MRC Centre for Neuromuscular Diseases

UCL

MRC Centre for Neuromuscular Diseases

Myotonic Dystrophy Workshop

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This workshop is supported by Genzyme and the MRC Centre for Neuromuscular Diseases.

Overview of the MRC Centre for Neuromuscular Diseases

Dear Colleagues,

I am delighted to welcome you to the MRC Centre for Neuromuscular Diseases.

Our centre aims to bring together clinicians, scientists, patient organisations and patients in order to advance UK translational research in neuromuscular disease. This is a particularly exciting time in the field as a range of basic science discoveries are revealing an increasing number of therapeutic targets. The centre aims to work with all its partners to support the development of a trials culture for patients with neuromuscular diseases. We will work hard to form reciprocal research and clinical links with other UK neuromuscular groups.

The MRC Centre is a joint partnership between the UCL Institute of Neurology, UCL Institute of Child Health, and the University of Newcastle-upon-Tyne. The centre is closely linked to its partner NHS organisations, University College London Hospitals NHS Foundation Trust, Great Ormond Street Hospital for Children and Newcastle Upon Tyne Hospitals NHS Foundation Trust.

I hope that you have a stimulating day in London!

Professor Michael G Hanna
Director, MRC Centre for Neuromuscular Diseases
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Introduction to the Myotonic Dystrophy Workshop

Dear Colleagues,

We are very pleased to welcome you to the first UK MRC Centre for Neuromuscular Diseases Myotonic Dystrophy Workshop which is supported by the MRC Centre for Neuromuscular Diseases and the British Myology Society. This is the second in a series of CPD approved practical workshops covering major muscle diseases which we hope will engage the clinical and scientific muscle community from throughout the UK, Ireland and beyond. We have aimed to invite colleagues who are actively involved in any aspect of myotonic dystrophy. The format for each of the workshops will be similar with the following broad aims:

- To establish or build on networks of clinicians, pathologists, geneticists, therapists, clinical nurse specialists, scientists, patient groups and other expert disciplines interested in specific muscle diseases that will work together on a long-term basis

- To agree network activities that are relevant to clinical practice and to which network members can contribute with minimal effort in the course of routine muscle practice

- Consider current practice regarding diagnosis and management and to form a consensus view from the workshop experts

- To provide an update in current research that has potential for translation into clinical trials and clinical practice

- Establish disease specific registries and databases held on web accessible servers

- To provide an update in possible natural history studies/new clinical trials that network members can participate in

- To publish a summary of the consensus views of the experts present at the workshop in Neuromuscular Disorders

- To report findings from the workshop to the annual BMS meeting and reconvene workshop at agreed intervals

We sincerely hope you find this workshop on myotonic dystrophy interesting and useful.

Best wishes

Prof. Michael Hanna
Director, London Newcastle MRC Centre for Neuromuscular Diseases,
UCL - London

Dr Chris Turner
Lead for Myotonic Dystrophy clinical service, MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery – London

Dr David Hilton-Jones
Director, MDC Oxford Muscle and Nerve Centre, University of Oxford

Aims of the MRC Centre Myotonic Dystrophy workshops

- Establish a DM network of UK clinicians/scientists/therapists
- Develop a National DM patient registry/database
- Develop National Clinical Guidelines for management of DM
- Groundwork for UK therapeutic and natural history trials in DM
- Seek and coordinate funding for basic science and clinical research in DM
- Develop international networks
- Establish a UK National Working Party for DM with key members
- Education and update in DM

Dr Chris Turner
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Programme

09:00-09:30	Coffee	
Session One	**Chairs: Professor Mike Hanna and Dr Chris Turner**	
09:30-09:45	Introduction	Prof Mike Hanna/ Dr Chris Turner
9:45-10:15	Excessive daytime sleepiness and respiratory failure in DM1	Dr David Hilton-Jones
10:15-10:45	The heart in DM: cardiac monitoring	Dr Perry Elliott
10:45-11:15	Muscle and brain in DM	Dr Chris Turner
11:15-11:45	GI involvement in DM	Dr Mark Roberts
11:45-12:15	Coffee	
Session Two	**Chairs: Professor Charles Thornton and Professor Darren Monckton**	
12:15-12:45	Unstable DNA in myotonic dystrophy: causes and consequences	Prof Darren Monckton
12:45-13:15	Treatments for myotonic dystrophy that target RNA	Prof Charles Thornton
13:15-14:15	Lunch, Old Board Room	
Session Three	**Chairs: Professor David Brook and Dr David Hilton-Jones**	
14:15-14:45	Developing assays for drugs to treat DM	Prof David Brook
14:45-15:15	Clinical databases and registries	Prof Hanns Lochmüller/ Dr Mark Rogers
15:15-15:30	Myotonic Dystrophy Support Group	Mrs Margaret Bowler
15:30-16:00	Coffee break	
16:00-17:00	Round Table discussion The next step: clinical databases, biobanks, natural history studies, therapeutic trials, DM-Net	
17:30 – 18:15	**MRC Centre Special Guest Lecture** Animal models and human treatments for Myotonic Dystrophy	**Prof Charles Thornton**
18:15 – 19:00	Drinks, lecture theatre foyer, 33 QS	

Speaker Abstracts

Excessive daytime sleepiness and ventilatory insufficiency in DM1
David Hilton-Jones, Oxford

Excessive daytime sleepiness is a common symptom of neuromuscular disorders associated with hypoventilation and sleep fragmentation. Ventilatory insufficiency and excessive daytime sleepiness are both very common in myotonic dystrophy, but there is surprisingly little correlation between the two.

Ventilatory insufficiency is a major cause of morbidity and mortality in myotonic dystrophy. Coupled with aspiration the major consequence is chest infection which is a common terminal event in all age groups. Anaesthesia not infrequently precipitates ventilatory failure.

Excessive daytime sleepiness is present to a greater or lesser extent in over 50% of patients with myotonic dystrophy and can have a major effect on quality of life. Despite frequent evidence of hypoventilation and disturbed sleep, the major cause of excessive daytime sleepiness seems to be an inherent feature of the disease itself, and may correlate with pathological changes noted in the brainstem. Even when present, treatment of hypoventilation (e.g. non-invasive ventilation) infrequently helps the sleepiness. Despite lack of large scale studies, psychostimulant drugs (e.g. modafinil) appear to be beneficial for many patients.

Further studies are needed of both hypoventilation, and its consequences, and excessive daytime sleepiness.

Muscle and central nervous system involvement in myotonic dystrophy
Chris Turner, Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, London

The defining features of myotonic dystrophy (DM) are progressive weakness of typical groups of muscles as well as myotonia. The weakness often causes significant morbidity and may contribute towards the early mortality associated with aspiration pneumonia caused by dysphagia, diaphragmatic weakness and possibly somnolence. Pharmacological treatment for muscle weakness and wasting has not proved effective and a better understanding of the dystrophic mechanisms will be important for development of future treatment. The myotonia of DM is traditionally described as being less clinically significant in comparison to the non-dystrophic myotonias and is usually not treated, especially if the patient has co-existent cardiac involvement. The molecular mechanisms underlying myotonia are better understood than dystrophy. Selective groups of patients may be suitable for treatment of myotonia.

Central nervous system (CNS) involvement in DM is increasingly recognised with several recent studies demonstrating focal brain atrophy associated with a dysexecutive syndrome and memory loss. CNS involvement may also explain problems with excessive daytime sleepiness as well as disturbances in behaviour and personality.

If cardiorespiratory complications of DM are monitored and treated successfully, progressive cognitive impairment and dementia may place CNS involvement as the most important organ to be affected in DM.

GI involvement in myotonic dystrophy

Mark Roberts
Salford Royal NHS Foundation Trust

Involvement of the gastrointestinal tract is increasingly recognised in patients with myotonic dystrophy (MD), and may be selective or affect its entire length: The frequent correlation between bulbar palsy and the attendant risks of often silent aspiration in pneumonia are emphasised. The utility of endoscopy (FESS) and barium swallow studies is emphasised. Oesophageal dysmotility with associated dysphagia and heartburn are common in MD patients. Gall bladder and hepatic dysfunction (which may lead to erroneous over investigation) are frequent issues in many patients. Small bowel involvement with smooth muscle atrophy and myotonia result in impaired peristalsis and bacterial overgrowth resulting in abdominal pain, bloating, steatorrhea and malabsorbtion. Colonic involvement with diarrhoea, constipation or an irritable bowel phenotype is frequently encountered. The significant impact of these gastrointestinal problems including pain, fatigue and weight loss, problems of habitual diet, and impaired nutrition are discussed.

