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Outcome measures for CMT and other neuromuscular disorders – utility and challenges (overview)

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We have prepared a list of clinical and paraclinical measures which have been developed during the last 15 years for clinical trial readiness and conduction in CMT, and provide a list of recent publication in the field of outcome measures for CMT and other neuromuscular disorders. A lot of work has been devoted to validate and standardize such measures and to prepare the best ground for EMA approval of trial design and new treatments.

1. Contribution of outcome measures to accelerating EMA approval

Although no single outcome measure is currently judged to be sufficient as a standalone regulatory endpoint in Charcot–Marie–Tooth disease, the availability of a portfolio of well-validated clinical outcome assessments (COA),

disease-specific patient-reported outcome measures (PROMs), and sensitive paraclinical tools represents an essential step toward regulatory readiness. In particular, the use of composite COA (or selected responsive individual items), complemented by PROMs and objective paraclinical measures such as quantitative muscle MRI and wet biomarkers showing strong correlation with clinical severity, may facilitate earlier detection of treatment effects and strengthen the overall evidentiary framework for EMA evaluation in CMT clinical trials.

2. Initiatives for standardization and harmonization of clinical outcome measures

Major international initiatives are currently addressing the need for standardization of clinical outcome measures in CMT, with a specific focus on reducing inter-rater variability and ensuring data reliability across multicentre trials. A key example is the development of a web-based platform providing real-time scoring tools, structured training materials, and a Global Certification Standard for clinical evaluators, which supports consistent administration, scoring, and quality assurance of outcome measures in both natural history studies and interventional trials (Cornett et al. Designing and Implementing a Web-Based Platform for Accurate and Reliable Clinical Outcome Measures and Global Certification for Evaluating Charcot-Marie-Tooth disease. J Peripher Nerv Syst. 2025 Sep;30(3):e70062). In parallel, substantial efforts are ongoing toward cross-cultural adaptation and validation of clinical outcome assessments and PROMs in multiple languages, a prerequisite for global studies and regulatory submissions, and a critical component for ensuring comparability and interpretability of outcome data across different healthcare systems.

3. Further educational materials

January 22, 2026, in a webinar on “CMT episode 3: Biomarkers and Outcome Measures for Clinical Trial Readiness in Charcot-Marie-Tooth disease (CMT)” organized by the ERN Euro NMD and ECRA and moderated by Kleopas Kleopa (Cyprus Institute of Neurology and Genetics (CING)), Mary Reilly (University College London, Department of Neuromuscular Diseases, UK), has given a deep and topical insight in the methods, challenges and perspectives of clinical outcome measures.

4. Main Outcome Measures (OM) for CMT

CLINICAL OUTCOME MEASURES

CMTNSv2	9 items: sensory/motor symptoms, sensory/motor examination, electrophysiology
CMTNS-R	9 items: sensory/motor symptoms, sensory/motor examination, electrophysiology, corrected with Rasch scores
CMTESv2	7 items: sensory/motor symptoms, sensory/motor examination
CMTES-R	7 items: sensory/motor symptoms, sensory/motor examination
ONLS	5-item arm score, 7-item leg score
CMT-PedS	11 items: hand dexterity, hand and leg strength, lower extremity sensation, balance, and gait
CMT-FOM	12 items: strength, arm and leg function, balance, mobility
CMT-InfS	15 items: fine motor skills (grasping, buttoning, tearing paper, scribbling), gross motor skills (sitting, crawling, rolling, running)
CMT-HI	105 questions: function, disability, quality of life
pCMT-QOL	QoL Scale for children (age 8-18 yrs) -Symptoms, Function, Social Activities, Feeling, Cognition, Social Skills - Physical and Mental Composite Domain Scores - Total pCMT-QOL Score; includes a parent-proxy version.
	PARACLINICAL OUTCOME MEASURES
qMRI	3 point Dixon sequences to assess Fat Fraction in Lower Limb Muscles
	WET BIOMARKERS
NfL	Structural axonal protein
miR 133a	Muscle-associated microRNA
miR 206	Muscle-associated microRNA
miR 223-3p	Schwann cell–associated microRNA
TMPRSS5	Schwann cell protein
NCAM1	Neuronal cell adhesion protein
GDF15	Hormone in the TGFβ family

Abbreviations: CMT = Charcot-Marie-Tooth disease; CMTES = CMT examination score; CMTES-R = Rasch-modified CMTES; CMT-FOM = CMT functional outcome measure; CMT-HI = CMT health index; CMT-InfS = CMT Infant Scale; CMTNS = CMT neuropathy score; CMTNS-R = Rasch-modified CMTNS; CMTNSv2 = CMTNS version 2; CMTPedS = CMT pediatric scale; GDF15 = growth and differentiation factor 15; NCAM1 = neural cell adhesion molecule 1; NfL = neurofilament light; ONLS = overall neuropathy limitation scale; pCMT-QOL: Pediatric Charcot-Marie-Tooth Disease Quality of Life Outcome Measure; qMRI = quantitative Magnetic Resonance Imaging. TMPRSS5 = trans- membrane protease serine 5.

