led to the naming of multiple “variant” variant subgroups which are still considered CIDP but with different clinical features. CIDP is a treatable disorder. Corticosteroids, intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg) and plasma exchange are proven effective therapies.2,3 Given the prognostic and treatment implications, it is critical that CIDP be confidently diagnosed and expeditiously treated early in the disease course before the development of irreversible disability. It is equally important to exclude the diagnosis in appropriate settings such that patients without CIDP avoid exposure to costly and potentially harmful interventions. Due to the heterogeneity and rarity of CIDP, this can be a challenging task.

One challenge with improving our diagnostic capabilities is a failure to fully understand the clinical and pathobiologic boundaries of CIDP and its variants. The rarity of the condition precludes individual centers or even national registries from recruiting sufficient patients to fully capture the spectrum of CIDP. To meet this challenge multicenter, multinational collaboration with large prospective observational cohorts are needed.

Three key aspects of CIDP that are in need of improved characterization are those of diagnosis, treatment and prognosis. Diagnosis is currently based on criteria derived by expert consensus, e.g. the 2021 EAN/PNS criteria for CIDP.4 While different criteria sets vary on specific recruitments, most need to meet at minimum a standardized clinical definition and have specific predefined abnormalities on electrophysiological studies. These criteria may lead to both erroneously excluding CIDP, for example in cases where electrophysiological signs of demyelination in motor nerves are absent, or erroneously diagnosing CIDP, for example in cases where electrophysiological results are misinterpreted.5 Given the consequences of withholding an effective treatment or starting a costly and possibly harmful intervention that is not indicated, the current criteria need to be improved. Particular attention need be given to “variants” of CIDP, as delayed diagnosis and over-diagnosis of these conditions is especially problematic. While currently classified as CIDP variants, it is unknown if some of these variants have distinct pathophysiological mechanisms, treatment responses and prognoses; and hence might be more appropriately classified as a unique disease.6,7

At present, the choice of first-line treatment is determined by patient preference and physician discretion. Although for some subgroups certain treatments may be more effective than others,4,8–10 in most with CIDP efficacy of the first line interventions is comparable. While efficacy of first line therapies (IVIG, corticosteroids, and plasma exchange) is well established, there is a dearth of data that informs on the optimal dose. Existing CIDP guidelinesrecommend optimizing treatment to individual patient needs, but the means by which to best achieve treatment optimization are unknown. The observation that between 37% and 62% of patients have a relapsing-remitting or a chronically progressive course requiring regular maintenance treatment magnifies the importance of better understanding how to personalize treatment protocols. 1,11–14 There are no known clinical or biological markers that can predict or assess disease activity or response to treatments, and as a result treatment optimization during routine clinical care is typically performed by trial and error. Changes in disability or impairment in patients on maintenance treatment may be subtle or occur on a single domain only. Patient reported outcome measures (PROMs) can capture non-specific symptoms such as fatigue, pain or exercise intolerance. It is currently not clear to what extent the fluctuation in PROMs reflect changes in disease activity, nor to what extent it should guide therapeutic decision making. From a practical perspective this leads to overtreatment in patients who have achieved remission but are still treated because withdrawal has not been attempted,15 as well as under-treatment of patients that are not properly monitored for disease progression. Improving our ability to select the best treatment for any individual patient at any specific point in their disease, and improving our ability to personalize that treatment over time with objective markers of disease activity and treatment response is an unmet need for the CIDP community.

To investigate these and other (future) issues an international collaboration is needed to include sufficient numbers of CIDP patients such that the full spectrum of disease can be captured. INCbase is an international research registry and biobank that will provide the infrastructure to achieve this goal. Participating institutions without an existing registry will be allowed direct access into the central INCbase network. Countries with freestanding national registries will be able to harmonize existing databases with INCbase for optimal worldwide collaboration and to ensure global coverage.

# OBJECTIVES

The primary objective of INCbase is to develop a prognostic model to predict long-term treatment response in CIDP patients at the start of treatment.

Secondary objectives of INCbase include:

1) to discover clinical, electrophysiological and biological biomarkers for diagnosis, disease activity and prognosis,

2) to describe variation in clinical and electrophysiological characteristics of CIDP to define the spectrum and boundaries of CIDP,

3) to describe short and long-term outcomes at impairment, disability and quality of life levels of (subgroups of) CIDP patients,

4) to discover clinical, electrophysiological and biological determinants of treatment response and long-term outcomes,

5) to describe physician and patient perspectives on and satisfaction with different treatments that may be used for CIDP, including plasma-exchange and subcutaneous immunoglobulin and

6) to deepen knowledge on CIDP pathophysiology, including investigating immunological pathways underlying CIDP.

# STUDY DESIGN

INCbase is an explorative multicenter prospective observational study using a modular web-based registry allowing collection of standardized prospective longitudinal data in CIDP. INCbase will collect clinical data and optional biomaterials at pre-specified time points and during periods of apparent disease activity (e.g., after treatment initiation or relapse). Patients in INCbase can either enter a core or extended module. The core is designed to capture a minimal set of data needed for the primary and some of the secondary aims of the study. The extended module was derived from the International CIDP Outcome Study (ICOS), a national registry that was initiated in the Netherlands18, and captures additional data that is needed for the other secondary endpoints by including more visits and extra outcomes. Furthermore, patients can be included in the home assessment module, comprised of additional questionnaires and home measurements of grip strength. Centers may choose to include patients in the core, the extended or the extended and home assessment (extended +) module based on patient related factors (i.e. decreased mobility impairing the ability for study visits), disease related factors (i.e. newly diagnosed, specific treatment started like SCIg or plasma-exchange) and center related factors (specific interests in certain secondary endpoints).