Potential treatments for myotonic dystrophy that target RNA

Charles Thornton, MD
University of Rochester Medical Center

The disease process in myotonic dystrophy is complicated and our understanding of it is still incomplete. Despite these limitations, events over the last three years are beginning to suggest that RNA-mediated mechanisms in myotonic dystrophy could prove to be unusually susceptible to therapeutic intervention. Most researchers who are working on the problem are using one means or another to target the toxic, repeat-containing RNA. For example, one approach taken by several research groups is to find “small molecule” drug-like compounds that can block the interaction of CUG repeat with RNA binding proteins. Because drug development traditionally has focused on protein targets rather than RNA, there is considerable uncertainty about the process whereby these compounds can be identified and the extent to which specific targeting of the repeat RNA is necessary or feasible. Another approach involves the use antisense oligonucleotides (ASOs). Impressive effects have been achieved in laboratory testing, but whether these can be translated into the clinic is an open question. This presentation will summarize recent efforts to find small molecule or ASO treatments for myotonic dystrophy.

Developing assays for drugs to treat DM

J David Brook
University of Nottingham

Over the past 20 years significant progress has been achieved in understanding the molecular pathology underlying Myotonic Dystrophy (DM). It is widely considered that DM1 is caused by a dominant RNA gain of function mechanism, in which the expansion of a repeated trinucleotide DNA sequence, CTG, is the primary event. Expression of the repeat sequence, which is located within the 3' untranslated region of the DMPK gene, results in repeat expansion transcripts that remain in the nucleus and do not get exported to the cytoplasm. Such transcripts have two effects; they activate one class of proteins, CUG-BP, and sequester another, MBNL. Together these actions result in the perturbation of alternative splicing, which affects many different transcripts producing an inappropriate ratio of isoforms. A better understanding of the molecular events underlying DM has led to the development of strategies and assays to identify compounds that may provide the starting points for therapeutic intervention in DM. Our group and others have set about identifying small molecules that may be useful in DM therapy. This presentation will outline the development of drug screening assays from our laboratory and summarise the published literature on attempts to identify drugs to treat DM.

Clinical Databases and Registries

Mark Thomas Rogers, University Hospital of Wales, Cardiff
Hanns Lochmüller, Institute of Human Genetics, Newcastle University

There are exciting developments in the field of myotonic dystrophy. Internationally progress has been made towards unravelling the molecular mechanisms behind DM and the prospects of developing clinical trials are starting to become realistic. Following a number of International Meetings within the DM clinical and research community there is a ground-swell of opinion that trials will only be feasible if there is a co-ordinated International effort at identifying and enrolling significant numbers of DM patients. An expert consensus workshop in Naarden, The Netherlands concluded that participant countries would aim to develop National Registries feeding into an International Registry that would be co-ordinated through TREAT-NMD (Thompson et al., 2009). The establishment of a UK Myotonic Dystrophy Research Database will be the beginnings of the UK contribution to this international pool of patients. A core dataset for the DM1 registries, comprising genetic and clinical data, and best practice guidelines for the registry were agreed and presented both at the IDMC-7 conference in Würzburg (Germany) and at a national meeting in Newcastle (July 16, 2009). Our presentation will outline the steps taken towards developing a UK Research Registry for Myotonic Dystrophy. The background to, aims of, and likely structure of the database will be presented.

Further reading:

Thompson R, Schoser B, Monckton DG, Blonsky K, Lochmüller H. Patient Registries and Trial Readiness in Myotonic Dystrophy--TREAT-NMD/Marigold International Workshop Report. Neuromuscul Disord. 2009 Dec;19(12):860-6.

Myotonic Dystrophy Support Group and clinical research
Mrs Margaret Bowler SRN SCM. (MDSG chairperson)

The MDSG currently has approximately 2000 members. This is the largest network of patients and relatives with DM in the UK. In the past, there has always a good response when members have been called upon to participate in research. Research contributions have included donations of the rare skin tumour associated with DM, the pilomatrixoma, as well as skin biopsies. Patients have also donated tissue from planned surgery, and post-mortem specimens.

The Annual MDSG Conference has always acted as an excellent source of spreading information to patients and relatives about DM research and sometimes research has been carried out during the conference such as anaesthetic research into the airway of patients with DM using jaw measurements.

The MDSG has been able to directly fund PhD students to attend IDMC meetings as well as raise money to fund small research projects and pieces of laboratory equipment.

The MDSG is keen to be involved in the development of A National DM Database as well as future fund raising for further clinical research.

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About the MRC Centre for Neuromuscular Diseases

The MRC Centre for translational research in neuromuscular diseases: a London-Newcastle partnership to form UK-wide translational research networks

Genetic and acquired neuromuscular diseases represent a major cause of mortality and morbidity in children and adults. There is a large gap between major science discoveries and patient benefit in these important disorders. Over the past two years, the MRC Centre has been working to reduce this gap by establishing a multidisciplinary translational research activity in these disabling diseases.

This is a joint centre between the UCL Institute of Neurology and the UCL Institute of Child Health, London and the University of Newcastle. The Centre is building on long-established UCL-Newcastle research and clinical links. The centre has established reciprocal clinical and research links with other neuromuscular research groups and patient organisations throughout the UK including the Muscular Dystrophy Campaign. The Centre is working with the very large adult and paediatric neuromuscular disease patient populations cared for at the co--located hospitals: Great Ormond Street NHS Trust, the National Hospital for Neurology and Neurosurgery -Queen Square, UCLH NHS Foundation Trust and Newcastle Upon Tyne Hospitals NHS Foundation Trust.

Highlights of the London-Newcastle Centre over the past 12 months

- Third annual MRC MDC UK translational research conference held in Oxford, attracting over 250 clinicians and scientists showcasing the best neuromuscular science

- Initiated and support over 25 separate neuromuscular UK clinical trials, natural history studies and MRI studies including muscular dystrophy, muscle ion channel disorders and inherited neuropathy. This is now the largest number of such trials in any European centre. We have recruited a further nationally commissioned service for young patients with metabolic muscle disease.

- Continued to develop the UK neuromuscular biobank as a tissue resource for research and for testing potential new therapies

- Established the Newcastle London MRC Centre national mitochondrial patient cohort study aiming to collect over one thousand mitochondrial patients for future clinical trials

- State of the art Neuromuscular Trials Unit opened in London and coordinating with Newcastle. The trials unit in the heart of the London part of the Centre is now full equipped with all the equipment essential to undertaking detailed muscle strength measures. We have recently commenced exercise physiology studies in the centre to systematically assess benefits of defined exercise regimes in specific muscle wasting diseases in young adults- in collaboration with Newcastle.

- In London Call clinical and research teams focussed on young adults with muscle wasting diseases brought together in new physical Centre. All the clinical and research teams - now amounting to over 60 staff - are located in the Centre and continue to provide an outstanding base to advance clinical research and clinical trials.

- A major mission of the London Newcastle Centre is to train young scientists to carry out research to advance treatments for patients with neuromuscular diseases. The Centre continues to be oversubscribed nationally and internationally. Professor Hanna and the team are actively fundraising to enable a greater number of young scientists to have the opportunity to train in this way and have been successful with certain muscle disease charities.

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Appendices

1. MRC Centre for Neuromuscular Diseases clinical trials
2. TREAT NMD database for DM1
3. Cardiff Protocol for the clinical assessment of patients with myotonic dystrophy
4. Myotonic Dystrophy Support Group
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1. MRC Centre for Neuromuscular Diseases clinical trials

Clinical trials linked to the MRC Centre and supported by different funding agencies including the Medical Research Council, Muscular Dystrophy Campaign, UK Department of Health, National Institutes of Health (USA), Food and Drug Administration (USA), AVI Biopharma and PTC Therapeutics.

