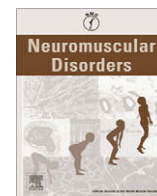




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## Workshop report

## Patient Registries and Trial Readiness in Myotonic Dystrophy – TREAT-NMD/Marigold International Workshop Report

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## 1. Introduction

A workshop entitled Patient Registries and Trial Readiness in Myotonic Dystrophy, jointly sponsored by TREAT-NMD ([www.treat-nmd.eu](http://www.treat-nmd.eu)) and the Marigold Foundation ([www.marigoldfoundation.org](http://www.marigoldfoundation.org)), was held from 12 to 14 June 2009 in Naarden, The Netherlands. The twenty-six participants represented eight countries and included scientists, clinicians, patient representatives and industry. The workshop built on the foundations established in two previous ENMC workshops on myotonic dystrophy and the myotonic dystrophy clinical working group set up by the Marigold Foundation, and took advantage of the tools developed within the TREAT-NMD network for patient registries and outcome measures.

Opening remarks from the workshop organizers, Hanns Lochmüller (TREAT-NMD) and Karla Blonsky (Marigold Foundation), showed that in recent years the need to collect patient data in a harmonized manner across multiple countries has become increasingly evident in the rare disease field, where locating patients suitable for a particular trial or therapy poses a particular challenge. Bziel van Engelen summarized previous ENMC (European Neuromuscular Centre) workshops on DM1 [1] which identified the need for international collaborations on outcome measures, natural history, patient registries and clinical trials. The present workshop also drew on the conclusions of the 157th ENMC International Workshop: Patient registries for rare, inherited muscular disorders, 25–27 January 2008 [2].

## 2. Patient registries and clinical trials

## 2.1. Industry and patient expectations

Charles Thornton began by providing an overview of completed and ongoing clinical trials in DM1 (see Table 1) and lessons learned. In the past, DM lagged behind other neuromuscular diseases, but recent changes in the field mean there is a real possibility that it will be one of the first conditions to reach a

meaningful trial, with increased industry interest and new preclinical research in novel gene approaches such as the recent study on RNA dominance reversal by antisense oligonucleotides in a mouse model of DM1 [3] opening up new therapeutic avenues. There have not been a great number of trials so far, but this is not a real reflection of trials to come.

Trials have not generally included the congenital or paediatric population, but most did not specifically exclude childhood onset forms of DM. Most have been in ambulatory patients, with modest muscle weakness, but few other restrictions regarding inclusion/exclusion criteria have been applied – no selection by repeat size or other genetic criteria. Overall, non-specific agents that promote muscle hypertrophy have not shown clear benefit, and the need for disease-specific, molecularly targeted therapies is thus evident. The anti-myotonia treatments that are available only provide partial relief, and it is doubtful whether these are protective against muscle injury or wasting. No trials to date have come from animal model preclinical results. Important from the point of view of future trials is the lesson that trials are feasible in the myotonic population: enrolment is not generally a hindrance, compliance is adequate, and patients are in general highly willing to take part even in complex trials and to undergo biopsies and other procedures.

Taking industry needs and expectations into account is key to any international initiative aiming to speed up the movement of therapies into the clinic, and the presence of three industry participants (Genzyme, Isis and Prosensa) helped focus the discussion on the prerequisites for this process. Bob Mattaliano presented Genzyme's interests in DM1 and their experience with registries for lysosomal storage diseases (Pompe, Gaucher, etc.). Genzyme's experience with registries dating back to 1991 (their Gaucher registry now has >5400 patients in 61 countries) reveals that registries can be highly valuable tools providing aggregated longitudinal data that increases understanding of the disease (sometimes even confounding long-held beliefs about prevalence and natural history), improves quality of care, and informs downstream clinical trials. Trials in rare diseases face many challenges owing to limited sample size, challenging patient enrolment, unclear clinical endpoints and the lack of prior clinical study pathways to follow. Longitudinal databases may help with endpoint definition and choice of statistical model and have the potential to be used as a

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**Table 1**  
Therapeutic trials carried out in DM1 (selection).