# STUDY POPULATION

## Population (base)

Both newly diagnosed and remotely diagnosed CIDP patients can be included in INCbase.

## Inclusion criteria

* Patients with the clinical diagnosis of CIDP, as judged by treating physician.
* Informed consent.

### Additional inclusion criteria for home assessment module

Patients eligible for the home assessment module are selected based on presumed disease activity:

Group 1) Active disease (newly diagnosed patients or patients without treatment for 1 year, with progressive disease)

Group 2) Stable disease (patients on maintenance treatment with IVIg or SCIg, who will start withdrawal or tapering at the discretion of treating physician)

Patients from group 1 can cross to group 2 at a later stage.

## Exclusion criteria

The presence of any condition, that at the discretion of the study investigator or study participant, impairs the participants ability to provide accurate study information in a timely and reliable manner.

## Sample size calculation

INCbase is an ongoing prospective study without a predetermined duration. For the sample size calculation, we will focus on the primary aim, i.e. the development of a prediction model for treatment response. We estimate that a population of 1000 newly diagnosed patients are needed to ensure sufficient numbers of patient not responding to treatment. To develop the prediction model, the cohort will be split into a development and validation cohort of equal parts. We estimate that around 20% of patients will not respond to treatment and, for external validation, the smallest outcome group should include around 100 patients.16,17 This number will also allow testing of multiple predictor variables and provide a safety margin for changes in diagnosis and patients lost to follow-up.

# TREATMENT OF SUBJECTS

Patients will be treated at the discretion of their treating physician. Participation in INCbase will in no way influence the choice, dose, or duration of the treatment.

# METHODS

## Study parameters/endpoints

### Main study parameter/endpoint

The clinical outcome assessed with disability scales at the different timepoints after start of treatment will be used as the primary outcome for the development of a prognostic model for treatment response. As disability scales the Inflammatory Rasch-Overall Disability Scale (I-RODS; supplement 1) and the Adjusted Inflammatory Neuropathy Cause and Treatment disability score (INCAT disability score; supplement 2) will be used. Clinical relevance of changes in disability will be based on the minimally clinically important different (MCID) for the I-RODS or a change greater 1 point for the adjusted INCAT score. Patients reaching clinically relevant changes in disability on the different timepoints will be categorized as responders or non-responders.

### Secondary study parameters/endpoints

The following secondary endpoints that have been predefined at the start of INCbase are:

- (changes in) impairment (assessed with MRC sum score, grip strength, Modified Inflammatory Neuropathy Cause and Treatment Sensory Sum score), disability (assessed with I-RODS, INCAT disability score) and quality of life (assessed with EuroQol quality of life, Pain intensity-numeric rating scale and Fatigue severity scale) at inclusion and at long-term follow-up timepoints for all CIDP patients and subgroups of CIDP patients

- associations between clinical data at baseline and follow-up, electrophysiological data and biological biomarkers (including but not limited to blood based immunological biomarkers) and impairment, disability and quality of life at different timepoints

- associations between clinical data at baseline and follow-up, electrophysiological data and biological biomarkers (including but not limited to blood based immunological biomarkers) and treatment response at different timepoints

- associations between clinical data at baseline and follow-up, electrophysiological data and biological biomarkers (including but not limited to blood based immunological biomarkers) and disease activity assessed with the CIDP disease activity status (CDAS) at different timepoints

- diagnostic accuracy of clinical data at baseline and follow-up, electrophysiological data and biological biomarkers (including but not limited to blood based immunological biomarkers) for the diagnosis of CIDP based on the current reference standard (i.e. the EAN/PNS 2021 criteria) and based on alternative reference standards like treatment response

- short and term patient satisfaction with different treatments that may be used for CIDP and changes in patient satisfaction in case of switching to other treatments

- short and long-term side effects of the different treatments that may be used for CIDP

- describing current clinical practice regarding the reasons for and use of plasma-exchange or similar therapies in CIDP

- describing current clinical practice regarding the reasons for and use of subcutaneous immunoglobulin in CIDP

Next to these predefined endpoints, new and other study parameters and endpoints will be employed during this study as a result of new insights and technical advances. These study parameters and endpoints will be bound to the scope of objectives of INCbase as defined in section 2.

## Study procedures

Whereas baseline assessments will be largely identical for all modules, for follow-up centers can choose a core module or they can choose the extended module that include more visits, with extra clinical, electrophysiological, immunological, parameters and treatment specific questions (Figure 1). A subset of patients can be included in the home assessment (extended +) module. The extent, complexity and use of other modules will depend on research interests, nature of the specific projects and patient features.

The extended module was derived from the International CIDP Outcome Study (ICOS), a national registry that was initiated in the Netherlands.18 In addition, relevant parameters from other currently running national registries were added. Tables 1 and 3 describe the outcome parameters collected for the core module at baseline and follow-up respectively. Tables 2 and 4 describe the additional outcome parameters collected at baseline and follow-up for the extended module. Table 5 describes outcome parameters for the home assessment module. For children included in INCbase, parameters that will be collected depend on the age and understanding which will be judged by the researcher. As a reference, for children between 6-12 the INCAT disability score, MRC sum score and grip strength may be collected, for younger children that which the researcher deems suitable and for children older than 12 all parameters may be collected.

