**Title:** Reliability of the Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM)

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## ABSTRACT

**Background and Aims:** The CMT-FOM is a 13-item clinical outcome assessment (COA) that measures physical ability in adults with Charcot-Marie-Tooth disease (CMT). Test-retest reliability, internal consistency and convergent validity have been established for the CMT-FOM. This current study sought to establish inter-rater reliability.

**Methods:** Following an in-person training of six international clinical evaluators we recruited 10 participants with genetically diagnosed CMT1A, (aged 18-74 years, 6 female). Participants were evaluated using the CMT-FOM over 2 days. Participants were given at least a 3 hour rest between evaluations, and were assessed twice each day.

**Results:** Following the provision of training by master trainers, all 13 items of the CMT-FOM exhibited excellent inter-rater reliability for raw scores ($ICC_{1,1}$ 0.825 to 0.989) and z-scores ($ICC_{1,1}$ 0.762 to 0.969). Reliability of the CMT-FOM total score was excellent ($ICC_{1,1}$ 0.983, 95% CI 0.958-0.995).

**Interpretation:** The CMT-FOM is a reliable COA used by clinical evaluators internationally. The next steps are to establish further validation through psychometric evaluation of the CMT-FOM in the Accelerate Clinical Trials in CMT (ACT-CMT) study.

**Key Words:** Measurement, Clinical Outcome Assessment, Functional measurement, Clinical evaluation, clinical evaluation

## Introduction

Charcot-Marie-Tooth disease (CMT) encompasses a group of clinically and genetically heterogeneous inherited peripheral neuropathies with a prevalence of 1/2,500 individuals [1]. CMT1A accounts for around 50% of all cases of CMT and results from a duplication of the gene encoding for peripheral myelin protein 22 (PMP22) [2]. CMT1A is slowly progressive and characterized by distal motor and sensory loss resulting in gait and balance disturbance, foot deformity and hand and foot weakness [3].

Clinical, genetic and pathomechanistic studies in CMT1A have led to the development of a range of candidate disease modifying therapies [4]. It is prudent now more than ever to ensure clinical trial readiness with well characterized clinical cohorts and clinically responsive outcome measures. Investigators within the Inherited Neuropathies Consortium have developed the CMTPedS [5] and CMTInfS [6] as responsive and reliable measures of functional disability from birth to 20 years of age. The Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM) is a Clinical Outcome Assessment (COA) developed to address the gap in clinically meaningful measurement of physical ability for adults with CMT [7]. The preliminary validity shows acceptable content validity, internal consistency and test-re-test reliability, although a full validation study is required [7].

As part of the validation process, it is important to establish consistency and accuracy amongst clinical evaluators. Inter-rater reliability has been established as part of the validation process for other CMT measures including the CMTNS [8,9], the CMTPedS [5] and CMTInfS [6]. Our current study, Accelerate Clinical Trials in CMT, (ACT-CMT) aims to concentrate international effort to validate and assess the responsiveness of a COA (CMT-FOM) and a range of biomarkers to enable the conduct of quality clinical trials of candidate

treatments for CMT1A. Therefore, as part of the ACT-CMT validation study, we sought to establish international, cross discipline inter-rater reliability of the CMT-FOM.

## Materials and Methods

### *Participants*

Ten adults with genetically confirmed CMT1A volunteered to participate through the University of Rochester. Ethical approval for this study was obtained from University of Rochester institutional review board and all participants provided informed consent to participate.

### *Procedures*

A training session was held prior to the 2 days of assessment where evaluators were provided with a presentation of all items in the CMT-FOM and a demonstration of each item. There was opportunity to practice each item amongst the evaluators during this session until proficiency was observed. Trainers were experts in the administration of peripheral neuropathy outcome measures (KE and JB). All 6 clinical evaluators had experience with CMT and clinical outcome assessment. The evaluators consisted of 2 females and 4 males from the following professions: physiotherapist, occupational therapist, research nurse, two neurologists and a physical medicine and rehabilitation physician.

Inter-rater reliability was established by five international sites with evaluators who assessed the 10 adult patients over 2 days. This approach is supported by previous work validating the CMTPedS based on multiple testing across 2 days [5]. Six clinical evaluators from 5 sites

participated in this study (Rochester: KE, Philadelphia: TE, Iowa: RZ, London: MP/MS, Milan: DP). Each participant was examined in the morning and afternoon on both days (4 assessments per patient). To avoid fatigue there was a >3 hour time gap between assessments on each day. Each clinical evaluator examined 4 adults each day (8 assessments over 2 days). Table 1 outlines the assessment schedule. All measurements were blinded to other clinical raters and collated by JB. The site with two evaluators (London) was treated as one clinical evaluator as evaluators were trained together and both completed all assessments together.