Links

CMTNSv2	https://pubmed.ncbi.nlm.nih.gov/22003934/
CMTNS-R	https://pubmed.ncbi.nlm.nih.gov/25400013/
CMTESv2	https://pubmed.ncbi.nlm.nih.gov/22003934/
CMTES-R	https://pubmed.ncbi.nlm.nih.gov/25400013/
CMT-PedS	https://pubmed.ncbi.nlm.nih.gov/22522479/
CMT-InfS	https://pubmed.ncbi.nlm.nih.gov/30476010/
CMT-FOM	https://pubmed.ncbi.nlm.nih.gov/30232254/
CMT-HI	https://pubmed.ncbi.nlm.nih.gov/30014533/
ONLS	https://pubmed.ncbi.nlm.nih.gov/16574730/
pCMT-QOL	https://pubmed.ncbi.nlm.nih.gov/33222249/; https://pubmed.ncbi.nlm.nih.gov/36748295/

Outcome Measures and biomarkers in CMT and other Neuromuscular Diseases (2024–2025) and recent reviews

Sorted by disease, then by year (descending). Columns: Year, Disease, Outcome type, Full citation, Link.

Year	Disease	Outcome measure / scale (Type)	Full citation	Link

Charcot-Marie-Tooth disease				
2025	Charcot–Marie–Tooth (CMT)	Platform for COA and certification	Cornett KMD, Estilow T, Bray P, Mandarakas MR, Donlevy GA, Baldwin JN, Eichinger K, Finkel RS, Burns J, McKay MJ. Designing and Implementing a Web-Based Platform for Accurate and Reliable Clinical Outcome Measures and Global Certification for Evaluating Charcot-Marie-Tooth disease. J Peripher Nerv Syst. 2025 Sep;30(3):e70062. doi: 10.1111/jns.70062. PMID: 40968111; PMCID: PMC12446152.	https://pubmed.ncbi.nlm.nih.gov/40968111/
2025	Charcot–Marie–Tooth (CMT) and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	Wet biomarker	Bellanti R, Keh RYS, Keddie S, Chou MKL, Misheva M, Smyth D, Baskozos G, Moodley K, Hart MS, Davies A, Reilly MM, Rinaldi S, Lunn MP. Plasma periaxin is a biomarker of peripheral nerve demyelination. Brain. 2025 Jun 23:awaf234. doi: 10.1093/brain/awaf234. Epub ahead of print. PMID: 40581376.	https://pubmed.ncbi.nlm.nih.gov/40581376/
2025	Charcot–Marie–Tooth (CMT)	Quantitative Muscle MRI	Evans MRB, Salhab HA, Sinclair CDJ, Shah S, Hanna MG, Yousry TA, Thornton JS, Morrow JM, Reilly MM. Twelve-month change in quantitative MRI calf muscle fat fraction in CMT1A predicts clinical change over 4 years. Ann Clin Transl Neurol. 2025	https://pubmed.ncbi.nlm.nih.gov/39957630/

			Apr;12(4):756-767. doi: 10.1002/acn3.52314. Epub 2025 Feb 17. PMID: 39957630; PMCID: PMC12040511.	
2025	Charcot–Marie–Tooth (CMT)	Nerve MRI	Zhu Y, Sun X, Fan D, Liu X. Nerve Diameter and DTI Parameters Maybe Potential Markers for Clinical Trial in Patients With Charcot-Marie-Tooth Disease Type 1A. Eur J Neurol. 2025 Jun;32(6):e70220. doi: 10.1111/ene.70220. PMID: 40511618; PMCID: PMC12163648.	https://pubmed.ncbi.nlm.nih.gov/40511618/
2025	Charcot–Marie–Tooth (CMT)	Wet biomarkers	Pretkalnina D, Kenina E, Gailite L, Rots D, Blennow K, Zetterberg H, Kenina V. Evaluating plasma biomarkers NfL, GFAP, GDF15, and FGF21 as indicators of disease severity in Charcot-Marie Tooth patients. Front Neurol. 2025 Jan 15;15:1490024. doi: 10.3389/fneur.2024.1490024. PMID: 39882365; PMCID: PMC11774688.	https://pubmed.ncbi.nlm.nih.gov/39882365/
2024	Charcot–Marie–Tooth (CMT)	CMT-FOM (Functional Outcome Measure) (PerfO)	Mandarakas MR, Eichinger KJ, Bray P, Cornett KMD, Shy ME, Reilly MM, Ramdharry GM, Scherer SS, Pareyson D, Estilow T, McKay MJ; for ACT-CMT Study Group; Herrmann DN, Burns J. Multicenter Validation of the Charcot-Marie-Tooth Functional Outcome Measure. Neurology.	https://pubmed.ncbi.nlm.nih.gov/38237108/