***Table 1: outcome parameters collected at baseline (all modules)***

|  |
| --- |
| Inflammatory Rasch-Overall Disability Scale (I-RODS; supplement 1) |
| Adjusted Inflammatory Neuropathy Cause and Treatment disability score (INCAT disability score; supplement 2) |
| CIDP disease activity status (CDAS) |
| Grip strength |
| EuroQol quality of life (EQ-5D; supplement 3) |
| CIDP (previous) treatment related adverse events |
| MRC sum score (supplement 4) |
| Modified Inflammatory Neuropathy Cause and Treatment Sensory Sum score (mISS; supplement 5) |

**Table 2: additional outcome parameters collected at baseline (extended module)**

|  |
| --- |
| Rasch- built Fatigue severity scale (R-FSS, supplement 6) |
| Pain intensity-numeric rating scale (PI-NRS; supplement 7) |
| Patient questionnaire relating to treatment preferences, treatment satisfaction, treatment effect and adverse effects (TSQM; supplement 8) |
| Hospital Anxiety and Depression Scale (HADS; supplement 10) |
| General Self Efficacy Scale (GSES; supplement 11) |

***Table 3: outcome parameters collected at follow-up for core module***

|  |
| --- |
| Inflammatory Rasch-Overall Disability Scale (I-RODS; supplement 1) |
| Adjusted Inflammatory Neuropathy Cause and Treatment disability score (INCAT disability score; supplement 2) |
| CIDP disease activity status (CDAS) |
| Grip strength |
| EuroQol quality of life (EQ-5D; supplement 3) |
| Optional impairment scale of choice (see table 4 for options) |
| Patient impression of change (supplement 9) |
| CIDP treatment related adverse events |

***Table 4: outcome parameters collected at follow-up for extended module (in addition to core module, based on the ICOS***18***)***

|  |
| --- |
| MRC sum score (supplement 4) |
| Modified Inflammatory Neuropathy Cause and Treatment Sensory Sum score (mISS; supplement 5) |
| Rasch-built Fatigue severity scale (R-FSS; supplement 6) |
| Pain intensity-numeric rating scale (PI-NRS; supplement 7) |
| Patient questionnaire relating to treatment preferences, treatment satisfaction, treatment effect and adverse effects (TSQM; supplement 8) |
| Patient global impression of change (PGIC; supplement 9) |
| Hospital Anxiety and Depression Scale (HADS; supplement 10) |
| General Self Efficacy Scale (GSES; supplement 11) |
|  |

## *Table 5: Parameters collected at home assessment*

|  |
| --- |
| Grip strength |
| Inflammatory Rasch-Overall Disability Scale (I-RODS; supplement 1) |
| EuroQol quality of life (EQ-5D; supplement 3) |
| Rasch- built Fatigue severity scale (R-FSS, supplement 6) |
| Pain intensity-numeric rating scale (PI-NRS; supplement 7) |
| Patient global impression of change (PGIC; supplement 9) |
| Hospital Anxiety and Depression Scale (HADS; supplement 10) |

*Baseline visit: clinical data and assessments*

The baseline visit may occur concurrently with a standard clinical visit or may be arranged as a separate study visit. Most data collected at baseline is part of standard clinical care. This includes epidemiological data (e.g. age, gender, medical history), diagnostic data (results from relevant diagnostic studies performed as part of routine clinical care like nerve conduction studies, imaging, etc.), disease history and disease related clinical information, (previous) treatment data (e.g. types of treatment, changes and reasons for changes in treatment, side effects, etc) and data on the neurologic examination (reported as MRC sum score, grip strength and mISS). Diagnostic studies solely performed as part of research for INCbase are not permitted. In addition to standard clinical care, patients will fill in questionnaires on patient reported outcomes (described in table 1 for the core module with additional questionnaires described in table 2 for the extended module).

*Follow-up visit: schedule and assessments*

Follow-up visits will be scheduled according to Figure 1 depending on whether a patient is in the core or extended module. For the core module visits are scheduled every 6 months. A margin of 2 months will be allowed. If treatment is started, additional visits can be planned in patients, concurrently with clinical visits at one/two months and at three months after start of new treatment. If treatment withdrawal or tapering is attempted, additional visits can be planned concurrently with clinical visits. In case of unscheduled visits planned because of clinical necessity, the individual researcher may decide to also collect follow-up research data. Follow-up duration is minimally two years, but patients can be followed as long as neurological monitoring is indicated. After two years, frequency of visits for stable individual patients can be reduced to once per year. An indication of the follow-up visit schedule for the different modules is provided in figure 1.

*Follow-up visits schedule: home assessment module*

Newly diagnosed patients or patients without treatment for over one year starting treatment (group 1), and patients stable on IVIg or SCIg maintenance treatment starting withdrawal (group 2) will be included. In accordance with the extended module, follow-up visits will be scheduled at one month (with a margin of two weeks), at three months, and at six months. In addition, there will be an optional visit at nine months depending on the tapering schedule (with a margin of four weeks), as displayed in figure 1. Patients from group 2 will perform home measurements at week 2, 4, 6, 8, 12 and 16 weeks after starting withdrawal, with the possibility of extension to 20 and 24 weeks. The decision for initiation of treatment and the regimen of treatment withdrawal will be with the treating physician.

**Figure 1: visit schedule and outcome measures collected**

**

*outcome parameters are described in the text*

*Follow-up visit: clinical data*

The following data will be collected that is part of standard care: treatment data (e.g. types of treatment, changes and reasons for changes in treatment, side effects, etc), disease related clinical information, the MRC sum score and mISS score (see table 3 and 4).

The following data will be collected that is not part of standard care: I-RODS, INCAT disability scale, EQ-5D, fatigue severity scale, pain severity scale, patient global impression of change, HADS, self-efficacy scale and a patient questionnaire relating to treatment preferences, treatment satisfaction, and treatment related adverse events (see table 3 and 4).

*Home assessment module follow-up: clinical data*

For the home assessment module, data that will be collected at visits is in accordance with aforementioned extended follow-up. Patients starting treatment withdrawal or tapering will additionally perform home measurements of grip strength and fill in the following questionnaires: I-RODS, PGIC, PI-NRS, R-FSS, EQ-5D and HADS (see table 5). This data will be collected by electronic CRF automatically sent to patient’s email, initially at an interval of two weeks and later at an interval of 4 weeks.