Completed Trials

RESTORING DYSTROPHIN EXPRESSION IN DUCHENNE MUSCULAR DYSTROPGY: A PHASE I/II CLINICAL TRIAL USING AVI-4658
Status: Completed (closed to recruitment)
Sponsor: Imperial College London
Funder: Department of Health (DoH)
PIs: Prof. Muntoni Bushby

The primary scope of the trial is to assess efficacy (dystrophin production) and safety of intramuscular administered morpholino oligomer directed against exon 51 (AVI – 4658 PMO).Antisense therapy with the use of antisense oligomers has the potential to restore effectively the production of dystrophin, the defective protein, in >70% of DMD. This could result in increased life expectancy through improved muscle survival and function. Recent scientific research has demonstrated the potential of this technique to skip mutated dystrophin exons, restore the reading frame and generate functional dystrophin protein. Having demonstrated proof-of-principle in human cell culture and animal model studies, we now intend to determine efficacy and safety of this approach to induce dystrophin exon skipping in children with DMD. This study is aimed at children with Duchenne muscular dystrophy above the age of 10 years with mutations than can be rescued by the skipping of exon 51 [45-50; 47-50; 48-50; 49-50; 50; 52; 52-63].

RANDOMISED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF LONG-TERM ASCORBIC ACID TREATMENT IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A
Status: Follow-up phase (closed to recruitment)
Sponsor: University College London
Funder: Muscular Dystrophy Campaign (MDC)
PI: Dr. Reilly

Charcot-Marie-Tooth disease 1A (CMT1A) is associated with a duplication of the peripheral myelin protein 22 (PMP22) gene. To date there is no pharmacological treatment for CMT1A patients. Treatments and therapy for CMT is restricted to symptomatic treatments such as physiotherapy and surgery for skeletal deformities.

Recently, treatment with ascorbic acid (AA) has been shown to be effective for transgenic mice over-expressing PMP22, a model of the human disease. Treated animals had much less severe neuropathy as compared to untreated controls as shown by clinical and histological findings. Some clinical parameters even improved during treatment.

This is a phase III prospective, multi-centre, randomized, double-blind, placebo-controlled study aiming to evaluate the efficacy of AA treatment in CMT1A.

The study has been running now almost for two years and it is now in the follow-up phase. Fifty participants were enrolled in the UK site at the National Hospital for Neurology and Neurosurgery.

For information about the study please contact Dr. Matilde Laura at m.laura@ion.ucl.ac.uk.

Open Trials

THERAPEUTIC TRIAL OF MEXILETINE IN NON-DYSTROPHIC MYOTONIA

Full Title: A Phase II Randomized, Double-Blind, Placebo controlled, Cross-Over Study to Investigate the Efficacy of Mexiletine in Patients with Non-Dystrophic Myotonia

Status: Open to recruitment
Sponsor: University College London (UCL)
Start date: June 2009
Funder: Food and Drug Administration (FDA – USA)
PI: Prof. Hanna

The non-dystrophic myotonia (NDM) is a group of rare neuromuscular disorders that causes episodes of muscle stiffness (known as myotonias) and paralysis. Predominantly the muscles of the face, hands and legs are affected. In addition to these episodes a permanent and debilitating muscle weakness can develop. The optimal treatment for these disorders is unknown.

Non-dystrophic myotonias are due to abnormalities of ion channels present in skeletal muscle membranes. There is experimental evidence that drugs like mexiletine which block the abnormal function of these ion channels allow the muscle to perform normally.

The study aims to test the efficacy of mexiletine in the treatment of the non-dystrophic myotonias. This proposal involves a multi-centre, double-blind, placebo-controlled cross over trial of a total duration of nine weeks. Approximately fifteen participants will be enrolled in the UK at the National Hospital for Neurology and Neurosurgery.

For information on the status of recruitment please contact Dr Dipa Raja Rayan at d.rajarayan@ion.ucl.ac.uk.

ECULIZUMAB FOR MYASTHENIA GRAVIS

Full Title: A Randomised, Double-Blind, Placebo-controlled, Cross-over, Multicenter Study of Eculizumab in Patients with Generalised Myasthenia Gravis (GMG) who have Moderate to Severe Muscle Weakness Despite Treatment with Immunosupressants

Status: Open to recruitment
Sponsor: Alexion Pharmaceuticals, Inc.
Planned start date: Dec 09
Funder: National Institutes of Health (NIH - USA)
UK PI: Prof. Dimitri Kullmann

This is a randomized, double-blind, placebo-controlled, cross-over, multicenter study to evaluate the safety and efficacy of eculizumab for the treatment of patients with myasthenia gravis. There are four stages in the study, the Screening Period, the first Treatment Period, the Wash-Out Period, and the second Treatment Period (the cross-over Treatment Period). Myasthenia gravis (MG) is an acquired autoimmune syndrome caused by the failure of neuromuscular transmission, which results from the binding of autoantibodies to proteins involved in signalling at the neuromuscular junction (NMJ). These proteins include the nicotinic AChR or, less frequently, a

muscle-specific tyrosine kinase (MuSK) involved in AChR clustering. Current available treatments for myasthenia gravis aim to modulate neuromuscular

transmission, to inhibit the production or effects of pathogenic antibodies, or to inhibit inflammatory cytokines. There is currently no specific treatment that corrects the autoimmune defect in MG.

Eculizumab is a humanized murine monoclonal antibody that blocks the activation of complement by selectively binding to C5 and preventing the enzymatic cleavage of C5 to C5a and C5b. The blockade of complement activation at this point in the cascade has been shown to prevent the proinflammatory effects of both C5a and C5b, especially the chemotaxis of inflammatory cells, and MAC (C5b-9)-mediated cell activation and lysis. Since eculizumab effectively inhibits complement, especially MAC formation, it is a potentially effective therapeutic approach for diseases such as MG in which the formation of the MAC and/or the release of C5a leads to localized destruction of the postsynaptic NMJ membrane and play a important role in the disease process.

Each patient who completes the study will receive approximately 22 infusions including 11infusions of eculizumab and 11 infusions of placebo. The estimated duration of a patient's participation is approximately 41 weeks.

For more information about the study please contact Dr. Jennifer Spillane at j.spillane@ion.ucl.ac.uk.

DMD HEART PROTECTION TRIAL
Full-Title: A double-blind randomised multi-centre, placebo-controlled trial of combined ACE-inhibitor and beta-blocker therapy in preventing the development of cardiomyopathy in genetically characterised males with DMD *without* echo-detectable left ventricular dysfunction.

Status: Site Specific Approval pending
Sponsor: Newcastle NHS Foundation Trust
Planned start date: 2010
Funder: British Heart Foundation
PI: Dr John Bourke, Prof. Muntoni

Duchenne muscular dystrophy [DMD] is an X-linked recessively inherited neuromuscular disorder due to a deficiency in the expression of the protein dystrophin on the inner aspect of cell sarcolemma. Its clinical course has traditionally been characterized by progressive weakness of proximal limb-girdle muscles and calf muscle hypertrophy. Duchenne-affected individuals typically lose ambulation and become wheelchair dependent before the age of 13 and die from cardio-respiratory failure at around the age of 20 years. From the cardiology perspective, some 90% of males with DMD develop a severe, progressive form of cardiomyopathy. Twenty to 30% have evidence of left ventricular impairment on echocardiography by age 10 years.

Abnormalities in left ventricular function are evident in an even larger proportion of patients at all ages when more sensitive imaging techniques, such as tissue Doppler, magnetic resonance or metabolic imaging, are deployed. Despite the severity of cardiac involvement in DMD, cardiologists have largely ignored this particular inherited form of cardiomyopathy. This is due to the fact that, because of their inability to exercise, cardiac symptoms only occur terminally in DMD patients when all cardiac reserve has been eroded. Even today in most hospitals, cardio-active drug therapy is

only started in patients with DMD when overt heart failure is evident and, even then, is typically deployed tentatively for symptom control, without any expectation that it can prolong life.

The objective of this trial is to determine whether the introduction of ACE-inhibitor combined with beta-blocker therapy, before the onset of echo-detectable left ventricular dysfunction, can delay the age of onset and/or slow the rate of progression of cardiomyopathy compared to placebo in males with DMD. This is a double-blind randomized, placebo-controlled Phase III trial of combined ACE inhibitor and beta-blocker therapy (perindopril and bisoprolol) over a minimum of three years and a maximum of five years. 140 participants (70 per arm) are to be enrolled and randomised.

For more information about the study please contact trial coordinator Rahela Choudhury at r.choudhury@ich.ucl.ac.uk.

