UK Myotonic Dystrophy Patient Registry

www.dm-registry.org/uk

Spring 2018 Edition

The registry is only able to operate with the support received from:

Myotonic Dystrophy Support Group | Muscular Dystrophy UK – Fighting muscle-wasting conditions | TREAT-NMD Neuromuscular Network

Registry Update and Participation Overview

March 2018 saw the UK Myotonic Dystrophy Patient Registry surpass 697 registered participants, an amazing achievement that could only have been achieved by the amazing support and contribution of every participant clinician, patient organisation and caregiver across the whole of the United Kingdom. Thanky you for all of your support!

The registry was first made live online in March 2012 and within one year had recruited 243 participants across the UK. This amazing recruitment drive was only possible due to the incredible support we received from the wider Myotonic Dystrophy community. The registry on average, recruits 10 new participants per month (Fig 2) and through this continued supply of participant information, the registry is still able to support recruitment into clinical research and development of potential treatments.

With the registry bringing together people with Myotonic Dystrophy; doctors, researchers and treatment developers are able to collect and share the anonymous disease information to help improve the standard of care for everyone with Myotonic Dystrophy, whilst opening doors to a greater understanding and future treatment of the disease.

Fig1: The UK Myotonic Dystrophy Patient Registry Homepage

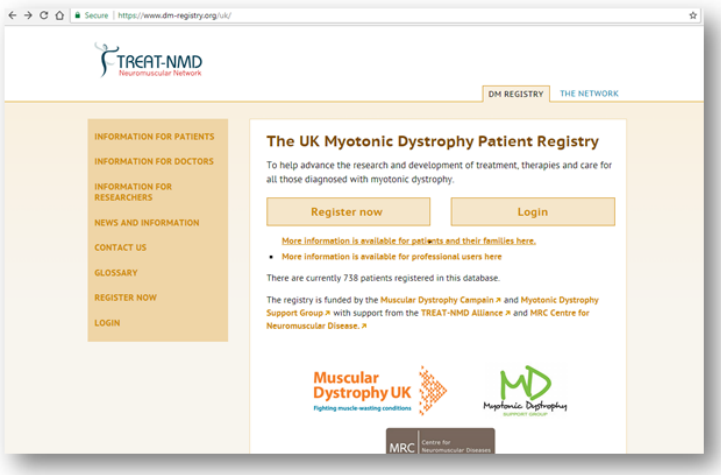


Fig 2: Number of Registrations to the UK Myotonic Dystrophy Patient Registry (2012 – 2018)

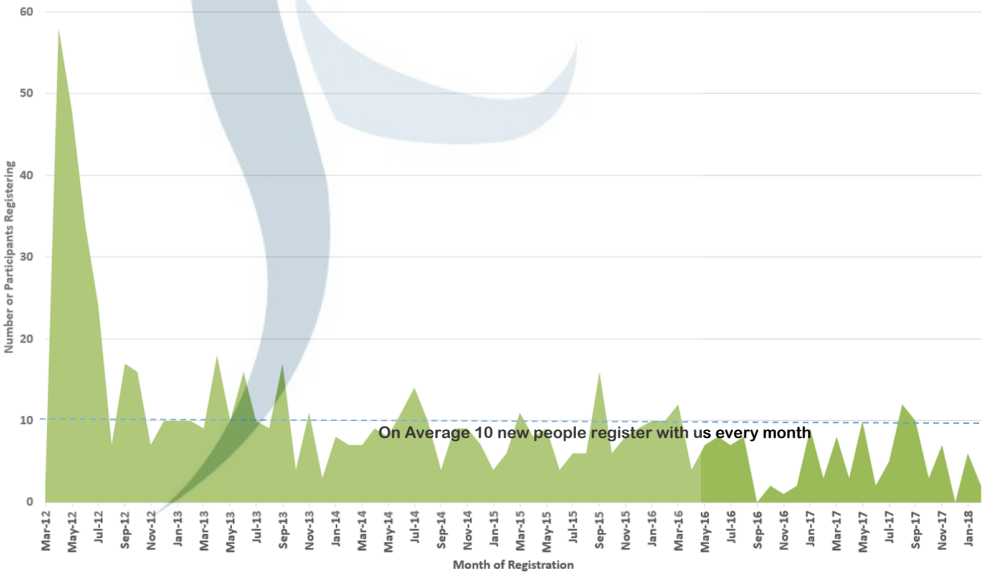
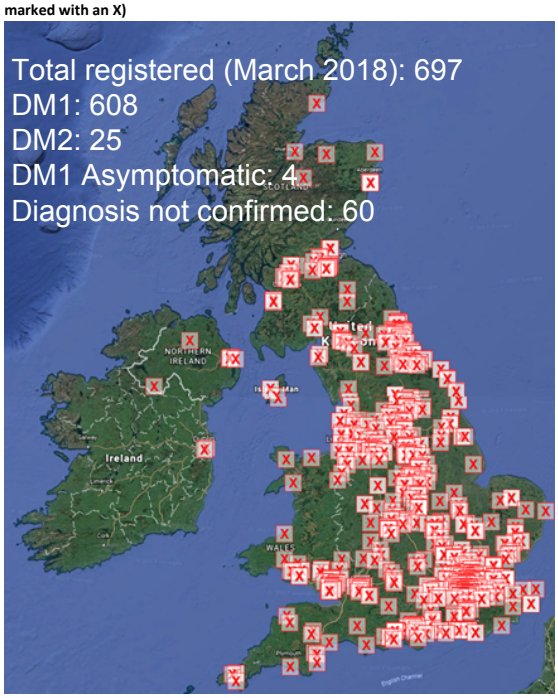