*Biomaterials*

Within INCbase, individual researchers will have the option to collect blood samples from individual patients at baseline and follow-up visits during the first year of participation. Collection of biomaterials is not mandatory. Additional sampling beyond one year may be performed for patients participating in the home assessment module. The biomaterial collection schedule in the Netherlands can be found in table 6. Blood samples may be processed to store as serum, plasma, DNA, RNA and peripheral blood mononuclear cells (PBMC). DNA is stored at baseline. RNA, PBMC and plasma are collected at baseline, in case of evident clinical improvement or stopping treatment (at either three or six months) and at relapse. Serum will be collected at all visits. Samples will be stored using the INCbase study ID and date of collection. The maximum amount of blood collected at an individual visit is 60 ml. Blood samples are the only biomaterial that will be collected specifically for INCbase. In children, up to 16 years of age, blood sampling will only be performed if there is also a clinical indication for blood sampling at that moment. A recommended standard for collection, isolation and storage of biomaterials will be provided separately. In addition, residual material from the diagnostic work-up can be stored, such as cerebrospinal fluid or (nerve/skin) biopsy samples.

**Table 5: frequency of biomaterial sampling for new patients in the Netherlands**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **baseline** | **M1** | **M3** | **M6** | **M9\*\*\*** | **M12** | **unscheduled****(relapse)** | **unscheduled****(restabilization)** |
| **Serum\*\*** | x | x | x | x | x | x | x | x |
| **RNA** | x |  | \*x or 🡪 | x |  |  | x |  |
| **PBMC** | x |  | \*x or 🡪 | x |  |  | x |  |
| **Plasma** | x |  | \*x or 🡪 | x |  |  | x |  |
| **DNA** | x |  |  |  |  |  |  |  |

\* In case of evident clinical improvement or stopping therapy at M3, sampling will be performed. If not, sampling will be performed at M6, or earlier if treatment is stopped (maximum of 4 weeks after stopping treatment).

\*\* For patients in the home assessment module, test for CIDP specific antibodies at baseline

\*\*\* Optional visit for patients in home assessment module depending on tapering schedule

## Withdrawal of individual subjects

Subjects can leave the study at any time for any reason without any consequences if they wish to do so. Investigators may withdraw a subject from study participation at any time if the investigator determines that the study participant is unable to fulfill the obligations of the study, or if study participation jeopardizes the health or well-being of the participant.

### Specific criteria for withdrawal (if applicable)

Not applicable

## Replacement of individual subjects after withdrawal

Not applicable

## Follow-up of subjects withdrawn from treatment

Not applicable

## Premature termination of the study

 Not applicable

# SAFETY REPORTING

## Temporary halt for reasons of subject safety

 <<add local/national>>

## AEs, SAEs and SUSARs

### Adverse events (AEs) and serious adverse events (SAEs)

Only those adverse events that are specifically related to the venipuncture for biomaterials collection and are reported spontaneously by the subject or observed by the investigator or his staff within 2 days after the procedure will be recorded and documented in the medical file and CRF. For hematomas related to venipuncture, only hematomas larger than 10x10 cm will be reported.

We do not expect any serious adverse events to occur. If a SAE related to the study procedures does occur, this will become apparent at the test day itself. The procedures for handling SAEs apply to (a) any SAE that occurs within 1 day after the intervention, and (b) has a possible or certain relation to the study procedures. The sponsor will report the SAEs <<add local/national>>.

### Suspected unexpected serious adverse reactions (SUSARs)

 Not applicable.

## Annual safety report

 Not applicable

## 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.

## 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.

# STATISTICAL ANALYSIS

To develop a prediction model of treatment outcome we will use univariable and multivariable logistic regression analysis to test the association between possible prognostic factors at start of treatment and treatment response (defined as clinically relevant changes in disability) as outcome variable. We will start with identifying possible prognostic factors by investigating a set of variables available at the start of treatment, like clinical, diagnostic, demographic variables, using univariate logistic regression analyses and treatment response as dependent variable. Identified possible prognostic factors will be combined into a multivariate model. 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 after which the model will be applied to a validation data set for external validation.

INCbase has various secondary objectives as stated above and statistical analyses have so far not been predefined. For research objectives requiring collective INCbase data, investigator will need to submit a research project proposal to the INCbase Steering Committee, that will include a samples size calculation and a statistical analysis plan.

# ETHICAL CONSIDERATIONS

## Regulation statement

This study will be conducted in accordance with the design and specific provisions of this IRB approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with ICH Good Clinical Practice (GCP) and the applicable local regulatory requirement(s). The principal investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the study participants. The principal investigator will promptly report to the IRB any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

## Recruitment and consent

Participants will be recruited when visiting the outpatient clinic or in case they are admitted to the hospital. When the selection criteria are fulfilled, the patient or the patient’s representative will be asked for written informed consent, in accordance with the guidelines of the local medical ethics committee (METC) or Institutional Review Board (IRB). 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 <<add local/national>> on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

## Objection by minors or incapacitated subjects (if applicable)

Minors can participate in this study, if consent is provided by their legal representatives*.* Participation in this study will not cause additional discomfort compared to standard care. In case the participating minor objects the <<add local/national>> will be applied.

## Benefits and risks assessment, group relatedness

Risks of participation are negligible; for adults the only interventions done extra for this study are the collection of questionnaires and blood through a venepuncture. For minors, blood will only be collected if there is a clinical indication for a venepuncture at that moment to minimize discomfort. No additional diagnostic studies will be performed solely for this study. There are no direct benefits for the individual participant. CIDP is heterogenous disorder with subtypes that may present predominantly in adults or minors. This study can only be done in this population, including minors, to capture the full diversity of CIDP.

