Congenital Muscular Dystrophy (CMD)
Common Data Element (CDE) Overview

Overview

The Congenital Muscular Dystrophies (CMDs) are a group of rare neuromuscular diseases with onset during the first two years of life. The diseases are characterized by hypotonia, contractures and progressive scoliosis with possible respiratory compromise. Distinct genetic and phenotypic subtypes have been characterized with a heterogeneous phenotypic spectrum.

Genetic discovery in the last decade has driven understanding of underlying pathophysiologic mechanisms highlighting potential therapeutic targets.

The CMD CDEs were developed at the request of members of the CMD clinical research community who were interested in using them for a planned natural history study and clinical trial. The NINDS plans to share the CMD CDEs and any feedback received about them with a larger Neuromuscular Disease (NMD) CDE Working Group that is currently being formed. The NMD CDE Working Group will review and evaluate the CMD CDEs and ultimately harmonize them with the NMD CDEs. The NMD CDEs should be available for public use on this Web site in the early 2012. In the meantime, the Institute welcomes your feedback about the CMD CDEs as the input will only serve to strengthen the NMD CDE effort.

Data standards include CDEs as well as case report form (CRF) Modules and Guidelines. The CRF Modules logically organize the CDEs for data collection, while the Guidelines provide further information about the CDEs. The CDEs, CRF Modules, and Guidelines presented are organized into domains which are intuitive and common in clinical research studies.

History and Acknowledgement

The CMD CDE Working Group would like to acknowledge the Pediatric Neuromuscular Clinical Research Network (PNCR) for sharing their data collection materials, specifically the CRFs developed through the network for Spinal Muscular Atrophy.

The CMD CDE Project grew from a series of meetings that began in late 2008. The NINDS CDE Team joined the project in early 2010.

The CMD CDE Working Group is currently comprised of two subgroups. The Working Group members actively develop the CDEs for their specific subgroups and also have an opportunity to review and comment on the recommendations of the other subgroups. The CMD CDE Working Group is supported by the NINDS CDE Team. The complete CMD CDE Working Group roster and the rosters by Subgroup are shown below

CMD International Registry Working Group, November 2008

On November 18-19th, a core working group of US CMD experts (representing diagnostics, pathology, genetics and neurology) together with a TREAT-NMD representative met with the Indiana University biogenetics registry experts and Cure CMD staff. The workshop targeted creating a CMD registry and defining how the registry would function within the current infrastructure both in the US and abroad. The CMD registry consists of a set of questions to be answered online or on paper by an affected person with CMD or their family member/representative.

Participants:

- Richard Cloud - Cure CMD, **Chair**
- Anne Rutkowski, MD - Cure CMD, **Vice Chair**
- Carsten Bönnemann, MD - Children's Hospital of Philadelphia
- Anne Connolly, MD - Washington University, St. Louis
- Tatiana Foroud, PhD - Indiana University
- Susan Iannaccone, MD - University of Texas Southwestern Medical Center
- Jackie Jackson, Research Coordinator - Indiana University
- Kathy Mathews, MD - University of Iowa
- Steven Moore, MD, PhD - University of Iowa
- Anna Sarkozy, MD - TREAT-NMD, Center for Life, Newcastle, England
- Susan Sparks, MD, PhD - Carolinas Medical Center
- Tom Winder, PhD - Prevention Genetics

Cure CMD/TREAT-NMD CMD International Registry Working Group, March 2009

TREAT-NMD hosted a conference with CMD expert neurologists and Cure CMD, an international CMD advocacy group based in the US. The meeting stressed the need for international consensus in building CMD infrastructure to support translational research and the goal of identifying drugs to slow disease progression.

Meeting participants focused on several key areas:

1. Application of TREAT-NMD tools and resources to CMD gaps of knowledge
2. A definition of the CMDs
3. The CMD International Patient Registry (CMDIR)
4. Placement of the CMDIR within existing infrastructure of current and planned locus specific databases (LSDB)
5. Harmonizing differences in national medical practice by pursuing consensus in launching the CMDIR with inclusion of both self report (patient directed) and physician report entries.

Participants:

- Richard Cloud - Cure CMD, **Chair**
- Anne Rutkowski, MD - Cure CMD, **Vice Chair**
- Christophe Béroud, PhD - Assistant Professor, Laboratoire de Génétique Moléculaire and INSERM U827, Montpellier, France
- Enrico Bertini, MD - Gesu Bambino Hospital

- Carsten Bönnemann, MD - Children's Hospital of Philadelphia
- Kate Bushby, MD - TREAT-NMD, Center for Life, Newcastle, England
- James Collins, MD, PhD - Cincinnati Children's Hospital Medical Center
- Emma Heslop, Assistant Project Manager - TREAT-NMD
- Stephen Lynn - TREAT-NMD Project Manager, Newcastle, England
- Susana Quijano-Roy, MD, PhD - de Reference Maladies Neuromusculaires (GNMH), Service de Pediatrie,
- Hôpital Raymond Poincaré, Garches, France
- Thomas Sejersen, MD - Karolinska Institut, Sweden
- Volker Straub, MD - TREAT-NMD, Newcastle Center for Life
- Rachel Thompson, UK SMA Patient Registry and SMA Clinical Research Communications - TREAT-NMD
- Tracey Willis, MD - TREAT-NMD, FKRP registry