*Measures*

All participants were assessed with the CMT-FOM, a 13 item measure with established test-re-test reliability, internal consistency and convergent validity [7]. This 13-item COA captures upper and lower limb strength, dexterity, balance, speed, ambulation and endurance. The CMT-FOM also includes a patient profile section which collects demographic information, patient reported symptoms, ankle flexibility, foot posture, gait and sensation.

Demographic variables include: age, gender, height, weight, assistive devices and dominant side. Disease severity was measured with the Charcot-Marie-Tooth Examination Score (CMTES). The CMTES is a sub score of the Charcot-Marie-Tooth Neuropathy Score CMTNS; calculated by summing the symptoms and signs excluding electrophysiology [8]. Each assessment is scored on a 0-4 point scale, with higher scores indicating increased impairment.

The patient reported symptoms include: presence of foot pain, hand weakness, leg cramps, hand tremor, unsteady ankles, daily trips and/or falls, hand pain and sensory symptoms. Foot posture is measured using the 6 item Foot Posture Index scored along a continuum of cavus (supinated) to planus (pronated) foot structure. A score of 0 denotes a neutral position, -2 clear signs of supination, and +2 clear signs of pronation. The aggregated score ranges from -12 (extremely supinated/pes cavus) to +12 (extremely pronated/pes planus) [10]. Ankle flexibility is measured in degrees by the weightbearing lunge test. Gait is categorized on a three point scale (no, some, yes) for foot drop, difficulty heel and toe walking. Sensation is measured by pinprick and vibration is measured with a tuning fork both scored on a 5 point scale described in the CMT Neuropathy Score [8]. The patient profile was only collected once for each participant as it does not contribute to the overall measure score of the CMT-FOM. Participants were asked to complete items in their regular footwear without the use of orthoses or ankle foot orthoses where safe and practical.

*Scoring*

To measure performance on the 13 CMT-FOM items, raw scores were converted to z-scores based on age and gender matched normative reference values collected mostly from the 1000 Norms project and published data [11-16]. This transformation of raw scores into a single unit of measure mirrors the well accepted and published approach for the CMTPedS [5] and CMTInfS [6].

To improve interpretation and calculate of an overall CMT-FOM measure score, z-scores were categorized along a continuum of disability levels: normal, very mild, mild, moderate and severe. Our approach mirrors the validated pediatric CMTPedS by collapsing to a 5-point

Likert response format based on age/gender derived z-scores: 0 is a z-score above normal or between 0-0.99 z-scores below normal; 1 is between 1-1.99 z-scores below normal; 2 is between 2-2.99 z-scores below normal; 3 is between 3-3.99 z-scores below normal; 4 is > 4 z-scores below normal [5].

*Data Analysis*

Data were analysed in SPSS v24 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Intraclass correlation coefficients ($ICC_{1,1}$) were calculated for all items using the one-way random model with absolute agreement single-measures option in SPSS 24.0. Both raw and z-scores were analysed, as well as a CMT-FOM total score. ICC values and 95% Confidence Intervals (95% CI) were considered excellent with a value of 0.75 or greater; fair to good for values between 0.40 to 0.75, poor if values were 0.40 or less [17].

**Results**

Ten adults (6 females) with genetically diagnosed CMT1A participated, aged 18-72 years (mean 44.6, SD 20.7) and 9 were right hand dominant. The CMTES scores showed a range of disease severity (mean 9.6, 5-19). Two participants wore ankle foot orthoses for testing. During daily activities the following symptoms were reported: 4 reported foot pain, 7 reported leg cramps, 6 unsteady ankles, 2 daily trips/falls, 2 hand pain, 5 hand weakness, 6 tremor and 8 sensory symptoms. Foot Posture Index ranged from -7 to 4 (mean 0, SD 4), lunge ranged from 4 to 32 degrees (mean 20, SD 8). Gait was characterised as nine had difficulty heel walking, 5 had difficulty toe walking and 5 had foot drop. Pinprick sensation was reduced in all 10 patients (8 decreased below or at ankle bones, 1 decreased at or below midline of calf, 1 decreased above calf midline up to and including knee). Vibration sensation

was reduced in 8 patients (3 reduced at first metatarsal bone, 3 reduced at ankle, 1 reduced at knee (tibial tuberosity), 1 absent at knee and ankle).

