Introduction to Muscular Dystrophy Ireland
Joe Mooney, Director MDI

- MDI’s mission statement is: Muscular Dystrophy Ireland aims to provide information, advice and support to people with neuromuscular conditions and their families through a range of support services. Our objective is to promote through practical empowerment, independent living for people with the condition muscular dystrophy. MDI supports advocating for a change in policy and services to enable people with neuromuscular conditions to fully participate in society and to live a life of their own choosing. MDI also aims to support and fund research into neuromuscular conditions.

- MDI provides support to people with a range of neuromuscular conditions. The membership is made up of people with the following conditions (figures from 28th February 2008):

<table>
<thead>
<tr>
<th>Type of MD</th>
<th>Number of Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne MD</td>
<td>90</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth</td>
<td>75</td>
</tr>
<tr>
<td>Myotonic Dystrophy</td>
<td>57</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>37</td>
</tr>
<tr>
<td>Limb-Girdle MD</td>
<td>35</td>
</tr>
<tr>
<td>Facioscapulohumeral MD</td>
<td>34</td>
</tr>
<tr>
<td>Myopathy</td>
<td>29</td>
</tr>
<tr>
<td>Becker MD</td>
<td>24</td>
</tr>
<tr>
<td>Congenital</td>
<td>14</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>7</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>3</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>3</td>
</tr>
<tr>
<td>Congenital MD</td>
<td>2</td>
</tr>
<tr>
<td>Inclusion Body Myositis</td>
<td>2</td>
</tr>
<tr>
<td>Arthrogryposis</td>
<td>1</td>
</tr>
<tr>
<td>Other / Unspecified</td>
<td>65</td>
</tr>
</tbody>
</table>

**Total Number of Members with MD: 478**

- MDI provides a range of support to members:
  - Nationwide information service
  - Family Support service: 8 FSWs throughout the country
  - Respite service: respite breaks, short term respite
  - Youth service: 5 YRWs throughout the country
  - Transport
  - Newsletter
  - Website: [www mdi ie](http://www mdi ie)
Muscular Dystrophy Treatment at the Central Remedial Clinic
Dr. Bryan Lynch, Consultant Paediatric Neurologist

- The CRC runs a multidisciplinary clinic for children and young people with muscular dystrophy. The services they have access to are a Paediatric Neurologist, Orthopaedic Surgeon, Physiotherapist, Occupational Therapist, Orthotist, Dietician, Social Worker and a Seating specialist. MDI also has a staff member in attendance at the clinic to provide support to families.
- The clinics are organised into a “young neuromuscular clinic” for ambulant children who do not need orthopaedic assessment or intervention, and a combined medical / orthopaedic clinic for those in need of orthopaedic assessment, particularly those using wheelchairs.
- More recent developments in the clinic include a steroid programme, respiratory input and cardiology input.
- There are currently 163 children enrolled in the neuromuscular clinics: 72 boys with Duchenne MD, 57 with a variety of other muscle disorders and 34 with hereditary motor and sensory neuropathy (also known as Charcot-Marie-Tooth Disease).
- The use of corticosteroids has been demonstrated to improve strength and function for a time, although there are side effects including weight gain.
- The steroid programme in the CRC started in 1996, when deflazacort was given at 0.9mg/kg/day, starting when boys were having difficulty staying on their feet.
- An audit in 1998 recommended starting steroid treatment earlier, and found that there was excellent benefit in some cases with effects lasting well beyond a year. The main side effects were weight gain and behavioural issues, and steroid treatment may be more difficult in boys already experiencing learning, behavioural and weight gain problems.
- In another audit from 1996 to 2004, 22 boys were treated with continuous steroids, on deflazacort at 0.9mg/kg/day. Treatment began when the boys were beginning to come off their feet, and were monitored with 2 to 6 monthly visits to the neuromuscular clinic.
- In 2004, the clinic reverted to prednisolone instead of deflazacort, and a new regimen was offered, with 10 days on and 10 days off (0.75mg/kg dosage). This helps to limit side effects but there is not much good research yet to show if the beneficial effects are as good as on continuous treatment. Steroids are also introduced earlier, in the early ambulant phase.
- The future directions are to link with new clinical treatments and research studies as they become available. As part of this, they are trying to source funding for a part-time research nurse to assist with this, medical audit and management of the clinics.
The Therapeutic Perspective in Duchenne muscular dystrophy
Prof. Kate Bushby