			2024 Feb 13;102(3):e207963. doi: 10.1212/WNL.0000000000207963. Epub 2024 Jan 18. PMID: 38237108; PMCID: PMC11097760.	
2024	Charcot–Marie–Tooth (CMT)	CMT-HI (MCID / trial-readiness) (PRO)	Rehbein T, Purks J, Dilek N, Behrens-Spraggins S, Sowden JE, Eichinger KJ; ACT-CMT Study Group; Burns J, Pareyson D, Scherer SS, Reilly MM, Shy ME, McDermott MP, Heatwole CR, Herrmann DN. Patient-reported disease burden in the Accelerate Clinical Trials in Charcot-Marie-Tooth Disease Study. J Peripher Nerv Syst. 2024 Dec;29(4):487-493. doi: 10.1111/jns.12662. Epub 2024 Oct 10. PMID: 39390667; PMCID: PMC11631656.	https://pubmed.ncbi.nlm.nih.gov/39390667/
RELEVANT OUTOCOME MEASURES PUBLISHED IN PREVIOUS YEARS				
2018	Charcot–Marie–Tooth (CMT)	CMTInfS (CMT Infant Scale) (PerfO)	Mandarakas MR, Menezes MP, Rose KJ, Shy R, Eichinger K, Foscan M, Estilow T, Kennedy R, Herbert K, Bray P, Refshauge K, Ryan MM, Yiu EM, Farrar M, Sampaio H, Moroni I, Pagliano E, Pareyson D, Yum SW, Herrmann DN, Acsadi G, Shy ME, Burns J, Sanmaneechai O. Development and validation of the Charcot-Marie-	https://pubmed.ncbi.nlm.nih.gov/30476010/

			Tooth Disease Infant Scale. Brain. 2018 Dec 1;141(12):3319-3330. doi: 10.1093/brain/awy280.	
2018	Charcot–Marie–Tooth (CMT)	CMT-HI (Charcot–Marie–Tooth Health Index) (PRO)	Johnson NE, Heatwole CR, Ferguson M, et al. The Charcot–Marie–Tooth Health Index (CMT-HI): evaluation of a disease-specific patient-reported outcome measure. Ann Neurol. 2018;84(2):225–233. doi:10.1002/ana.25282	https://pubmed.ncbi.nlm.nih.gov/30014533/
2014	Charcot–Marie–Tooth (CMT)	CMTNSv2 (CMT Neuropathy Score v2) (ClinRO)	Sadjadi R, Reilly MM, Shy ME, Pareyson D, Laura M, Murphy S, Feely SM, Grider T, Bacon C, Piscosquito G, Calabrese D, Burns TM. Psychometrics evaluation of Charcot-Marie-Tooth Neuropathy Score (CMTNSv2) second version, using Rasch analysis. J Peripher Nerv Syst. 2014 Sep;19(3):192-6. doi: 10.1111/jns.12084. PMID: 25400013; PMCID: PMC4303498.	https://pubmed.ncbi.nlm.nih.gov/25400013/
2012	Charcot–Marie–Tooth (CMT)	CMTPedS (CMT Pediatric Scale) (PerfO)	Burns J, Ouvrier R, Estilow T, Shy R, Laurá M, Pallant JF, Lek M, Muntoni F, Reilly MM, Pareyson D, Acsadi G, Shy ME, Finkel RS. Validation of the Charcot-Marie-Tooth disease pediatric scale as an outcome measure of disability. Ann Neurol. 2012 May;71(5):642-52. doi:	https://pubmed.ncbi.nlm.nih.gov/22522479/

			10.1002/ana.23572. PMID: 22522479; PMCID: PMC3335189.	
REVIEWS / EDUCATION MATERIAL ON CMT COA				
2025	Charcot–Marie–Tooth (CMT)	Pain management	Steve S Scherer - Webinar	https://www.youtube.com/watch?v=KELsjGPvMYQ
2025	Charcot–Marie–Tooth (CMT)	Review	De Grado A, Serio M, Saveri P, Pisciotta C, Pareyson D. Charcot-Marie-Tooth disease: a review of clinical developments and its management - What's new in 2025? Expert Rev Neurother. 2025 Apr;25(4):427-442. doi: 10.1080/14737175.2025.2470980. Epub 2025 Mar 7. PMID: 40014417.	https://pubmed.ncbi.nlm.nih.gov/40014417/
2024	Charcot–Marie–Tooth (CMT)	Review	McCray BA, Fridman V. Clinical Outcome Assessments and Biomarkers in Charcot-Marie-Tooth Disease. Neurology. 2024 Dec 24;103(12):e210120. doi: 10.1212/WNL.0000000000210120. Epub 2024 Nov 25. PMID: 39586049; PMCID: PMC11590233.	https://pubmed.ncbi.nlm.nih.gov/39586049/