ARIMOCLOMOL FOR SPORADIC INCLUSION BODY MYOSITIS (IBM)
Full Title: A Randomized, Double-blinded, Placebo-controlled Pilot Study Assessing the Safety and Tolerability of Arimoclomol in Adult Patients with Sporadic Inclusion Body Myositis

Status: Open to recruitment
Sponsor: University College London (UCL)
Planned start date: June 2010
Funder: Medical Research Council (MRC)
PI: Prof. Hanna

Sporadic Inclusion Body Myositis (IBM) is the commonest acquired disease of muscle affecting people aged 50 years and over. This is a progressive and debilitating disease with both muscle weakness and wasting, characteristically of the quadriceps and finger flexors. Over time the condition can lead to severe disability, falls and swallowing impairment. Affected muscle tissue demonstrates inflammation and degeneration.

Arimoclomol is a new compound which acts by enhancing a normal, inbuilt protective cell reaction to stresses. The products of this response are 'Heat Shock Proteins (HSPs) which counteract processes that end up leading to abnormal protein deposition and to damage mediated by inflammation.

This proposal involves a multi-centre, double-blind, placebo-controlled parallel study of total duration twelve weeks.

This study proposal aims to assess the safety and tolerability of Arimoclomol (100 mg TDS) as compared with placebo over 4 months of treatment in patients with IBM.

Recruitment will take place at the National Hospital for Neurology and Neurosurgery and twelve patients will be enrolled.

For information on the status of recruitment please contact Dr Adrian Miller at a.miller@ion.ucl.ac.uk.

A PHASE IIb EFFICACY AND SAFETY STUDY OF PTC124 IN SUBJECTS WITH NONSENSE MUTATION-MEDIATED DUCHENNE AND BECKER MUSCULAR DYSTROPHY

Status: Ongoing (closed to recruitment)
Sponsor: PTC Therapeutics
Funder: PTC Therapeutics
PIs: Prof. Bushby, Prof Muntoni

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder affecting young boys. The condition is disabling and life-threatening. A small subset of boys are classified as having Becker muscular dystrophy (BMD), a phenotypically milder form of the dystrophic muscle disease.

In approximately10 to 15% of boys with DMD and BMD the causative defect is the presence of a nonsense mutation in the dystrophin gene that truncates dystrophin protein production by introducing a premature stop codon into the dystrophin messenger ribonucleic acid (mRNA).

PTC124 is a novel, orally bioavailable, small-molecule drug that promotes ribosomal read-through of mRNA containing a premature stop codon. Through this mechanism of action, PTC124 has the potential to overcome the genetic defect in boys for whom a nonsense mutation causes DMD/BMD.

In vitro studies in cell lines with dystrophin nonsense mutations have shown that PTC124 can restore production of the missing dystrophin gene.

This is an international, multi-centre, randomized, double-blind, placebo-controlled, dose-ranging, efficacy and safety study.

The study primary aim is to evaluate the effect of PTC124 on ambulation as assessed by the distance walked during a 6-minute walk test (6MWT).

The double-blind arm of the study randomised 174 participants worldwide which were followed for a period of 12 months. At the completion of the blinded treatment, eligible and compliant participants went on to receive PTC124 (Atularen) in an open-label extension study. However, this study was prematurely discontinued based on a decision made by the Data Monitoring Committee, following the analysis of 6-minute walk-test (primary endpoint) data showing no statistical difference in placebo and active treatment in the main study. Dystrophin expression data is yet to be fully analysed.

(Ataluren is now the non-proprietary generic name for PTC124).

New PTC 124 in non-ambulant DMD has been suspended
PI Prof Katie Bushby

ANTISENSE OLIGONUCLEOTIDE INDUCED EXON SKIPPING IN DUCHENNE MUSCULAR DYSTROPHY

This initiative is led by the MDEX consortium (The MDEX consortium led by Professor Muntoni, is a multidisciplinary enterprise to promote translational research into muscular dystrophies, and is formed by the clinical groups of Professor Francesco Muntoni (UCL Institute of Child Health) and Professor Kate Bushby and Professor Volker Straub (Newcastle University), and scientists from Imperial College London (Professor Dominic Wells), UCL Institute of Child Health (Dr Jennifer Morgan), Royal Holloway University of London (Professor George Dickson and Dr Ian Graham),

Oxford University (Dr Matthew Wood) and University of Western Australia (Prof Steve Wilton). In addition, the charities Muscular Dystrophy Campaign (MDC), Action Duchenne and Duchenne Family Support Group also participate in the Consortium, www.mdex.org.uk).

The current two trials led by the consortium are mentioned below.

DOSE-RANGING STUDY OF AVI-4658 TO INDUCE DYSTROPHIN EXPRESSION IN SELECTED DUCHENNE MUSCULAR DYSTROPHY (DMD) PATIENTS – (Systemic study)Status: Ongoing (closed to recruitment).
Sponsor: AVI Biopharma
Funder: Medical Research Council (MRC) and AVI Biopharma
PIs: Prof. Muntoni Bushby

This is a safety study of AVI-4658 (a 30-base phosphorodiamidate Morpholino oligomer [PMO]), to skip exon 51 of the dystrophin gene in relevant subjects with DMD.This is an open-label, two-centre, dose-ranging comparative clinical study of duration twelve weeks.

The objectives of the study are to assess safety and to select the optimum dose that elicits at least 10% *de novo* dystrophin-positive fibres and dystrophin in a sentinel muscle group after an intravenous AVI-4658 dosing regimen. A total of up to 16 subjects (ambulatory paediatric males, aged ≥5 and ≤15 years of age) will be enrolled in this study, consisting of four treatment cohorts and four subjects per cohort. It is expected that there will be four treatment arms ranging from 0.5 mg/kg to 4 mg/kg. All subjects will receive 12 weekly intravenous infusions of AVI-4658.Precedent studies have demonstrate that AVI-4658 might have therapeutic relevance in managing DMD for boys whose frame-shifted dystrophin gene lesion could be restored after excision of exon 51 if sufficient drug is translocated into the nucleus of the afflicted muscle cell. This trial is being conducted in London and Newcastle. All participants have completed treatment. Analysis of results is ongoing. For further information please contact Guru Ganeshaguru, MDEX Clinical Trials Coordinator (Dr K. Ganeshaguru k.ganeshaguru@ich.ucl.ac.uk) or Geoff Bell, Trials Coordinator (MRC centre Newcastle site) at geoff.bell@nuth.nhs.uk.

CCRN 165 (NDS mito function)
Status: Open to recruitment
PI: Prof Chinnery

A phase 2a, double blind, randomised, placebo-controlled, 28 day, two-arm, parallel group study of A0001 in patients with the A3243G mitochondrial DNA point mutation and evidence of impaired mitochondrial function.

PI – Professor P.F. Chinnery, Department of Neurology, Newcastle University, and Newcastle upon Tyne Foundation Hospitals NHS Trust.

The primary objective of this study is to establish proof of concept of the efficacy of A0001 in the treatment of patients with an established mitochondrial disorder using metabolic imaging, a number of functional assessments, biochemical measures and patient/clinical-rated scales.

Secondary objectives of the study are to evaluate the tolerability and safety of A001 in this patient population and to establish pharmacokinetics of A0001 in this patient population.
Patients will be invited to participate if they fit the inclusion criteria which briefly consists of aged 18 – 70 (male or female), confirmed carriers of the A3243G mitochondrial DNA point mutation, with one or more of the associated symptoms and are capable of performing the required tests associated with this study (MRI,MRS, 6 minute walk test).
The study will recruit approximately 30 patients, which should ensure 21 (14 on treatment, 7 on placebo) evaluable patients, which will give sufficient power to detect an improvement of 50% on one of the outcome variables, the primary endpoint being improvement in the rate of ATP recovery in cardiac muscle as measured by P-MRS.
Following informed consent and screening, patients will be randomized to receive 28 days of either A0001 capsules (to be taken orally) at dose level of 0.75g BID (1.5g total daily dose) or placebo.
PK samples will be collected at Baseline and days 4,7,11,14,21 and 28
Safety will be evaluated by history updates, physical examinations, vital sign assessments, 12 lead ECG, routine blood lab analysis and adverse event assessments.
This study is open to recruitment, for further information contact P.F.Chinnery p.f.chinnery@newcastle.ac.uk, Dr G Gorman Grainne.Gorman@newcastle.ac.uk or Mr G Bell Geoffrey.bell@ncl.ac.uk

Exercise Studies

STRENGTHENING HIP MUSCLES TO IMPROVE WALKING DISTANCE IN PEOPLE WITH CHARCOT- MARIE-TOOTH DISEASE
Status: Closed to recruitment
Sponsor: University College London Hospitals
Funder: Muscular Dystrophy Campaign (MDC)
PI: Dr. Reilly
Charcot-Marie-Tooth (CMT) disease is a form of hereditary peripheral neuropathy. People with CMT present with weakness, wasting and sensory loss as a result of degeneration of the long peripheral nerves supplying the distal muscles.
The aim of this study will be to investigate the efficacy of a 16 week home based programme of training to increase hip flexor muscle strength and walking endurance. Additional measures of gait speed, exertion, fatigue, disability and general activity will also be recorded. Baseline impairment measures will be obtained to ascertain predictors of strength gains.