Fig 3: Geographical Spread of Registered Paricipants (Each participants location marked with an X)



Remember To Update Your Details

The registry is only as useful as the information it contains. Please remember to update your information on a regular basis and if you change things such as your postal address, telephone number, email address or other personal information, please make sure you update this on the registry - otherwise you may miss out on important information relating to Myotonic Dystrophy.

Tips for all Registry Participants

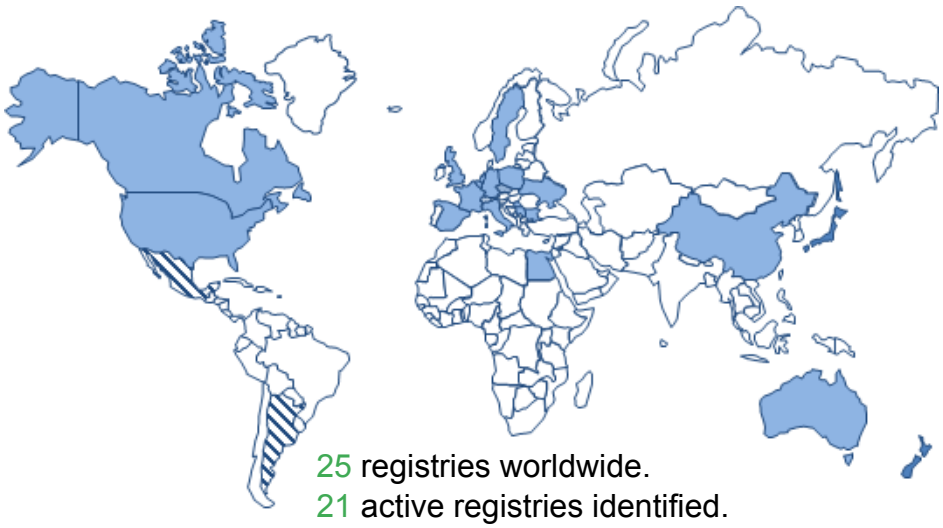
- Keep a Record of your username (this will be the email address you used when registering) and password so that you don't have any problems accessing your registry account – but remember to keep your details secure!
- If you do have any problems accessing your account on the registry contact the curation team at myotonicdystrophyregistry@treat-nmd.eu
- Ensure that you answer as many questions in each questionnaire as you are able to – each answer provides vital information that helps power research in to Myotonic Dystrophy.
- If you are ever unsure about your participation in the registry get in touch with us
- If you are a caregiver, friend or family member of a participant in the registry whose circumstances may have changed which affects their participation in the registry, please let us know.

Global Picture: Myotonic Dystrophy Registries

The UK Myotonic Dystrophy Patienty Registry is proud to operate alongside other national patient registries across the world, as part of a larger network of registries collecting information about the disease. Through registries working together and collecting similar information on participants in each country, we are able to coordinate resources and knowledge about the disease, which is essential in order to move towards larger and more successful clinical trials and ultimately better management.

By participating in the UK DM registry you are playing an an important part of the establishment of a 'global' registry with your information. This huge network (coordinated by TREAT-NMD - www.treat-nmd.eu) shares advice and promotes the inclusion of more countries and data in order to generate benefits for all. We are making an global impact!

Figure 4: Location of registries collecting data on myotonic dystrophy. The countries shaded with stripes are in the set up phase of registries.



25 registries worldwide.
21 active registries identified.
2 recently launched.
2 in set-up.