Other NEUROMUSCULAR DISORDERS (2024-2025)

2025	Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	Review	Rajabally YA, Boggia GM, Riley D, Riley S, Peatman J, Noel W, Gary C, Nobile-Orazio E. Outcome measures in CIDP: A scoping and mapping review. J Neurol Sci. 2025 Oct 15;477:123654. doi: 10.1016/j.jns.2025.123654. Epub 2025 Aug 12. PMID: 40839897	https://pubmed.ncbi.nlm.nih.gov/40839897/
2025	Facioscapulohumeral Dystrophy (FSHD)	FSHD-RODS (PRO)	Teeselink S, Vincenten SCC, Voermans NC, van Alfen N, van Engelen BGM, Mul K. The Facioscapulohumeral Muscular Dystrophy Rasch-Built Overall Disability Scale (FSHD-RODS): Longitudinal Assessment of a Disease-Specific Patient Reported Outcome. Eur J Neurol. 2025 Aug;32(8):e70238. doi: 10.1111/ene.70238. PMID: 40781929; PMCID: PMC12334892.	https://pubmed.ncbi.nlm.nih.gov/40781929/

2024	Limb-Girdle Muscular Dystrophies (LGMD)	LGMD-HI (Health Index) (PRO)	Stouffer JA, Bates K, Thacker LR, Heatwole C, Johnson NE. The Limb Girdle Muscular Dystrophy Health Index (LGMD-HI). Neuromuscul Disord. 2024 Jun;39:48-53. doi: 10.1016/j.nmd.2024.04.008. Epub 2024 Apr 29. PMID: 38795602; PMCID: PMC11176010.	https://pubmed.ncbi.nlm.nih.gov/38795602/
2024	Limb-Girdle Muscular Dystrophies (LGMD)	Quantitative muscle MRI (qMRI)	Forsting J, Wächter M, Froeling M, Rohm M, Güttsches AK, De Lorenzo A, Südkamp N, Kocabas A, Vorgerd M, Enax-Krumova E, Rehmann R, Schlaffke L. Quantitative muscle magnetic resonance imaging in limb-girdle muscular dystrophy type R1 (LGMDR1): A prospective longitudinal cohort study. NMR Biomed. 2024 Oct;37(10):e5172. doi: 10.1002/nbm.5172. Epub 2024 May 25. PMID: 38794994.	https://pubmed.ncbi.nlm.nih.gov/38794994/
2025	Myasthenia Gravis (NMJ)	PASS	Spagni G, Verza MU, Cornacchini S, Beretta F, Sun B, Lotti A, Falso S, Barilaro A, Massacesi L, Evoli A, Damato V. Validation of the "Patient-Acceptable Symptom State" Question as Outcome Measure in AChR Myasthenia Gravis: A Multicentre, Prospective Study. Eur J Neurol. 2025 Jun;32(6):e70262. doi:	https://pubmed.ncbi.nlm.nih.gov/40556475/

			10.1111/ene.70262. PMID: 40556475; PMCID: PMC12188101.	
2024	Myasthenia Gravis (NMJ)	MG-ADL (PRO)	Janssen MF, Dewilde S, Wolfe GI, Muppidi S, Phillips G. Psychometric properties of MG-ADL items and MG-ADL score: An assessment of distributional characteristics, validity and factor structure in two large datasets. J Neurol Sci. 2024 Aug 15;463:123135. doi: 10.1016/j.jns.2024.123135. Epub 2024 Jul 22. PMID: 39068745.	https://pubmed.ncbi.nlm.nih.gov/39068745/
2024	Spinal Muscular Atrophy (SMA)	HFMSE / RULM responsiveness (PerfO)	Hagenacker T, Maggi L, Coratti G, Youn B, Raynaud S, Paradis AD, Mercuri E. Effectiveness of Nusinersen in Adolescents and Adults with Spinal Muscular Atrophy: Systematic Review and Meta-analysis. Neurol Ther. 2024 Oct;13(5):1483-1504. doi: 10.1007/s40120-024-00653-2. Epub 2024 Sep 2. PMID: 39222296; PMCID: PMC11393259.	https://pubmed.ncbi.nlm.nih.gov/39222296/