Trial	Trial type and number of patients (n)	Reference	Results overview
IM testosterone enanthate, 3 mg/kg/wk, 12 months	n = 40 (men), Randomized Controlled Trial (RCT)	Griggs RC et al. <i>Neurology</i> 1989	No improvement in strength (Manual Muscle testing, myometry scores) or function scores
Pituitary-derived human growth hormone	n = 4, open-label, uncontrolled	Chyatte SB et al. <i>South Med J</i> 1974	Positive nitrogen and potassium balance, no improvement in strength
Recombinant human growth hormone	n = 8, open-label, uncontrolled	Thornton CA et al. <i>Neurology</i> 1993; 43:A280	Improvement in muscle mass, no improvement in strength
Subcutaneous rIGF-1, 5 mg every 12 h, for 4 months	n = 18, RCT	Vlachopapadopoulou E et al. <i>J Clin Endocrinol Metab</i> 1995	Increased insulin sensitivity, protein synthesis, lean body mass. Post hoc analysis suggested increased strength and function in a subgroup
Exercise training for 24 weeks	n = 36, RCT	Lindeman E et al. <i>Arch Phys Med Rehabil</i> 1995	None of the measurement techniques showed any training effect or deterioration
Intravenous DHEAS, 200 mg/d for 8 weeks	n = 11, open-label, uncontrolled	Sugino M et al. <i>Neurology</i> 1998	Improved strength, activities of daily living, myotonia, insulin sensitivity, cardiac conduction
Oral DHEA 100 mg/d vs. 400 mg/d vs placebo	n = 75, RCT	Pénisson-Besnier I et al. <i>Neurology</i> 2008	No improvement in strength, function scores, QOL
Amitriptyline, 50 mg/d + weight training) for 4–6 months	n = 12, open-label, uncontrolled	Milner-Brown HS et al. <i>Arch Phys Med Rehabil</i> 1990	No improvement in strength
Imipramine, 150 mg/d for 6 weeks	n = 12, double-blind, crossover	Gascon GG et al. <i>Am J Phys Med Rehabil</i> 1989	Grip strength improved and grip myotonia improved slightly. Depression scores fell
Selenium and vitamin E for 2 years	n = 27, RCT, dose escalating	Orndahl G et al. <i>J Intern Med</i> 1994	No improvement in strength or function

control group for a futility trial design. With regard to trial design, a large treatment effect is required to mitigate the risk of type II error in a trial in a small cohort; there is a need for discussion with regulatory authorities on clinical development plans and endpoints, particularly prospective biomarker use, as clinical endpoints are generally preferred and clinical data will always overrule results with biochemical or histological markers. Phase IV (post-marketing) clinical verification studies may often be required for rare disease therapy approval, and these are a substantial commitment that can diminish industry interest in a particular therapeutic area.

Robert MacLeod gave an overview of Isis Pharmaceuticals' DM1 development program. Isis focus on antisense technology as a therapeutic platform for various conditions. In DM1 the targets are the *DMPK* transcript and the repeat, with the aim of splicing out the repeat sequence. Challenges remain in terms of muscle targeting, improving delivery to tissue and establishing the safety and efficacy of new chemistries, and also crucially in the need for standardization of endpoints for trials.

Lisa Vittek from the Myotonic Dystrophy Foundation (MDF, [www.myotonic.com](http://www.myotonic.com)) presented the work that patient advocacy groups such as the MDF play in terms of patient empowerment and support and online community development as well as fundraising and funding research. Lisa's own experience with her daughter Kayla, who suffers from congenital myotonic dystrophy, provided a real example of the costs for society, with medical bills for the first 3 months amounting to 2 million US Dollars, and 24-h care at home requiring the input of multiple care providers. Lisa and the other patient advocacy representatives present (Valerie Cwik from the Muscular Dystrophy Association, MDA and Virginie Picard from the Association Française contre les Myopathies, AFM) stressed the importance of the collaboration of the whole DM community and two-way communication with patients: families want to be part of the solution,

and patient registries can provide an opportunity for feedback to help patients and families understand what is going on in DM research.

