

## MRC Centre for Neuromuscular Diseases – milestones and deliverables

### What this document contains

This document sets out the originally agreed added value, deliverables, milestones and success criteria in each of the core areas and describes the evidence showing how we have achieved all the deliverables that were set in each core area

### Core Activity- 1: Neuromuscular Clinical Trials

Responsible PI's - Mike Hanna and Katie Bushby. *Neuromuscular Trials Milestones-core deliverable table agreed with MRC*

<b>Added value</b>	<ul style="list-style-type: none"> <li>• New clinical trials centre of excellence for all aspects of UK neuromuscular trials</li> <li>• Development of UK nm clinical trials culture that compares well with those in other countries eg USA</li> </ul>
<b>Deliverables</b>	<ul style="list-style-type: none"> <li>• New core clinical trials group</li> <li>• UK register phase I/II nm clinical studies</li> <li>• Access to standardised patient database</li> <li>• A resource to support nm trial design</li> <li>• UK clinical networks for nm trials</li> <li>• New disease-specific outcome measures</li> <li>• New MRI outcome measures developed jointly with MRI core group</li> <li>• Database/resource of published nm clinical trials in collaboration with Cochrane nm group</li> <li>• Initiate/complete at least 2 natural history studies.</li> <li>• Initiate/complete agreed clinical trials at least 5 clinical trials.</li> </ul>
<b>Milestones</b>	<ul style="list-style-type: none"> <li>• Months 1-6 core trials group agenda and work plan set-existing databases, informal networks scoped reorganised and established. Trials registry established, Collaborative Cochrane database established.</li> <li>• Months 12-18 new natural history studies agreed and initiated</li> <li>• Months 12-24 new clinical trials agreed and initiated</li> <li>• All the deliverables listed to be monitored and updated throughout the 5 years.</li> <li>• New natural history studies and treatment trials [both investigator lead and with pharma] will continue to be initiated and completed through the five years</li> </ul>
<b>Success criteria</b>	<ul style="list-style-type: none"> <li>• Centre recognized by professional organizations, charities and pharma as the UK national nm clinical trials portal. Measured by number of trials with pharma, number of investigator lead trials funded by non-pharma eg charities. At least one of each.</li> <li>• Develop UK nm trial design and outcomes measures complete at least one natural history study and intervention trial.</li> <li>• Develop role of MRI as outcome measure in trials- complete at least one natural history study with MRI as outcome tool.</li> <li>• Trials and natural history studies initiated and completed- at least one of each completed.</li> <li>• Collaborations with pharma leading to trials- at least one pharma-linked trial completed.</li> <li>• UK national neurology nm trials networks facilitated and coordinated by the centre-provide evidence of network meetings/contributions to natural history studies/trials</li> <li>• Publications on natural history trials and clinical intervention trials</li> </ul>

**1. Staffing** The two clinical trials coordinators have been working in London and Newcastle in MRC Centre-funded posts since March 2008. They have been involved in all phases of different trials including set-up phase, recruitment and close down phases (table and list of trials attached). In London an additional trials coordinator has been appointed following an application to the Muscular Dystrophy campaign (MDC) as part of a UCL joint paediatric adult centre award, and has worked closely with the other two trials coordinators. LCRN funding on the back of NIHR portfolio status has been leveraged to support additional

ad hoc clinical trial coordinator time, but the MRC Centre trials coordinator has been critical for all activities in London and Newcastle.

2. Trials mapping to the centre Currently **over 30** different trials and natural history studies map to the centre and these are fully listed in the attached document. Trials are considered to map to the centre if they have been undertaken by MRC Centre PI's and/or have been supported by the centre, for example through the trials coordinators.

3. Trials support Newcastle receive support for trial design, biostatistics and regulatory advice through their research and development offices and clinical trials units including Elaine McColl MRC Centre PI. Recently in London a dedicated trials support unit has been established at Queen Square with CBRC host support lead by Professor Reilly that includes a dedicated statistician time, pharmacy support and trial design support. This new Queen Square Centre is host support mapping to the MRC Centre and is a resource to potentially support cross centre new trials in the design, protocol and statistics stages.

4. Clinical trials units Full paediatric and adult neuromuscular clinical trials research facilities are available in Newcastle and in London. Host support has been significant in both sites. For example in London CBRC support combined with charity support raised £2m to deliver a new adult neuromuscular trials centre and London hub for the MRC Centre opened in Dec 2009. Several trials are now being run jointly by London and Newcastle partners allowing patients to be recruited at a geographically most convenient site. In addition, both centres now have exercise physiology testing capability for exercise trials.

The core aim of the trials activity is to make the UK trials ready and trials active. The activities of the MRC centre trials platform include

1. Support trial design, statistics, protocol development.
2. Support ethics MHRA R and D and other regulatory approvals
3. Support platform for national UK patient cohorts that are
4. Portal for pharma lead trials
5. Support investigator lead trials including licensing of novel compounds for use in human studies eg arimoclomol.
6. Support the development of outcome measures, especially MRI
7. Support natural history studies.
8. Conduct clinical trials

Funded studies from centre PI's can take advantage of the Centre's trial support activity. The strategy regarding decisions about which natural history studies to undertake and which IMP's to prioritise has been based on peer review by external funding agencies in all cases. Therefore PI's will make funding applications to outside agencies to support the trial of interest (which maps to one of the core diseases). The centre support can be used to help in the design phase prior to funding application and successfully funded studies can take full advantage of the trials support to run the trial.

Description of delivery against deliverables, milestones, success criteria

### **Deliverables:**

#### **D1.New core clinical trials group**

Cross links between Clinical trial groups in London and Newcastle have been established focussed on paediatric or adult trials, cohorts and MRI studies:

Muntoni Bushby Straub in relation to the MDEX consortium.

Hanna, Turnbull, Reilly, Chinnery, McFarland in relation to the mitochondrial cohort and mitochondrial exercise trials.

Straub, Thornton, Bushby, Hanna, Yousry in relation to MRI studies including the LGMD2I study

Reilly Chinnery Horvarth regarding to neuropathy cohort and trials.

## **D2. UK register phase I/II nm clinical studies**

The MRC Centre London trials coordinator keeps a register of all trials across the MRC Centre and is compiling a register of all trials across the UK available of the MRC Centre website. There has been a tenfold increase in active clinical trials and natural history studies in the period 2008-2011 since the centre commenced. Phase III trials are already registered nationally.

## **D3 Access to standardised patient database/registries**

Joint London Newcastle MRC Centre mitochondrial cohort database has been established and is jointly run by MRC Centre PI's in Newcastle and London having now entered >600 patients with mitochondrial diseases.

MRC centre PIs lead Northstar cohort and DMD and SMA registries.

MRC Centre PIs lead TREATNMD registries.

MRC Centre PI's lead IBM-net.

## **D4 A resource to support nm trial design**

Dr McColl is a PI in the MRC Centre.

Professor Reilly leads UCL ION trials unit which supports the MRC Centre trials activity.

## **D5 UK clinical networks for nm trials**

Networks/cohorts for DMD, SMA, IBM, CMD established. New intra UK cohorts for Myotonic Dystrophy (Lochmuller Turner), CMT (Reilly Horvarth), Channelopathies (Hanna Lochmuller) being developed.

## **D6 New disease-specific outcome measures**

New outcome measures in relation to MRI have developed and correlate with strength-see MRI core activity report.

MRC investigators have produced TREAT-NMD registry of outcome measures see [www.TREAT-NMD](http://www.TREAT-NMD)

## **D7 New MRI outcome measures developed jointly with MRI core group**

Joint LGMD2I MRI project abstracts published first publication submitted.

Prospective IBM-CMT abstracts published.

See list of MRI publications below.

## **D8 Cochrane unit moved to MRC Centre for Neuromuscular**

Diseases Queen Square in September 2008. Professor Richard Hughes and Dr Michael Lunn are members of the MRC Centre. Joint working between MRC Centre and Cochrane unit commenced e.g. MRC Centre PIs of systematic reviews, Cochrane databases is a resource for MRC Centre PIs designing new trials. Series of MRC Centre Cochrane reviews in press/progress.

## **D9 Initiate/complete at least 2 natural history studies.**

Two muscle channelopathy studies in NMD and ATS completed abstracts published first two papers in press.

IBM cohort study natural history study in its 2<sup>nd</sup> year now includes 164 patients

Mitochondrial cohort study recruited > 600 patients

NorthStar SMARtnet CM all in progress over 100 patients recruited.

CMT natural history study initiated May 2010, 111 pts recruited to date.

### **D10 Initiate/complete agreed clinical trials at least five clinical trials.**

Six Clinical trials completed and 27 clinical trials/natural history started or in set up phase. Completed trials are listed with all other studies below and are also summarised in section 1 of the case for support.

#### **Milestones**

Months 1-6 core trials group agenda and work plan set-existing databases, informal networks scoped reorganised and established. Trials registry established, Collaborative Cochrane database established. *London trials coordinator has collated lists of existing databases.*

*Move of Cochrane and working links established.*

Months 12-18 new natural history studies agreed and initiated.  
*Commenced-see trials list.*

Months 12-24 new clinical trials agreed and initiated.  
*Commenced see trials list.*

All the deliverables listed to be monitored and updated throughout the five years.

New natural history studies and treatment trials (both investigator lead and with pharma) will continue to be initiated and completed through the five years.

*Commenced see trials list.*

#### **Success criteria**

Centre recognised by professional organisations, charities and pharma as the UK national nm clinical trials portal. Measured by number of trials with pharma, number of investigator lead trials funded by non-pharma e.g. charities. At least one of each.  
*See trials list.*

Develop UK nm trial design and outcomes measures. Complete at least one natural history study and intervention trial.  
*See trials list.*

Develop role of MRI as outcome measure in trials - complete at least one natural history study with MRI as outcome tool.  
*IBM CMT natural history MRI –cross sectional phase completed, one year interval study to complete sprin 2012*

Trials and natural history studies initiated and completed - at least one of each completed.  
*See trials list.*

Collaborations with pharma leading to trials- at least one pharma-linked trial completed.  
*See trials list.*

UK national neurology nm trials networks facilitated and coordinated by the centre - provide evidence of network meetings/contributions to natural history studies/trials.

## **MRC Centre Clinical Trials of Investigational Medical Products CTIMPs**

*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, Alexion Pharmaceuticals, GlaxoSmithKline.*

### **MRC Centre CTIMPs Set-up Phase trials**

#### **1. 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)**

**PI: Prof Hanna**

**Recruitment target: 12**

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 or Gisela Barreto, Trials Coordinator at Gisela.barreto@uclh.nhs.uk.

#### **2. 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: Set-up phase**

**Sponsor: Newcastle NHS Foundation**

**Planned start date: 2011**

**Funder: British Heart Foundation**

**PI: Prof. Muntoni**

**Recruitment target: 140**

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 characterised 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 randomised, 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 the trial coordinator on 020 7905 2639.

### **3. A Pilot Study of Valproate Sodium for McArdle Disease**

**Status: Set-up phase**

**Sponsor: UCL**

**Planned start date: 2011**

**Funder: Muscular Dystrophy campaign**

**PI: Prof. Ros Quinlivan**

**Recruitment target: 15**

McArdle disease (Glycogen storage disease type V, GSDV) is an inherited metabolic disorder of skeletal muscle. Affected patients are unable to produce lactate during ischaemic exercise [McArdle 1951] because they have a congenital absence of the enzyme muscle glycogen phosphorylase, which is essential for glycogen metabolism [Mommaerts 1959, Schmidt and Mahler 1959]. The condition is caused by homozygous or compound heterozygous mutations in the muscle glycogen phosphorylase gene (*PYGM*) located at chromosome 11q13 [Beynon 2002]. This enzyme deficiency results in the inability to mobilise muscle glycogen stores that are normally required for energy during anaerobic metabolism. In affected people, symptoms of fatigue and cramp occur within minutes of initiating any activity and during strenuous activity such as lifting heavy weights or walking uphill, if the activity is continued despite severe cramping, a contracture occurs which leads to muscle damage (rhabdomyolysis), myoglobinuria and, when severe, acute renal failure.

Currently, there is no satisfactory treatment that can be recommended for the condition [Quinlivan 2008]. Taking glucose prior to exercise may alleviate muscle symptoms by inducing a second 'second wind', but this is not a good strategy for daily living as it may result in significant weight gain [Vissing 2003]. There is limited evidence for subjective benefit from creatine supplementation in five out of nine subjects from a randomised controlled trial [Vorgerd 2002], although this has not been confirmed in the clinic setting.

Although most people with McArdle disease have complete absence of skeletal muscle phosphorylase, there are a small minority of patients who possess splice site mutations that enable production of very small amounts (1-2%) of functional enzyme [Vissing]. These people have a milder phenotype with less severe symptoms, and functional exercise assessments have shown better exercise capacity than typical patients with the condition. Findings from these atypical individuals suggest potential therapeutic agents might only need to produce very small amounts of enzyme for significant functional improvement. Furthermore, finding a therapeutic agent to 'switch on' expression of the foetal isoenzyme may be a potential therapeutic strategy.

Sodium Valproate (Valproic acid) is one of a group of drugs known as histone deacetylase inhibitors (HDACIs) that can affect gene expression by acetylating lysine residues, which in turn has a direct effect on chromatin [Thiagalingam 2003]. There is some evidence from animal studies to suggest that sodium valproate can 'switch on' the foetal phosphorylase isoenzyme.

A recent clinical trial of the drug in McArdle sheep that were given sodium valproate for three months showed the presence of phosphorylase positive muscle fibres, in the absence of muscle necrosis and/or regeneration [Howell 2010].

The current proposes an open label uncontrolled pilot study to evaluate safety and efficacy of Sodium valproate (slow release) 20mg /kg once daily for six months. 15 subjects, adult male and post menopausal women attending specialist centres for McArdle disease will be recruited across three sites: London, Copenhagen and Dallas.

## **MRC Centre CTIMPs Open Trials**

### **4. Phase II, multicenter, randomized, adaptive, double-blind, placebo controlled Study to assess Safety and Efficacy of Olesoxime (TRO19622) in 3-25 year old Spinal Muscular Atrophy (SMA) patients**

**Status: Open**

**Sponsor: TROPHOS**

**Funder: Association Francaise contre les Myopathies**

**PIs: Francesco Muntoni, Hanns Lochmuller, Helen Roper**

**Recruitment target (UK): 30; due for completion by 31<sup>st</sup> September 2013**

The UCL Institute of Child Health and Great Ormond Street Hospital for Children (London), Birmingham Heartlands Hospital, and Newcastle upon Tyne Hospitals Royal Victoria Infirmary have been invited to collaborate in this phase II clinical trial in non-ambulant patients with SMA II and III with a documented homozygous absence of SMN1 exon 7 and/or deletion and mutation on the other allele. This is a multicentre, double-blind, randomized, placebo-controlled study in patients with SMA type 2 or non-ambulant type 3. The study will be conducted in multiple centres across Europe and will be sponsored by Trophos (a biopharmaceutical company based in France) and funded by AFM (Association française contre les myopathies). The aim is to assess efficacy, futility, safety and tolerability of a new drug called olesoxime. This is a neuroprotective drug that acts by interacting with protein components of the mitochondrial permeability transition pore (mPTP), preventing the release of apoptotic factors and in turn neuronal death. Olesoxime has displayed an excellent safety profile and has been well tolerated in phase I clinical trials in healthy subjects. For each participant, this phase II study will involve a 4 week screening period followed by a 24 month (104 week) treatment period. Following screening procedures and confirmation of eligibility, subjects will be randomised to receive either olesoxime or placebo in a 2:1 ratio. Olesoxime (or matched placebo) will be taken daily with evening meal as a liquid formulation at a dose of 10mg/kg. 150 subjects in total will be recruited, with a target of 30 patients in the UK. Recruitment is planned to be completed in 6 months. It is possible a dose adjustment may be made once 45 patients across Europe have been received study drug for 3 months based on a review by a designated independent Data Monitoring Committee. The patients to be recruited should be at least 3 years of age but younger than 26 years at the time of enrolment, with the age of onset of symptoms to be at 3 years of age or younger. They should not be taking any medication intended for the treatment of SMA within 30 days prior to being enrolled on the study. Eligible patients can be taking oral salbutamol as long as this has been commenced at least six months prior to enrolment on the study and remains at a stable dose during the study period. Participation in another investigational drug or therapy study within 3 months of enrolment is an exclusion criterion, as well as a hypersensitivity to sesame oil and use of medications that could interfere with olesoxime absorption (including cholestyramine, fibrates, fish-oils, niacin, phytosterols and ezetimibe). Further information about this study can be obtained from the Clinical Trials Coordinator on 020 7905 2639.