- DMD is a treatable condition, with predictable complications in different systems. Steroid treatment, physiotherapy, respiratory support and cardiac surveillance all have recognised benefits.
- 20 years on from identifying the dystrophin gene, there are a number of research strategies entering the clinical arena.
- Exon skipping has entered clinical trials. The principle is to “force” the skipping of one or more exons to allow some dystrophin protein to be produced. The MDEX Consortium are running phase 1 of a trial (exon 51 targeted), and a Dutch group has established proof of principle in intra muscular injection (also exon 51).
- Exon skipping is a promising therapy, but systemic trials have yet to be performed and there are concerns over the production of some of the reagents. It is possible that viral vector delivery of splice factors may produce better benefits. The exon specific nature of the target means that people need to know their precise mutation and register for identification for clinical trials. Also, it will not be a therapeutic option for ALL people with DMD.
- Another area under investigation is stop codon suppression, which could help around 15% of people with DMD who have this type of mutation. The principle is to bypass the premature stop codon so protein production can continue through to the normal stop. PTC Therapeutics has concluded a proof of principle trial in the USA and will recruit for an international trial over the next few months. A centre in the UK is participating in this.
- Cell transplantation is being looked at. However, the timescale for clinical translation may be prolonged, as there are issues to address including production, method of delivery, and prevention of immune reactions. Some clinics currently offering “stem cell treatments” are not endorsed by the scientific community.
- Upregulation of alternative proteins is another possible option. Summit plc is hoping to begin a clinical trial in 2008/9.
- Blocking myostatin is another option that has been explored. Wyeth ran the first phase of a trial but results were not enormously promising so they may not continue with the trial. Other companies are expressing an interest in getting involved however.
- Other researchers and companies, e.g. Santhera Pharmaceuticals, are looking into addressing the downstream pathology (e.g. cardiomyopathy), identifying testing systems for new molecules and looking at already approved drugs for other conditions that might emerge for fast tracking into muscular dystrophy trials.
- The challenges for the future are to make sense of animal studies, to engage industry, identify participants for clinical trials and bring together people with the condition, researchers and clinicians. We also need to manage people’s expectations, so as not to offer false hope.
TREAT-NMD was also introduced. This is an EU network whose aim is to accelerate the pathway of promising treatments to the clinic. More information can be found at [www.treat-nmd.eu](http://www.treat-nmd.eu).

In order to prepare for trials, TREAT-NMD is developing standards of care, registries, and looking at trial site feasibility.

Standards of care are being developed in order to create a “level playing field for all people with neuromuscular conditions across the world”. Standards have been developed for spinal muscular atrophy and an interim document is available for DMD.

TREAT-NMD has also been standardising registries. People with DMD can register their details, which would be useful for researchers looking for clinical trial participants and for clinicians in the event of a treatment becoming available. Action Duchenne has a registry which is now available to Irish families and you can register online at [www.dmdregistry.org](http://www.dmdregistry.org).

**Orthopaedic Involvement in DMD**

Mr. Damien McCormack, Orthopaedic Surgeon

- Foot surgery could be advocated to facilitate the wearing of splints to prevent or correct foot deformity, and to allow comfortable shoe wear.
- Scoliosis, curvature of the spine, can progress after the loss of ambulation. There is a small space of time in which it is possible to perform this surgery, as the bigger the curve, the more difficult it is to perform and the older the child is so there can be a larger chance of problems with the anaesthetic.
- Mr. McCormack uses the single rod technique, which is not moulded to the pelvis. This may not be technically the most perfect surgery, but he believes it to be safest for people with DMD as it is quick, taking approximately one hour and so there is less time under anaesthetic.

**Physiotherapy Management of DMD**

Pamela Foley, Physiotherapist

- A consistent stretching programme is important for people with DMD, so a routine should be established. The reason for this is to delay the development of contractures, maintain symmetrical posture for as long as possible, and to encourage mobility.
- The achilles tendons are probably the most important stretch at the beginning, and others like hamstrings, hands etc. can be worked with later when required.
- Night splints are good to keep a stretch on the achilles tendons, so the physiotherapist works with an orthotist. The orthotic must fit well and needs to be worn every night. If a child outgrows a night splint, you should contact the physio or orthotist. If there is a positive attitude towards night splints, there is a better chance of success. However, daytime ankle-foot orthoses or moulded insoles are not suitable for boys with DMD.
Regarding footwear, boots are not suitable for boys with DMD as they need to push up on their toes when walking and down on their heels for balance when standing. Comfortable shoes or trainers are best.

Regular mobility is recommended, particularly for younger boys with DMD. This could include swimming, horse riding or cycling. However, resisted exercises or those that use the “eccentric” muscles are not recommended.

In the early stages, the physiotherapist would see the family weekly / two-weekly until a Home Programme was established, and then monthly once the programme is working well.