## Compensation for injury

<<add local/national>>

## Incentives (if applicable)

 Not applicable.

# ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

## 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 <<add local/national>> and other guidelines, regulations and Acts. Data management and reporting of the study will be performed in accordance with the ICH GCP guidelines. All data will be entered in a web-based data entry system and stored online, taking in account all safety measures and ICH-GCP regulation on privacy. Participant email addresses will be encrypted and stored in the database, and will only be accessible to the local investigator. Data will be compartmentalized in a way that investigators will have access only to data from patients included in their own center. In addition, investigators and functional administrators of the central coordinating center (Amsterdam University Medical Center) will have access to the complete data set, excluding participant email addresses from other centers. Relevant data from the complete data set will be distributed to investigators for analysis, only after approval of the INCbase steering committee.

For each participating country and/or center, the study will be initiated, coordinated, and if applicable, monitored and insured via local or national coordinators and under regional legislation using the current study protocol as a template. When applicable, a country will have a single coordinating center that will act as study sponsor within that country. The national sponsor can make adjustments to the protocol to accommodate local and national requirements. Each center and/or national coordinating center will be responsible for ethics approval and amendments, and monitoring if required by national or local regulations. According to national and local regulations, individual centers will store and archive all essential documents on site (such as Informed Consent forms, privacy assessment, clinical trial agreement, biobanking log if applicable). Responsibilities of the central coordinating center, national coordinating center and participating center are defined in the INCbase Data Registry and Biomaterial Policy.

Each site will be the owner of their data that such participating member has entered into the INCbase Database and all intellectual property therein, and may use such data for its further research and education and patient care purposes. Use of collective data has to be preceded by approval of the INCbase Steering Committee. Participating centers can make use of an opt-out procedure if a particular center does not want their data to be used for analysis for a certain project. Collaboration in the sharing of data will be further defined and arranged in the INCbase Data Registry and Biomaterial Policy which will be signed by all participating centers and physicians and after approval of the INCbase Steering Committee.

**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 hospital codes. The key to this code is only known in the including center and with the treating physician. The list with codes of the participating center will be kept locally and can accessed only by the investigators of the participating center, and if appropriate, by the national sponsor. This code will also be used to store reports with electrophysiological data, serum, DNA, RNA, PBMC, cerebrospinal fluid, nerve biopsy and ultrasonography images. <<add local/national>> will have access to source documents.

**Access to data by commercial parties**

INCbase is co-funded by pharmaceutical companies based on investigator-initiated grants, for example the development of a prediction model for long-term treatment outcome. Primary and secondary outcomes and statistical analysis of these projects need to be prespecified, but explorative analysis within these proposals will be allowed. According to these proposals, commercial parties will not have access to the database or the (pseudonimised) individual data of participants. In some projects, agreement was reached to share the analysis of results with the funding parties. Within the informed consent, participants will be asked to provide a specific consent for sharing data and/or non-identifiable biomaterials with industry in the future. Sharing of data with any party will only be possible upon reasonable request and after approval of the INCbase Steering Committee.

##

**Storage and analysis of biomaterials**

Biosamples collected for INCbase will be stored locally at the participating center. Biosamples in local biobanks will be owned and governed by the participating site and can be used locally for studies without approval of the INCbase Steering Committee. Centers can participate in collaborative projects approved by the INCbase Steering Committee by using an opt-in procedure and a material transfer agreement which will part of the INCbase Data Registry and Biomaterial Policy. 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 a maximum of <> years after this project has ended.

## Monitoring and Quality Assurance

The risk classification of this study is considered as negligible. Independent monitoring will be established in the central administrative center (Amsterdam UMC) overseeing the whole dataset for completeness. Data quality will be improved through automated data checks built within the online web-based entry system. Data checks will be done at regular intervals during the study. In addition, local monitoring will be instituted if required locally and/or nationally. In general, the central administrative center encourages participating centers to include local monitoring to strive the highest possible quality of data and study conduct. See for further details the INCbase monitoring plan. If centers already participate in a national CIDP registry that includes monitoring, no additional monitoring will be required for sharing data with INCbase.

## Amendments

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

## Annual progress report

The sponsor/investigator will submit a summary of the progress of the study to the accredited METC or IRB 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.

## End of study report

The investigator will notify the accredited METC or IRB 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. As previously stated, there is no predefined end of this study as this is an ongoing study.

In case the study is ended prematurely, the investigator will notify the accredited METC or IRB 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.

## Public disclosure and publication policy

The INCbase Steering Committee is responsible for all decisions regarding publication of data for scientific purposes that makes use of collective INCbase data. Financial sponsors of the study will only have an advisory role in the study design, data collection, data analysis and interpretation or results. Scientific reports and presentations will be prepared by the INCbase investigators. Further regulations regarding the ownership and usage of the data and biosamples collected in INCbase is defined in the INCbase Data Registry and Biomaterial Policy.