### **5. HYP HOP: DICHLORPHENAMIDE vs. PLACEBO FOR PERIODIC PARALYSIS**

Full Title: Double-blind, placebo-controlled, parallel group, phase III study comparing dichlorphenamide vs. placebo for the treatment of periodic paralysis

**Status: Open to Recruitment**

**Sponsor: University Rochester**

**Funder: National Institutes of Health (NIH - USA)**

**PI: Prof. Hanna**

**Patients recruited:14; target 40**

This is a phase III trial into Periodic Paralysis. 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, Hypokalemic periodic paralysis). The 9-week studies will investigate the prevention of attacks of weakness and it will be followed by 1-year extensions without placebo to compare the long term effects of DCP 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 or Gisela Barreto, Trials Coordinator at Gisela.barreto@uclh.nhs.uk.

## **6. ARIMOCLOMOL FOR SPORADIC INCLUSION BODY MYOSITIS (IBM)**

Full Title: A Randomised, Double-blinded, Placebo-controlled Pilot Study Assessing the Safety and Tolerability of Arimoclomol in Adult Patients with Sporadic Inclusion Body Myositis

**Status: Closed to Recruitment**

**Sponsor: University College London (UCL)**

**Funder: Arthritis Research UK and Myositis Support Group**

**PI: Prof. Hanna**

**Patients recruited: 12; target 12**

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. Pedro Machado at p.machado@ion.ucl.ac.uk or Gisela Barreto, Trials Coordinator at Gisela.barreto@uclh.nhs.uk.

## **7. GSK/Prosensa clinical trial in DMD boys with study drug GSK2402968 (PRO051)**

Full Title: 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: Ongoing**

**Sponsor: GlaxoSmithKline**

**Funder: GlaxoSmithKline**

**PIs: Volker Straub, Francesco Muntoni**

**Patients recruited: 8; target (UK) 8**

A multicentre trial with this study drug is recruiting DMD boys in UK at the Great Ormond Street Hospital (GOSH), London and at the Royal Victoria Infirmary, Newcastle. It is a Phase IIa, double blind, exploratory, parallel clinical trial to assess the optimal dose of GSK2402968 for safety, tolerability and efficacy, in ambulant patients with DMD. This study is designed to explore efficacy and safety of GSK2402968 given as a continuous regimen and an intermittent regimen over 24 and 48 weeks.

Objective(s)

Primary objective:

- To assess the efficacy of 2 different dosing regimens of subcutaneous GSK2402968 administered over 24 weeks in ambulant subjects with DMD.

Secondary objectives:

- To assess the safety and tolerability of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.
- To assess the PK of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.
- To assess long term efficacy of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.



## Study Design

The study aims to randomise 54 subjects. There will be 2 parallel cohorts. Each cohort will include 16 subjects on GSK2402968 and 8 subjects on matched placebo (2:1 ratio). Further information about this study can be obtained from the MRC Centre Clinical Trials Coordinator on 020 7905 2639.

## **8. Investigation of the ability of Otelixizumab to inhibit in vitro antigen-specific T cell responses from Myasthenia Gravis patients**

**Status: Open to Recruitment**

**Sponsor/Funder: GlaxoSmithKline**

**PI: Prof Kullmann**

**Patients recruited: 39; target 40**

Myasthenia Gravis (MG) is the best understood autoimmune disease (a disease in which the immune system attacks some part of the body). This attack is directed by various parts of the immune system.

There is a continued search for newer drugs that will be of benefit in the treatment of MG. Otelixizumab has been identified as a possible treatment for MG. However before clinical trials can be considered additional information is needed to determine how it interacts with the immune system of patients with MG.

In this study adult patients with MG will be invited to provide blood samples (50 ml) for research purposes. Blood collected from patients will be used for Tcell assay and autoantibody assay development. Patients may be asked to provide a repeat blood sample (additional 50ml) after 46 months following the initial collection to see if T cell activation changes over time. Up to 40 participants will be enrolled in the UK. The study is being sponsored by GlaxoSmithKline group of companies.

For information on recruitment contact Natalie James (natalie.James@uclh.nhs.uk).

## **9. THERAPEUTIC TRIAL OF LITHIUM CARBONATE IN MND/ALS (LiCALS)**

**Full title: A double-blind, randomised, placebo controlled trial of lithium carbonate in patients with amyotrophic lateral sclerosis.**

**Status: Ongoing (closed to recruitment)**

**Sponsor: University College London Hospitals NHS Foundation Trust**

**Start date: June 2009**

**Funder: Motor Neurone Disease Association, and NIHR**

**UCL PI: Dr Richard Orrell**

**Patients recruited: 22, target: open-ended**

Recent research suggested that lithium carbonate may be effective in lowering the progression of MND/ALS. Lithium may protect motor neurons through a range of mechanisms, including improving the transport of proteins along the motor neuron, improving the transport of mitochondria, and activating cell survival factors. In one study, lithium prolonged survival in a mouse model of MND/ALS. This is a multi-centre UK study, involving 215 patients with MND/ALS, taking lithium or placebo, for 18 months. The trial is designed to assess the safety, efficacy and tolerability of lithium in combination with riluzole as a treatment for MND/ALS. Assessments include survival, symptoms, quality of life, and function. Participants are randomised to take lithium or placebo, the level of lithium in the blood is monitored, and the dose of lithium (and placebo) adjusted as needed.

## **10. LiCALS Open Label Extension**

**Full title: LiCALS open label extension trial of lithium carbonate in amyotrophic lateral sclerosis.**

**Status: Recruiting.**

**Sponsor: University College London Hospitals NHS Foundation Trust**

**Start date: March 2011**

**Funder: Motor Neurone Disease Association, and NIHR**

**UCL PI: Dr Richard Orrell**

**Patients recruited: 3 of 8 recruited**

This is an open label extension study for those who have completed the randomised double blind trial of lithium carbonate in ALS. The objective is to obtain further evidence of the safety of lithium carbonate in doses achieving levels of 0.4-0.8 mmol/l.

### **GSK1223249 in MND/ALS (the Nogo-A study)**

Full title: A Phase I, multi-center, randomized, placebo-controlled, double-blind, single and repeat dose escalation of a drug to treat ALS.

**Status: Recruiting**

**Sponsor: Royal Free Hampstead NHS Trust**

**Start date: September 2010**

**Funder: GlaxoSmithKline**

**UCL PI: Dr Richard Orrell**

**Patients recruited: 2, target: 2**

GSK 1223249 is a new drug developed by GlaxoSmithKline, that targets a protein called Neurite Outgrowth Inhibitor (Nogo-A), which impairs neurone regeneration. There is evidence of increased Nogo-A, which impairs neuron regeneration, in muscle of people with MND/ALS. By blocking the effect of Nogo-A, GSK1223249 may be an effective treatment for the disease. GSK1223249 delays symptom onset and prolongs survival in a mouse model of MND/ALS. The trial will provide safety and tolerability information, together with biomarker and functional information. This may lead to further trials to assess effectiveness. The study includes an infusion of the drug (or placebo), with a muscle biopsy taken before and following the infusion, together with other monitoring assessments. For further information please contact Dr Richard Orrell (r.orrell@ucl.ac.uk)

### **11. BIOMARKER STUDIES IN MND/ALS**

Full title: Characterisation of a panel of disease biomarkers in peripheral blood from individuals with motor neuron disease

**Sponsor: University College London Hospitals NHS Foundation Trust**

**Start date: May 2009**

**Funder: Motor Neurone Disease Association**

**UCL PI: Dr Richard Orrell**

Motor neuron disease (MND) is an adult-onset neurodegenerative disease and one of the commonest neuromuscular disorders. The speed of progression of MND varies among individuals and the condition can develop with different clinical manifestations. Currently, there are no blood tests that could help us to predict the speed of progression of the disease and the likely clinical manifestations (e.g. predominant involvement of speech and swallowing or of the limb muscles). We are testing specific disease biomarkers in the blood. To assess change over time, a blood sample is taken every 3 months. The sample has to be carefully processed as soon as it is taken to preserve the quality of the blood contents. We are studying a range of blood constituents including proteins, DNA and RNA. From some participants we also collect samples of cerebrospinal fluid. If repeated samples are not possible, a single sample of blood for DNA studies is also helpful. We also examine samples from participants without MND/ALS, and individuals with similar but unrelated neuromuscular conditions. Parallel studies of biomarkers in an animal model of ALS are informing our choice of biomarkers. The study is in collaboration with Queen Mary University of London, and other participating centres.

## **MRC Centre CTIMPs Completed Trials**

### **12. RANDOMISED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF LONG-TERM ASCORBIC ACID TREATMENT IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A**

**Status: Completed.**

**Sponsor: University College London**

**Funder: Muscular Dystrophy Campaign (MDC)**

**PI: Prof. Reilly**

**Patients recruited: 50 target 50**

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, randomised, double-blind, placebo-controlled study aiming to evaluate the efficacy of AA treatment in CMT1A.

The study is now complete. Fifty participants were enrolled in the UK site at the MRC Centre for Neuromuscular Diseases. Paper published in Lancet Neurology 2010.

### **13. THERAPEUTIC TRIAL OF MEXILETINE IN NON-DYSTROPHIC MYOTONIA**

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

**Status: Completed**

**Sponsor: University College London (UCL)**

**Funder: Food and Drug Administration (FDA – USA)**

**PI: Prof. Hanna**

**Patients recruited: 14; target 15**

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 total duration nine weeks. Fifteen participants have been enrolled in the UK at the MRC Centre. For information on the status of recruitment please contact Dr. Dipa Raja Rayan at [d.rajarayan@ion.ucl.ac.uk](mailto:d.rajarayan@ion.ucl.ac.uk) or Gisela Barreto, Trials Coordinator at [Gisela.barreto@uclh.nhs.uk](mailto:Gisela.barreto@uclh.nhs.uk)

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

**Status: Completed**

**Sponsor: PTC Therapeutics**

**Funder: PTC Therapeutics**

**PIs: Prof. Muntoni, Prof. Bushby**

**Patients recruited: 11**

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 approximately 10 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, randomised, 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 are to be followed for a period of 12 months. At the completion of the blinded treatment, all compliant participants were eligible to receive open-label PTC124 in a separate extension study.

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

This work has been completed.

The preliminary findings from the Ataluren Study 007 did not show significant muscle improvement in the patients who participated in the study. The study was therefore discontinued. An update on this study was presented at the International Congress on Neuromuscular Diseases, Naples, Italy, 17-22 July 2010 by Professor Kate Bushby. Details of this presentation is available on [www.ptcbio.com](http://www.ptcbio.com) Briefly, analysis showed that, on average, patients treated with low-dose ataluren experienced better outcomes on measures of efficacy than patients treated with high-dose ataluren or placebo - this phenomenon is not unique for ataluren and has been observed with other drugs for other diseases. Further analysis of efficacy data is ongoing.

## **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](http://www.mdex.org.uk)).

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

### **15. RESTORING DYSTROPHIN EXPRESSION IN DUCHENNE MUSCULAR DYSTROPHY: A PHASE I/II CLINICAL TRIAL USING AVI-4658**

**Status: completed**

**Sponsor: Imperial College London**

**Funder: Department of Health (DoH)**

**PI: Prof. Muntoni**

**Patients recruited: 8**

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 that can be rescued by the skipping of exon 51 [45-50; 47-50; 48-50; 49-50; 50; 52; 52-63].

This work has been completed and outcome data published in the journal Lancet Neurology ([Volume 8, Issue 10](#), Pages 918 - 928, October 2009)

## **16. DOSE-RANGING STUDY OF AVI-4658 TO INDUCE DYSTROPHIN EXPRESSION IN SELECTED DUCHENNE MUSCULAR DYSTROPHY (DMD) PATIENTS – (Systemic study)**

**Status: Completed**

**Sponsor: AVI Biopharma**

**Funder: Medical Research Council (MRC) and AVI Biopharma**

**PI: Prof. Muntoni**

**Patients recruited: 19**

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  $\geq 5$  and  $\leq 15$  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 demonstrated 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 was conducted in London and Newcastle.

A total of 19 subjects (12 at GOSH and 7 at RVI, Newcastle) were recruited and final data is being analysed for submission to regulatory authorities in Europe and the USA. Outcome data were presented at the World Muscle Society, 12-16 October 2010 in Japan and published.

[www.thelancet.com](http://www.thelancet.com) Published online July 25, 2011 DOI:10.1016/S0140-60756-3.

## **17. 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 Immunosuppressants

**Status: Closed**

**Sponsor/Funder: Alexion Pharmaceuticals, Inc.**

**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. 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 signaling 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.

Patients will receive approximately 22 infusions including 11 infusions 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 [jspillane@ion.ucl.ac.uk](mailto:jspillane@ion.ucl.ac.uk) or Natalie James at [Natalie.James@uclh.nhs.uk](mailto:Natalie.James@uclh.nhs.uk).

**CTIMPs: Studies in negotiation**

<b>Collagen VI Disorder</b>				Planning phase				ICH - MRC London	F. Muntoni					
<b>DMD</b>			Steroid trial	Awaiting funding		NIH	UNEW/ICH		Kate Bushby					
<b>DMD</b>			ACE-031	Planning phase		Acceleron			John Oram					
<b>LGMD</b>				Planning phase			UNEW, ION, UNCLON/ICH							
			SEPN1	Planning phase					Ana Ferreira / Volker Straub					

**CTIMPs**

Study/Disease	R&D/REC	EudraCT	Drug	General Status	Study Design/Duration	Funder/Sponsors	Legal Rep.(CRO) / Partners	Lead Institution	PI/Contract	Fellow	Phase	Sites	Total Patients	UK Patients/Status
<b>Arimoclonol / IBM</b>	08/0168; 09/H0714/22	2008-00820-8-42	BRX-345 100mg tds placebo	Closed to recruitment	Placebo controlled 4 months dosing and 8 months f/up	ARC/UCLH -UCL	MSG	MRC London	MG.Hanna	Pedro Machado/Adrian Miller	Ila	US/UK	24	12 aged>50yrs /active
<b>Mexiletine / NDM</b>	08/0169; 09H0714/21	2009-01118-4-36	Mexiletine 200mg tds placebo	Completed	Placebo controlled cross-over/ 9wks	FDA-Orphan Prod. Dvlp./UCL H&UCL	CINCH MRC MSG ION	MRC London	MG.Hanna	Dipa Raja Rayan/Emma Matthews	Ilb	US(4 ) Canada UK	60	15/ closed