Discussion brought up several unresolved issues regarding trials in DM1. The natural course of progression of the disease is so variable that endpoint selection is a challenge. Questions remain as to whether muscle strength measurements are a valid outcome measure, and increase in muscle mass does not appear to be reflected in muscle strength improvement. No study so far has been powered to show a slowing of deterioration; all have been powered to show improvement. Studying the trajectory of the disease in each patient for a year before intervention has been performed in a recent study in inclusion body myositis [4] and this might be applied to DM1 to enable powering for slowing of deterioration. A suggestion was raised that a highly restricted patient cohort of more severely affected patients (such as adult patients with respiratory difficulties) might be one in which therapeutic effect could be more easily studied. Biomarkers are important to obtain an early understanding of effect, and are often critical to guiding internal decisions for industry. Without a suitable biomarker that gives an indication of therapeutic efficacy in a reasonable timeframe, trials for a small market disease like DM may simply not be feasible for many corporate sponsors. However, regulatory authorities are aware that an effect on a biomarker may not translate into clinical benefit and thus will always prefer clinical endpoints. There was consensus that the correlation between repeat length and progression has not been sufficiently studied and a retrospective analysis of data from preceding trials would be of value but may not be feasible owing to lack of genetic data. There was also agreement that more natural history data would help inform this debate, and a valuable suggestion was raised as to whether placebo group data from past trials could be pooled in a freely accessible database.

**Table 2**  
Existing patient data collections.

PI/country	Scope	Clinician/patient reported	Date established	Total DM1 patients	Total DM2 patients	Genetic diagnosis required
Campbell Canada	National	Both	2005	20	0	Y
Groh USA	National	Both	1997	406	0	Y
Meola Italy	National	Clinician	2007	250	150	N
Rogers Cardiff, UK	Regional	Clinician	1998	237	0	N
Schooser Germany	National	Both	2008	53	143	Y
Thornton USA	National	Patient	2000	676	107	N
Udd Finland	National	Clinician	2004	0	160	Y
v.Engelen Netherlands	National	Clinician	2004	272	23	Y
Eymard France	National	Clinician	1998	200	0	Y
Puymirat Quebec, Canada	Regional	Clinician	1998	280	0	Y

## 2.2. Existing registries and patient data collections

The second session provided an overview of the patient data collections already in existence (see Table 2). Cheryl Swaby and Don MacKenzie presented the development of a Canadian Neuromuscular Disease Registry (CNDP). This new initiative, supported by the Marigold Foundation, is being rolled out across Canada in the second half of 2009 as an online interface for professionals to input patient data during clinic appointments, beginning in 2–3 centres but later extending to 25 neuromuscular centres across the country. It will begin with myotonic dystrophy and Duchenne muscular dystrophy, and will include all mandatory and highly encouraged items from the TREAT-NMD global registries plus additional items representing common clinical practice in Canada. Additional neuromuscular diseases are expected to be added in subsequent years.

Guillaume Bassez presented the GENEMU registry on behalf of Jack Puymirat. This is a French Canadian longitudinal data and natural history registry with 3200 patient records, of which 280 are DM1 patients from 96 families. Its objectives are the identification of genes and of cohorts of patients for clinical trials, and the collection of biomaterials. The recruitment questionnaire is extensive, with 158 items, and some patients have been followed up for as long as 10 years. It is linked to a biomaterials collection with more than 5000 samples (DNA, blood, muscle, organs) covering a range of different conditions.

Dr. Bassez then described the French Registry for Myotonic Dystrophy, which has the overall aim of enabling the standardized characterization of the French DM1 population. It uses the same clinical grid as GENEMU but has slightly differing objectives including clinical management, natural history, genotype–phenotype correlations, comparison of DM1 and DM2, comparison of prognostic factors, identification of homogeneous patient subgroups and recruitment for trials. The registry has ethical approval and currently contains 200 patient records, which are created during clinical consultations on paper forms that are sent for central data input. No specific patient consent has been implemented, so sharing of data is not possible unless patients are re-consented. There is no biobank currently associated with the French registry, but there is an initiative to link AFM's tissue collection effort with the patient data. A comparison between the two patient populations in the French and French Canadian registries is ongoing.

Charles Thornton described the National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy ([www.urotc.rochester.edu/nihregistry/](http://www.urotc.rochester.edu/nihregistry/)).