This study will use a single blinded, randomized cross over design to investigate if training the hip flexor muscles will strengthen the hip flexor muscle and improve walking endurance in people with all types of CMT.
The trial will included people, aged between 18 and 70 years, who have been diagnosed with CMT on the basis of genetic tests (where possible), family history and neurophysiology testing. Each subject will be involved with the study for a 40 week period. For further information please contact Dr Gita Ramdharry, Research Physiotherapist at g.ramdharry@ion.ucl.ac.uk.

EXERCISE TRAINING IN PATIENTS WITH MITOCHONDRIAL DISEASE: ASSESSING THE BENEFITS
Status: Open to recruitment
Sponsor: University Newcastle
Funder: Muscular Dystrophy Campaign (MDC)
PI: Prof. Turnbull
Mitochondrial myopathies are a very important group of muscle diseases associated with weakness, pain and fatigue. At present, treatment options are very limited. Exercise therapy has been found to have some benefit in this group of patients and we wish to explore this further in terms of both strength and endurance.
The aim of this study is to demonstrate that strength exercise training is an effective approach to therapy in certain patients with mitochondrial myopathy, specifically those with sporadic mutations in mitochondrial DNA. Based on our previous research studies, we believe that such training will improve muscle strength, mitochondrial function, exercise tolerance and overall quality of life.
The main objectives will be:
1) To confirm that endurance training in patients with mitochondrial abnormalities improves quality of life, exercise tolerance and oxidative capacity.
2) To determine the ability of resistance muscle strength training to improve skeletal muscle strength and oxidative capacity by incorporation of satellite cells into mature myofibres.
Participants are expected to commit to an exercise training and testing over a period of 4 to 8 months.
The study will include patients between the ages of 18 and 65 years who have had a previous muscle biopsy showing a defect in skeletal muscle mitochondrial DNA that is either in the form of a sporadic point mutation or single large-scale deletion. Patients who have this type of mutation and do not have any family members that are affected and have no major cardiac involvement, hypertension, pulmonary or peripheral vascular disease that may complicate findings.
For information about recruitment contact Geoff Bell at geoff.bell@nuth.nhs.uk.

Open Natural History – Longitudinal Studies

NON-DYSTROPHIC MYOTONIAS: GENOTYPE AND PHENOTYPE CORRELATION AND LONGITUDINAL STUDIES
Status: Closed to recruitment
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
UK PI: Prof. Hanna

This multi-centre project involves a prospective, cross-sectional and longitudinal natural history in non-dystrophic myotonias (NDM).
The aim is to collect standardized data from NDM patients, to include clinical symptoms, exam findings, as well as the results of strength, functional, and electrophysiological testing. Genetic testing will permit precise identification of individual NDM subtype. This information will allow for the identification and implementation of appropriate endpoints in studies of potential treatments.
This is a NIH funded study. Twenty patients were enrolled at the National Hospital for Neurology and Neurosurgery.
For more information about the study please contact Dr Dipa Raja Rayan at d.rajarayan@ion.ucl.ac.uk.

ANDERSEN-TAWIL SYNDROME: GENOTYPE AND PHENOTYPE CORRELATION AND LONGITUDINAL STUDY
Status: Open to recruitment
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
UK PI: Prof. Hanna

Andersen-Tawil syndrome is a neuromuscular disorder caused by a mutation in the KCNJ2 gene which codes for the inwardly rectifying potassium channel Kir2.1. A number of different mutations in this gene have already been identified in affected individuals. This disorder is characterized by the triad of periodic paralysis, developmental abnormalities and cardiac arrhythmias.
This project is a natural history trial into Andersen-Tawil Syndrome. The aim of the trial is to study the relationship between the genetic abnormalities underlying the disorder and the diverse clinical features.
Eight patients have been enrolled so far at the National Hospital for Neurology and Neurosurgery.
For more information about the study please contact Dr Dipa Raja Rayan at d.rajarayan@ion.ucl.ac.uk.

CHARCOT-MARIE-TOOTH DISEASE AND RELATED DISORDERS: A NATURAL HISTORY STUDY
Status: Open to recruitment
Sponsor: UCLH NHS Foundation Trust
Funder: National Institute of Health, USA
PI: Dr M Reilly
Co-PI: Prof F Muntoni, Dr M Laura
The main aims of this study are to:
Collect natural history data on CMT and related disorders Identify genetic factors that cause and modify Charcot-Marie-Tooth neuropathies.
CMT is the most common inherited neurological disorders for which there are no established treatments and there is a need to fully characterise the disease and the different genetic components.
Other aims are to:
Establish a scoring system for quantifying impairment in young children with various forms of CMT (most patients with CMT develop their first symptoms in the first two decades of life - in childhood).
The success of the paediatric scoring system will be determined by whether it can reproducibly quantify disease progression in children with various types of CMT.
Establish a Website Resource for the Inherited Neuropathies for patients, families and investigators.
For further information, please contact Rahela Choudhury at r.choudhury@ich.ucl.ac.uk.

Planned Trials

HYP HOP: DICHLORPHENAMIDE vs. PLACEBO FOR PERIODIC PARALYSIS
Status: Open to recruitment
Sponsor: University College London (UCL)
Funder: National Institutes of Health (NIH - USA)
UK PI: Prof. Hanna
This is a phase III trial into Periodic Paralysis planned to start in 2010. This proposal involves a multi-centre, double-blind, placebo-controlled parallel group, nine-week studies comparing the effects of dichlorphenamide(DCP) vs placebo in patients with period paralysis (Hyper, Hypokalaemic periodic paralysis). The 9-week studies will investigate the prevention of attacks of weakness and it will be followed by 1-year double-blind extensions without placebo to compare the long term effects of DCP vs ACZ on the course of the diseases and on inter-attack weakness. Approximately 40 participants will be recruited from the United Kingdom.

For information on the status of recruitment please contact Dr. James Burge at James.burge@uclh.nhs.uk.

A PHASE II, DOUBLE BLIND, EXPLORATORY, PARALLEL-GROUP, PLACEBO CONTROLLED CLINICAL STUDY TO ASSESS TWO DOSING REGIMENS OF GSK2402968 FOR EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS IN AMBULANT SUBJECTS WITH DUCHENNE MUSCULAR DYSTROPHY
Status: Set-up phase
Sponsor: GlaxoSmithKline
Funder: GlaxoSmithKline
PI: Profs F. Muntoni, V. Straub & K. Bushby
GSK2402968 has been explored at doses up to 6mg/kg subcutaneous (s.c.) weekly initially for 5 weeks in ambulant subjects with Duchenne Muscular Dystrophy (DMD). An open-label extension protocol is ongoing, and to date subjects have received GSK2402968 6mg/kg/week for at least 3 months. GSK2402968 appears to be well-tolerated, and has the potential to be efficacious based on the dystrophin expression previously observed in muscle biopsies. However, more information is needed to determine dosing regimens for optimal therapeutic safety margin in relation to efficacy.