<b>Tapp / ATS</b>	08/0327	2009-01344-4-36	Acetazolamide 250mg BD/Liquid potassium 40mEq BD/Placebo	Set-up phase: sponsorship, pharmacy, REC MHRA R&D	Multiple cross over study-individual randomised, placebo controlled 'n of 1' trial	NIH/UCLH &UCL	CINCH	MRC London	MG.Hanna	James Burge	III?	US/UK	16	10/ not yet recruiting
<b>Hyp-Hop / Periodic Paralysis</b>	07/N126	2008-00230-619	Dichlorphenamide 50mg BD vs Placebo	Recruiting	Placebo controlled Parallel 9 wks + 1 year extension	NIH (\$3300/pt)/UCL&UCLH	Aptuit(CRO)/MRC MSG ION	MRC London	MG.Hanna	James Burge	III	US Canada UK Italy Netherlands	14 1 Hyp 11 1 Hop	Aged>18 20 Hypo 20 Hyper/recruiting
<b>Charcot-Marie-Tooth (CMT-TRAUK)</b>	06/N056	2006-00460-0-39	ascorbic acid 1500g od vs placebo	Completed	RCT Placebo controlled / two years	MDC/UCL &UCLH	BPNS	MRC London	M.Reilly	Matilde Laura	III	UK Italy	27 2	50 pts aged 18-70/ completed Sep 2009
<b>RMC trial / CIDP</b>	06/N020-05/Q060-3/148	2005-00338-2-16	Methotrexate	Completed	RCT, oral methotrexate or placebo plus folic acid for 40 wks	GBS/CIDP Foundation International		MRC London	M.Reilly	Michael Lunn	III	23 european sites	62 aged 18-70	completed 2008
<b>AVI IM</b>			AVI-4658 (PMO)	Completed	Antisense therapy assessing the efficacy and safety of intramuscular	DoH/Imperial College	Imperial College/ UNEW/ICH	Imperial college	F.Muntoni	Maria Kinali/ S.Cirak	I/II	UK only		Completed 2009



					administered morpholino oligomer directed against exon 51 in DMD									
<b>AVI - 4658 X2 / DMD</b>	08/H0713 /117	2007-00469 5-3	AVI-4658	Completed	Dose ranging study of antisense oligonucleotide sequence for targeted skipping of exon 51 in DMD/ 18 months duration. Weekly IV treatment for 12 weeks followed by 9 months F-up.	AVI Biopharma/ MRC	Veristat Inc.	ICH - MRC London	F.Muntoni/Kate Bushby	S.Cirak	IIb	London/Newcastle	19	Completed 2010 ICH 12; UNEW 7
<b>PTC 124- Nonsense Mutation / DMD &amp; BMD</b>	08/H0408 /29	2007-00547 8-29	PTC124 20, 20,40 mg/kg tds 10, 10, 20 mg/kg tds	Completed	RCT, dose-ranging/4 8 wks + Long term open label (at least 48	PTC therapeutics	Kendle	MRC Newcastle	F.Muntoni - ICH K. Bushby - Newcastle	S.Cirak	IIb	23 sites, US, UK, Israel	16 5	ICH-3; UNEW -11 Completed 2010

					wks)									
<b>DMD Heart Protection Trial</b>		2007-005932-10	Combination of perindopril/bisoprolol or matching placebo	Set-up phase MHRA/REC approved	RCT ACE-inhibitor and beta blocker therapy in preventing cardiomyopathy in males DMD without echo-detectable left ventricular dysfunction/ 60 months (5 yrs)	BHF/Newcastle upon Tyne NHS Trust	ICH, UNEW	MRC Newcastle	Jonh Bourke-UNEW; F.Muntoni -ICH	To be assigned	II	5 UK sites	140	140
<b>Myasthenia Gravis</b>	09/H0714/61	2009-014669-13	Eculizumab (11 infusions/11 infusions placebo )	Closed	Placebo-controlled, cross-over, multicenter study/ patients to be included for a period of 41 weeks. Study period: 2yrs	Alexion	Sue Clarke, Medical Research Network	MRC London	Dimitri Kullman	Jane Spillane	II	TBC	24	Closed to Recruitment in London

<b>GSK/Myasthenia Gravis</b>	10/H0311/8	N/A	Otelixizumab	Ongoing	Blood study - samples used for Tcell assay and autoantibody assay development.	GlaxoSmith Kline	N/A	MRC London	Dimitri Kullman	Jane Spillane		UK, US	40	40/recruiting
<b>DMD/(GSK/Prosensa)</b>	10/H0906/29	2010-018412-32	GSK2402968	Ongoing	Phase IIa double-blind exploratory parallel RCT designed to explore efficacy and safety of GSK2402968 given as a continuous/intermittent regimen over 24 and 48 weeks in ambulant s DMD patients	GlaxoSmith Kline	ICH, UNEW, (CRO-I3 Research)	MRC Newcastle	Volker Straub, F.Munttoni		IIa	London/Newcastle	54	8/active
<b>SMA/Trophos</b>	10/H0720/92	2010-020386-24	TRO19622	Set-up phase	Phase II, Multicentre, double-blind, RCT study in	AFM/Trophos		MRC London	F.Munttoni		II	European sites, UK: Newcastle	150	30/not yet recruiting

<p><b>McArdle</b></p> <p><b>GSK1223249 in MND/ALS (the Nogo-A study)</b></p> <p><b>Biomarkers in MND/ALS Therapeutic trial of lithium carbonate in MND/ALS LiCALS</b></p>	TBC	TBC	Sodium Valproate	Set-up phase	patients with SMA type II or non-ambulant type III Open-label uncontrolled pilot study to evaluate safety/efficacy of Sodium Valproate in McArdle disease	DMC/UCL	ION, MDC	MRC London	Ros Quinlivan	TBC		e, GOSH, Birmingham  London Copenhagen, Dallas	15	Not recruiting yet
						GSK			R. Orrell					2 (fully recruited)
									R. Orrell					22
									R. Orrell					

LiCALS Open Label Extensio n									R. Orrell				3/8 recruited
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## **Natural History – Longitudinal Studies**

### **Set-up Phase**

#### **18. OUTCOME MEASURES IN SMA TYPE II AND III**

**Status: Recruitment to commence shortly**

**Funder: SMA Europe**

**PI: Prof Muntoni**

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 across Europe 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 with SMA II and III.

Further information can be obtained from the Trials Coordinator or Research Physiotherapist on 020 7905 2639.

### **Open Trials**

#### **19. 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)**

**PI: Prof. Hanna**

**Patients recruited: 11 target >10**

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 characterised 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.

Eleven patients have been enrolled so far 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](mailto:d.rajarayan@ion.ucl.ac.uk).

#### **20. EPISODIC ATAXIA SYNDROME: GENOTYPE-PHENOTYPE CORRELATION AND LONGITUDINAL STUDY**

**Status: Recruiting**

**Sponsor: University College London**

**Funder: National Institutes of Health (NIH – USA)**

**PI: Prof. Hanna**

**Patients recruited: 36 target >20**

Episodic Ataxia Syndrome is a rare, genetic disease that causes recurrent episodes of dizziness and incoordination.

The majority of cases are likely caused by an inherent genetic mutation. However in some patients the mutation is unidentifiable. The purpose of this study is to collect prospective standardized data from subjects to better define the clinical phenotype of the EAs and to establish clinically relevant endpoints for use in therapeutic trials.

The study will also :

- Fully characterize the clinical spectra and the natural history of genetically defined EA.
- Systematically investigate phenotypic differences between EA subjects harboring KCNA1/CACNA1A mutations and those that do not.

This proposal involves a multi-center cross-sectional data collection analysis as well as a prospective longitudinal study. Since EA is a chronic disease whose course is measured in years rather than months, the subjects will be followed longitudinally at a yearly interval for a period of two years.

For information about the study please contact Tracey Graves at [tracey.graves@btinternet.com](mailto:tracey.graves@btinternet.com).

## **21. CMT: A NATURAL HISTORY STUDY**

Full Title: Charcot-Marie-Tooth Disease and related disorders: A Natural History Study

**Status: Open to Recruitment**

**Sponsor: University College London Hospitals**

**Funder: National Institutes of Health (NIH – USA)**

**PI: Dr Reilly/Prof Muntoni**

**Patients recruited: 162; target (UK) >50**

Charcot-Marie-Tooth Disease (CMT) and related disorders (distal hereditary motor neuropathy (dHMN) and hereditary sensory and autonomic neuropathy (HSAN)) are a clinically and genetically heterogeneous group of disorders affecting approximately 1 in 2500 people.

People with this condition present with upper and lower limb weakness, wasting and sensory loss as a result of degeneration of the long peripheral nerves supplying the distal muscles. Despite the clinical similarities among patients with CMT the group is genetically heterogeneous. Advances have been made in identifying the genes that cause CMT and the molecular organisation of the peripheral nervous system (PNS) nevertheless the optimal management and treatment of the different variants of this disorder is not known and moreover natural history data is lacking for most forms of inherited neuropathies.

This is a 5 year study that will be conducted by four centres in United States and two centres in the UK (National Hospital for Neurology and Neurosurgery and Great Ormond Street Hospital). The aim of the project is to fully characterise the features of different types of CMT and the longitudinal progression of the disease. The data will also be used to establish clinically relevant endpoints for use in therapeutic trials. The identification and genetic characterisation of patients will facilitate the recruitment of participants for future therapeutic trials. Ultimately the information gained with this study will lead to the improvement in the treatment and management of CMT.

The study is also seeking to establish an appropriate paediatric impairment scoring method for CMT and establish a database for the inherited neuropathies. The study will include both adult and paediatric patients. Evaluations will consist of a neurological history and examination, nerve conduction velocity (NCV) study and in some selected cases skin biopsy.

This is a NIH funded study. At least fifty patients will be enrolled at the National Hospital for Neurology and Great Ormond Street Hospital.

For more information about the study please contact Dr. Matilde Laura at [m.laura@ion.ucl.ac.uk](mailto:m.laura@ion.ucl.ac.uk).

## **22. MITOCHONDRIAL DISEASE COHORT**

**Status: Open to Recruitment**

**Sponsor: The University of Newcastle Upon Tyne**

**Funder: MRC**

**PI: Dr R McFarland, MG Hanna, DM Turnbull**

**patients recruited: 871; target 1000**

The current project proposes to develop a cohort of UK patients with mitochondrial diseases. The details are to be stored in a database that will enable clinicians to gain adequate information for future clinical trials.

Mitochondrial diseases present a huge challenge to patients and doctors because no effective treatment is available. The extremely diverse phenotypic presentation of mitochondrial disease has previously limited cohort development.

The cohort will comprise symptomatic adults and children, in whom a mitochondrial disease phenotype and (where possible) genotype, have been confirmed. Asymptomatic individuals who have requested genotyping and proved positive will also be included. Genotyping is important because the same mitochondrial phenotype may be caused by several distinct mutations in either the mitochondrial or nuclear genomes. Phenotype will be characterized in all individuals (symptomatic and asymptomatic) on the basis of clinical history, clinical examination and detailed investigation.

Two centres will receive referrals (Newcastle University and University College London Hospitals). The database will physically be stored at Newcastle University and it will have a dedicated, electronic secure server.

The project anticipates collecting details on 1000 patients in total.

For information on the status of recruitment please contact Dr. Robert Pitceathly (London) [r.pitceathly@ion.ucl.ac.uk](mailto:r.pitceathly@ion.ucl.ac.uk) or Geoff Bell (Newcastle) [geoff.bell@nuth.nhs.uk](mailto:geoff.bell@nuth.nhs.uk).

## **23. THE NATURAL HISTORY OF INCLUSION BODY MYOSITIS (IBM Net)**

**Status: Open to Recruitment**

**Sponsor: University College Hospitals**

**Funder: MDC**

**PI: Dr Matt Parton/Mike Hanna**

**Enrolled 164 Target 200**

Inclusion body myositis (IBM) is probably the commonest muscle disease beginning in those aged over 50. It leads to progressive disability with, classically, a characteristic pattern of muscle involvement. However it is poorly understood: its cause is unknown, there is no conclusive diagnostic test and it has no treatment. Furthermore, information on the pattern and prognosis of IBM is more based on anecdote from clinical experience, rather than firm fact. The largest published series of data on the natural history of the illness followed only eleven patients for six months.

The current project seeks to better characterise IBM by gathering clinical data from as many cases as possible.

Serial standardised assessment (annually for five years) will chart disease progression and so both expand and strengthen knowledge of the natural history of the illness. Furthermore, establishment of a cohort of reliably-defined cases will build a valuable resource that could potentially form the starting-point for future studies.



For information on the status of recruitment please contact Dr. Pedro Machado at p.machado@ion.ucl.ac.uk

## **24. PERIPHERAL NEUROPATHY OUTCOME MEASURES STANDARDISATION STUDY (PERINOMS)**

**Status: Open**

**Sponsor: Erasmus Medical Center**

**PI: Dr M Lunn**

**Patients recruited: 110; overall target 120**

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.

### **Closed Natural History Trials**

## **25. 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)**

**PI: Prof. Hanna**

**Patients recruited: 20**

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](mailto:d.rajarayan@ion.ucl.ac.uk).

**Non-CTIMPs/ Longitudinal Studies**

Study/Disease	R&D/REC	Status	Study Design/Duration	Funder/Sponsors	Collaborators	Lead Institution	PI/Contact	Fellow	Sites	Total Patients	UK Patients/Status
<b>NDM (ION channel Study) - NH</b>		Closed to recruitment	Prospective, cross-sectional and longitudinal Nat. Hist. to better define the clinical phenotype of NDM/4yrs	NIH/UCLH	CINCH	MRC London	M.Hanna	Emma Matthews	US, Canada, UK	150	20 completed
<b>Episodic Ataxia Syndrome - NH</b>	05/Q0505/108	Enrolling	Prospective, cross-sectional and longitudinal Nat. Hist. to better define the clinical phenotype of EA	NIH/UCLH	CINCH	MRC London	M.Hanna	Tracey Gravis	UK, Canada, US	125	20
<b>ATS (Andersen-Tawil Syndrome) NH</b>	05/Q0505/109	Enrolling	Prospective, cross-sectional and longitudinal Nat. Hist. to better define the clinical phenotype of ATS	NIH/UCLH	CINCH	MRC London	M.Hanna	Sanjeev Rajakulendran	US UK	20	11
<b>SMA - Longitudinal NH validation of outcome measures in SMA II &amp;</b>	10/H0808/77	Set-up phase	The study will provide data on SMA II and III for a 12 month period	SMA Europe	ICH, UNEW, Amsterdam Univ. Inst. Myology Paris, Bambino Gesù	MRC london	F.Muntoni	TBC	EU sites	130	TBC

<b>III</b>					Children's Hospital (Italy), Catholic Univ. (Belgium)						
<b>Collagen VI: Nat. History Study</b>	TBC	Set-up phase	Natural History	TBC	ICH, UNEW	MRC London	F.Muntoni /UNEW	TBC	TBC	TBC	TBC
<b>CMT Nat study</b>	09/H0716/61	Enrolling	Prospective, longitudinal Nat. Hist. study to characterise the pathogenicity of CMT and related neuropathies/ 5yrs	NIH/UCLH	ION	MRC London	M.Reilly	Matilde Laura	ION/NHNN	>50	>50Enrolling
<b>Validation of New Outcome Measures in pediatrics CMT</b>	09/H0716/61	Enrolling	Prospective study to establish a scoring system for quantifying impairment in ped. CMT	NIH/UCLH	ION, ICH/GOSH	MRC London	M.Reilly/ F.Muntoni	TBC	ICH/GOSH		Enrolling
<b>Genetic Modifiers of the CMT1A Phenotype</b>	TBC	Enrolling		MDA(US)	ION	MRC London	M.Reilly	Henry Houlden	NHNN		30 enrolling
<b>X-inactivation in X-linked CMT</b>	TBC	Enrolling			ION	MRC London	M.Reilly	Sinead Murphy	NHNN		Enrolling

<b>Hereditary Sensory and Autonomic Neuropathy Type 1 (HSAN1): A Natural History Study</b>	TBC	Set-up phase	Study aims to carry out a two year natural history study to identify outcome measures for proposed trial of serine in HSAN1	UCLH/UCL National Institute for Health Research CBRC ?	ION	MRC London	M.Reilly	TBC	NHNN	30-50	Set-up phase
<b>Perinoms</b>	TBC	Enrolling	Parallel Cross-sectional and longitudinal study of outcome measures for GBS, CIDP, MMNCB and paraproteinemic neuropathy. 2 yrs duration	Erasmus Medical Center, Univ. Maastricht/?KCL	Erasmus Medical Center, Rotterdam; Univ. Hospital Maastricht, ION, KCL	MRC London	Mike Lunn	TBC	12 sites: USA, UK, Canada, Italy, Netherlands, France, Belgium	250 (120 Sectional - Netherlands only; 130 longitudinal)	120 enrolled
<b>North Star</b>		Ongoing	Nat. Hist./DMD database	MDC	ICH, UNEW	MRC London	F.Muntoni	N/A	North centres and south centres	not limited	not limited
<b>MusQoL UK</b>	08/H0907/118	recruiting	Nat. Hist. Assessing QoL in adults with muscle disease/45mins self report	MDC/KCL	KCL, ION	MRC London	M.Hanna	A.Miller, J.Burge, R. Pitceathly	KCL, ION	450	450
<b>Mitochondrial Cohort</b>	09/0235	recruiting	Natural History/Mitochondrial Database. 3 yrs project	MRC/UNEW	UNEW, ION	MRC NEW	M.Hanna	Rob Pitceathly	UNEW, ION	1500	1500

<b>Fatigue in children with MG</b>	TBC	Applying for funding	PhD programme: development of OM, comparison of home and clinic based measures	Applying for NIHR and MDC PhD studentships	MRC Centre, ICH	MRC London	Francesco Muntoni (NIHR) and Gita Ramdharry (MDC)	Andrew Hiscock	NHNN, GOSH		
<b>IBM Net</b>	10/H072 1/28	Open	Nat. Hist. study on IBM	MDC/UC H	MRC centre, ION	MRC London	Matt Parton	Pedro Machado	NHNN		

## **Exercise Studies**

### **Set-up Phase**

#### **26. Aerobic training in Charcot-Marie-Tooth disease and Inclusion Body Myositis.**

**Status: In set-up**

**Sponsor: University College Hospitals**

**Funder: TBC**

**PI: Dr Gita Ramdharry**

The specific objective of the present study is to investigate the effect of aerobic training in two common neuromuscular diseases (NMD): Charcot-Marie-Tooth disease (CMT) and Inclusion Body Myositis (IBM). These diseases result in progressive muscle wasting and substantial morbidity and disability. The effect of aerobic training on fitness levels, muscle strength and function will be systematically examined. This study will also monitor the safety, feasibility and impact on quality of life of this type of exercise training in these groups.