This registry, which is funded by the US National Institutes of Health, NIH, has the primary goal of facilitating research in DM and FSHD by establishing a mechanism for contact between researchers and patients. Secondary goals include collection of self-reported data from patients, education of patients and care providers, and promoting a sense of community and involvement in the research process. Annual updates are performed via a self-report renewal form which has a relatively high response rate (70% at 5 years). The registry currently contains records on 850 patients with DM (676 with DM1, 107 with DM2). Only 50% of these have genetic confirmation of their diagnosis. The registry has been used for 15 studies [5], by a standard mechanism by which researchers can contact the registry for anonymized data or to have the registry pass on their information for patient recruitment (patient data is not disclosed directly to researchers).

Mark Rogers presented the Cardiff Myotonic Dystrophy Database. Set up in 1998, this database contains 237 patient records. Entries are based on a detailed clinical assessment questionnaire carried out during a patient consultation. All patients are consented for enrolment in the database and most with consent to take part in trials. There is also an annual update element.

Benedikt Schooser gave an overview of the German DM registry, which began in 2002 and covers eight diagnostic centres in Germany. A more comprehensive registry using data items from the Rochester registry was established in 2008 and this contains completed records of 53 DM1 patients and 143 DM2 patients (from 47 and 134 families, respectively) collected in the Munich centre. Specific aims of this registry include obtaining data on cardiovascular risk profiles (lipid profiles and statin therapy), complications under anaesthesia, cardiac manifestations, long-term outcomes and natural history (particularly in DM2), and disease manifestation in offspring.

William Groh described the Registry of Arrhythmias in DM1. This was launched in 1996 and contains records of 406 genetically confirmed DM1 patients who have been followed for an average of seven years. The goals of the registry are to determine the natural history and risk factors for cardiac issues in DM1 in the context of the underlying disease, to develop cardiac referral guidelines, and to study interventions for arrhythmias. The ultimate aim is to decrease the unacceptably high rate of sudden death in DM1 patients. The registry began as a clinical trial (23 sites) with a cohort from MDA clinics of adult patients with clinical diagnosis of DM, and methods comprised collecting natural history data by questionnaire, obtaining genetic confirmation of the diagnosis,

performing a 12-lead ECG and 24-h ambulatory ECG and echocardiography, and then following patients with observation but no recommendations or interventions. Follow-ups were on a yearly basis or after an event (death, sudden death, unexplained syncope, pacemaker or implantable cardioverter-defibrillator (ICD) implantation, arrhythmia). Eight publications have resulted from registry data, including a study showing that atrial arrhythmia and severe conduction abnormalities are risk factors for sudden death in DM1 [6].

### 2.3. Concept of an international registry

The existing registries are seen as valuable resources that have already moved the understanding of DM1 forward substantially, but it is clear that the data collected is not consistent from registry to registry and their differing goals make direct comparisons and use on an international level challenging. Hanns Lochmüller gave an overview of the TREAT-NMD patient registries initiative ([www.treat-nmd.eu/patientregistries](http://www.treat-nmd.eu/patientregistries)). The TREAT-NMD registries were set up primarily with future trials and therapies in mind and have a clear set of aims and objectives, including streamlined, internationally harmonized core datasets enabling trial planning, feasibility and patient recruitment (genetic report mandatory; quality control through curation; data updated annually); a clear ethos of patient involvement, patient feedback, patient consent, ethical governance and oversight; links with clinical trial and care sites; and the possibility of incorporating broader datasets/additional modules on a national level for natural history and longitudinal data collection.

Christophe Bérout summarized the lessons learned from the TREAT-NMD international registries for DMD and SMA, which have now been operational for around a year and are already being used by pharmaceutical companies for trial planning and recruitment. The success of the DMD and SMA registries has re-emphasized that expectations from stakeholders (patients on the one hand and industry on the other) regarding upcoming clinical trials have driven international collaboration to fill a significant unmet need. The endorsement from industry and use of the registries for trial planning has been a key driving force. A particular strength of the current system is its flexibility and the fact that while it insists on harmonization of a streamlined, trial-focused dataset, it allows this dataset to be collected within a wide range of local systems, thus it does not force participants to use a particular IT solution and is able to work with existing practices. Other important factors are the rigour of the curation process (reliability of data is key), the availability of guidelines and annual training for curators, and the integral involvement of patient organizations, who are essential to the running of many of the national systems. An important recognition is that major international collaboration of this sort (recent feasibility enquiries into the DMD registry have involved 20 countries) gives registry initiatives a much higher impact and more power to negotiate with third parties, as well as the opportunity to share experiences and avoid duplication of effort.