ENMC CMD Outcome Measure Working Group, March 2010

The 173rd European Neuro Muscular Centre (ENMC) Workshop organized by Dr. Francesco Muntoni, Dr. Eugenio Mercuri, Dr. Carsten Bönnemann and Cure CMD complemented current efforts to support CMD clinical trial readiness, including launch of an international CMD registry and development of CMD Care Guidelines. An opening introduction by Dr. Jeremy Hobart and Stefan Cano reviewed both the purpose of outcome measures and the importance of getting the outcome measure scale right, based upon an iterative process involving statistical analysis of existing data and an understanding of clinical disease progression.

The workshop focused upon meeting two concrete objectives: 1) a review of available CMD data with regard to natural history and motor function to identify a set of clinical functional classes and the need of appropriate scales that could be used as outcome measures; 2) a review of available CMD CRFs to launch an international CMD longitudinal study. Each clinician presented CMD subtype specific patient cohort data with an emphasis on assessing functional vital capacity decline, start of assisted ventilation and weight/diet supplementation versus age. The physiotherapists presented limited data sets regarding CMD cohorts across a variety of motor scales. A new upper limb scale validated in spinal muscular atrophy, an upper limb strength test developed for nonambulatory boys with Duchenne and a novel motriplate were presented. Complex integrated motor scales, including the EK2 scale and actimetry by accelerometry were described, along with existing neuromuscular-oriented quality of life and caregiver burden scales that are not currently validated in the CMD population.

Participants:

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- Eunice Kim - Cure CMD, **Vice Chair**
- Enrico Bertini, MD - Unit of Molecular Medicine, Dept. of Laboratory Medicine, Ospedale Bambino, Rome, Italy
- Carsten Bönnemann, MD - Children's Hospital of Philadelphia
- Stefan Cano, Chartered Psychologist - Senior Lecturer in Psychometrics, Peninsula College of Medicine and Dentistry

- Michelle Chatwin, Consultant Physiotherapist - Respiratory Support, Royal Brompton Hospital
- Nicholas Coppard, PhD - Senior Vice President Development, Santhera Pharmaceuticals Holding Ltd.
- Michelle Eagle, PhD, MSc, MCSP - Consultant Physiotherapist, University of Newcastle
- Ana Ferreiro, MD, PhD - UMR 787 Groupe Myologie Faculté de Médecine, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
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- Jeremy Hobart, MD - Senior Lecturer and Honorary Consultant Neurologist, Department of Clinical Neuroscience,
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- Linda Hynan, PhD - Professor of Biostatistics, Departments of Clinical Sciences and Psychiatry at UT Southwestern Medical Center
- Marion Main, MA, MCSP - Consultant Physiotherapist in Paediatric Neuromuscular Disorders, Dubowitz Neuromuscular Center
- Kathy Mathews, MD - University of Iowa
- Anna Mayhew - Consultant Research Physiotherapist, England
- Elena Mazzone, Physiotherapist - Pediatric Neurology Unit, Catholic University, Rome
- Thomas Meier, PhD - Chief Scientific Officer, Santhera Pharmaceuticals Holding Ltd.
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- Christine Payan, MD - Institut de Myologie, Hôpital Pitié-Salpêtrière
- Susana Quijano-Roy, MD, PhD - Centre de Reference Maladies Neuromusculaires (GNMH), Service de Pediatrie,
- Hôpital Raymond Poincaré, Garches, France
- Laurent Servais, PhD - - Institut of Myology, Paris, France
- Volker Straub, MD - TREAT-NMD, Center for Life, Newcastle, England

CMD Comparative Outcome Measure Study, June 2010

This study led by Dr. Kenneth Fischbeck (NIH), Dr. Carsten Bönnemann (CHOP) and Cure CMD will focus upon two functional classes of CMD: ambulatory and nonambulatory children (5-18 years of age). A total of 22 children with either Merosin Deficient or Ullrich CMD were recruited through the CMD International Registry (CMDIR).

The study has four aims focused on determining inter-rater reliability and validity of a particular set of outcome measure scales in these two most common CMD subtypes using seven pediatric neurologist/physical therapist rating teams. Outcome measure scales chosen will reflect decisions made at ENMC workshop and will include: a pediatric quality of life scale, a motor function scale, a standard clinical assessment tool, pulmonary function testing and a caregiver burden

scale (completed by parents). To determine ability to ascertain significant change with disease progression, study participants will be invited to participate in a one year follow up exam.

- Aim#1: To determine clinician and therapist inter-rater reliability when evaluating disease severity using a clinical assessment tool and motor scale.