# STRUCTURED RISK ANALYSIS

## Potential issues of concern

Not applicable

## 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 negligible.

# REFERENCES

1. Lunn MP, Manji H, Choudhary PP, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. [Internet]. J. Neurol. Neurosurg. Psychiatry 1999;66(5):677–80.Available from: http://www.ncbi.nlm.nih.gov/pubmed/10209187

2. Oaklander AL, Lunn MP, Hughes RA, et al. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews. [Internet]. Cochrane database Syst. Rev. 2017;1:CD010369.Available from: http://www.ncbi.nlm.nih.gov/pubmed/28084646

3. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. [Internet]. Lancet. Neurol. 2018;17(1):35–46.Available from: http://www.ncbi.nlm.nih.gov/pubmed/29122523

4. Joint Task Force of the EFNS and the PNS, Van den Bergh PYK, Hadden RDM, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripher [Internet]. Eur. J. Neurol. 2010;17(3):356–63.Available from: http://www.ncbi.nlm.nih.gov/pubmed/20456730

5. Allen JA, Ney J, Lewis RA. Electrodiagnostic errors contribute to chronic inflammatory demyelinating polyneuropathy misdiagnosis. [Internet]. Muscle Nerve 2018;57(4):542–549.Available from: http://www.ncbi.nlm.nih.gov/pubmed/29053880

6. Iijima M, Yamamoto M, Hirayama M, et al. Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP. [Internet]. Neurology 2005;64(8):1471–5.Available from: http://www.ncbi.nlm.nih.gov/pubmed/15851750

7. Rajabally YA, Narasimhan M, Chavada G. Electrophysiological predictors of steroid-responsiveness in chronic inflammatory demyelinating polyneuropathy. [Internet]. J. Neurol. 2008;255(6):936–8.Available from: http://www.ncbi.nlm.nih.gov/pubmed/18438699

8. Viala K, Renié L, Maisonobe T, et al. Follow-up study and response to treatment in 23 patients with Lewis-Sumner syndrome. [Internet]. Brain 2004;127(Pt 9):2010–7.Available from: http://www.ncbi.nlm.nih.gov/pubmed/15289267

9. Kimura A, Sakurai T, Koumura A, et al. Motor-dominant chronic inflammatory demyelinating polyneuropathy. [Internet]. J. Neurol. 2010;257(4):621–9.Available from: http://www.ncbi.nlm.nih.gov/pubmed/20361294

10. Querol L, Rojas-García R, Diaz-Manera J, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. [Internet]. Neurol. Neuroimmunol. neuroinflammation 2015;2(5):e149.Available from: http://www.ncbi.nlm.nih.gov/pubmed/26401517

11. Chiò A, Cocito D, Bottacchi E, et al. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. [Internet]. J. Neurol. Neurosurg. Psychiatry 2007;78(12):1349–53.Available from: http://www.ncbi.nlm.nih.gov/pubmed/17494979

12. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. [Internet]. Neurology 1997;48(2):321–8.Available from: http://www.ncbi.nlm.nih.gov/pubmed/9040714

13. Gorson KC, van Schaik IN, Merkies ISJ, et al. Chronic inflammatory demyelinating polyneuropathy disease activity status: recommendations for clinical research standards and use in clinical practice. [Internet]. J. Peripher. Nerv. Syst. 2010;15(4):326–33.Available from: http://www.ncbi.nlm.nih.gov/pubmed/21199104

14. Mygland A, Monstad P. Chronic acquired demyelinating symmetric polyneuropathy classified by pattern of weakness. [Internet]. Arch. Neurol. 2003;60(2):260–4.Available from: http://www.ncbi.nlm.nih.gov/pubmed/12580713

15. Adrichem ME, Eftimov F, van Schaik IN. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyradiculoneuropathy, a time to start and a time to stop. [Internet]. J. Peripher. Nerv. Syst. 2016;21(3):121–7.Available from: http://www.ncbi.nlm.nih.gov/pubmed/27241239

16. Bunschoten C, Jacobs BC, Van den Bergh PYK, et al. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Lancet Neurol. 2019;

17. Vergouwe Y, Steyerberg EW, Eijkemans MJC, Habbema JDF. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. [Internet]. J. Clin. Epidemiol. 2005;58(5):475–83.Available from: http://www.ncbi.nlm.nih.gov/pubmed/15845334

18. Bunschoten C, Eftimov F, van der Pol W-LL, et al. International chronic inflammatory demyelinating polyneuropathy outcome study (ICOS): Protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome. [Internet]. J. Peripher. Nerv. Syst. 2019;24(1):34–38.Available from: http://www.ncbi.nlm.nih.gov/pubmed/30570196

19. van Nes SI, Vanhoutte EK, van Doorn PA, et al. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. [Internet]. Neurology 2011;76(4):337–45.Available from: http://www.ncbi.nlm.nih.gov/pubmed/21263135

20. Hughes RAC, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. [Internet]. Lancet. Neurol. 2008;7(2):136–44.Available from: http://www.ncbi.nlm.nih.gov/pubmed/18178525

21. van Nes SI, Vanhoutte EK, Faber CG, et al. Improving fatigue assessment in immune-mediated neuropathies: the modified Rasch-built fatigue severity scale. [Internet]. J. Peripher. Nerv. Syst. 2009;14(4):268–78.Available from: http://www.ncbi.nlm.nih.gov/pubmed/20021568

#  SUPPLEMENTS

**SUPPLEMENT 1 – Rasch-built Inflammatory Neuropathy - Overall Disability Scale (I-RODS)**17

INSTRUCTIONS: This is a questionnaire about the relationship between daily activities and your health. Your answers give information about how your polyneuropathy affects your daily and social activities and to what degree you are able to perform your usual activities.

Answer each question by marking the correct box (“x”). If you are not sure about your ability to perform a task, you are still requested to mark an answer that comes as close as possible to your judged ability to complete such a task. All questions should be completed. You can only choose one answer to each question. If your situation fluctuates, your answer should be based on how you usually perform the task.