### 2.4. Mandatory dataset

Wide-ranging discussion covered the need to balance collection of as much valuable information as practicable with the need to maximize enrolment – a minimal dataset will avoid onerous time burden on participating clinicians and patients, facilitating uptake by a larger population, but its range of use will be more limited. It was agreed that the purpose of the international registry should be primarily identification of patient cohorts for trials, and that natural history and longitudinal data collection could be linked with the registry at a national level or could be the aim of a separate specific research project linked to the registry but should not be

a requirement for the international registry, as exhaustive data collection is not feasible in most cases. The solution reached was to create a highly focused set of “mandatory” items – these items are considered most likely to inform inclusion/exclusion criteria for trials and so only patient records including these data are eligible for inclusion in the international registry – and to supplement this with a secondary set of “highly encouraged” items – patient records that do not contain these additional items are still eligible for inclusion in the international registry, but those that do may help refine inclusion criteria for a particular trial and may also help answer additional questions in DM1 (see Table 3).

## 3. Outcome measures for DM

Outcome measures are tests or scales designed to measure a particular attribute that is expected to change as a result of a trial or intervention – essentially to reliably monitor whether a treatment is having an effect. Measures must be reliable (with both test-retest and inter-rater reliability), valid, responsive to change, and clinically meaningful. Benedikt Schoser gave an overview showing that although various functional assessments do exist, there is no real consensus about their use in specific conditions, including DM. Questions to be resolved for DM include which outcome measures are most appropriate for assessment of efficacy, which cohorts they should be used on, and at which stage of disease.

Joanne Auld presented the TREAT-NMD Registry of Outcome Measures ([www.researchchrom.com](http://www.researchchrom.com)), a freely accessible and regularly updated online resource that is intended to be a convenient first stop for important baseline information about existing outcome measures and clear directions to key points of contact and comprehensive sources of information. It contains detailed summary information about outcome measures, including a description, information about availability, contact details for providers (e.g. device suppliers, distributors of outcome measures), and references to related documents including manuals and training videos. Outcome measure (OM) records are created and maintained using an online form and input is welcomed from anyone with an appropriate understanding of a particular measure – whether the person or group responsible for developing the measure or investigators or medical practitioners with a sound working knowledge of it through use or research. Workshop participants were invited to contribute to the provision of additional OMs.

Charles Thornton provided an overview of outcome measures used in past DM trials. In DM, clinically meaningful events (death, loss of employment, pacemaker, ventilation, bracing, walker,

**Table 3**  
Core dataset for International DM1 Registry.

Mandatory items
Demographic details (name, date of birth, contact details)
Clinical and genetic diagnosis
Motor function: ambulation (clinical, wheelchair use)
Highly encouraged items
Myotonia (clinical, medication)
Cardiac (clinical, implant/device, ECG result, Echo result, medication)
Pulmonary (clinical, use of ventilator, FVC)
Swallowing/feeding (clinical, use of feeding device)
Fatigue, daytime sleepiness (clinical, medication)
Cataract surgery
Age at onset
Family history
Ethnic origin
Signed up to other registry
Genetic testing details (name of laboratory, date of test, method of test, repeat length)

wheelchair use etc.) are too rare to use in a trial of reasonable time-frame. Surrogate measures are therefore required. Strength measurements, muscle mass (size), myotonia, biochemical measures (e.g. insulin sensitivity) and functional measures (e.g. the six-minute walk test, 6MWT) may be acceptable to the regulatory authorities as valid surrogate measures; there is nonetheless a need to make sure that surrogate markers correlate closely with clinically meaningful events. Quantitative myometry using a fixed myometer has good test–retest reliability in DM1, but is relatively expensive both in terms of apparatus and testing time, and has other issues associated with tolerability, training and responsiveness. Grip strength may be a good measure in DM1. Manual Muscle Testing (MMT) takes more effort to ensure reliability, but is low cost, and reliability can be improved with evaluator training. For muscle mass assessment, the DEXA scan is a fairly cheap system with very good test–retest reliability. For myotonia, the standard measure is a timed test: grip relaxation time, either voluntary or electrically stimulated. Outcome measures based on muscle strength measurements do however have a number of drawbacks: it is unknown which set of muscles is most likely to respond to a drug, there is a substantial amount of variability day-to-day, there are numerous confounding factors (e.g. order of testing), and progression may be too slow to show improvement in a clinical trial of reasonable length.