- Aim #2: To determine the "spread" of the disease across the motor scales (what is the dynamic range of the each outcome scale used)

- Aim #3: To determine how accurately the self assessment using a pediatric quality of life scale correlates with both clinician and motor scale assessment.

- Aim #4: To determine how closely pulmonary function tests: FVC sitting and supine, correlates with the clinician and motor scale assessment and disease severity.

Participants:

- Anne Rutkowski, MD - Cure CMD, **Chair**
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- Courtney Broadley, PT, DPT - Kennedy Krieger Institute
- James Collins, MD, PhD - Cincinnati Children's Hospital Medical Center
- Robert Fee, MA - Project Coordination, Columbia University DMD/BMD Project
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- Linda Hynan, PhD - Professor of Biostatistics, Departments of Clinical Sciences and Psychiatry at UT Southwestern Medical Center
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- Ami Mankodi, MD - NINDS

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- Katy Meilleur, RN, NP - NINDS
- Kathryn North, M.D., F.R.A.C.P. - Children's Hospital at Westmead Clinical School Faculty of Medicine, University of Sydney
- Shamaine Price - Coordinator, NINDS
- Kristy Rose - Physiotherapist, Institute for Neuroscience and Muscle Research, Children's Hospital at Westmead
- Alice Schindler, MS, CGC - Genetic Counselor, Neurogenetics Branch, National Institutes of Health/NINDS
- Kathryn Wagner, MD, PhD - Director of the Center for Genetic Muscle Disorders, Kennedy Krieger Institute

CMD Common Data Element Working Group Kick-off Meeting, September 2010

The first meeting of the CMD CDE Working Group took place at NINDS in Bethesda, MD on September 29, 2010. The purpose of the meeting was to identify and define the CMD Core CDEs that are essential and need to be collected for any CMD clinical study (registry, longitudinal study, genotype/phenotype study, clinical trial) to make them comparable. The Working Group also began to identify a list of measurements to include in the CMD CDEs and to discuss developing standard protocols and procedures for their collection. Following the in-person meeting the Working Group continues its CDE development work over conference calls.

Participants:

- Anne Rutkowski, MD - Cure CMD, **Chair**
- Eunice Kim - Cure CMD, **Vice Chair**
- Carsten Bönnemann, MD - Senior Investigator, NINDS
- James Collins, MD, PhD - Cincinnati Children's Hospital Medical Center
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- Reghan Foley, MD - Neuromuscular Research Fellow, Dubowitz Neuromuscular Center, London
- Stacie Grinnon, MS - CDE Co-Project Manager, KAI Research, Inc. (An Altarum Company), Rockville, Maryland, USA
- Susan Iannaccone, MD - Southwestern Medical Center, UT Southwestern Medical Center at Dallas
- Cynthia Joyce - Executive Director, Spinal Muscular Atrophy Foundation
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- Rachel Richesson, MS, PhD, MPH - University of South Florida
- Ulrike Schara, MD - Universitätsklinikum Essen, Zentrum für Kinderheikunde, Essen, Germany
- Karen Lohmann Siegel, PT, MA - Chief Therapist Officer, Agency for Healthcare Research and Quality
- Christina You, MSPH - CMD CDE Lead, KAI Research, Inc. (An Altarum Company), Rockville, Maryland, USA

CMD Motor Data Working Group, October 2010

The working group will focus on desired outcome measures in the CMD population and a review of the following data:

A. retrospective CMD patient chart review of motor scales used at Dubowitz Neuromuscular Center over the last two decades, subjected to Rasch analysis
B. retrospective CMD patient chart review of MFM in various centers, subjected to Rasch analysis
C. data from CMD Comparative Outcome Measure study, June 2010

Participants:

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- Reghan Foley, MD - Neuromuscular Research Fellow, Dubowitz Neuromuscular Center, London
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References

Publications

- Allamand V, Merlini L, Bushby K on behalf of the Consortium for Collagen VI-related myopathies.166th ENMC International Workshop on Collagen type VI related Myopathies, 22-24 May 2009, Naarden, The Netherland. Neuromuscular Disorders 20(2010):346-354
- Bönnemann C G (2009) Congenital Muscular Dystrophy. In: Squire LR (ed.) Encyclopedia of Neuroscience, volume 3, pp. 67-74. Oxford: Academic Press.
- Mercuri E, Messina S, Bruno C, Mora M, Pegoraro E, Comi GP, et al. Congenital muscular dystrophies with defective glycosylation of dystroglycan: a population study. Neurology 2009; 26:1802-1809.
- Nadeau A, Kinali M, Main M, Jimenez-Mallebrera C, Aloysius A, Clement E, North B, Manzur AY, Robb SA, Mercuri E, Muntoni F. Natural history of Ullrich congenital muscular dystrophy. Neurology 209 Jul 7;73 (1): 25-31.

Additional References

- Congenital Muscular Dystrophy International Registry (CMDIR)
- Cure CMD

Disclaimer

CDEs were developed as part of a natural history study.