Myotonic Dystrophy: Disease Characteristics

In this edition of the newsletter, we would like to go in to a little more detail about Myotonic Dystrophy and its disease characteristics; from the general knowledge of the disease, which many of you know well, and about preclinical steps of the clinical trials.

Myotonic dystrophy is a very complex disease. Its symptoms and progression can vary widely from one patient to another, so it is difficult to predict how the disorder will affect you or your family in the future. A person may have only mild muscle pains or cataracts that develop in the adulthood, while another person with DM may be born with severely breathing problems.

The most characteristic symptoms of DM are muscle weakness, difficulty in relaxing muscles (myotonia), and loss of muscle mass. However, it is a mistake to think that DM is only a muscle disease, because it also affects many other functions of the body, including heart, respiratory or digestive system, to name but a few. This variability in symptoms presents unique challenges in both the diagnosis and management of the disease.

Brain
-Difficulty with thinking and problem solving
-Emotional and behaviour problems
-Excessive daytime sleepiness
-Nerve damage in feet and hands

Vision
-Cataracts
-Damage to the retina
-Drooping eyelids (ptosis)

Skin
-Higher risk of benign tumor (pilomatrixoma)

Respiratory system
-Breathing problems in newborns
-Frequent lung infections
-Aspiration of food or fluids into airways
-Inability to breathe in enough oxygen
-Sleep apnoea

Cardiovascular System
-Heart rhythm problems (arrhythmias)
-Enlarged heart muscle
-Low blood pressure
-Sudden death

Hormones
-Insulin resistance
-Premature frontal balding in men

Gastrointestinal
-Difficulty swallowing
-Pain and bloating after meals
-Constipation, diarrhoea, irritable bowel syndrome
-Gallstones
Enlarged colon

Reproductive system
-Small testes, low sperm count, low testosterone
-Higher risk of miscarriage and stillbirth; early menopause
-Problems with pregnancy and delivery
-Newborn complications

Muscle
-Muscle weakness (myopathy)
-Muscle stiffness and trouble relaxing a muscle (Myotonia)
-Muscle wasting that gets worse overtime (atrophy)
-Severe muscle weakness and delayed development in newborns

Figure 5: Characteristics of Myotonic Dystrophy in the human body

Myotonic Dystrophy: Route to Diagnosis

The route to which a person with Myotonic Dystrophy is eventually given a confirmed diagnosis can difer depending upon the Health Care professional they intially visit. In order to make an initial diagnosis, begins with a complete family history and physical examination (Usually carried out by a specialist nurse, doctor and physio during a visit to a specialist centre). A person will undergo a series of medical tests, dependent upon the symptoms he or she first presents with. An important part of the evaluation is a proceedure called an electromyography (EMG). This procedure (usually carried out by a specialist clinican) detects the presence of myotonia in a high proportion of people with DM1 or DM2. If the results of this test point strongly toward a diagnosis of myotonic dystrophy, the disorder can then be confirmed by genetic testing. The diagram below shows the various Health Care Professionals a person in the UK may have visited at some point leading up to their diagnosis and the symptoms they would address in the pathway to diagnosis.

General Practitioner (GP)

Exhaustion, inability to sleep well, excessive daytime sleepiness, feeling faint.

Hearing loss, delayed or impaired speech, swallowing difficulties. Jaw and mouth bone deformities that disturb chewing and speech.

Chronic diarrhea, constipation, unexplained stomach pain, gallstones, swallowing problems.

Depression, personality abnormalities such as excessive apathy, socialization issues, and attention deficit.

Chronic respiratory problems, sleep apnea, frequent chest colds that do not go away, aspiration pneumonia caused by swallowing issues.

Pediatrician

Hypotonia (also known as floppy baby syndrome) or child with learning and behavioural problems.

Neurologist

Nerve and muscle complaints including weakness, stiffness, and chronic muscle pain, cognitive development delays, reduced executive function.

Ophthalmologist

Blurry or dimmed vision (possible cataracts), eye muscle weakness, droopy eyelids (ptosis).

Cardiologist

Abnormal heartbeat, heart damage (cardiomyopathy), fainting spells.

Treatment of Myotonic Dystrophy

Myotonic dystrophy tends to worse gradually over several decades. While no treatment exists that slows the progression of it, management of symptoms can greatly improve quality of life. Taking steps to prevent or treat problems as they come up can help avert complications.