**Table 4**  
Recent and ongoing natural history studies in DM1 (selection).

Location and PI	Cohort type and no. of patients (n)	Status	Measures used
London, Canada Craig Campbell (Canadian National Surveillance)	Paediatric/congenital DM1, n = 29	Ongoing	Incidence study with 5 year follow-up. Medical parameters (genetic characteristics, length of ventilation, neonatal complications), developmental profile, quality of life, long-term medical morbidity
Rochester, USA Charles Thornton/ Dick Moxley	Adult DM1, n = 80	Completed	Quality of life, functional status, muscle mass (DEXA), neuromuscular impairment (strength, quantitative, MMT), myotonia (EMG, action myotonia), function (6MWT, upper-limb function) and biopsy
Paris, France Gallais, Eymard	Adult DM1, n = 40	Ongoing	Neuropsychological battery: MMSE (mini mental state examination), frontal assessment battery, Stroop test, digit span, TMT (Trail Making Test) and D2
Paris, France Angeard, Eymard	Paediatric DM1, n = 19	Ongoing	Wechsler Intelligence Scale, Stroop, TMT A and B, Rey Complex Figure Test, French Memory Battery Evaluation (BEM84)
Finland Udd	Adult DM2, n = 170	Completed	Clinical and MRI
Milan, Italy Meola	Adult DM1 and DM2, n = 187	Completed	INQoL
Munich, Germany Schoser	Adult DM2, n = 143	Completed	Quality of life, functional status, neuromuscular impairment (strength, quantitative, MMT)

Discussion of muscle-related outcome measures focused on their responsiveness, reliability and clinical meaningfulness. Grip strength was agreed to be a useful measure, but it was commented that there is a need to ensure that it is correlated with progression/impairment – i.e. that it is clinically meaningful and impacts on quality of life. There is a need for an upper-limb equivalent of the six-minute walk test. An overview of recent natural history studies is provided in [Table 4](#).

William Groh presented on cardiac outcome measures in DM1. Most measures used for cardiac assessments of DM1 patients are the same as those used in everyday clinical situations in large patient populations, so there are few issues with validation and reliability. The resting 12-lead ECG (PR interval, QRS duration) is a useful measure in DM1. A rhythm other than sinus, PR interval >240 ms and QRS >120 ms are sensitive measures indicative of cardiac problems in DM1. The Holter ECG (ambulatory, performed over 24 h) does not have substantial additional prognostic value over the resting 12-lead ECG. Other monitoring options include insertable loop recorder (ILR), echocardiography, cardiac nuclear imaging, exercise testing, cardiac catheterization and electrophysiological studies. An important point to note with regard to DM1 trials is that regulatory authorities may require evidence that a therapy does not increase cardiac mortality. Since proof of this in a short-term trial situation would be prohibitive, such evidence would have to come from animal models or use of appropriate surrogate markers in the trial.

Bruno Eymard presented the results of two ongoing studies into the cognitive effects of DM1 (see [Table 4](#)). In adult patients, global intelligence and short-term memory were found to correlate with CTG repeat count and disease onset, while performance related to executive function correlated with age and disease duration, indicating progressive and selective ageing-related damage to the anterior part of the CNS. In children, visuo-constructive abilities were poor, and there was no clear difference between short and long-term memory; but differences were seen between verbal and visual memory, and between verbal and performance IQ. The suggestion was made that the Stroop test might be an appropriate cognitive measure in adults. It is validated and standardized, takes 15 min and can be administered by a psychologist or general practitioner, and longitudinal results are available in adult DM1 [7]. In children, the Wechsler Intelligence Scale for Children (WISC 4) is of great interest to highlight the dissociation between the four indexes (verbal comprehension, perceptual reasoning, speed of processing and working memory). The Rey Complex Figure task is a useful measure to test visuo-constructive ability, which is frequently impaired.

