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Deliverable D.5.2.

Standardization of clinical outcome assessments for CMT – chances, limitations, and strategies

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ECRA's position on clinical outcome assessments: why so important?

Charcot-Marie-Tooth disease (CMT) represents a biologically and clinically heterogeneous group of slowly progressive disorders lacking sensitive and universally applicable biomarkers or functional scales. Ongoing research aims to refine composite scores, digital mobility measures, and imaging biomarkers to address these gaps. But why is this so important, especially now? Clinical outcome assessments (COAs) are crucial to translate subjective symptoms into a comparable, repeatable, and objectifiable unit that quantitatively captures disease severity and progression as well as treatment response. With molecular understanding on CMT pathomechanisms growing at a galop, trial-readiness means to have validated measurements for all of the above at hand. For this, several ECRA members have previously and are currently engaged in the conduction of natural history studies, including the attached list of references.

Discussing the importance of COAs, following aspects need to be taken into account:

1. **Patient-Centered Care**: COAs focus on measuring outcomes that are important to patients, such as mobility, pain levels, and quality of life. This patient-centered approach ensures that treatment developments align with the needs and preferences of those affected by CMT.

2. **Regulatory Requirements**: Regulatory agencies, including FDA and EMA, increasingly require evidence from COAs to support drug approvals. Demonstrating that a treatment improves meaningful clinical outcomes is essential for gaining regulatory approval.

3. **Standardization of Measurements**: The use of standardized COAs allows for consistency in data collection across different studies and populations. This standardization facilitates comparisons between studies and helps in understanding the effectiveness of interventions.

5. **Enhancing Clinical Trial Readiness**: Including COAs in clinical trials (as opposed to measuring secondary biomarkers only) can improve their design by identifying relevant endpoints that reflect real-world impacts on patients' lives. This can lead to more robust evidence regarding a therapy's efficacy.

6. **Informed Decision-Making**: By incorporating COAs into research and clinical practice, healthcare providers can make better-informed decisions about treatment options based on

outcomes that matter most to their patients. COAs can not only inform about potential treatment options, but also about other important life decisions and overall prognosis.

Reflection on current practice: How to quantify disease progression, how to capture treatment response?

Deliverable 5.1 provides a detailed list of COAs and other outcome parameters that have recently been used or are currently in use for clinical validation or in ongoing trials. It is important to consider the diversity of these outcome parameters. Whereas some direct outcome parameters such as foot dorsiflexion strength have ceiling effects, composite scores such as the CMTES score have been designed to follow a Gaussian distribution, enabling more representative stratification. Since all clinical outcome assessments are (to some extent) examiner-dependent, a combination with electrophysiological, imaging, and serum biomarkers has been commonly used in several trial settings.

Limitations and need for standardization: what is special for CMT?

Standardizing clinical outcome parameters for Charcot–Marie–Tooth (CMT) disease is difficult due to several interrelated scientific and clinical challenges:

1. **Heterogeneity**: CMT is not a single disease but a group of inherited neuropathies with over 100 known disease-associated genes across many subtypes. Different mutations lead to variable disease mechanisms and clinical presentations, making a single standardized outcome measure inadequate for all subtypes.
2. **Slow Progression**: CMT progresses very slowly, often over decades. Detecting meaningful clinical change over a short trial period (e.g., 1–2 years) is challenging, requiring outcome measures that are both highly sensitive and reliable despite minimal short-term changes.
3. **Limitations of Existing Scales**: Commonly used scales or single parameters might have ceiling or floor effects, lack sensitivity to small improvements, and sometimes rely on patient-reported outcomes that can be subjective. Some scales mix impairments (like strength loss) with disability (like walking performance), complicating interpretation. Some scales emphasize sensory disturbances, therefore not fully capturing disease severity for motor neuropathies. Points assigned for reduced amplitudes upon nerve conduction studies might underestimate the severity of demyelinating neuropathies.
4. **Lack of Robust Biomarkers**: Objective measures such as nerve conduction studies, quantitative muscle MRI, or biochemical markers are still being validated. Nerve conduction studies might be less informative in advanced disease stages. Muscle MRI might not be available or considered too expensive in some countries. Serum biomarkers such as NfL levels might be sensitive to axonal loss but not specific to CMT, where its clinical meaningfulness remains to be further determined.
5. **Pediatric vs. Adult Cohorts**: CMT often starts in childhood, but children's natural growth can mask disease progression, whereas in adults, progression may plateau. This makes it hard to create one standard measure applicable across ages. Pediatric and adult neurologists use different scales, potentially complication transition.
6. **Rarity of Subtypes**: Even though CMT is considered one of the most frequent rare diseases, the different subtypes range in frequency from the rare to the ultrarare spectrum. With relatively few patients available for clinical trials worldwide, the community is being chal-

lenged to collaborate in global networks to ensure sufficient power and statistical robustness of data. Small, diverse study populations make validation and comparison of outcome metrics more complex.

Strategies to overcome these challenges: how can ECRA contribute?

ECRA brings together a combination of experts representing clinical, basic science, and patient perspectives. We leveraged the Antwerp meeting to report on existing trials and outcome parameters (see deliverable 5.1) and discuss the respective strengths' and weaknesses.

- To increase representative study cohorts, ECRA itself forms a network that propagates collaboration and data sharing (see deliverable 3.1).
- To address examiner dependence of clinical outcome assessments, ECRA plans to improve and harmonize the training situation (see 5-year work plan).
- To overcome statistical limitations of COAs (such as ceiling effects or non-Gaussian distributions), ECRA suggests to use composite scores that have been validated for CMT.
- To increase objectiveness of results, ECRA suggests to combine COAs with imaging biomarkers such as fat fraction on muscle MRI.
- To ensure a trial result is clinically meaningful and specific to the disease mechanism of interest, ECRA suggests to combine COAs with disease-specific biomarkers (such as serum sorbitol measurements in CMT-SORD).
- To reduce costs, increase availability, and ensure repeatability of measurements, ECRA suggests to explore new outcome parameters as a complementary source to the established ones (for example combine muscle MRI and ultrasound).

Summary and conclusions: COAs in CMT – where are we now?

The CMT community is right now getting into the privileged situation that pathomechanism-specific, potentially disease modifying treatments are coming into clinical trials for some CMT subtypes. Never before have COAs been so urgently needed. The ideal outcome parameter is sensitive, specific, clinically meaningful, easily repeatable, available at low cost, and statistically robust. There is no such outcome parameter for CMT (and probably not for the preponderance of diseases). ECRA harbors the important chance of bringing together experts from clinical, basic science, and patient perspectives. At the same time, ECRA represents a diversity of countries and backgrounds. The Antwerp conference was a crucial step for the assessment of COAs currently in use (see deliverable 5.1) and a starting point for further improvement.

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