If you need assistance or you are using special devices to perform the activity, you are requested to mark "possible, but with some difficulty ". In case you never perform the activity due to your polyneuropathy mark "not possible".

|  |  |  |
| --- | --- | --- |
|  | **Are you able to** | **Mark the best option with “x”** |
|  |  | **0** | **1** | **2** |
|  | **Task** | **Not possible to perform** | **Possible, but with some difficulty** | **Possible, without any difficulty** |
| 1 | read a newspaper/book? |  |  |  |
| 2 | eat? |  |  |  |
| 3 | brush your teeth? |  |  |  |
| 4 | wash upper body? |  |  |  |
| 5 | sit on a toilet? |  |  |  |
| 6 | make a sandwich? |  |  |  |
| 7 | dress upper body? |  |  |  |
| 8 | wash lower body? |  |  |  |
| 9 | move a chair? |  |  |  |
| 10 | turn a key in a lock? |  |  |  |
| 11 | go to the general practitioner? |  |  |  |
| 12 | take a shower? |  |  |  |
| 13 | do the dishes? |  |  |  |
| 14 | do the shopping? |  |  |  |
| 15 | catch an object (e.g., ball)? |  |  |  |
| 16 | bend and pick up an object? |  |  |  |
| 17 | walk one flight of stairs? |  |  |  |
| 18 | travel by public transportation? |  |  |  |
| 19 | walk and avoid obstacles? |  |  |  |
| 20 | walk outdoor < 1 km? |  |  |  |
| 21 | carry and put down a heavy object? |  |  |  |
| 22 | dance? |  |  |  |
| 23 | stand for hours? |  |  |  |
| 24 | run? |  |  |  |

**SUPPLEMENT 2 – INCAT disability score**18

**Arm disability**

0 No upper limb problems

1 Symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zips and buttons; washing or brushing hair; using a knife and fork together; handing small coins

2 Symptoms, in one arm or both arms, affecting but not preventing any of the above mentioned functions

3 Symptoms, in one arm or both arms, preventing one or two of the above mentioned functions

4 Symptoms, in one arm or both arms, preventing three or all of the functions listed, but some purposeful movements still possible

5 Inability to use either arm for any purposeful movement

**Leg disability**

0 Walking not affected

1 Walking affected, but walks independently outdoors

2 Usually uses unilateral support (stick, single crutch, one arm) to walk outdoors

3 Usually uses bilateral support (sticks, crutches, frame, two arms) to walk outdoors

4 Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with help

5 Restricted to wheelchair, unable to stand and walk a few steps with help

**Overall disability (**results fromsum of arm and leg disability scores). For calculating changes in INCAT scores the adjusted INCAT score will be used.

|  |
| --- |
|  |

 **SUPPLEMENT 3 – EuroQol (EQ-5D) Health Questionnaire**

*UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group.*

Under each heading, please tick the ONE box that best describes your health TODAY.

**MOBILITY**

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

**USUAL ACTIVITIES**

**(e.g. work, study, housework, family or leisure activities)**

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

We would like to know how good or bad your health is TODAY

**10**

0

**20**

**30**

**40**

**50**

**60**

**80**

**70**

**90**

**100**

**5**

**15**

**25**

**35**

**45**

**55**

**75**

**65**

**85**

**95**

**The best health**

**you can imagine**

**The worst health**

**you can imagine**

This scale is numbered from 0 to 100.

* 100 means the best health you can imagine; 0 means the worst health you can imagine.
* Mark an X on the scale to indicate how your health is TODAY.
* Now, please write the number you marked on the scale in the box
* below.

YOUR HEALTH TODAY =

**SUPPLEMENT 4 – 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.

|  |  |
| --- | --- |
| **0** | **No visible contraction.** |
| **1** | **Visible contraction without movement of the limb.** |
| **2** | **Active movement of the limb, but not against gravity.** |
| **3** | **Active movement against gravity over (almost) the full range.** |
| **4** | **Active movement against gravity and resistance.** |
| **5** | **Normal strength.** |

**SUPPLEMENT 5 – Modified INCAT sensory Sum Score (mISS)**

#

The mISS 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).

**In case of an asymmetric distribution note the sensory deficit at the most affected side.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Sensation** |  | **Normal** | **Abnormal** |
|  | **Grade** | **0** | **1** | **2** | **3** | **4** |
| **Pinprick** | **Arms** | at index finger | at index finger | at ulnar styloid process | at medial humerus epicondyle | at acromio-clavicular joint  |
| **Legs** | at hallux | at hallux | at medial malleolus | at patella | at anterior superior iliac spine |
| **Light touch** | **Arms** | at index finger | at index finger | at ulnar styloid process | at medial humerus epicondyle | at acromio-clavicular joint  |
| **Legs** | at hallux | at hallux | at medial malleolus | at patella | at anterior superior iliac spine |
| **Vibration sense** | **Arms**  | at index finger | at index finger | at ulnar styloid process | at medial humerus epicondyle | at acromio-clavicular joint  |
| **Legs** | at hallux | at hallux | at medial malleolus | at patella | at anterior superior iliac spine |
| **Joint position** | **Arms** | DIP joint index finger | DIP joint index finger | at wrist | at elbow | at shoulder joint |
| **Legs** | DIP joint hallux | DIP joint hallux | at ankle | at knee | at hip joint |
| **Two-point discrimination** | **Index finger** | at index finger\* | at index finger\* |  |  |  |

DIP=distal interphalangeal. \* Normal values are provided in the following table. \* In case of an asymmetric distribution note the sensory deficit at the most affected site should.