Giovanni Meola gave a synopsis of the involvement of other systems in DM1. There is a lack of consensus on the appropriate timing for use of non-invasive ventilation [8]. Potential respiratory outcome measures include reversal/improvement of symptoms related to daytime hypoventilation, number of unplanned hospital admissions, mortality, reversal of daytime hypercapnia, lung function measurements (FVC), and improvement of parameters in sleep studies. In a review of gastrointestinal manifestations [9], the following measures were noted: stabilization of previously documented weight loss/weight gain of >5 kg for 6 months after intervention, reduction in laryngeal penetration of bolus and/or aspiration observed on videofluoroscopy, reduction in chest infections from aspiration over 6 months. Quality of life studies in DM1 have shown that health-related QoL is severely impaired in DM1 and that disease duration and severity negatively correlate with QoL. A recent study in Italy [10] concluded that the INQoL measure can be recommended for use in neuromuscular patients.

Craig Campbell summarized the specific obstacles in assessment of children with congenital DM. Cognitive and mental status

differences dominate the clinical picture but testing for these deficits is resource-heavy, and rarely possible in a single measure. Children with DM1 are on a normal developmental trajectory similar to any other child, albeit one that is negatively affected by developmental delays and hypotonia. Moreover, tone and muscle strength do improve over time, so outcome measures and trials are aiming at a moving target. This and the fact that time points for symptom onset are still unclear means that pharmaceutical and other clinical trials rarely include children. Campbell reported on the Canadian CDM surveillance and cohort study, an extensive survey that uses a monthly questionnaire sent to paediatric physicians to enrol patients in a cohort study with telephone and physician record follow-up every six months over a period of five years (see Table 4). A systematic review of the literature is currently being performed and an inventory of potential outcome measures created. In additional work by Campbell's group, 20 outcome measures are being tested in the paediatric population for assessment of reliability and validity. A 2-min writing test and 2-min typing test were proposed as possible correlates of the 6MWT for the upper limbs. In validity studies, the 6MWT did not correlate with age or with CTG size, but did correlate with quality of life using PedsQL. Overall, relevant outcome measures for the congenital population include length of neonatal ventilation, number of hospital admissions, length of assisted feeding, scoliosis, mental status (IQ), ambulatory status, strength and functional testing.

Bjarne Udd provided an overview of the phenotypic differences between DM2 and DM1 based on a study of 170 DM2 patients in Finland (see Table 4), and reviewed potential outcome measures. Potential outcome measures for DM2 could include cardiac conduction defects, insulin resistance, muscle changes by imaging, brain MRI changes, clinical muscle weakness. Muscle pain would be a clinically meaningful outcome measure, but establishing the best assay is a challenge. Muscle MRI may be a highly useful outcome measure for DM2 in the future as it targets the main clinical manifestation, muscle degeneration, but technical improvements will be necessary. DEXA parameters may be of interest to reveal changes in muscle tissue compared to fat and connective tissue over time.

Discussion revealed some interesting candidates for DM1 outcome measures on which a certain amount of evidence has already been accrued, but also clearly revealed the need for additional natural history research and outcome measure validation to inform trial planning. Studies to establish correlations between surrogate markers and clinically meaningful events may need to be large-scale and long-term, and international collaboration and sharing of information is essential in this regard to avoid duplication of effort and wasting of limited resources. Establishing a dialogue with the regulatory authorities on surrogate markers and biomarkers will become increasingly important in the near future.

#### 4. Genetics of DM with relevance for clinical trials and patient registries

Future therapies for DM1 may be based on modification of the underlying genetic defect, and genetic confirmation of the disease will be required for any patient entering a clinical trial even where the therapy itself is not gene-based. The necessity of including genetic data in the international DM1 registry is thus clear from a trials perspective. Darren Monckton gave an overview of DM1 genetics and the important considerations for therapeutic development. Key to this is an understanding of the underlying genetic variability of the disease. The size of the CTG repeat not only varies from generation to generation, but is also unstable through the lifetime of an individual patient and differs from tissue to tissue.