There is no exact time at which to introduce a manual wheelchair. The time varies according to the individual. However, it is advisable to get a manual wheelchair when needed and not to use a buggy. The time of beginning to use a powerchair will also vary according to the individual.

When a child starts to use a wheelchair, a new phase of management begins with a baseline spinal x-ray after 6 months and follow up spinal x-rays every 6 months.

The key points are to get an early and regular assessment, employ a consistent stretching programme, use night splints, and get a timely referral for a seating assessment. Physiotherapy management can make a real difference to the quality of life.

Respiratory Care of the Person with DMD
Dr. Dubheasa Slattery, Respiratory Paediatrician

- There are a number of respiratory complications in DMD. These can include recurrent respiratory tract infections, sleep disordered breathing, swallow difficulties, anaesthetic and post surgery problems, other respiratory disorders such as asthma and associated disorders such as gastro-oesophageal reflux. Respiratory failure, along with cardiac problems, leads to the reduced lifespan seen in DMD.
- The idea then, is to predict problems, prevent, arrest and treat.
- The American Thoracic Society (ATS) released a consensus statement in 2004. This looked at evaluation and anticipatory guidance, including routine evaluation of respiratory function, nutrition, sleep evaluation and cardiac involvement, and also management, including airway clearance, non invasive ventilation, corticosteroids, and patient education.
- Routine evaluation of respiratory function is necessary because people can be unaware of the loss of their respiratory muscle strength, and evaluation helps to predict those who will require assistance. Regular GP visits are recommended as well as access to a specialist respiratory paediatrician, pneumococcal and annual influenza vaccines, and a pre surgery respiratory and cardiac review.
- It can be difficult to get to the ideal body weight, but being over OR under weight has a negative effect on lung function. The involvement of a dietician is important.
- Sleep evaluation can be used to detect the subtle onset of respiratory insufficiency. Symptoms of sleep hypoventilation can include wakening
at night, daytime sleepiness and morning headache. Recommendations are to review sleep quality and symptoms at each visit, have an annual evaluation when this is indicated clinically or when using a wheelchair (sleep study or overnight pulse oximetry with CO2 monitoring or blood gas).

- Managing airway clearance: if a person with DMD does not have an effective cough, a physiotherapist can assist with manual techniques, or mechanical techniques such as suction machines can be used.
- Non invasive nocturnal ventilation: intermittent positive pressure ventilation with a BiPAP and humidified oxygen apparently improves survival, quality of sleep, quality of life, independence, decreases daytime sleepiness and slows the rate of decline in pulmonary function compared with those not using ventilation. There are different sizes and types of masks available.
- Daytime non invasive ventilation should be considered when O2 levels are below 92%. Continuous invasive ventilation (tracheostomy) can be considered for some people.
- The majority of people with DMD develop scoliosis after losing independent ambulation. Surgery should be timed so it can take place before lung and cardiac problems are too severe. Respiratory monitoring should be performed two months pre surgery and pre op.
- Oral corticosteroids are associated with a significant sparing of lung function. Dose regime and age at which to start treatment needs further research.
- Patient education is very important in order to recognise signs and symptoms of lung complications early and to make informed decisions regarding ventilation.

Cardiac Function in DMD
Dr. Colin McMahon, Paediatric Cardiologist

- DMD is not just a skeletal disorder, it affects multiple systems.
- Most people with DMD and 70% of those with Becker have dilated cardiomyopathy by 20 years, even though there may be no outward signs. There is a need to monitor early, as someone may be asymptomatic but damage can still be occurring.
- Heart muscle can recover to an extent if it is allowed to, eg. with ACE inhibitors or beta blockers.
- There appears to be a genetic susceptibility to dilated cardiomyopathy (DCM), with deletions of exons 12 and 14-17 having a strong association with DCM while those of exons 51 and 52 are protective against DCM. This was found in a small study with limited follow up in Heuston, Texas.
- The protocol currently followed in Our Lady’s Hospital is:
  - First review at 10-12 years of age
  - Annual review thereafter
- Clinical history is taken, and tests include a physical exam, ECG, BNP test (to measure levels of natriuretic peptide), and echocardiogram.
- There does not appear to be a correlation between hand grip strength and cardiomyopathy.
- Treatment depends on the results of these tests. If there are normal left ventricular dimensions / ejection fraction, then continue to monitor. If symptomatic, then diuretics, beta blockers and ACEi can be considered.
- Follow up is important. If asymptomatic with normal ECG features, there should be an annual review, if symptomatic, there should be a 6 monthly review.
- Future: earlier detection and more aggressive therapy strategies are predicted.