**Normative static and dynamic Normative values for (Rydel-Seiffer) Tuning Fork**

**two-point discrimination values**

|  |  |  |
| --- | --- | --- |
| **Age (years)** | **Static assessment** | **Dynamic assessment** |
| **20-39** | 4.0 | 3.5 |
| **40-49** | 4.5 | 4.0 |
| **50-59** | 5.0 | 4.0 |
| **60-69** | 6.0 | 5.0 |
| **70-79** | 7.0 | 6.0 |
| **≥ 80** | 8.5 | 6.5 |

|  |  |
| --- | --- |
| **Arms** | **Legs** |
| **Age (yr)** | **Value**  | **Age (yr)** | **Value** |
| **< 40**  | > 6.5 | **< 40**  | > 4.5 |
| **41 - 85** | > 6.0 | **41 - 60** | > 4.0 |
| **> 85** | > 5.5 | **61 - 85** | > 3.5 |
|  | **> 85** | > 3.0 |

**SUPPLEMENT 6 - Rasch-built Fatigue Severity Scale (R-FSS)**19

The higher the score you choose, the more you agree with the question (the lower the score the less you agree).

 disagree agree

1. Exercise brings on my fatigue 0 1 2 3
2. I am easily fatigued 0 1 2 3
3. Fatigue interferes with my physical functioning. 0 1 2 3
4. Fatigue causes frequent problems for me. 0 1 2 3
5. My fatigue prevents sustained physical functioning. 0 1 2 3
6. Fatigue interferes with carrying out certain duties and responsibilities. 0 1 2 3
7. Fatigue interferes with my work, family, or social life.

**SUPPLEMENT 7 - Pain intensity-numeric rating scale (PI-NRS)**

Please choose the number best resembling your symptoms.

* How would you rate your pain today?

0 🞎 1 🞎 2 🞎 3 🞎 4 🞎 5 🞎 6 🞎 7 🞎 8 🞎 9 🞎 10 🞎

0 = no pain maximal pain = 10

* How would you rate the most severe pain in the past 4 weeks?

0 🞎 1 🞎 2 🞎 3 🞎 4 🞎 5 🞎 6 🞎 7 🞎 8 🞎 9 🞎 10 🞎

0 = no pain maximal pain = 10

* How would you rate the your pain on average in the past 4 weeks?

0 🞎 1 🞎 2 🞎 3 🞎 4 🞎 5 🞎 6 🞎 7 🞎 8 🞎 9 🞎 10 🞎

0 = no pain maximal pain = 10

**SUPPLEMENT 8 - Treatment Satisfaction Questionnaire**

1) How satisfied are you with your therapy?

very satisfied 🞎

satisfied 🞎

neither satisfied nor dissatisfied 🞎

dissatisfied 🞎

very dissatisfied 🞎

2) Considering all the different ways your disease is affecting you, if you would stay in this state for the next few months, do you consider that your current state is satisfactory?

 Yes 🞎

 No 🞎

**SUPPLEMENT 9 – Patient impression of change**

Since the last change in medication, how would you describe the change (if any) in symptoms, related to CIDP?

very much improved 🞎

much improved 🞎

minimally improved 🞎

no change 🞎

minimally worse 🞎

much worse 🞎

very much worse 🞎

Since the last visit for this study, how would you describe the change (if any) in symptoms, related to CIDP?

very much improved 🞎

much improved 🞎

minimally improved 🞎

no change 🞎

minimally worse 🞎

much worse 🞎

very much worse 🞎

**SUPPLEMENT 10- Hospital Anxiety and Depression Scale (HADS)**

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your clinician to know how you feel. Read each item below and underline the reply which comes closest to how you have been feeling in the **past week**. Ignore the numbers printed at the edge of the questionnaire. Don’t take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

1. **I feel tense or “wound up”**

3 – Most of the time

2 – A lot of the time

1 – From time to time, occasionally

0 – Never

1. **I enjoy the things I used to enjoy**

0 – Definitely

1 – Not quite so much

2 – Only a little

3 – Hardly at all

1. **I get a sort of frightened feeling as if something awful is about to happen**

3 – Very definitely and fairly badly

2 – Yes, but not too badly

1 – Sometimes, but it doesn’t worry me

0 – Never

1. **I can laugh and see the funny side of things**

0 – As much as I always could

1 – Not quite so much

2 – Definitely not so much now

3 – Never

1. **Worrying thoughts go through my mind**

3 – A great deal of the time

2 – A lot of the time

1 – Not too often

0 – Almost never

1. **I feel cheerful**

3 – Never

2 – Not often

1 – Sometimes

0 – Most of the time

1. **I can sit at ease and feel relaxed**

0 – Always

1 – Usually

2 – Not often

3 – Never

1. **I feel as if I am slowed down**

3 – Nearly all the time

2 – Very often

1 – Sometimes

0 – Never

1. **I get a sort of anxious feeling like "butterflies" in the stomach**

0 – Never

1 – Occasionally

2 – Often

3 – Very often

1. **I have lost interest in my appearance**

3 – Definitely

2 – Often I don’t take as much care as I should

1 – Sometimes I don’t take as much care as I should

0 – I take just as much care as ever

1. **I feel restless as if I have to be on the move**

3 – Definitely

2 – Quite a lot

1 – Not very much

0 – Never

1. **I look forward with enjoyment to things**

0 – As much as I ever have

1 – Somewhat less than I used to

2 – Much less than I used to

3 – Rarely

1. **I get sudden feelings of panic**

3 – Very often

2 – Often

1 – Not very often

0 – Never

1. **I can enjoy a good book, radio or television program**

0 – Often

1 – Sometimes

2 – Not often

3 –Very seldom

**SUPPLEMENT 11- General Self-Efficacy Scale (GSES)**

1 = Not at all true 2 = Hardly true 3 = Moderately true 4 = Exactly true

|  |  |
| --- | --- |
| 1. I can always manage to solve difficult problems if I try hard enough.
2. If someone opposes me, I can find the means and ways to get what I want.
3. It is easy for me to stick to my aims and accomplish my goals.
4. I am confident that I could deal efficiently with unexpected events.
5. Thanks to my resourcefulness, I know how to handle unforeseen situations.
6. I can solve most problems if I invest the necessary effort.
7. I can remain calm when facing difficulties because I can rely on my coping abilities
8. When I am confronted with a problem, I can usually find several solutions.
9. If I am in trouble, I can usually think of a solution.
10. I can usually handle whatever comes my way.
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