Sixty subjects, (30 from each disease group, aged between 18 and 75), will be recruited from the neuromuscular clinics at Queen Square. Both disease groups will be investigated concurrently with the same methods but will be viewed and analysed as separate studies. A crossover design will be used with training and control periods. The trial will span three years with each subject participating for a 34 week period. For the training intervention, participants will train in select local gyms and train on a bicycle ergometer.

The primary outcome measure for this study is maximum aerobic capacity during exercise testing. There will also be measures of muscle strength, body composition, and activity levels. In addition the study will investigate non-motoric effects of exercise such as mood, motivation, sleep and fatigue.

#### **27. Full Title: Exploring the causes of falls and balance impairments in people with neuromuscular diseases**

**Status: In set-up**

**Sponsor: University College Hospitals**

**Funder: NIHR**

**PI: Dr Gita Ramdharry**

Falls are commonly reported by people with neuromuscular disorders but to date there has been little formal investigation of this problem. Frequent falling increases the risk of injury and reduces mobility due to avoidance of activities perceived to increase the threat of falls.

The aim of this study is to ascertain falls risk from measurement of falls incidents, balance impairment and clinical presentation in people with different types of Charcot-Marie-Tooth (CMT), Distal Myopathy (DM) and Sensory Neuropathy (SN) with healthy controls. Measurements of static, anticipatory and reactive balance impairment and prospective falls events will be used to ascertain relationships with clinical presentation in people with different types of CMT, DM and SN. The three pathologies have been chosen for comparison as this will allow some discernment between the sensory and motor contributions to falls

## Open Trials

### **28. EXERCISE TRAINING IN PATIENTS WITH MITOCHONDRIAL DISEASE: ASSESSING THE BENEFITS**

**Status: Recruiting**

**Sponsor: University Newcastle**

**Funder: Muscular Dystrophy Campaign (MDC)**

**PI: Prof Turnbull**

**Collaboration site MRC Centre London (Hanna)**

**Patients recruited: 6- 5 Newcaslte 1 London**

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 are:

To confirm that endurance training in patients with mitochondrial abnormalities improves quality of life, exercise tolerance and oxidative capacity.

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](mailto:geoff.bell@nuth.nhs.uk) or Dr Robert Pitceathly at [r.pitceathly@ion.ucl.ac.uk](mailto:r.pitceathly@ion.ucl.ac.uk).

### **29. CARDIAC ADAPTATIONS TO EXERCISE IN MITOCHONDRIAL DISEASE**

**Status: Recruiting**

**Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust**

**Funder: MRC**

**PI: Prof D M Turnbull/Dr MI Trenell,**

**Patients recruited: 9; target 24**

Twenty four people with mitochondrial disease will take part in the study. Participants will undergo cardiac, cognitive and movement examination and then they will be randomised into two groups. They will receive either; exercise counselling and support (n = 12) or continue standard care (n = 12) over a 16 week period. At the end of the 16 week period baseline measures will be repeated. Participants to be studied will have biopsy proven mitochondrial disease (age 18–60 years; BMI 20–35 kg/m<sup>2</sup>; and do not take part in regular exercise). Subjects with heart disease that would produce an adverse response to exercise will be excluded. Subjects with significant kidney disease or in vivo ferrous material will be excluded



also as these are contra-indications to the use of gadolinium-based contrast agents and magnetic resonance imaging respectively. Magnetic resonance and echocardiographic evaluation of cardiac function as well as movement and cognitive function will be assessed at baseline and at 16 weeks. A progressive exercise test will be undertaken at baseline to establish maximal aerobic capacity and evaluate for an adverse response to exercise.

The patient exercise group will be matched with a control group of individuals without known mitochondrial disease who will undergo the same evaluation and training regime (n = 12).

In total, the study will require each participant to attend the research facility for three visits for metabolic examination. The exercise groups will be requested to attend 48 exercise sessions over 16 weeks.

For information about recruitment contact Geoff Bell at [geoff.bell@nuth.nhs.uk](mailto:geoff.bell@nuth.nhs.uk).

### **30. PHYSICAL ACTIVITY AND INCLUSION BODY MYOSITIS**

**Status: Recruiting**

**Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust**

**Funder: MRC**

**PI: Dr M Trenell**

**Collaborating site MRC Centre London**

**Recruitment: 500 recruits expected, across 5 disease sites (all not open yet), stroke arm has 36 recruited, 100 expected**

The aim of this study is to collect data on day to day physical activity levels and metabolic control in individuals with chronic disease.

#### **DESIGN:**

Participants will be identified from chronic disease clinics by the following lead clinicians: Stroke-Prof Gary Ford, Neuromuscular disorders-Prof Kate Bushby, Metabolic disorders-Prof Roy Taylor, fatigue-Prof Julia Newton and Ageing-Prof Julia Newton. An equal sample of male and female participants will be used in the study which will be up to 100 patients in each disease group.

#### **METHODOLOGY:**

Step 1: Relevant practitioners will highlight possible candidates for the study.

Step 2: Visit 1: At the start of the study participants will either be asked to attend Newcastle University's Campus for Ageing and Vitality (Newcastle General Hospital), or if they are an inpatient will be visited on the ward. Participants will be provided with an information sheet about the study. They will be given the opportunity to talk with the team and ask questions. Once fully informed, participants will provide signed informed consent.

Participants will be asked to fill in a disease screening questionnaire at the start of the process. The height and weight of the participants will be recorded and this information will be entered into the physical activity monitors. Instructions will be provided as to how to use the monitors. A resting blood sample may also be taken at this point. This will be analysed for glucose, insulin, lipid profile and liver function.

Step 3: Participants will wear the arm monitors for five days including one weekend day.

Step 4: Visit 2: At the end of the five day period participants will attend the research centre again or attend a pre-arranged session either at their home work place or on the ward to

return the activity monitor. Here they will complete a brief physical activity questionnaire and two brief fatigue questionnaires. Data from the physical activity monitor will be fed into a computer. Each participant will be provided with a printout of their weekly activity levels and given the opportunity to discuss their results.

For information about recruitment contact Geoff Bell at [geoff.bell@nuth.nhs.uk](mailto:geoff.bell@nuth.nhs.uk).

### **31. EXERCISE AND SARCOPENIA**

**Status: Recruiting**

**Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust Funder: MRC**

**PI: Prof DM Turnbull**

**Collaborating site MRC Centre London**

**Patients recruited: 0; target: 36**

Sarcopenia, which is a complex multifactor process, has significant implications on quality of life, performance of daily activities, maintenance of independence and on projected healthcare costs.

Studies show that low physical activity correlates with poor mitochondrial function. Conversely, exercise correlates with better mitochondrial function, clinical improvement and improved perceived quality of life. Endurance training has been proven to be safe and efficacious in mitochondrial disease which may provide a model for the aging process albeit in an accelerated form with biochemical, histological and genetic changes seen in aged muscle also found in various mitochondrial conditions.

**Aims:**

1. To assess the rate and extent of motor unit loss in the eighth decade of life- cross-sectional (time 0) and longitudinal analysis (end of study)
2. To correlate the extent of motor unit loss with histological correlates and the development of sarcopenia
3. To assess the impact of exercise on the rate and extent of motor neuron loss
4. To observe whether endurance training initiated in late middle age prevents loss of muscle strength and mass in senescence
5. To assess the impact of neuronal loss on the inability to retain gains made in muscle strength following training after the 7th decade of life
6. To characterise effects of exercise upon neural activity, muscle oxidative capacity and mitochondrial and satellite cell plasticity with age.

**Method:**

Thirty six (36) female participants, matched for body mass index who do not take regular exercise will be invited to participate: 40- 45 years (12), 60-65 years (12) and 80- 85 years (12). Inclusion criteria will be capacity to undertake cycling exercise and ability to give informed consent. Exclusion criteria will be co-existing active coronary artery disease or steroid therapy.

These patients will be recruited via the media and social support groups. All expenses (travel, accommodation and meals) will be paid for from the research grant.

The study will take place over 24 weeks. Participants will attend the study centre for 7 visits in total. The study will include 2 main visits at the beginning and end of the study. Each main visit will last 3 days. There will also be 5 one day visits.

For information about recruitment contact Geoff Bell at [geoff.bell@nuth.nhs.uk](mailto:geoff.bell@nuth.nhs.uk).

### **Closed Trials**

#### **32. STRENGTHENING HIP MUSCLES TO IMPROVE WALKING DISTANCE IN PEOPLE WITH CHARCOT- MARIE-TOOTH DISEASE**

**Status: Completed**

**Sponsor: University College London Hospitals**

**Funder: Muscular Dystrophy Campaign (MDC)**

**PI: Dr. Reilly**

**Patients recruited: 32 target: 32**

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, randomised 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 include 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.

Data being analysed for publication.

Exercise Studies

Study/Disease	R&D/REC	Status	Study Design/Duration	Funder/Sponsors	Collaborators	Lead Institution	PI/Contact	Fellow	Sites	Total Patients	UK Patients/Status
<b>Exercise trial for CMT</b>	09/0049 09/H072 3/6	Completed	Exercise Randomised Controlled Trial (RCT)	MDC/UC LH	N/A	MRC London	M.Reilly	Alex Pollard	NHNN MRC London	32	32 closed
<b>Exercise trial for mitochondrial disease</b>	09/0235	Enrolling	Exercise RCT duration 48 weeks: 16 wks resistance training plus 32 weeks aerobic conditioning	MDC	UNEW; London	Lead MRC Newcastle Collab MRC London	Doug Turnbull	Grainne Gorman/Jane Newman	MRC UNEW, London MRC London	10	10/5 enrolled
<b>Cardiac adaptations to exercise in mitochondrial disease</b>	TBC	Enrolling	Exercise RCT involving 48 exercise session over 16 weeks to assess effect on mitochondrial disease	MRC	UNEW	Lead MRC Newcastle Collab MRC London	Doug Turnbull		UK	24	9
<b>Physical activity and IBM</b>	TBC	Enrolling	Study aiming to collect data on day to day physical activity levels and metabolic control in individuals with chronic	MRC	UNEW	Lead MRC Newcastle Collab MRC London	Dr M Trenell		UK MRC Newcaslte Collab MRC London	100	36

			disease								
<b>Exercise and sarcopenia</b>	TBC	Enrolling	Exercise study duration 24 weeks involving female participants	MRC	UNEW	Lead MRC Newcastle Collab MRC London	Doug Turnbull		UK	36	0
<b>Aerobic training in NMD</b>	TBC	Applying for funding	Exercise cross over trial: 12 weeks aerobic training at local Fitness First gyms	Applying to CRDC fast track and MDC	MRC Centre London, Department Psychology, University of Surrey	MRC London	Ramdharry Hanna Reilly		NHNN	60	60
<b>Frequency and circumstances of falls in NMDs</b>	10/H0803/70	Completed	Survey of people with CMT and distal myopathy	NIHR	MRC Centre, St George's University of London	MRC London	Gita Ramdharry	Gita Ramdharry	NHNN	100	100
<b>Falls and balance in NMDs</b>	TBC	Ongoing	Exploratory lab study	NIHR	MRC Centre, St George's University of London	MRC London	Gita Ramdharry	Gita Ramdharry	NHNN	20	20

## **Imaging Studies**

### **Set-Up Phase**

#### **33. Full Title: Evaluation and Optimisation of Muscle Imaging Biomarkers in Support of Non-ambulant Duchenne Muscular Dystrophy Studies**

**Sponsor: Great Ormond Street Hospital/Institute of Child Health**

**Funder: GSK**

**PI: Prof Francesco Muntoni**

Duchenne muscular dystrophy (DMD) is the most frequent inheritable lethal childhood disease. In the recent years, there have been promising advances for new potential genetic treatments (including the development of exon skipping with anti-sense oligomers producing dystrophin restoration). The current way to assess successful outcomes in early genetic experimental therapies is to measure the restoration of the defective protein in muscle, which involves a muscle biopsy, a significantly invasive procedure. It is therefore required to design and validate non-invasive markers, which allow measuring response to treatments in the ambulant and non-ambulant population.

Magnetic resonance imaging (MRI) has become a valuable tool to image the change in signal characteristics in dystrophic muscle. MRI provides non-invasive indices of muscle atrophy, fibro-fatty replacement, oedema, and structural abnormalities in DMD muscle that may offer valuable markers of efficacy for exon-skipping treatments. The time-course of these MRI indices are currently unknown, and particularly unclear in the non-ambulatory population.

The primary aim of this study is to characterise through MRI differential involvement of muscle groups occurring with disease progression, more precisely by defining which muscle groups are best markers for therapeutic response in the non-ambulant boys. In addition we aim to define quantitative imaging changes in these muscle groups by optimising quantitative metrics for detecting change in these muscles over time (and, thus, by inference, with a therapeutic intervention) – ensuring that robust statistical methods are in place for interventional studies of non-ambulatory boys.

A related aim of the study is to correlate the MRI findings with clinical assessments currently in use in the non-ambulant population.

This is a prospective longitudinal natural history study. Subjects with DMD will be followed over a one year period. MRI datasets will be collected at baseline, 3 months, 6 months, and 12 months. Clinical observations will be performed at baseline, 6 months, and 12 months.

Healthy boys may also be scanned using MRI for the purposes of testing scan test/retest and for investigating differences in the MRI biomarkers between the DMD population and healthy boys. Healthy controls will be scanned either once or twice, for test/retest purposes.

All subjects will be asked not to undertake organized or unaccustomed physical exercise (i.e. participation in school sports, training clubs,) from 1 week before imaging and clinical

assessments. This is to eliminate exercise as a confounding factor. Normal playing with friends is permitted.

For more information about the study please contact Dr Valeria Ricotti at [v.ricotti@ich.ucl.ac.uk](mailto:v.ricotti@ich.ucl.ac.uk).

## **Open Trials**

### **34. 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: MRC**

**PI: Prof T Yousry/Dr J Thornton**

**Patients recruited: 52; target 80**

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) and 40 patients with genetically confirmed Charcot Marie Tooth Disease (CMT). 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 characterise 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](mailto:j.morrow@ion.ucl.ac.uk).

### **35. MRI IN FKRP-RELATED LGMD2I**

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 NHS Trust**

**Funder: MRC**

**PI - Prof V 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.

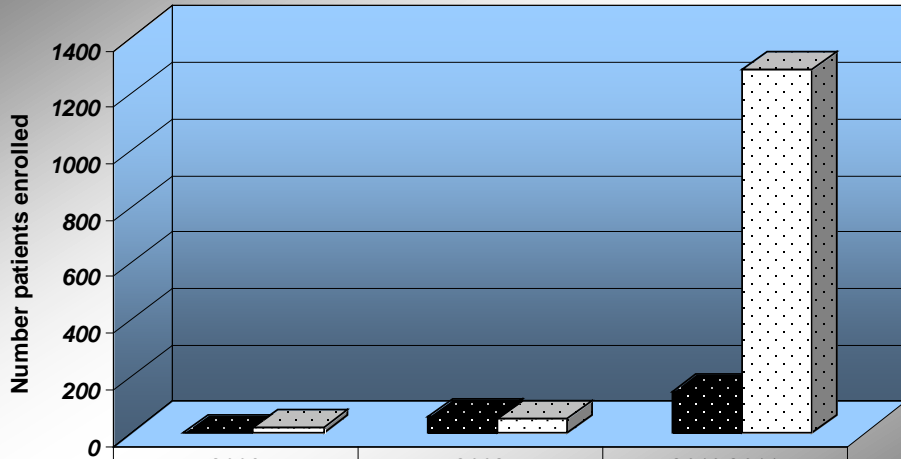
For further information about the study please contact Dr. Jasper Morrow at [j.morrow@ion.ucl.ac.uk](mailto:j.morrow@ion.ucl.ac.uk).