This study is designed to explore efficacy and safety of GSK2402968 given as a continuous regimen over 24 and 48 weeks. For further information please contact Rahela Choudhury, Clinical Trials Coordinator at r.choudhury@ich.ucl.ac.uk. .
NOTE: GSK2402968 formerly know as PRO051

TAPP: THERAPEUTIC TRIAL OF POTASSIUM AND ACETAZOLAMIDE IN ANDERSEN-TAWIL SYNDROME
Status: Set-up Phase
Sponsor: University College London (UCL)
Funder: National Institutes of Health (NIH – USA)
UK PI: Prof Hanna
Andersen-Tawil Syndrome (ATS) is a rare form of periodic paralysis that is associated with serious heart-rhythm abnormalities. ATS is characterized by a triad of episodic muscle weakness, long-QT syndrome with potentially fatal cardiac dysrhythmias and skeletal developmental anomalies. The underlying cause of this potentially fatal condition is only partly understood and there are no established treatments. Mutations in the KCNJ2 gene encoding Kir2.1, an inward-rectifying potassium channel account for

approximately 60% of ATS cases (termed ATS1), the remaining 40% are presumed to have an as yet undetermined gene lesion and are designated ATS2. ATS1 and ATS2 are phenotypically indistinguishable.
The treatment of ATS has been largely anecdotal and empirical.
This proposal involves a multi-centre, placebo-controlled 'n of 1' study design of total duration 45 weeks. The expected total enrolment for this multi-centre study is 16 participants.
The aim of this study is to determine whether potassium supplements and/or acetazolamide alter the duration of muscle weakness and potentially life-threatening heart rhythm abnormalities in patients with ATS.
For information on the status of recruitment please contact Dr. James Burge at James.burge@uclh.nhs.uk.

OUTCOME MEASURES IN SMA TYPE II AND III
Status: Set-up phase
Funder: SMA Europe
PI: Profs Muntoni, Straub, Bushby
This project provides an excellent opportunity as for the first time, ten leading neuromuscular centers in Europe which have been involved in the development and validation of functional scales for SMA will collaborate to validate and cross validate measures that have been suggested to be the most suitable for multicentric trials by a large international consensus, but have not been tested in large multicentric studies yet.
One hundred and thirty patients affected by type II and type III SMA will be enrolled and assessed at baseline and 6 and 12 months later. Non ambulant patients will be assessed using the modified version of the Hammersmith Motor Functional Scale while ambulant patients will be assessed using the extended module of the Hammersmith Motor Functional Scale and timed items, the 6 minute walk and a step activity monitor. All patients will also be assessed using the MFM, that covers the whole range of activities for both ambulant and non ambulant patients. All measures will undergo a process of validation including inter observer reliability. This information will be most valuable for any future trial and will make the groups involved ready to participate to future collaborative studies saving a lot of time on the preliminary aspects (validation, reliability, training) that will be fulfilled by the present study. The study will also provide natural history data for a 12 month period on patients. Please contact Rahela Choudhury, Clinical Trials Coordinator at r.choudhury@ich.ucl.ac.uk for further details.

PERIPHERAL NEUROPATHY OUTCOME MEASURES STANDARDISATION STUDY (PERINOMS)
Status: set-up phase
Sponsor: Erasmus Medical Center
PI: Dr M. Lunn

The current study aims to expand the clinimetric knowledge on outcome measures at various levels of outcome (pathology, impairment, activity & participation limitation, and quality of life) in autoimmune polyneuropathies, particularly in GBS, CIDP, MMN, MGUSP, and autoimmune small fibre neuropathies (AI-SFN). Also, the general applicability of an autonomic symptoms scale plus some selected activity limitation scales will be examined.

Outcome measures will be assessed in a cross-sectional and longitudinal group of patients at the level of:

-Pathology: Intraepidermal nerve fibre (IENF) density will be assessed in patients with GBS, CIDP, MGUSP, and AI-SFN (in sarcoidosis). IENF density will be examined regarding its correlation with other outcome measures (validity), its reliability (intra observer and inter-observer), and its responsiveness to clinical changes over time.

-Impairment: comparison studies, evaluating the validity, reliability, and responsiveness will be performed between MRC sumscore versus NIS motor subset, INCAT sensory sumscore versus NIS sensory sumscore, and hand-held Vigorimeter versus Jamar dynamometer. Also, the correlation of electrophysiological studies with other impairment outcome measures will be evaluated. Finally, the scientific soundness of the modified Dutch composite autonomic symptoms scale (mdCompass) will be examined.

-Activity limitation: comparison studies, evaluating the validity, reliability, and responsiveness will be performed between the ODSS and an overall neuropathy limitations scale (ONLS). Also, a newly devised weighted (based on Rasch analyses) activity and participation scale will be constructed, aiming specifically on the limitations in patients with polyneuropathy.

-Quality of life: Disease-specific versus generic quality of life measures will be assessed, determining their clinimetric soundness and by comparison studies in the various polyneuropathy groups.

The ultimate goal of the current study will be the presentation of a *specific* minimum core set of outcome measures to be used in future clinical and follow-up studies in patients with polyneuropathy, mainly those patients with autoimmune mediated polyneuropathies. The study will be performed in collaboration with several local, European, and USA neurological centres with great experience in dealing with inflammatory neurological disorders.

Imaging Studies

MRI in IBM and CMT

Full Title: A Study of Quantitative Magnetic Resonance Imaging and the Clinical Features of Inclusion Body Myositis and Charcot Marie Tooth
Disease Status: Open to recruitment
Sponsor: University College London Hospitals
Funder: Medical Research Council
PI: T Yousry / J Thornton / MM Reilly / M Koltzenburg / MG Hanna

Magnetic resonance imaging (MRI) is a key tool in the diagnosis and management of a number of diseases. Despite the wide use of MRI in several clinical settings, so far its role in neuromuscular disease has not been well established. The current standard for the diagnosis of neuromuscular disorders includes clinical examination, electrophysiological investigations, biopsy and genetic testing. Due to the nature of the involvement of prominent muscles and peripheral nerves in these disorders it is proposed that MRI could play a prominent role in understanding of neuromuscular disease.

This study aims to investigate the use of MRI as a tool in the study of nerve and muscle diseases by focusing on two particular neuromuscular diseases, one primarily neuropathic and one principally myopathic. Two separate patient cohorts with neuromuscular disease will be recruited. Forty patients with Sporadic Inclusion Body Myositis (IBM) will be recruited and 40 patients with genetically confirmed Charcot Marie Tooth Disease (CMT) will be recruited. In addition to the two patient cohorts, two groups of healthy volunteers each of size 40 will act as comparators for the disease groups. Each of the patients enrolled in the study will undergo an MRI scanning session in which the quantitative MR techniques developed in Phase 1 with the health volunteers will be applied. In addition to the MRI scanning sessions, each patient will undergo a clinical examination to record the main clinical features of their disease status including an electrophysiological nerve conduction assessment. In the final phase of the study, a sub-group of the patients will then be followed-up at 6 month intervals for 5 years in a longitudinal natural history study of IBM and CMT that focuses on the MR methods and clinical findings that were shown to be most illuminating.

Changes over time in the MRI parameters in the diseased groups and Healthy volunteers will be compared.

Objectives:

To detect, using quantitative magnetic resonance imaging (qMRI), the changes in the nerves and muscles of patients with inclusion body myositis or Charcot Marie Tooth disease, and to relate these changes to the measurable clinical and neurophysiological features in these diseases. This will allow the value of various

qMRI techniques as markers of disease activity and progression to be tested.
Secondary objectives of the study include:
-The development of novel quantitative MR techniques for targeted assessment of the human neuromuscular system
-To more fully characterize both the magnetic resonance imaging and clinical features of inclusion body myositis or Charcot Marie Tooth disease as compared with healthy individuals and to study the progression of these characteristics with time over a period of 5 years.
For more information about the study please contact Dr. Jasper Morrow at j.morrow@ion.ucl.ac.uk.