SYMPTOM	TREATMENT
Treat high blood sugar levels Mange mild diabetes symptoms	Anti-diabetic drugs
Control myotonia that impairs nomal activities	Anti-myotonic drugs
Manage muscle pain	Nonsteroidal Anti-inflammatory drugs
Control excessive daytime sleepiness	Wakefulness promoting agents

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Using Gene Editing to Correct Myotonic Dystrophy

A potentially revolutionary technology may lead to the development of a drug for DM, that can correct a patient's DNA by selectively removing the expanded CTG and CCTG repeats in DM1 and DM2, respectively.

This new gene editing technology has emerged from the discovery of how bacteria protect themselves from invading viruses. They're will very likely will be a Nobel Prize awarded to the scientists who discovered how this bacterial defence mechanism could be used to edit human gene defects.

Is this gene editing going to be available soon for DM?
The direct answer is, no. Several issues need to be resolved before any clinical application of gene editing is realised. The specificity and efficiency of gene editing will also need to improve. Delivery of the gene editing reagents also must be optimized, these are large molecules that will have to be delivered by intravenous injections and must then gain access to cells throughout the body of DM patients in order to correct the multiple symptoms of the disease.

www.myotonic.org/using-gene-editing-correct-dm

Compliance with Prescribed Medication among Patients Living with Myotonic Dystrophy

A recent study at the University of Rochester titled “Medication adherence in patients with myotonic dystrophy and facioscapulohumeral muscular dystrophy,” (www.ncbi.nlm.nih.gov/pubmed/27734165) was motivated in part by the fact that DM patients need to take multiple prescriptions. The study also sought to understand how difficulty in swallowing, limited mobility, and reduced employment may impact DM and facioscapulohumeral muscular dystrophy (FSHD) patient compliance with prescribed medicine.

For both DM1 and DM2, muscle weakness was the symptom that patients most commonly viewed as an unmet treatment need, and for which they wanted new therapies to be developed. Patients also cited the need for treatments to improve mobility and reduce fatigue as high-priority issues in DM1, while DM2 patients reported pain as an unmet need. Many patients surveyed took six or more medications. Improved access to physical therapy, exercise, and mobility devices may help reduce reliance on some medications.

Most DM patients reported a good understanding of both their disease and the reasons that they were taking specific medications. Most participants in the study (93% of DM1, 88% of DM2 patients) reported that cost/ insurance coverage was not a barrier to compliance with medications prescribed for their DM symptoms. Side effects of one or more medications were important compliance factors for a significant number of DM patients (35% in DM1, 49% in DM2), and were a factor that led to many patients discontinuing a medication (37% in DM1, 60% in DM2). Patients also identified difficulty in swallowing medicines in tablet or capsule form as a barrier to compliance with prescribed medication (33% in DM1, 21% in DM2).

Dr. Moxley and colleagues concluded that the symptoms of DM did not significantly impair patient adherence to medications prescribed for their multi-system disease. DM1 patients identified more of a need for new medications to manage their disease symptoms than patients with DM2. DM patient compliance with medications was, overall, better than literature reports for other chronic diseases.
www.myotonic.org/compliance-prescribed-medication-among-patients-living-myotonic-dystrophy

prefer.

PATIENT PREFERENCES

Patients are often faced with different treatment options, each of which has unique advantages and disadvantages. Patient preferences refer to the choices that patients make regarding different treatments and the characteristics of the treatments that influence their decisions. This can be about existing treatments or treatments in development. For example, a patient preference study could investigate whether patients with sleep problems would prefer to use a new drug for sleep apnoea or the traditionally recommended continuous positive airway pressure (CPAP) mask.

Patient preference information can be used for many different purposes, such as:

- **informing medical companies about the desired characteristics of a new medical product or drug**
- **helping regulatory bodies understand what trade-offs patients are willing to make**
- **guiding healthcare providers to develop interventions that are respectful to the individual preferences of the patient**

Although patient preference information is very valuable, there is currently little guidance on how and when to collect it.

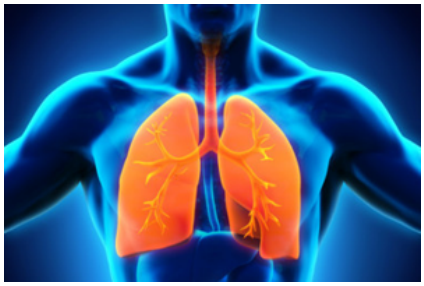
Fig 1: The life cycle of a drug. The PREFER project will find out when and how patient preferences should be incorporated into this cycle.

The PREFER project will identify methods for measuring patient preferences and evaluate some of these methods in real scenario preference studies. One of these studies will include patients with Myotonic Dystrophy (DM1). The results from this study might provide an insight into the preferences of the DM1 community regarding potential medical products or lifestyle changes targeting disease symptoms such as daytime sleepiness.