**Imaging Studies**

**Non-\*CTIMPs/ Longitudinal Studies**

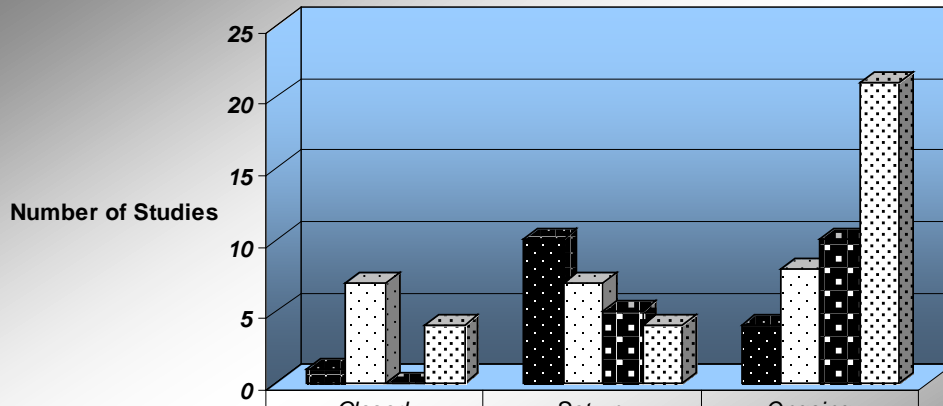
Study/Disease	R&D/REC	Status	Study Design/Duration	Funder/Sponsors	Collaborators	Lead Institution	PI/Contact	Fellow	Sites	Total Patients	UK Patients/Status
<b>MRI study (CMT/IBM)</b>	08/H0715/17	open to recruitment	Prospective cohort CMT-IBM using MRI to detect changes in muscle of 40 IBM patients and changes in nerve of 40 CMT patients /5 years	MRC/UC LH	ION	MRC London	T.Yousry	Chris Sinclair Jasper Morrow	ION	160 participants from which 80 are patients	80
<b>MRI study (FKRP related LGMD2I)</b>	09/H0907/29	Open to recruitment	Natural History	Newcastle NHS Trust	ION, UNEW	MRC NEW	M.Hanna	Jasper Morrow	UNEW, ION	50-60	50-60 enrolling
<b>MRI in DMD</b>	TBC	Set-up	Prospective longitudinal natural history study of 12 months duration	GOSH/ICH, GSK	GOSH/ICH, NHNN, ION	MRC London	F.Muntoni	Valeria Ricotti	GOSH/NHNN	15	15

### Accrual Progression 2006-2011

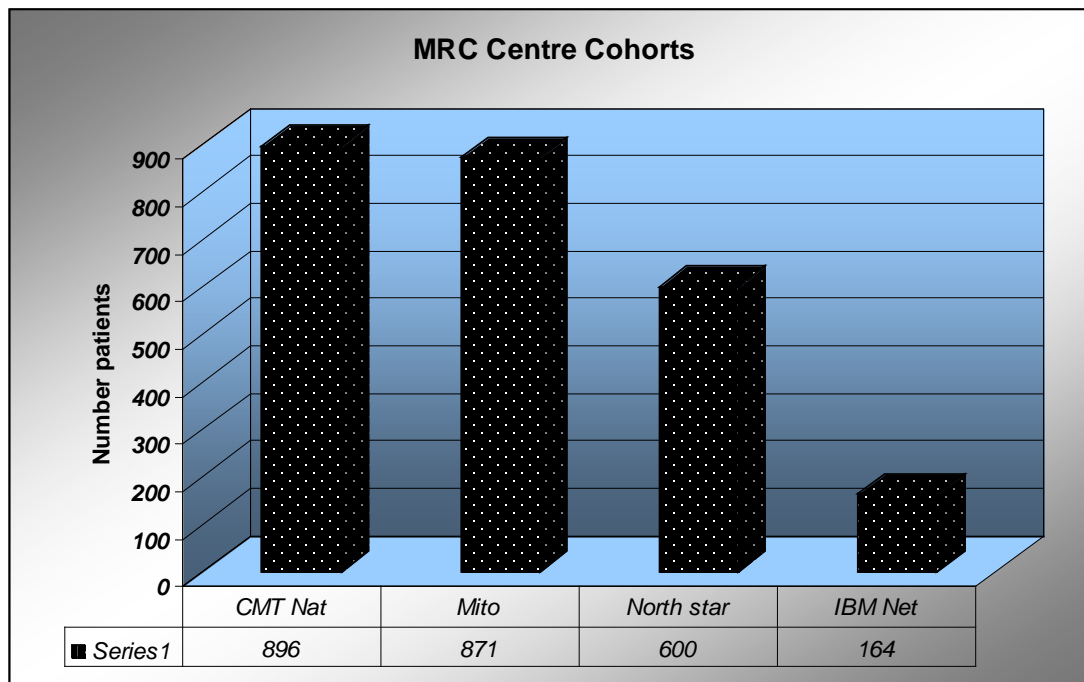


	2006	2008	2010-2011
■ CTIMPs	1	58	142
□ Non-CTIMPs	20	47	1286

### Studies Progression 2009-2011



	Closed	Set-up	Ongoing
■ CTIMPs 2009	1	10	4
□ CTIMPs 2011	7	7	8
■ Non-CTIMPs 2009	0	5	10
□ Non-CTIMPs 2011	4	4	21



## Clinical Trials, Outcome Measures, Natural history Studies Publications

### Papers

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Cirak S *et al.* Exon skipping and dystrophin restoration in Duchenne Muscular Dystrophy patients after systemic phosphorodiamidate morpholino oligomer treatment. *The Lancet*, 2011, Aug 13;378(9791):595-605

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Richard Hughes, *Neuromuscular Disorders in press*

Double-blind, placebo-controlled, parallel group, phase III study comparing dichlorphenamide vs. placebo for the treatment of periodic paralysis (HYP HOP trial).

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Genotype-phenotype correlation and longitudinal three year natural history study in the Non-dystrophic myotonias in the UK D.L. Raja Rayan, E. Matthews, S. Rajakulendran, G. Barreto, S.V. Tan, L. Dewar, J. Burge, R.C. Griggs, R.Barohn, M.G. Hanna and the CINCH group *Neuromuscular Disorders in press*

Assessing the efficacy of Mexiletine in UK patients with Non-dystrophic Myotonia

D.L. Raja Rayan, E. Matthews, G. Barreto, S.V. Tan, L. Dewar, J. Burge, R Barohn, M.G. Hanna and the CINCH group. *Neuromuscular Disorders in press*

Genotype-phenotype correlation and longitudinal study of Andersen-Tawil Syndrome in the UK D.L. Raja Rayan, S. Rajakulendran, G. Barreto, S.V. Tan, L. Dewar, R.C. Griggs, M.G. Hanna and the CINCH group. *Neuromuscular Disorders in press*

Charcot-Marie-Tooth Disease and Related Disorders: A Natural History Study

M.Laurá, S. Murphy, A. Rossor, A. Hiscock, M. Main, M.E. Shy, F. Muntoni, M.M. Reilly *Neuromuscular Disorders in press*

A randomised, double-blinded, placebo-controlled pilot study assessing the safety and tolerability of Arimoclomol in sporadic Inclusion Body Myositis (IBM)

P. Machado, A. Miller, M. Parton, L. Dewar, J. Holton, M. Dimachkie, L. Herbelin, L. Greensmith, R. Barohn, M. Hanna *Neuromuscular Disorders in press*

The Effects of Arimoclomol on Pathological Outcome Measures of Inclusion Body Myositis *in vitro*

Adrian Miller, Mhoriam Ahmed, Michael Hanna, Linda Greensmith *Neuromuscular Disorders in press*

An MRI study of the effects of metoprolol on *in vivo* cardiac calcium homeostasis

Alison Blain, Elizabeth Greally, Steve Laval, Volker Straub, Guy MacGowan. *Neuromuscular Disorders in press*

An integrative database for clinical and research studies in neuromuscular diseases  
Thomas Müller, Sebahattin Cirak, Matthew Parton, Michael Lunn, Mike Hanna, Francesco Muntoni  
*Neuromuscular Disorders in press*

The Natural History of Sporadic Inclusion Body Myositis: Development of an Electronic Database IBM-net. A Miller, P Machado, J Morrow, A Hiscock, L Dewar, S Brady, D Hilton-Jones MG Hanna, M Parton,  
*Neuromuscular Disorders in press*

The MRC Centre for Translational Research in Neuromuscular Disease: Mitochondrial Disease Patient Cohort Study UK V Nesbitt,<sup>1</sup> RDS Pitceathly, S Rahman, J Poulton, DM Turnbull, MG Hanna, R McFarland  
*Neuromuscular Disorders in press*

Benefits and adverse effects of glucocorticoids in boys with Duchenne Muscular Dystrophy: a UK perspective Ricotti V, Manzur AY, Scott E, Muntoni F, on behalf of NorthStar Clinical Network  
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Current progress with the systemic administration trial of AVI-4658, a novel Phosphorodiamidate Morpholino Oligomer (PMO) skipping dystrophin exon 51 in Duchenne muscular dystrophy (DMD)  
Sebahattin Cirak, Michela Guglieri, Steve Shrewsbury, Kate Bushby, Francesco Muntoni  
*Neuromuscular Disorders in press*

Translation related clinical trials in duchenne muscular dystrophy (DMD) in the UK  
Rahela Choudhury, Gisela Barreto, K Ganeshaguru, Sebahattin Cirak, Mariacristina Scoto, Francesco Muntoni  
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Exploring emotional impact in a proof-of-principle single-blind, controlled, two-doses escalation intramuscular study of a morpholino splice-switching oligonucleotide (AVI-4658) trial to induce dystrophin restoration in children with Duchenne muscular dystrophy Elena M. Garralda, Maria Kinali, Sebahattin Cirak, Francesco Muntoni  
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UK NorthStar Neuromuscular Clinical Network (NSCN): National Audit results in Duchenne Muscular Dystrophy (DMD) Corticosteroid practice, Vitamin D status and bone health Adnan Y Manzur, Elaine Scott, Pinki Munot, Kayal Vijaykumar, Francesco Muntoni, on behalf of UK NorthStar

The genetic skeletal muscle channelopathies: Genotype-Phenotype correlation and longitudinal studies S Rajakulendran, E Matthews, SV Tan, L Dewar, RC Griggs, MG Hanna and the CINCH group  
*Neuromuscular Disorders*  
double-blind placebo controlled cross-over study to investigate the efficacy of Mexiletine in patients with Non-dystrophic Myotonia in the UK  
D. Raja Rayan, E. Matthews, G. Barreto, V.S.Tan, L. Dewar, J. Burge and M.G. Hanna. *Neuromuscular Disorders*

MRC Mitochondrial Cohort Study: Development of a UK Database  
Pitceathly, R.D.S.; Nesbitt, V.; Rahman, S. McFarland, R. Hanna M.G. and Turnbull, D.M.  
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Development and validation of a mitochondrial disease-specific quality of life scale (Mito-QOL) J L Elson, M Cadogan, S Apabhai, A Phillips, R McFarland, R Whittaker, R Horvath, E McColl, D M Turnbull, G S Gorman  
*Neuromuscular Disorders in press*

IBM-Net: a clinical database of inclusion body myositis patients  
Matt Parton, Mike Hanna, Adrian Miller, Jasper Morrow  
*Neuromuscular Disorders in press*

Using MRI as a diagnostic tool in the skeletal muscle channelopathies  
E. Matthews, R. Sud, R. Labrum, L.Strycharczuk, C Sinclair, T. Yousry and M.G.Hanna  
*Neuromuscular Disorders in press*

### **Core Activity - Neuromuscular Animal Models**

<b>Added value</b>	<ul style="list-style-type: none"> <li>• Establishing a comprehensive behavioural test battery for neuromuscular disease with existing resource and support for animal research from the host institution</li> <li>• Establishing translational imaging and electrophysiological techniques for the assessment of animals models of neuromuscular disease (MRI,QTRAC)</li> </ul>
<b>Deliverables</b>	<ul style="list-style-type: none"> <li>• A standard battery for the investigation of animal models of neuromuscular disease used in publications</li> </ul> <p>We have established a range of behavioural, histological and electrophysiological techniques.</p> <ul style="list-style-type: none"> <li>• Translation of novel assessment techniques between animal and humans (e.g. MRI, QTRAC)</li> </ul> <p>Several projects have used nerve excitability profiling (Qtrac) in animals and humans (details see below). Cardiac MRI has been applied to mouse models and patients.</p> <p>There are plans for MRI studies on antisense treatment in mdx mice and in a model of Kennedy's disease facilitated by appointment of an animal physicist partly funded by the MRC Centre.</p>
<b>Milestones</b>	<ul style="list-style-type: none"> <li>• 2008 Establishing core techniques for behavioural assessment of mouse models of neuromuscular disease</li> <li>• 2010 Establishing MRI and QTRAC standards</li> </ul>
<b>Success criteria</b>	<ul style="list-style-type: none"> <li>• Publication of battery for the assessment of neuromuscular models 2010</li> <li>• Liaising with EUmorphia consortium on harmonization of MRC Centre tests into the EU consortium.</li> </ul>
<b>Responsibilities</b>	<ul style="list-style-type: none"> <li>• <b>Martin Koltzenburg Linda Greensmith Lizzy Fisher, Dimitri Kullmann</b></li> </ul>

***Progress in Neuromuscular animal model core area:***

The table below lists the investigational techniques for neuromuscular diseases. Tests highlighted in blue and black are those suggested for neuromuscular phenotyping of mice by EMPReSS and Treat-NMD, respectively. Those that are available in the centre or are currently developed are in red. Some of the techniques suggested by EMPReSS and Treat-NMD are not going to be implemented as we feel that they are not adding significant new information over other test or we were not able to fund within the current budget.



## Readouts

## Protocol/Method

## Status

## GLOBAL BEHAVIOUR

EMPreSS	Global score (mainly behaviour)	Modified SHIRPA	yes
EMPreSS	Coordination	Tail suspension	yes
Treat-NMD	Forelimb strength	Grip strength	yes
Treat-NMD	Fatigue	4 limb grid test/Inverted suspension	yes
EMPreSS	Limb strength	Grip strength forelimbs and 4 limbs	yes
Treat-NMD	Exercise	Voluntary wheel	to be established
Treat-NMD	Contraction properties	Dynamometer	not to be established
Treat-NMD	Spontaneous locomotor activity	Open field (Digiscan)	not to be established
Treat-NMD	Spontaneous locomotor activity	Accelerometer	not to be established
EMPreSS	Spontaneous locomotor activity	Open field	not to be established
Treat-NMD	Fatigue/Coordination	Rotarod	yes
EMPreSS	Fatigue/Coordination	Rotarod	yes
EMPreSS	Global reflex	Acoustic startle	not to be established
EMPreSS	Fatigue	Swim Ability Test	not to be established
Treat-NMD	Acute and sustained force	Wire test	not to be established
Treat-NMD	Acute and sustained force	Whole body tension test	not to be established
EMPreSS	Nociceptive reflex	Tail flick	to be implemented
MRC Centre	Nociceptive reflex	Paw withdrawal/ Radiant heat	to be implemented
MRC Centre	Spontaneous locomotion/nociception	Temperature preference	to be implemented
MRC Centre	Nociceptive reflex	von Frey hair (manual, electronic)	to be implemented

## MORPHOLOGY

Treat-NMD	Muscle morphology (qualitative)	MRI	to be implemented
MRC Centre	Muscle morphology quantitative	MRI	to be implemented
MRC Centre	Nerve morphology	MRI	to be implemented
Treat-NMD	Joint contracture	Tibiotarsal joint angle	yes
Treat-NMD	Muscle morphology	H&E: diameter, centronucleation	yes
Treat-NMD	Muscle morphology	Van Gieson, Sirius Red	yes
Treat-NMD	Muscle morphology	Masson's trichrome stain	yes
Treat-NMD	Muscle membrane integrity	Evans blue/Procion orange/albumin/fibronectin	yes
Treat-NMD	Muscle membrane integrity	Parvalbumin	yes
EMPreSS	Protein Expression	Immunohistochemistry/WB	yes
EMPreSS	Gene Expression	In situ hybridization	yes
MRC Centre	Peripheral nerve quantification	Plastic sections LM - myelinated fibres	yes
MRC Centre	Ventral and dorsal root L5 quantification	Plastic sections LM - myelinated fibres	yes
MRC Centre	Peripheral nerve/roots ultrastructure	Plastic section EM	yes
MRC Centre	DRG quantification	Stereological measurement	yes
MRC Centre	DRG neuronal typing	IHC, vital stain	yes
MRC Centre	Spinal cord morphology and motor neuron quantification	IHC	yes
MRC Centre	Epidermal nerve fibres density	PGP9.5 IHC	yes