Full-Title: A study using Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) in Patients with Limb Girdle Muscular Dystrophy 2I; an assessment of muscle damage.
Status: Open to recruitment
Sponsor: Newcastle upon Tyne NHS Trust
Funder: MRC Centre for Neuromuscular diseases
PI: Prof. Volker Straub
Re-defined in 1995, the LGMDs are face sparing, proximally predominant, progressive muscular dystrophies with elevated creatine kinase levels and dystrophic features on muscle biopsy. In the current classification system, LGMDs are divided into autosomal dominant (LGMD1) and autosomal recessive (LGMD2) disorders with a superimposed lettering system denoting the chronological order of the chromosomal linkage.
Limb Girdle Muscular Dystrophy 2I (LGMD2I) is caused by a mutation in the fukutin related protein gene (FKRP)1 and manifests temporal variability. Clinically the age of onset, rate of progression and severity varies greatly between cases and even within the same family. They range from asymptomatic patients with mildly raised creatine kinase levels to those severely affected and non ambulant. The respiratory and cardiac complications, well known to occur in this type of muscular dystrophy, in 30% and 60% of patients respectively, occur independently of the general muscle weakness and also cardiac complications occur independently from respiratory compromise.
Magnetic Resonance imaging (MRI) has been increasingly used in imaging in patients with neuromuscular disorders over the past 5 years.
Studies have shown that whilst there is considerable overlap in muscle involvement there is also striking differences that can be of diagnostic value. In both patients with LGMD2A and LGMD2I there is a prominent pattern of involvement of the posterior thigh muscles, however in LGMD2A there is also selective involvement of the medial gastrocnemius and soleus muscles in the lower leg, which was not seen

in LGMD2I. Although it is clearly demonstrated that MRI findings mirror those obtained from clinical examination, it has been reported recently that in fact MRI abnormalities can be detected in patients with neuromuscular disorders when clinical examination of particular muscle groups have been normal. MRI can therefore be useful to show early manifestations of a disease and to monitor the effect of early therapeutic interventions.
Beside MRI another non-invasive technique to consider is phosphorus magnetic resonance spectroscopy (P-MRS). P-MRS studies have demonstrated several metabolic abnormalities in the skeletal muscle of patients with Duchenne Muscular Dystrophy (DMD)/ Becker Muscular Dystrophy (BMD) and in the group of autosomal recessive LGMDs, associated with sarcoglycan deficiency (LGMD2C-F) . These changes are thought to be specific for dystrophies secondary to deficits in the dystrophin-glycoprotein complex. In these patients there appears to be an increased cytosolic pH in both groups, however there is also abnormal concentrations of phosphorylated compounds (in particular, decreased phosphocreatine and increased inorganic phosphate concentrations).
The study overall aim is to develop and evaluate non-invasive techniques to quantify muscle pathology and the rate of change over time in LGMD2I, which is potentially a useful tool for monitoring response to treatment and therapies. This shall be achieved by measuring static MRI over a 2 year period and comparing this to age matched adult controls including the quantitative 3-point Dixon technique for measuring fat. At the same time we will also be measuring the Pi and cytosolic pH, ATP and ADP via MRS to see whether a specific pattern of metabolic abnormality is detected in these patients.
For further information about the study please contact Dr. Jasper Morrow at j.morrow@ion.ucl.ac.uk.

2. TREAT NMD database for DM1

The TREAT-NMD network brings together clinicians and researchers in the neuromuscular field with industry and patient advocacy partners. It provides an infrastructure to support the development of new therapies, provide training and education, and disseminate best practice.

TREAT-NMD was established to address the bottlenecks that have held back translational research and therapeutic development in the neuromuscular field. The network has developed partnerships across the world to help prepare the neuromuscular field for clinical trials and implement best practice in patient care. The resources it has developed are freely available to clinicians, researchers and patients worldwide.

The Care and Trial Site Registry

We encourage all clinicians interested in neuromuscular trials or with expertise in neuromuscular patient care to register with the TREAT-NMD Care and Trial Site Registry (CTSR), a database of information on clinical sites set up to facilitate the selection of centres with the expertise to take part in clinical trials. Companies have already made use of the CTSR to assist in their site selection for upcoming trials.

www.treat-nmd.eu/ctsr

Standard operating procedures for animal models

As the result of collaborations between leading animal model specialists worldwide, a set of SOPs for various experimental protocols on animal models have been drafted and made available on the TREAT-NMD website for the use of researchers working in this area.

www.treat-nmd.eu/animalmodels

Registry of Outcome Measures (ROM)

The TREAT-NMD Registry of Outcome Measures is a freely accessible online resource for information on outcome measures. It contains detailed summary information about outcome measures, including a description, availability information, contact details for providers, and references to related documents including manuals and training videos.

www.treat-nmd.eu/ROM

Standards of care guidelines

Variations in care standards not only impact on quality of life but also make comparison of trial results from different centres a challenge. Recent international initiatives have resulted in academic publications of consensus guidelines for best-practice care of SMA and DMD, and family-friendly versions have been created in multiple languages in collaboration with patient groups. Similar processes are ongoing for other conditions such as the congenital muscular dystrophies.

SMA care standards: www.treat-nmd.eu/sma-care

DMD care standards: www.treat-nmd.eu/dmd-care

TREAT-NMD Advisory Committee for Therapeutics (TACT)

TACT is an expert multidisciplinary body that provides applicants with independent, objective guidance on advancing new therapies for neuromuscular diseases. Its goal is to position the potential therapy along a realistic pathway to clinical trial and registration by evaluating preclinical data as well as drug development considerations, and providing information on optimal trial design and resources available for trial planning and conduct.

www.treat-nmd.eu/TACT

Biobanks

EuroBioBank is a network of biobanks providing human DNA, cell and tissue samples as a service to the scientific community conducting research on rare diseases, in particular neuromuscular conditions. A total of approximately 400,000 samples are available to researchers worldwide via the online catalogue.

www.eurobiobank.org

Patient registries

The TREAT-NMD patient registries were set up primarily with future trials and therapies in mind. The global registries for DMD and SMA are recognised as the leading resource for trial planning and recruitment in these diseases at an international level and are already being used by pharmaceutical companies for this purpose. The registries are open to enquiries from academic colleagues, and clinicians are invited to make use of the registries for their own research questions.

www.treat-nmd.eu/patientregistries

3. Cardiff DM protocol

Cardiff Myotonic Dystrophy Muscle Clinic Record

SECTION A – Patient Registration Details

1.Personal Details

Personal I.D. Number …… Sex ……

Genetic number …… D.O.B. ……

Surname ……First Name…… D.O.D. ……

Address …… Phone No ……

…… Occupation ……

Post Code …… Date of 1st appt ……

2. Diagnostic Details

Type: dm1 / dm2

Classification: congenital / early childhood / adult

Status: clinically affected / presymptomatic / gene carrier / unaffected

Repeat No: …….

3. Age

Of onset of symptoms…… Of diagnosis ……

Of lens opacities ……

4.Patient Awareness

(*Please tick to indicate the following have been discussed)*

Consent form and information sheet: verbal consent given/written consent given.

Carecard

Fact Sheet

Support Group

Anaesthetic Risks

5. Transmitting Parent Details

Sex of transmitting parent ……

Personal I.D. No ……

Genetic No ……

D.O.B ……..

D.O.D ……..

6. Patient Contact Details

Type of contact: Cardiff Clinic/Oswestry Clinic/Home/Other (specify……) / none.

Frequency of contact: ……

Signed …… Date ……..

SECTION B – Clinic Details

Name …… Personal I.D. Number ……
Appointment date …… Genetic Number ……
Weight …… BMI …… Height ……. Visual Acuity ……
No. of Chest Infections past 6 months … Urine Analysis ……..
Mobility(*delete as appropriate)* Assisted/Independent R.M.I. Score ……..
Falls None/Some no change/falls increasing Epworth score ……

Current Problems According to the Patient

……
……
……
……
……
……
……

Current Medication

1)
2)
3)
4)
5)
6)
7)
8)

Genetic Counselling

Self Yes/Declined/Not offered/Unknown **Presymptomatic Self** Yes/Declined/Not offered/Unknown
Family members Yes/Declined/Not offered/Unknown **Prenatal** Yes/Declined/Not offered/Unknown

Swallowing

1.Do you cough when eating or drinking?
Never or<2/month ≥2/month but<1week ≥2/week.
2.Do you have to cut your food up finely or mince it before eating?
Yes No
3.Do you avoid certain foods because of difficulty in swallowing them?
Yes No
4.Does food tend to stick in your throat?
Never or<2/month >2/month

Cardiovascular

Breathlessness None/uphill only/on flat/at rest
Chest pain Yes/No
Palpitations Yes/No Details……...
Faints/Blackouts Yes/No Details……

Somnolence

Change in daytime sleepiness Yes/No Morning headaches Yes/No

Vaccinations

Influenza: Yes/No Pneuomococcal: Yes/No Other: Yes/No

Lens Opacities

Absent/visible with ophthalmoscope/mature or operated/recurrent.