The case study in DM1 is planned to begin later this year. Participants enrolled in the patient registry will be notified about recruitment via email from the registry curator.

This is a five year project that has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115966. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This public-private partnership includes 16 pharmaceutical companies, 10 academic institutions (including Newcastle University), 4 patient organizations (one of which is MDUK), 1 Health Technology Assessment body and 2 small enterprises. www.imi-prefer.eu/

Determinants of Respiratory Function in DM1



Respiratory dysfunction is a major contributor to morbidity and mortality in DM. An evidence-based approach is essential to understanding the underlying risk factors and appropriate actions in management of respiratory status in DM patients. Such an understanding of the natural history and relative value of interventions for respiratory dysfunction is also essential in the design of interventional clinical trials. Careful natural history studies are the path forward to improved clinical care and informed clinical trials.

UNDERSTANDING THE RISK FACTORS BEHIND RESPIRATORY FUNCTION IN DM1

Dr. Ghilas Boussaïd (Hôpital Raymond Poincaré, Garches, France) and colleagues have evaluated the relationship of DM1 genotype and other respiratory function determinants in the progression of respiratory dysfunction. Their prospective observational study provided data on 283 subjects, followed for five years or until loss to follow-up, for regression modeling of functional changes over time.

Respiratory function parameters associated with CTG repeat length were determined via a multivariate linear regression analysis. Higher peak cough impairment and lower vital capacity and maximum inspiratory pressure were associated with longer CTG repeats. Observed decline over time in vital capacity was associated with longer CTG repeats, older baseline age, and higher baseline BMI values. Longer CTG repeats also correlated with larger decreases in maximum inspiratory pressure, maximum expiratory pressure, and increased risk of death. Very long repeats (>1000) were associated with annual vital capacity declines as high as 36%--these rapid declines flag adult CDM patients for very close respiratory monitoring.

IMPACT OF RESPIRATORY CARE

Non-invasive ventilation was in use for 13% of study subjects at baseline and was initiated in 41% of the remaining subjects during follow-up. Decision to initiate non-invasive ventilation was associated with lower peak cough flow after accounting for age and arterial CO2 tension. Non-invasive ventilation improved vital capacity. The authors posit that closer respiratory follow-up is warranted for patients with long CTG repeats and/or high BMI. They also noted the compliance issues with non-invasive ventilation in DM1 patients and highlighted the importance of considering sociological and psychological variables in future studies of respiratory function and non-invasive ventilation.

Taken together, the authors established that long CTG repeats are associated with a more severe respiratory phenotype and faster functional decline. Obesity was also identified as an important risk factor for respiratory status. They did not identify an association between non-invasive ventilation and many measure of improvements in respiratory status, but concede limitations in this study. Overall, starting early with regular peak cough flow assessments and following patients closely, particularly in adults with CDM, were seen as an effective means of reducing risks of respiratory dysfunction.

Improving Clinical Trials in Myotonic Dystrophy: Thurman Wheeler, M.D

Dr. Wheeler, assistant professor of neurology at Harvard Medical School and a clinical neurologist at Massachusetts General Hospital, received a grant to develop new serum-based biomarkers in adults and children with type 1 and 2 myotonic dystrophy (DM1 and DM2).

Dr. Wheeler's grant, will allow him and his team to begin initial exploration of the viability of developing DM biomarkers that can be measured in blood and urine, reducing or avoiding the need for muscle biopsies, which are invasive and risky, to support data collection in clinical studies and trials. The results of this study are yet to be published. Further infomration can be found here:

www.myotonic.org/improving-clinical-trials-myotonic-dystrophy-thurman-wheeler-md

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Developing an advanced molecular patch therapy for DM1

Professor Matthew Wood at Oxford University is developing a molecular patch that could be a potential treatment for people with myotonic dystrophy type 1. This research, titled 'Advanced peptide-oligonucleotide therapy for myotonic dystrophy type 1' and been ran at Oxford University, will also help to further enhance molecular patch technology, which will be beneficial for the neuromuscular field in the long-term.

The aim of this project (due to be completed in 2019) is to develop an advanced molecular patch that binds to the mutant DMPK RNA and blocks its toxic effects. This could therefore be a potential treatment for people with myotonic dystrophy type 1. Further information can be found at the MD UK website: www.musculardystrophyuk.org/grants/developing-an-advanced-molecular-patch-therapy-for-myotonic-dystrophy-type-1/

If you would like to participate in a future edition of the UK FSHD Patient newsletter, please email the project team: fshdregistry@treat-nmd.eu