## NERVE AND MUSCLE FUNCTION

Treat-NMD	Single muscle force	Isometric force measurement (in vivo)	yes
Treat-NMD	Single muscle force	Isometric force measurement (in	yes

		vitro)	
MRC Centre	Assessment of motor nerves	Motor nerve conduction, QTRAC	yes
MRC Centre	Assessment of motor nerves	MUNE	yes
MRC Centre	Assessment of motor nerves	Fatigue test	yes
MRC Centre	Assessment of muscle	EMG	yes

## NERVE FUNCTION

MRC Centre	Assessment of sensory nerves	Sensory nerve conduction studies	yes
MRC Centre	Assessment of sensory nerves	QTRAC in vitro and in vivo	yes
MRC Centre	Assessment of sensory nerves	Single unit recordings	yes

## ORGAN FUNCTION

Treat-NMD	Respiratory function	Plethysmography	?
Treat-NMD	Cardiac function	Echocardiography	?
Treat-NMD	Cardiac function	P/V loops	yes
EMPreSS	Cardiac function	Left ventricular haemodynamics	yes
EMPreSS	Cardiac function	ECG	yes
EMPreSS	Cardiovascular function	Blood Pressure and heart rate	yes
MRC Centre	Cardiac function	MRI	yes

## BIOCHEMISTRY

Treat-NMD	Muscle Dystrophin/Utrophin content	WB, IHC	yes
Treat-NMD	Muscle proteins	WB, IHC	yes
Treat-NMD	Muscle collagen content	Hydroxyproline	yes

Treat-NMD	Muscle membrane integrity	CK, LDH, Pyruvate kinase	yes
EMPreSS	Blood chemistry	Haematology	yes
EMPreSS	Blood chemistry	Clinical Chemistry	yes
EMPreSS	Body composition	Dexa-scan analysis	Currently not implemented

## CELLULAR FUNCTION

Treat-NMD	Muscle Ion channel function	Voltage/Current clamp	yes
Treat-NMD	Muscle calcium homeostasis	Calcium imaging	yes
Treat-NMD	Muscle calcium homeostasis	Total calcium measurement	yes
UCL	Neuronal function	Voltage/Current/Patch clamp	yes
UCL	DRG function	Calcium imaging	yes
UCL	Mitochondrial function	Confocal microscopy in vitro	yes

## MOLECULAR BIOLOGY

EMPreSS	Gene Expression	In situ hybridization	yes
EMPreSS	Gene Expression	Immunohistochemistry	yes
EMPreSS	Gene Expression	Whole mount staining of embryos	yes
EMPreSS	Gene Expression	Gene expression by qrtPCR	yes

Several publications have arisen from the animal work of the centre:

### Full Publications

Achilli, F., Bros-Facer, V., Williams, H., Banks, G., AlQatari, M., Chia, R., Tucci, V., Groves, M., Nickols, C., Seburn, K., Kendall, R., Cader, M., Talbot, K., van Minnen, J., Burgess, R., **Brandner, S.**, Martin, J., **Koltzenburg, M.**, **Greensmith, L.**, Nolan, P., **Fisher, E.M.C.** (2009) An ENU-induced mutation in a mouse glycyl-tRNA synthetase (GARS) causes peripheral sensory and motor phenotypes creating a model of Charcot-Marie-Tooth type 2D peripheral neuropathy. *Dis Model Mech* 2: 359-373

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Boërio, D., Kalmar, B., **Greensmith, L.**, **Bostock, H.** (2010) Changes in excitability of mouse motor axons in the mutant SOD1<sup>G93A</sup> model of amyotrophic lateral sclerosis. *Muscle and Nerve* 41(6):774-84

Banks, G.T., Haas, M.A., Line, S., Shepherd, H.L., AlQatari, M., Stewart, S., Rishal, I., Philpott, A., Kalmar, B., Kuta, A., Groves, M., Parkinson, N., Acevedo-Arozena, A., **Brandner, S.**, Bannerman, B., **Greensmith, L.**, Hafezparast, M., **Koltzenburg, M.**, Deacon, R., Fainzilber, M., **Fisher, E.M.C.** (2011)

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Malik, B., Nirmalanathan, N., Bilsland, LG., La Spada, AR., **Hanna, MG.**, Schiavo, G., Gallo JM., **Greensmith, L** (2011) Absence of disturbed axonal transport in Spinal and Bulbar Muscular Atrophy Human Molecular Genetics

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## **Abstracts**

Joyce P, Fratta P, Phatak V, McGoldrick P, Greensmith L, Fisher EMC, Acevedo-Arozena A (2011) A new mouse model of ALS carrying a point mutation in the mouse Sod1 gene. UK Neuromuscular Translational Research conference, London, UK *in press Neuromuscular Disorders*

Ricketts T, Fratta P, Joyce P, McGoldrick P, Kent R, Greensmith L, Acevedo-Arozena A, Fisher, EMC (2010) Functional characterization of mouse TDP-43 point mutations generated by chemical mutagenesis. American Society of Neuroscience Annual meeting, San Diego, USA

McGoldrick P, Dick J, Ricketts T, Acevedo-Arozena A, Fisher E, Greensmith L (2010) Investigating novel mutant mouse models of motor neuron disease. UK Neuromuscular translational research conference, Oxford, UK

Joyce P, Fratta P, Phatak V, McGoldrick P, Greensmith L, Fisher EMC, Acevedo-Arozena A, (2010) A new mouse model of ALS carrying a point mutation in the mouse Sod1 gene. Society for Neuroscience meeting, San Diego, USA

AlQatari M, Vastani N, Bros-Facer V, Groves M, Greensmith L, Fisher EM, Koltzenburg M (2009) A mutation of the cytoplasmic dynein heavy chain gene Dync1h1 causes a severe sensory neuropathy J. Periph. Nerv. Syst. 14, Suppl. 2, 6

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Stevens J, Hendriks, W, Bros-Facer V, Greensmith, L, Martin, J, Schiavo, G, Fisher, E. (2009) An investigation of SOD1 behaviour in amyotrophic lateral sclerosis. Association of British Neurologists, Liverpool, UK. Platform presentation

Banks G, Kuta A, Bros Facer V, Schiavo G, Koltzenburg M, Greensmith L, Fisher EMC (2009) Working with mouse mutants to uncover the roles of transport proteins. EMBO Conference on spatial dynamics of intracellular communication – overcoming distance in signalling networks, Maale Hachamisha, Israel

Stevens J, Hendriks, W, Bros-Facer V, Greensmith, L, Martin, J, Schiavo, G, Fisher, E. (2009) An investigation of SOD1 behaviour in amyotrophic lateral sclerosis. American Academy of Neurology, Seattle, USA

## **Core Activity – Biobank**

### **Summary**

The MRC for Neuromuscular Diseases Biobank aims to be a unique resource of human muscle and nerve tissue and cell cultures available to the basic science community for a range of activities including testing of new therapies in defined neuromuscular disorders. The biobank has been established in close collaboration at both sites (UCL London and Newcastle University) and is since run by biobank technicians Diana Johnson and Mojgan Reza under the responsibility of Professors Francesco Muntoni and Hanns Lochmüller. Deliverables of the biobank were defined in the MRC grant application as: (i) An established UK neuromuscular biobank (ii), new basic science projects and collaborations utilising biobank tissues (iii), education, training and PhD projects related to biobank and (iv) publications arising out of biobank utilisation. Success criteria for the first 5 years were set as: (i) New basic science added value collaborations, (ii) new therapies tested on biobank tissues, (iii) PhD projects offered, (iv) publications related to biobank projects, (v) use of biobank by groups outside the centre (vi) new groups joining and contributing tissues to the biobank initiative, (vi) linkage and collaborations with EuroBioBank and TREAT-NMD initiatives. Milestones were set out in detail (see below), and have been reached or surpassed for the first 3 years of operation. Considering that our infrastructure and network of collaborations is in full operation, we are confident that we will reach and surpass the milestones for years 4 and 5. Within the first 3 years of existence the MRC centre biobank has benefited a large number of basic, translational research and research & development projects within the centre, has supported PhD students and high-profile publications and integrated successfully in UK and international networks. Moreover, the biobank was indispensable in attracting significant subsequent funding from national (MRC and Wellcome Trust) and European (EC, 7<sup>th</sup> framework program) agencies.

### **Progress versus milestones**

#### **1. Samples collected by the biobank**

Period	Target per site (as defined in milestones)	Target combined (as in milestones)	Samples received Newcastle	Samples received London	<b>TOTAL</b>
2008 (from 1 <sup>st</sup> July)	50	100	73	53	<b>126</b>
2009	75	150	238	92	<b>330</b>
2010	75	150	539	181	<b>720</b>
2011 (to 21 <sup>st</sup> Jan.)	75	150	34	18	<b>52</b>
<b>TOTAL</b>	<b>275</b>	<b>550</b>	<b>884</b>	<b>344</b>	<b>1228</b>

The original milestone targets for sample collection were exceeded by more than 2-fold. This is in part due to the strong influx of serum/plasma samples through the BIO-NMD project (which was not anticipated when the original milestones were set). Even if those samples were not counted, the number

of samples (primarily myoblasts and fibroblasts) exceeds the targets for the first 3 years. The following pathologies are now available through the biobank, many of them from multiple donors:

BETHLEM MYOPATHY

BILATERAL OPTIC ATROPHY

CARNITINE DEFICIENCY, SYSTEMIC PRIMARY; CDSP

CENTRAL CORE DISEASE OF MUSCLE

COMPLEX III DEFICIENCY

CONGENITAL DISORDER OF GLYCOSYLATION

CONGENITAL DISORDER OF GLYCOSYLATION, TYPE I/lix

CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Ia; CDG1A

DYSTROPHIA MYOTONICA I

EMERY-DREIFUSS MUSCULAR DYSTROPHY, AUTOSOMAL DOMINANT; EDMD2

EMERY-DREIFUSS MUSCULAR DYSTROPHY, X-LINKED; EDMD

FRAGILE X MENTAL RETARDATION SYNDROME

GLYCOGEN STORAGE DISEASE II

INFLAMMATORY MYOPATHY

KEARNS-SAYRE SYNDROME; KSS

LEBER'S OPTIC ATROPHY

MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 1; MHS1; KING SYNDROME, INCLUDED

MINICORE MYOPATHY WITH EXTERNAL OPHTHALMOPLEGIA

MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY; MADD; GLUTARIC ACIDURIA IIA, INCLUDED

MUSCLE-EYE-BRAIN DISEASE; MEB

MUSCULAR DYSTROPHY, BECKER TYPE; BMD

MUSCULAR DYSTROPHY, BECKER TYPE; BMD FEMALE CARRIER

MUSCULAR DYSTROPHY, CONGENITAL MEROSIN-DEFICIENT, 1A; MDC1A

MUSCULAR DYSTROPHY, CONGENITAL, 1C; MDC1C

MUSCULAR DYSTROPHY, DUCHENNE TYPE; DMD

MUSCULAR DYSTROPHY, DUCHENNE TYPE; DMD FEMALE CARRIER

MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2A; LGMD2A; MYOSITIS, EOSINOPHILIC, INCLUDED

MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2B; LGMD2B

MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2E; LGMD2E

MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2K; LGMD2K

MYASTHENIA, LIMB-GIRDLE, FAMILIAL

MYASTHENIC SYNDROME, CONGENITAL, SLOW-CHANNEL; SCCMS

MYOPATHY, CENTRONUCLEAR, AUTOSOMAL RECESSIVE

MYOTONIC EPILEPSY WITH RAGGED RED FIBERS (MERRF)

MYOTUBULAR MYOPATHY 1; MTM1

NEMALINE MYOPATHY 2; NEM2

NEMALINE MYOPATHY 3; NEM3; NEMALINE MYOPATHY 3 WITH INTRANUCLEAR RODS, INCLUDED

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 1; NBIA1

OPTIC ATROPHY, AUTOSOMAL DOMINANT, OPA1 MUTATION

POLYGLUCOSAN BODY CARDIOMYOPATHY

RETT SYNDROME; RTT

RIGID SPINE MUSCULAR DYSTROPHY 1; RSMD1

SENSORY AXONAL NEUROPATHY

SPINAL MUSCULAR ATROPHY, DISTAL, CONGENITAL NONPROGRESSIVE

SPINAL MUSCULAR ATROPHY, TYPE I; SMA1

SPINAL MUSCULAR ATROPHY, TYPE II; SMA2

SPINAL MUSCULAR ATROPHY, TYPE II; SMA3

ULLRICH CONGENITAL MUSCULAR DYSTROPHY; UCMD

WALKER-WARBURG SYNDROME; WWS; MUSCULAR DYSTROPHY, CONGENITAL, PLUS MENTAL RETARDATION, INCLUDED

## 2. Samples given out for research by the biobank

Period	Samples distributed	Samples distributed	<b>TOTAL</b>
	Newcastle	London	
2008 (from 1 <sup>st</sup> July)	22	20	<b>42</b>
2009	36	55	<b>91</b>
2010	328	88	<b>416</b>
2011 (to 21 <sup>st</sup> January)	11	56	<b>67</b>
<b>TOTAL</b>	<b>397</b>	<b>219</b>	<b>616</b>

There was no specific target set in the original for number of samples distributed. However, it should be noted that the biobank resources have been extensively used right from the start of the biobank, and have been increased ever since. A large increase in the distribution in 2010 is in part due to BIO-NMD



related samples. More than 53 scientists have received samples for research, some of them for several research projects (affiliations listed for external researchers only; MRC centre PhD students marked with \*):

### **London UCL**

Caroline Godfrey; Silvia Torelli; Elisabeth Stevens; Haiyan Zhou; Francesco Muntoni; Nisha Bhardwaj; Rivka Steimberg; Mike Hanna; Karen Anthony; Katie Heath; Victoria Castleman; Sarah Farmer; Sebahattin Cirak; Irina Zaharieva; Iulia Oprea; Jacqueline Jonuschies; Jihee Kim; Katie Heath; Dwi Sarengat; Isabelle Breloy; Mhoriam Ahmed\*; Neta Baruch\*; Placido Navas and Thomas Merritt.

### **Newcastle University**

Hanns Lochmüller; Debbie Hicks; Kate Bushby; Doug Turnbull; Volker Straub; Patrick Chinnery; Rita Barresi, Cynthia Yu-Wai-Man; Matthew Bates; Gabriele Saretzki; Juliane Müller; Kamil Sitarz; Phillippa Carling; Richard Charlton; Rob Taylor; Kim Clugston; Sally Spendiff\* and Vivienne Neeve

### **Royal Veterinary College**

Marta Fernandez-Fuente

### **Nottingham University**

Chris Denning; Emily Dick;

### **Leiden University, Netherlands**

Annemieke Aartsma-Rus; Peter-Bram 'tHoen

### **Oxford University**

Aurelie Goyenvalle; Kay Davies

### **Perth University**

Carl Adkin; Steve Wilton; Sue Fletcher

### **National Institute, Tokyo**

Ichizo Nishino

### **Basel University, Switzerland**

Susan Treves

### **Heidelberg University, Germany**

Jan Ksienzyk, Oliver Müller

The project titles provided by the requesting scientists were encompassing both basic and translational research projects, while some had direct (diagnostic) relevance for patients or were R&D projects to identify better diagnostic markers. Pathologies requested included DMD, COL6-disorders, congenital muscular dystrophies (glycosylation defects), limb girdle muscular dystrophies (FKRP, ANO5), LHON, mitochondrial myopathies, Leigh syndrome, congenital myasthenic syndromes, myotonic dystrophy, congenital myopathies (CCD, PTRF, choline kinase defect), IBM, chanellopathies.

### **Major outcomes of research supported by the biobank**

#### Research publications

Despite the time lag between the time of sample request by a scientist and the time of a publication based on research with this sample, it is highly encouraging that 13 research publications have made use of MRC centre biobank resources and acknowledge them.

Kinali M, Arechavala-Gomez V, Feng L, Cirak S, Hunt D, Adkin C, Guglieri M, Ashton E, Abbs S, Nihoyannopoulos P, Garralda ME, Rutherford M, McCulley C, Popplewell L, Graham IR, Dickson G, Wood MJ, Wells DJ, Wilton SD, Kole R, Straub V, Bushby K, Sewry C, Morgan JE, Muntoni F. Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. *Lancet Neurol*. 2009 Oct;8(10):918-28.

Arbogast S, Beuvin M, Fraysse B, Zhou H, Muntoni F and Ferreira A. Oxidative stress in SEPN1-related myopathy: from pathophysiology to treatment. *Annals of Neurology*, 2009;65(6):677-686.

Boldrin L, Zammit PS, Muntoni F, Morgan JE. Mature adult dystrophic mouse muscle environment does not impede efficient engrafted satellite cell regeneration and self-renewal. *Stem Cells*. 2009 Oct;27(10):2478-87.