Muscle Force

Eye closure : normal/mild/moderate (eyes closed, lashes not buried)/severe

Cervical flexion	5 4+ 4 4- 3 2 1 0
Cervical extension	5 4+ 4 4- 3 2 1 0

	R	L
Shoulder abduction	5 4+ 4 4- 3 2 1 0	5 4+ 4 4- 3 2 1 0
Elbow flexion	5 4+ 4 4- 3 2 1 0	5 4+ 4 4- 3 2 1 0
Wrist extension	5 4+ 4 4- 3 2 1 0	5 4+ 4 4- 3 2 1 0
Wrist flexion	5 4+ 4 4- 3 2 1 0	5 4+ 4 4- 3 2 1 0
Pinch grip	5 4+ 4 4- 3 2 1 0	5 4+ 4 4- 3 2 1 0
Hip Flexion	5 4+ 4 4- 3 2 1 0	5 4+ 4 4- 3 2 1 0
Knee extension	5 4+ 4 4- 3 2 1 0	5 4+ 4 4- 3 2 1 0
Ankle dorsiflexion	5 4+ 4 4- 3 2 1 0	5 4+ 4 4- 3 2 1 0

MRC grades 5=normal 4=active movement against resistance 3=can overcome gravity
2=movement if gravity eliminated 1=flicker/trace 0=no movement at all

Hand grip(dynamometer)……Kgf …… Kgf

Myotonia absent/percussion only/mild/moderate/severe

Myometry Yes/No

Swallowing

Total volume (usually 100mls) ……Presence of double swallows……..

Time …… Cough while swallowing……

No. of Swallows ……

Cardiovascular

ECG requested/Not required

Rate…… P.R interval ……

Rhythm SR/AF or Flutter/SVT/LBBB/RBBB/LAH/LPH/bifasc.block

Pulse rate …… B.P ……

	Lying	*sitting/standing*
FVC	…… …… ……	…… …… ……
FEVI	…… …… ……	…… …… ……

M.D.T.Referral OT/Physio/FCO/Psychology/Social Work/Speech Therapy/ Respiratory/ Orthotist/ Cardiology/Psychiatry/Support Group/Research/Other (……..)

Comments……
……
……

Signed ……

4. The development of the Myotonic Dystrophy Support Group over two decades.

“Myotonic Dystrophy…” When I first heard these words mentioned, it was in a hospital consultation room, with my husband, Keith, and our 12 year old son, Peter. At this consultation with a Paediatric Neurologist , my husband learnt that his medical problems and our sons were associated with DM 1. It had taken 9 years for the diagnosis to be made in my son. Peter, at the age of 3yrs, had constipation which became soiling. He had clumsy fingers, and wouldn’t use crayons, make jigsaws or play with Lego, unlike his 2 brothers and sister. We had seen a Paediatrician regularly until at the age of 8 the Paediatrician told me over the telephone ‘the sooner your child is put into care, the better’!

I was devastated. This followed numerous complaints from the school, including asking me to ‘teach him to eat with his mouth closed’, ongoing toileting problems, and the school refusing to take him on outings. The bullying continued at school even after his diagnosis. Peter was transferred to a school for disruptive children associated within the Nottingham Mental Hospital. I was told he had to be resident for a year and would not be allowed home at anytime, as his everyday living problems were caused by stress in the home.

This short introduction is to share with you why the Myotonic Dystrophy Support Group was founded in 1989. I wanted to help people to avoid going through the awful 9 years that our family had experienced.

Between 1985 and 1989, I contacted agencies, radio and newspapers to increase awareness of Myotonic Dystrophy. A few family contacts and I met in a house and Ian, my eldest son who was a medical student at Cardiff, sat on the floor and drew a diagram of basic genetics. Ian is now a Consultant Anaesthetist, and has developed a strong interest in Anaesthetics and Myotonic Dystrophy.

Following the diagnosis of my son, we were encouraged to visit Professor Peter Harper, and ordered his book on Myotonic Dystrophy from the Library. Reading the text, Ian couldn’t understand why so many medical professionals had missed diagnosing my affected son?

An article in the Independent newspaper described a BMJ report of a patient with Myotonic Dystrophy who could not smile and I was asked to give a reply. An Independent newspaper Editor came to our home to discuss our experiences of Myotonic Dystrophy. This was published 7 months later as an article in the Independent newspaper and subsequently I received 50 calls from affected families.

The contacts grew from there and the first national DM meeting was held in 1989. Professor Peter Harper spoke at the Postgraduate Centre in Nottingham and 72 medical professionals attended. Ian and I were interviewed on Radio Derby, and the first gathering of 90 people met.

Professor Harper's talk was recorded and transcribed by the Muscular Dystrophy Group, who also bought our first phone and answering machine. This article was called 'Lecture Notes', and travelled throughout the UK and abroad. The article was found in the belongings of a family in which 3 family members were killed in a road traffic accident. The father had left his home and money to the Myotonic Dystrophy Support Group. We had never met this family before and the MDSG was built on this initial legacy of £139,000. Professor Harper became our first Patron.

From these humble beginnings, the MDSG grew into a national Support Group. We have a helpline, a quarterly newsletter, a recently modernised website, and an Office employing 2 part-time secretarial staff and a book-keeper. There are 28 regional contact families, and several areas have regular meetings. There are a selection of clearly-presented leaflets written by Consultants who have a real passion for helping families with DM.

We became a Registered Charity and had 15 Trustees. In 2010, the MDSG also become a Company limited by Guarantee. We have 10 Directors and 8 Medical Advisors. We meet 3-4 times per year.

Our Annual Conferences continue to grow and typically we will have 200 delegates attend from all parts of the UK. At the heart of the conference, is a series of presentations, given mostly by medical professionals, who provide updates in the basic and clinical science of DM in language we understand. There are also several more informal discussion groups about specific topics related to DM and medical professionals speak informally to the delegates during the day. Our Present Patron is Prof. David Brook of Nottingham University Medical School. The MDSG is invited to attend the IDMC meetings. We currently support research work in Glasgow and Nottingham, and have assisted PhD students to attend IDMC meetings.

In 2004, I felt honoured to be asked to contribute to the book "Myotonic Dystrophy: Present Management, Future Therapy", which was written after a meeting of 24 doctors in Naarden. The DM 'Facts Book' has also been a real life line to many families, and again I was thrilled to be asked to write a' forward' to the second edition.

The MDSG includes 1830 members from throughout the UK. I am positive that the MDSG will act as an excellent framework around which a National TREAT-NMD DM Database can be formed in conjunction with Hanns Lochmuller, Mark

Rogers and Chris Turner. The MDSG also recognises that generating funding is critical to the development of basic and clinical research in the UK and will be an active participant in future charitable events.

Mrs Margaret Bowler SRN SCM. (MDSG chairperson)

5. About the Muscular Dystrophy Campaign

The Muscular Dystrophy Campaign is the leading UK charity focusing on all muscular dystrophies and allied neuromuscular disorders. We have pioneered the search for treatments and cures for over 50 years and we are dedicated to improving the lives of all children and adults affected by muscle disease.

We fund world-class research to find effective treatments and cures; provide free practical and emotional support; campaign to raise awareness and bring about change, and award grants towards the costs of specialist equipment.

Fighting for change

An important part of the work the Muscular Dystrophy Campaign does is to campaign on behalf of the 70,000 people in the UK that are affected by muscle-wasting diseases. We do this by putting pressure on decision makers in Westminster, the NHS and local authorities to:

- ensure access to essential service for the people affected by these conditions
- end the current postcode lottery in the provision of health and social services
- increase the number of specialist Care Advisors across the UK.

We also continually strive to:

- persuade the government to increase investment in research into muscular dystrophies and allied disorders
- improve access to and for funding home adaptations, powered wheelchairs and specialist equipment
- secure better support for the transition into adulthood for young people with these conditions
- make the voices of people affected heard by securing extensive local and national media coverage.

Campaigning all year round, in every part of the UK, we make a difference to the lives of families living with these disorders.

“In isolation our voices are too quiet to be heard; together we have a louder voice and we can make real changes.” Sharon Kitcher, whose son James has Duchenne muscular dystrophy

6. Notes