Yet another factor is that of variant repeats: an interruption of the CTG repeat by other sequences may occur in around 5% of cases and may result in a less severe disease course and slower progression [11]. This has clear implications for trial design, as results may be biased if this effect is not controlled for. The predictive value of the size of the repeat expansion for an individual patient is low, and many diagnostic labs therefore do not provide an actual number of repeats; however, Monckton presented a method of increasing the predictive value of the repeat count in determining age of onset based on the length of the progenitor allele. Repeat-primed PCR, now a commonly used testing method, provides no indication of repeat length above 50 repeats, and most methods may not identify variant repeats. European Molecular Genetics Quality Network (EMQN) best practice guidelines and recommendations on myotonic dystrophy types 1 and 2 have recently been published [12], but do not incorporate recent findings relating to the existence of variant repeats.

Christopher Pearson expanded on the issues of repeat instability and somatic mosaicism, including the questions of rate of change and inter-tissue variability. Somatic instability may contribute to disease progression and severity. The process of instability also reveals targets for repeat modulation: DNA replication, DNA repair, and epigenetics all contribute to repeat expansion [13], so a greater understanding of these processes may provide future possibilities to modulate expansion.

Ralf Krahe provided a comprehensive description of genetic analysis in DM2. The DM2 repeat comprises four nucleotides (CCTG) and may be very large, up to 11,000 CCTG, and very complex. In DM2 there is no clear correlation between repeat size and disease severity, and no anticipation is seen: based on peripheral blood leukocyte testing, there appears to be an equal occurrence of expansion and contraction in parent-offspring pairs. To date there have been no studies of the DM2 CCTG repeat in primary affected tissues. A premutation allele pool for DM2 [14] contains alleles that have lost cryptic interruptions and are very unstable.

Discussion focused on the challenges of DM1 genetics and what genetic data can realistically be captured in the international DM1 registry. It was agreed that the only mandatory item to be captured would be confirmation of the molecular diagnosis itself; however, a range of additional items were suggested as supplementary (highly encouraged) questions that might help provide more valuable genetic data (Table 3). With respect to future clinical trials, there were discussions surrounding the importance of considering whether treatments may have a negative effect on repeat stability, particularly with chromatin remodelling drugs. Identification of variant repeat carriers may be a challenge in trials, as variant sequence may result in milder or unusual clinical phenotypes potentially confounding trial results.

#### 5. Conclusions and future plans

This meeting achieved an important goal in reaching consensus on an international registry for myotonic dystrophy type 1. It was clearly signalled by all those present, in particular the industry participants and patient representatives, that harmonization of key patient data on an international level is a timely initiative that will facilitate translational research in DM1 by easing the path for industry and researchers to move therapies forward to the clinical trial stage. It was recognized that further natural history studies and work to more accurately predict disease course and progression will be required in order to enable the validation of additional outcome measures for DM1. Work to set up the DM1 International Registry will commence, in a collaboration between TREAT-NMD, the existing DM1 registries

presented here, the patient advocacy groups and in future with other groups worldwide wishing to contribute patient data to this global initiative.

## 6. Participants

Joanne Auld (TREAT-NMD, UK)  
 Guillaume Bassez (Paris, France)  
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 Craig Campbell (London, Canada)  
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 Valerie Cwik (Muscular Dystrophy Association, USA)  
 Baziel van Engelen (Nijmegen, The Netherlands)  
 Bruno Eymard (Paris, France)  
 Bill Groh (Indiana, USA)  
 Ralf Krahe (Houston, USA)  
 \*Hanns Lochmüller (Newcastle, UK)  
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 Robert MacLeod (Isis Pharmaceuticals, USA)  
 Giovanni Meola (Milan, Italy)  
 Bob Mattaliano (Genzyme, USA)  
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 Christopher Pearson (Toronto, Canada)  
 Virginie Picard (Association Française contre les Myopathies, France)  
 Mark Rogers (Cardiff, UK)  
 \*Benedikt Schoser (Munich, Germany)  
 Cheryl Swaby (Marigold Foundation, Canada)  
 Rachel Thompson (TREAT-NMD, UK)  
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 Bjarne Udd (Helsinki, Finland)  
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