All 13 items of the CMT-FOM exhibited good to excellent inter-rater reliability for raw scores ($ICC_{1,1}$ 0.825 to 0.989) and z-scores ($ICC_{1,1}$ 0.762 to 0.969) (Table 2). Inter-rater reliability of the CMT-FOM total score was excellent ($ICC_{1,1}$ 0.983, 95% CI 0.958-0.995).

**Discussion**

Establishing feasible, valid and sensitive measures of function is essential to clinical trial readiness for adults with CMT1A. We established inter-rater reliability of the CMT-FOM across 5 international clinical sites during a 2 day meeting. All items of the CMT-FOM exhibited good to excellent inter-rater reliability for raw scores, z-scores and the total score.

Development of disease-specific psychometrically valid COAs is necessary to ensure clinical trial readiness [18]. This process requires international effort, especially in rare disease to achieve adequate power to validate tools. With promising therapies on the horizon, it is now the time to ensure we have whole of life COAs that demonstrate the reliability and validity necessary to both power and conduct clinical trials [19]. In CMT1A we have measures that have overlap from birth to 20 years of age. The CMT-FOM addresses a critical gap in measurement of disability for adults with CMT1A.

Inter-rater reliability has been established for the CMT-FOM across all 5 international sites and data collection for the Accelerate Clinical Trials in Charcot Marie Tooth Disease (ACT-CMT) NIH grant # NIH 1 U01 NS109403-02 study is underway. This study will explore the

psychometric properties of the scale using Rasch analysis including item redundancy, construct validity, multicenter inter-rater reliability, responsiveness and the minimal clinically important change. This approach dovetails already validated disease measures and complete a whole of life COA measurement system for CMT1A [5-7]

In conclusion, the CMT-FOM displays excellent intra-rater reliability between clinical evaluators from 5 international sites. A larger longitudinal study is underway to validate the CMT-FOM and to determine its responsiveness and utility for clinical trials in CMT1A.

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**Table 1.** Schedule of evaluations for subjects 1-10 across 2 days

| Site | Sat | Sat | Sat | Sat | Sun | Sun | Sun | Sun |
|---|---|---|---|---|---|---|---|---|
| Evaluator | 9.30 | 11.00 | 1pm | 2pm | 9.30 | 11.00 | 1pm | 2pm |
| 1 | S1 | S6 | S2 | S7 | S3 | S8 | S4 | S9 |
| 2 | S2 | S7 | S3 | S8 | S4 | S9 | S5 | S10 |
| 3 | S3 | S8 | S4 | S9 | S5 | S10 | S1 | S6 |
| 4 | S4 | S9 | S5 | S10 | S1 | S6 | S2 | S7 |
| 5 | S5 | S10 | S1 | S6 | S2 | S7 | S3 | S8 |

**Table 2.** Inter rater reliability for each of the 13 items and the CMT-FOM total score.

| Item | Raw | z-score |
|---|---|---|
| 1. Hand grip (N) | .957 (95%CI .896-.988) | .887 (95%CI .743-.966) |
| 2. Foot plantarflexion (N) | .849 (95%CI .669-.954) | .762 (95%CI .521-.923) |
| 3. Foot dorsiflexion (N) | .922 (95%CI .816-.977) | .912 (95%CI .796-.974) |
| 4. Functional Dexterity Test (sec) | .889 (95%CI .747-.967) | .849 (95%CI .669-.954) |
| 5. Nine-hole peg test (sec) | .924 (95%CI .821-.978) | .875 (95%CI .720-.962) |
| 6. 10-meter walk/run (sec) | .980 (95%CI .951-.994) | .955 (95%CI .891-.987) |
| 7. Stair climb (sec) | .980 (95%CI .949-.994) | .935 (95%CI .844-.981) |
| 8. 30-second chair stand test (#) | .969 (95%CI .922-.991) | .811 (95%CI .603-.941) |
| 9. Stance with feet apart on line with eyes open (10 sec) | .825 (95%CI .626-.946) | .779 (95%CI .549-.930) |
| 10. Stance with feet apart on line with eyes closed (20 sec) | .954 (95%CI .887-.987) | .953 (95%CI .886-.987) |
| 11. Single leg stance with eyes closed (20 sec) | .891 (95%CI .751-.967) | .841 (95%CI .656-.951) |
| 12. Timed up and go (sec) | .987 (95%CI .968-.996) | .969 (95%CI .922-.991) |
| 13. 6-minute walk test (m) | .989 (95%CI .971-.997) | .965 (95%CI .912-.990) |
| **Total Score (0-52)** | $\tilde{x}$ 16 (SD 12, range 3-38) | .983 (95%CI .958-.995) |