Mitropant C, Adams AM, Meloni PL, Muntoni F, Fletcher S, Wilton SD. Rational design of antisense oligomers to induce dystrophin exon skipping. *Mol Ther*. 2009 Aug;17(8):1418-26.

Arechavala-Gomez V, Kinali M, Feng L, Guglieri M, Edge G, Main M, Hunt D, Lehovsky J, Straub V, Bushby K, Sewry CA, Morgan JE, Muntoni F. Revertant fibres and dystrophin traces in Duchenne muscular dystrophy: Implication for clinical trials. *Neuromuscul Disord*. 2010 May;20(5):295-301

Wamsley GL, Arechavala-Gomez V, Fernandez-Fuente M, Burke MM, Nagel N, Holder A, Stanley R, Chandler K, Marks SL, Muntoni F, Shelton GD, Piercy RY. A Duchenne muscular dystrophy gene hot spot mutation in dystrophin-deficient cavalier king charles spaniels is amenable to exon 51 skipping. *PLoS One*. 2010 Jan 13;5(1):e8647.

Arechavala-Gomez V, Kinali M, Feng L, Brown SC, Sewry C, Morgan JE, Muntoni F. Immunohistological intensity measurements as a tool to assess sarcolemma-associated protein expression. *Neuropathol Appl Neurobiol*. 2010 Jun;36(4):265-74.

Forrest S, Meloni PL, Muntoni F, Kim J, Fletcher S, Wilton SD. Personalized exon skipping strategies to address clustered non-deletion dystrophin mutations. *Neuromuscul Disord*. 2010 Dec;20(12):810-6.

John P. Kemp, Paul M. Smith, Angela Pyle, Vivienne C. M. Neeve, Helen A. L. Tuppen, Ulrike Schara, Beril Talim, Haluk Topaloglu, Elke Holinski-Feder, Angela Abicht, Birgit Czermin, Hanns Lochmüller, Robert McFarland, Patrick F. Chinnery, Zofia M.A. Chrzanowska-Lightowlers, Robert N. Lightowlers, Robert W. Taylor and Rita Horvath. Nuclear factors involved in mitochondrial translation cause a subgroup of combined respiratory chain deficiency. *Brain* 2011 Jan; 134(Pt 1):183-95.

Emily Dick, Elena Matsa, Jayson Bispham, Mojgan Reza, Michela Guglieri, Andrew Staniforth, Sue Watson, Rajendra Kumari, Hanns Lochmüller, Lorraine Young, David Darling, Chris Denning. Two new protocols to enhance the production and isolation of human induced pluripotent stem cell lines. *Stem Cell Res*. 2010 Nov 20. [Epub ahead of print] PMID: 21095172

Muscle histology vs MRI in Duchenne muscular dystrophy. Kinali M, Arechavala-Gomez V, Cirak S, Glover A, Guglieri M, Feng L, Hollingsworth KG, Hunt D, Jungbluth H, Roper HP, Quinlivan RM, Gosalakkal JA, Jayawant S, Nadeau A, Hughes-Carre L, Manzur AY, Mercuri E, Morgan JE, Straub V, Bushby K, Sewry C, Rutherford M, Muntoni F. *Neurology*. 2011 Jan 25;76(4):346-53.

Enhanced excitation coupled Ca<sup>2+</sup> entry induces nuclear translocation of NFAT and contributes to IL-6 release from myotubes from patients with Central core disease. Treves S, Vukcevic M, Jeannet PY, Levano S, Girard T, Urwyler A, Fischer D, Voit T, Jungbluth H, Lillis S, Muntoni F, Quinlivan R, Sarkozy A, Bushby K, Zorzato F. *Hum Mol Genet*. 2011 Feb 1;20(3):589-600

Jan Senderek, Juliane S. Müller, Marina Dusl, Tim M. Strom, Velina Guergueltcheva, Irmgard Diepolder, Steven H. Laval, Susan Maxwell, Judy Cossins, Sabine Krause, Nuria Muelas, Juan J. Vilchez, Jaume Colomer, Cecilia Jimenez Mallebrera, Andrei, Nascimento, Shahriar Nafissi, Ariana Kariminejad, Yalda Nilipour, Bitra Bozorgmehr, Hossein Najmabadi, Carmelo Rodolico, Jörn P. Sieb, Ortrud K. Steinlein, Beate Schlotter, Benedikt Schoser, Janbernd Kirschner, Ralf Herrmann, Thomas Voit, Anders Oldfors, Christopher Lindbergh, Andoni Urtizberea, Maja von der Hagen, Angela Hübner, Jacqueline Palace, Kate Bushby, Volker Straub, David Beeson, Angela Abicht, Hanns Lochmüller. Hexosamine biosynthetic pathway mutations cause neuromuscular transmission defect. *American Journal of Human Genetics*, in press.

## 2. Grant applications

It has been recognized that the biobank of the MRC centre is an excellent platform for further research. Therefore, 4 successful grant applications have included work that will be carried out by the biobank. Notably, 3 of these applications are joint applications between London and Newcastle.

Medical Research Council – “New in vitro models of Duchenne Muscular Dystrophy by induced pluripotency in patient biopsies and gene knockdown in human ES cells”. Prof. Chris Denning (Nottingham University), Prof. Hanns Lochmüller, Prof. Volker Straub (Newcastle University)

Medical Research Council – “Lentivirally-modified stem cells to treat Duchenne muscular dystrophy”. Dr Jenny Morgan, Prof. Francesco Muntoni, Prof. Adrian Thrasher and Prof. Olivier Danos (UCL London); Dr. S. Laval, Prof. Hanns Lochmüller (Newcastle University).

European Commission, 7<sup>th</sup> Framework Program – “BIO-NMD” biomarker discovery in dystrophin- and COL6-related muscular dystrophies. European consortium led by Prof. Alessandra Ferlini (Ferrara, Italy), including Prof. Francesco Muntoni, Dr. Jenny Morgan (UCL London), Prof. Volker Straub, Prof. Hanns Lochmüller (Newcastle University).

Wellcome Trust. Advanced Antisense Technology for exon skipping in Duchenne Muscular Dystrophy. Led by Dr Matthew Wood (Oxford) and F. Muntoni, and with Morgan, Dickson; Wells; Straub and Bushby as co-applicants.

## 3. Support for MRC centre PhD students

Three MRC centre PhD students have made use of the biobank (Mhoriam Ahmed and Neta Baruch, both UCL London; Sally Spendiff, Newcastle University). They describe the importance of the biobank for their research as follows

The focus of my PhD project is on the impact that mutations in muscle membrane ion channels have on intracellular signaling pathways, and how these pathways alter mitochondrial biogenesis and cell death. Understanding this could clarify the link between such mutations and muscle dystrophy, and could thereby highlight potential targets for therapeutic drug action. The Biobank provides me with control and patient fibroblasts and myoblasts, which I can then stimulate and image, to determine differences between physiological and pathophysiological responses. These human cells serve as better models for my research than the alternative which is rodent tissue, not only because they are of the same species as the disease of interest, but also because rodents with relevant mutations are difficult to acquire or produce. My project would thus be extremely limited without the Biobank, and I would like to take the opportunity to thank you for supporting it (Neta Baruch).

As part of my project I am investigating whether the pathological features of inclusion body myositis can be recapitulated in a rodent cell in vitro model, in order to assess the possible benefits of novel therapeutic agents. To add to this I am also using the outcome measures from the rodent cultures to study the effects on human cultured myoblasts. For this, I require human myoblasts from both sIBM patients and normal (non-muscle disease) patients. I have been able to obtain ‘normal’ cells from the Biobank already and hope to also get some IBM patient cells shortly. The MRC Centre Biobank is therefore essential for my project, without which these novel drugs would only be limited to testing in artificially-modeled disease cells, rather than actual patient cells. Maintaining a Biobank means all the

samples are well catalogued with their diagnosis complete. This makes choosing the most appropriate sample to use very easy (Mhoriam Ahmed).

Myopathy occurs in many patients with mitochondrial disease caused by sporadic large scale deletions of the mitochondrial genome (mtDNA). The presence of both wild type (WT) and mutated mtDNA in the muscles of these patients has opened up the possibility of favorably changing the balance of WT to delete mtDNA, thus reducing clinical severity. This project involves examining mtDNA deletion levels in the muscle stem cells of patients and tracking how these levels change during muscle growth. Samples of patient's myoblasts have been received from the Biobank in order to determine the changes in mtDNA deletion levels as the cells divide and head towards differentiation. We have also been able to obtain control myoblast cell lines from the Biobank, with which we can compare our patient cells to. Initial findings suggest that while deletions are present in satellite cells at relatively high levels, they are reduced as the myoblasts divide and differentiate (Sally Spendiff).

#### 4. Cooperation/link with EuroBioBank

The MRC centre biobanks in London and Newcastle adopted all SOPs and requirements for becoming a member of the EuroBioBank network. At the annual assembly of EuroBioBank in Paris (June 2010) the MRC centre biobanks were accepted as members by unanimous vote and participate in all EuroBioBank activities since. From March 2011, all MRC centre biobank samples will be displayed in the EuroBioBank online catalogue and will be accessible to neuromuscular researchers world-wide. Furthermore, EuroBioBank participates in the prototype project of a wider European infrastructure, called BBMRI. The BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) is a pan-European initiative to integrate data and facilitate the exchange of biobank materials. However, EuroBioBank does not receive any funding through BBMRI.

#### Core Activity – Neuromuscular MRI

Objectives Our aim is to address unmet needs for diagnosis and treatment monitoring in patients with neuromuscular diseases through MRI methodological development and systematic patient studies correlating MRI findings with clinical and functional assessment.

The MRC Centre MRI activities are focussed principally on the development of MRI as a biomarker /outcome measure in neuromuscular diseases.

#### UCL Staff (funding/support)

Prof Tarek Yousry (UCL) – Neuroradiology Lead; MRC Centre PI for Imaging  
Dr John Thornton (NHS/NIHR CBRC) – Neuromuscular MRI Physics lead  
Prof Xavier Golay (UCL) – UCL MRI Physics Academic Lead  
Dr Chris Sinclair (MRC Centre; NIHR CBRC) – MRI Physics Research Associate  
Dr Rob Janiczek (NIHR CBRC/GSK) – MRI Physics Research Associate  
Dr Jasper Morrow (MRC Centre) – Clinical Research Fellow  
Dr Arne Fischmann – Visiting Neuroradiology Fellow  
Dr Ibrahim Ali Amer – Neuroradiology PhD Student  
Dr Rexford Newbould – (GSK) Industrial collaborator

#### UCL Funding

New Funding for Neuromuscular MRI research additional to MRC Centre support:

£160,000 (2010-2012) NIHR CBRC; Congenital superior oblique weakness: clinical findings, MRI and genes; PI Annegret Dahlmann-Noor (J Thornton co-I; T. Yousry Co-I)

£90,000 (2010-2012) NIHR CBRC; Longitudinal assessment of regional and total muscle mass using MRI (T. Yousry PI; J Thornton co-I; Industrial collaboration with GSK)

£46,785 (2011) NIHR CBRC; Flexibility and Sustainability Funding award (PA J Thornton)  
Funding application submitted

NIHR CBRC 2 year project grant: Immediate application of advanced MRI to improve diagnosis and monitor treatment outcomes in muscle wasting Neuromuscular Diseases (PI J Thornton, + centre members as Co-Is)

## Newcastle Staff

Professor Volker Straub

Professor Andy Blamire

Dr Kieran Hollingsworth

## Funding: MRC MDC

## Methodological Developments

### **Magnetization Transfer MRI of Skeletal Muscle**

We have demonstrated for the first time an association between skeletal muscle magnetisation transfer ratio (MTR) and a clinical measure of function (MRC Dorsiflexion score) in patients with CIDP and CMT1A (CDJ Sinclair *et al.* submitted to JNNP 2011). This provides key evidence supporting the potential value of muscle magnetization transfer (MT) imaging as a measure of myopathology. The first systematic evaluation of quantitative MT in human lower-limb muscle at 3 Tesla has confirmed the clinical feasibility of the qMT approach and provided normative values from healthy adults (CDJ Sinclair *et al.* *Magnetic Resonance in Medicine*, 64 (6): p1739-1748; 2010). A methodological improvement has been implemented to correct error due to B1 inhomogeneities resulting in a more robust pathological marker (CDJ Sinclair *et al.* under review *Magnetic Resonance in Medicine* 2011). A study is underway to assess the pathological sensitivity of qMT measures across a range of severity in a group of patients with IBM.

### **Quantitative MRI using vendor-supplied acquisition sequences**

Although MRI scanner manufacturer-supplied acquisition sequences may not be optimal for the purposes of MRI quantification, with careful protocol design it is possible to obtain accurate and reproducible measurements. This approach has the advantage of speed of implementation, and potential roll-out across centres. We have established protocols for radiological assessment, T2 and T1 relaxometry, MTR, and Dixon fat-water separation in skeletal muscle, and visualisation and cross-sectional area measurement in peripheral nerves. Test-retest data has been collected from control subjects and patients with IBM and CMT in order to establish reproducibility and normative values (manuscript under preparation). Correlation of MRI measures with clinical assessments, and sensitivity to disease progression will be established in our IBM/CMT1A cohort study (see below).

### **IDEAL-CPMG Fat-water T2 Relaxometry**

Concurrent muscle damage, oedema and fat infiltration are common in neuromuscular diseases. Standard imaging techniques preclude accurate separation and quantification of oedema and fat infiltration when these processes overlap. IDEAL-CPMG combines iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) with a Carr-Purcell-Meiboom-Gill (CPMG) imaging sequence. This new method yields, from a single acquisition, a series of fat and water images with multiple T2-weightings enabling measurement of tissue-water T2 and lip T2 from the isolated fat and water signals along with a T2-corrected fat fraction. The method has been demonstrated in phantoms, healthy controls and a representative patient (RL Janiczek *et al.* *Magnetic Resonance in Medicine*, under review 2011) and clinical applicability is being tested in a cohort of IBM patients.

### **Variable Field-of-View Continuous Moving Table Acquisition**

Whole-body muscle bulk is a measurement target for monitoring a number of neuromuscular conditions, and the common proximal-distal nature of neuromuscular pathology can require a longer longitudinal field of view (FOV) than can be accommodated within the homogeneous region of the MRI scanner. In contrast to conventional multi-station MRI, continuously moving table (CMT) acquisitions collect data as the patient moves through the scanner, potentially interrogating the whole-body in a single scan. Current CMT approaches use a constant FOV for entire acquisition. We have developed a method which continuously adapts the imaged FOV to reflect the patient geometry passing through the imaging volume (manuscript in preparation). This acquisition technology significantly reduces the scan time, and will improve the efficiency and quality of quantitative MRI methods such as fat-water separation.

### **Peripheral Nerve Cross-sectional Area**

Peripheral nerve hypertrophy is a common feature of peripheral neuropathies. We have demonstrated that it is possible to quantify sciatic nerve cross-section areas on conventional MRI, and that this

approach has promise as a disease marker in CMT1A, and a potential diagnostic role in CIDP (CDJ Sinclair *et al.* Journal of Neurology, Neurosurgery & Psychiatry, published online October 2010). We are investigating the applicability of this method in distal peripheral nerves, and other diseases.

#### Patient Studies - current

##### **Quantitative MRI in IBM and CMT (part MRC centre funded)**

A study of the quantitative MRI and clinical features of inclusion body myositis (IBM) and Charcot-Marie-Tooth disease (CMT1A). Subjects: patients with IBM (40), CMT1A (40), healthy volunteers (80). Clinical assessment; CSMi HUMAC NORM Myometry; Qualitative MRI: T1, T2, STIR; Quantitative MRI: T1M, T2M, MTR, Dixon, Diffusion; Neurophysiology.

STATUS: Phase 1: Development and test-retest in healthy volunteers  
Complete - MRI reproducibility study manuscript in preparation  
Phase 2: Cross sectional study (baseline)  
Acquisitions close to completion; preliminary analysis underway  
Phase 3: Longitudinal (1 year follow up)  
Acquisitions commenced February 2011

Investigation of the clinical feasibility and pathological sensitivity of qMT and IDEAL-CPMG MRI in 10 IBM patients compared with 10 controls.

STATUS: Acquisitions commenced February 2011

##### **MRI in Progressive External Ophthalmoplegia (Non MRC centre funded)**

The first study addressing radiological and quantitative MRI features of extra-ocular muscles in mitochondrial disease (9 patients + 9 controls).

STATUS: Acquisitions complete; analysis underway

##### **Congenital superior oblique weakness: Clinical phenotype, MRI and genes (Non MRC centre funded)**

Cohort of 100 individuals with congenital superior oblique muscle weakness; genetic characterization; ophthalmic assessment; MRI of 4<sup>th</sup> cranial nerve and extra-ocular muscles.

STATUS: Recruitment underway; MRI examinations to commence March 2011

##### **MRI in LGMD2I (European multi-centre study – MRC Centre funded Newcastle leading)**

First systematic multicentre study in LGMD2I – 4 centres (Newcastle, London, Copenhagen, Paris), 38 patients in total, 3 repeats. London: 6 patients.

STATUS: baseline measurements complete; 12 month follow-up measurements commence January 2011

##### **A cross-sectional study of magnetic resonance imaging in non-dystrophic myotonias (Non MRC centre funded)**

Retrospective audit of conventional MRI findings in 11 patients with CLCN1 mutation and 10 with SCN4A.

STATUS: Audit complete and formally presented, manuscript in preparation.

#### Patient Studies – to commence 2011

##### **MRI in inflammatory Neuropathies(Non MRC centre funded)**

10 patients CIDP, 10 patients MMN, 20 controls; Single scan and clinical assessment; MRI: Nerve roots, Sciatic nerve (CIDP, controls), Forearm nerves (MMN, controls)

STATUS: REC approved, R+D approval application in process

##### **MRI in Hypokalaemic Periodic Paralysis(Non MRC centre funded)**

An investigation of the value of MRI to quantify muscle water-balance and response to treatment in hypokalaemic periodic paralysis patients.

STATUS: REC forms complete, final protocol in preparation

Small-scale studies investigating the value of established conventional and quantitative MRI protocols in well characterized inherited neuropathy patient groups are under urgent consideration.

## Cross-Centre Collaboration

### **Treat-NMD Participation and SOPs**

Members of the MRC Centre (from both London and Newcastle) have participated in a European MRI working group, under the auspices of TREAT-NMD (meetings held Stockholm 2<sup>nd</sup> May 2010 and hosted at the MRC Centre London June 21<sup>st</sup> 2010), to define consensus SOPs for the use of MRI as an outcome measure (T1w images for qualitative evaluation of muscle involvement and topography of lesion; Quantification of muscle fat infiltration using 3-point Dixon or spectrally selective excitation techniques; Quantitative evaluation of muscle oedema or inflammation in using T2 measurement). These SOPs will be disseminated via a peer-reviewed publication and the TREAT-NMD website.

### **LGMD2I Multi-Centre Study**

The process of developing these SOPs was partially driven by collaborative work that has taken place as part of the multicentre MRI study of patients with LGMD2I. There were valuable interactions between MRI physicists in Newcastle and London in establishing an accurate MRI protocol realisable on 3T scanners from different vendors at each site with a proper cross-centre validated quality control procedure.

## UCL Industrial Collaboration

The post of Dr Rob Janiczek is jointly funded by Glaxo-Smith-Kline and his MRI development work has been hosted at the GSK Clinical Imaging Centre as part of collaborative project to develop MRI muscle-volume assessment as an outcome measure.

We have agreed with Siemens that neuromuscular MRI development will be a key theme within the UCL-Siemens research framework under the research agreement signed in 2010.

## Translation into clinical imaging service

We have recently revised the clinical service neuromuscular MRI protocols at Queen Square in the light of improvements demonstrated in our research imaging protocols. We have established a regular review cycle to ensure that research developments feed in directly to improving the quality and efficiency of our clinical MRI service for these patient groups.

## Publications and Conference Abstracts

### Published

Christopher D. J. Sinclair, Mario A. Miranda, Peter Cowley, Jasper M. Morrow, Indran Davagnanam, Hiten Mehta, Michael G. Hanna, Martin Koltzenburg, Mary M. Reilly, Tarek A. Yousry, and John S. Thornton. Magnetic Resonance Imaging Shows Increased Sciatic Nerve Cross-sectional Area in Inherited and Inflammatory Neuropathies. *Journal of Neurology, Neurosurgery & Psychiatry*; 2011 Nov; 82(11):1283-6. Epub 2010 Oct 22. PMID: 20971754

Christopher D. J. Sinclair, Rebecca S. Samson, David L. Thomas, Nikolaus Weiskopf, Antoine Lutti, John S. Thornton and Xavier Golay; Quantitative magnetization transfer in in vivo healthy human skeletal muscle at 3T Magnetic Resonance in Medicine, *Magn Reson Med*. 2010 Dec;64(6):1739-48. doi: 10.1002/mrm.22562. Epub 2010 Jul 27. PMID: 20665899

Sinclair CD, Morrow JM, Hanna MG, Reilly MM, Yousry TA, Golay X, Thornton JS. Correcting radiofrequency inhomogeneity effects in skeletal muscle magnetisation transfer maps. *NMR Biomed*. 2011 Jul 27. doi: 10.1002/nbm.1744. [Epub ahead of print] PMID: 21796708

Janiczek RL, Gambarota G, Sinclair CD, Yousry TA, Thornton JS, Golay X, Newbould RD. Simultaneous T(2) and lipid quantitation using IDEAL-CPMG. *Magn Reson Med*. 2011 Nov;66(5):1293-302. Epub 2011 May 20. PMID: 21604292.

Sinclair CD, Morrow JM, Miranda MA, Davagnanam I, Cowley PC, Mehta H, Hanna MG, Koltzenburg M, Yousry TA, Reilly MM, Thornton JS. Skeletal muscle MRI magnetisation transfer ratio reflects clinical severity in peripheral neuropathies. *J Neurol Neurosurg Psychiatry*. 2012 Jan; 83(1):29-32. Epub 2011 May 25. PMID: 21613652

## Under Review

Tracey A. Willis, Kieren G. Hollingsworth, Anna Coombs, Marie-Louise Sveen, Soren Anderson, Tanya Stojkovic, Michelle Eagle, Anna Mayhew, Paulo Loureiro de Sousa, Liz Dewar, Jasper M. Morrow, Chris D. Sinclair, John S. Thornton, Katie Bushby, Hanns Lochmuller, Michael G. Hanna, Jean-Yves Hogrel, Pierre G. Carlier, John Vissing, Volker Straub MRI muscle fat quantification in Limb Girdle Muscular Dystrophy 2I is more sensitive to detect disease progression than clinical Assessments of muscle strength and function.

## In Preparation

Author list to include: Jasper M Morrow, Emma Matthews, Dipa L Raja Rayan, Arne Fischmann, Ibrahim Amer, Christopher JD Sinclair, John S Thornton, Mary M Reilly, Tarek A Yousry, Michael G Hanna. Skeletal muscle MRI shows distinct abnormalities in genetically proven non-dystrophic myotonias.

Author list to include: Arne Fischmann, Christopher DJ Sinclair, Jasper M Morrow, Mary M Reilly, Michael G Hanna, John S Thornton, Tarek A Yousry. Effects of patient positioning and anatomical localisation upon reproducibility of quantitative MRI of lower limb muscles.

Author list to include: Morrow JM, Sinclair CDJ, Fischmann A, Reilly MM, Hanna MG, Thornton JS, Yousry TA. Quantitative MRI of skeletal muscle in healthy volunteers: inter-scan reproducibility and normal inter-subject and between muscle variation.

Author list to include: Morrow JM, Sinclair CDJ, Fischmann A, Thornton JS, Yousry TA, Reilly MM, Hanna MG. Validation as an outcome measure of quantitative MRI of skeletal muscle in Charcot-Marie-Tooth disease and inclusion body myositis.

Author list to include: Fischmann A, Morrow JM, Sinclair CDJ, Thornton JS, Reilly MM, Miller J, Yousry TA, Hanna MG. Pattern of Involvement in Inclusion Body Myositis: a new scoring system.

Author list to include: Pitceathly RDS, Sinclair CDJ, Ali N, Bremner F, Morrow JM, Davagnanam I, Rahman S, Plant G, Thornton JS, Yousry T, Hanna MG. Quantitative MRI of extra-ocular muscles in single mitochondrial DNA deletion disorders.

Author list to include: Tracey A. Willis, Kieren G. Hollingsworth, Marie-Louise Sveen, Tanja Stojkovic, Michelle Eagle, Anna Mayhew, Paulo Loureiro, Jasper Morrow, Chris D. Sinclair, John S. Thornton, Katie Bushby, Hanns Lochmüller, Mike Hanna, Pierre G. Carlier, John Vissing, Volker Straub. Muscle involvement in Limb Girdle Muscular Dystrophy 2I; a multicentre comparison of semi quantitative and quantitative MRI techniques.

## Conference Proceedings

*Quantitative Magnetization Transfer in In Vivo Healthy Human Skeletal Muscle at 3T* C.D.J. Sinclair, R.S. Samson, D.L. Thomas, N. Weiskopf, A. Lutti, J.S. Thornton, X. Golay Proc. Intl. Soc. Mag. Reson. Med. 18 (2010) p871

*Test-Retest Reproducibility of MTR, T2 and 3-point Dixon Fat Quantification in Muscle MRI* C.D.J. Sinclair, J. M. Morrow, T.A. Yousry, X. Golay and J.S. Thornton; Proc. Intl. Soc. Mag. Reson. Med. 18 (2010) p852

*Continuously Moving Table Whole-Body MRI using Variable Field of View.* Janiczek RL, Howard JW, Gambarota G, Thornton JS, Golay X, Newbould RD; Proc ISMRM Annual Meeting (2010), Stockholm, Sweden.

*Extra-orbital muscle T2 relaxation time and clinical activity in thyroid eye disease* L Mancini, R. Rajendram, J Uddin, RW Lee, GE Rose, T Yousry, K Miszkiel, JS Thornton. 18th Scientific meeting of the ISMRM, Stockholm, Sweden, May 2010

*Quantitative Magnetization Transfer MRI: A Potential New Source of Biomarkers in Skeletal Muscle?* C.D.J. Sinclair, R.S. Samson, D.L. Thomas, N. Weiskopf, A. Lutti, J.S. Thornton, X. Golay



United Kingdom Neuromuscular Translational Research Conference 2010, Oxford, England, 25Mar 2010 - 26 Mar 2010. Neuromuscular Disorders. Pergamon-Elsevier Science Ltd. 20: S28-S29. Mar 2010

*Inter-Scan Reproducibility of Quantitative Neuromuscular MRI* C.D.J. Sinclair, J. M. Morrow, T.A. Yousry, M.M. Reilly, M.G. Hanna, X. Golay and J.S. Thornton United Kingdom Neuromuscular Translational Research Conference 2010, Oxford, England, 25Mar 2010 - 26 Mar 2010. Neuromuscular Disorders. Pergamon-Elsevier Science Ltd. 20: S28-S28. Mar 2010

*Quantitative Magnetization Transfer in In Vivo Healthy Human Skeletal Muscle at 3T* C.D.J. Sinclair, R.S. Samson, D.L. Thomas, N. Weiskopf, A. Lutti, J.S. Thornton, X. Golay 19th British Chapter ISMRM Annual Symposium, Kings College London, 2010 O14

*Assessing the Inter-Scan Reproducibility of MTR, T2 and Fat Quantification in Muscle MRI* C.D.J. Sinclair, J. M. Morrow, M.M. Reilly, M.G. Hanna, T.A. Yousry, X. Golay and J.S. Thornton 19th British Chapter ISMRM Annual Symposium, Kings College London, 2010 P9

*Magnetic Resonance Imaging and Sciatic Nerve Cross-sectional Area in Inherited and Inflammatory Neuropathies* C.D.J. Sinclair, J.M. Morrow, M.A. Miranda, P. Cowley, I. Davagnanam, H. Mehta, M.G. Hanna, M. Koltzenburg, M.M. Reilly, T.A. Yousry and J.S. Thornton; United Kingdom Neuromuscular Translational Research Conference 2010, Oxford, England, 25Mar 2010 - 26 Mar 2010. Neuromuscular Disorders. Pergamon-Elsevier Science Ltd. 20:S29-S29. Mar 2010

*The reliability of quantitative MRI measures in neuromuscular disease* J.M. Morrow, C.D.J Sinclair, M.M. Reilly, M.G. Hanna, T.A. Yousry, X. Golay, J.S. Thornton Presented at the Muscle Study Group Meeting, Beaver Hollow, NY, USA. September 2010

*Magnetic Resonance Imaging and Sciatic Nerve Cross-sectional Area in Inherited and Inflammatory Neuropathies* J.M. Morrow, C.D.J. Sinclair, M.A. Miranda, P. Cowley, I. Davagnanam, H. Mehta, M.G. Hanna, M. Koltzenburg, M.M. Reilly, T.A. Yousry and J.S. Thornton; Joint British and Italian Peripheral Nerve Society Meeting, Trieste, 2010

*Using MRI as a diagnostic tool in the skeletal muscle channelopathies* E. Mathews, R. Sud, R. Labrum, L. Strycharczuk, C.D.J. Sinclair, T.A. Yousry, M.G. Hanna United Kingdom Neuromuscular Translational Research Conference 2010, Oxford, England, 25Mar 2010 - 26 Mar 2010. Neuromuscular Disorders. Pergamon-Elsevier Science Ltd. 20: S29-S30. Mar 2010

*The reliability of quantitative MRI measures in neuromuscular disease* J.M. Morrow, C.D.J Sinclair, M.M. Reilly, M.G. Hanna, T.A. Yousry, X. Golay, J.S. Thornton; XII International Congress on Neuromuscular Disorders, Naples, Italy, 2010 Acta Myologica 29 TW156 p279

*Quantitative Magnetization Transfer MRI: A Potential New Source of Biomarkers in Skeletal Muscle?* C.D.J. Sinclair, R.S. Samson, D.L. Thomas, N. Weiskopf, A. Lutti, J.S. Thornton, X. Golay; XII International Congress on Neuromuscular Disorders, Naples, Italy, 2010 Acta Myologica 29 TW158 p280

*Correlation between muscle magnetization transfer ratio and muscle strength in chronic inflammatory demyelinating polyneuropathy* Sinclair CD, Miranda MA, Cowley P, Reilly M, Thornton JS, Yousry TA; Proceedings of the 17th Annual Meeting of ISMRM, Honolulu, Hawaii, USA, 2009;17:3958.

*Quantitative neuromuscular MRI: Correlation between magnetization transfer ratio and muscle strength in a peripheral neuropathy* C.D.J. Sinclair, M.A. Miranda, P. Cowley, M. Reilly, J.S. Thornton, T.A. Yousry; 18th British Chapter ISMRM Annual Symposium, Imperial College London, 2009

*Association between magnetization transfer ratio and muscle strength in chronic inflammatory demyelinating polyneuropathy* CDJ Sinclair, MA Miranda, P Cowley, M Reilly, M Koltzenburg, JS Thornton, TA Yousry; UK Neuromuscular Translational Research Conference, Newcastle-Upon-Tyne, 2009

*Using MRI as a diagnostic tool in the skeletal muscle channelopathies* E. Mathews, R. Sud, R. Labrum, L. Strycharczuk, C. Sinclair, J. Thorpe, T. Yousry and M.G. Hanna Muscle Study Group, Beaver Hollow, USA, 2009

*Histogram segmentation using Dixon fat-fraction maps for characterizing skeletal muscle disease* C.D.J Sinclair, X. Golay and J.S. Thornton; 15<sup>th</sup> Annual Meeting of the British Chapter of the ISMRM, Cardiff University, 2009 p61

**Forthcoming Conference Contributions**

*Simultaneous T2 and Lipid Quantitation using IDEAL-CPMG* R. L. Janiczek, G. Gambarota, C. D. Sinclair T. A. Yousry, J. S. Thornton, X. Golay, and R. D. Newbould Accepted for ISMRM Conference (2011), Montreal, Canada

*Correcting RF Inhomogeneities in Skeletal Muscle Magnetization Transfer Maps* CDJ Sinclair, JM Morrow, MG Hanna, MM Reilly, TA Yousry, X Golay and JS Thornton Accepted for ISMRM Conference (2011), Montreal, Canada

*3Tesla gradient-echo 3-point Dixon imaging for robust water-only imaging of the extra-ocular muscles* CDJ Sinclair, R Pitceathly, I Davagnanam, MG Hanna, MM Reilly, TA Yousry, X Golay, JS Thornton Accepted for ISMRM Conference (2011), Montreal, Canada

*Magnetic resonance imaging in the non-dystrophic myotonias*J.M. Morrow, E. Matthews, D. L. Raja Rayan, I. Amer, A. Fischmann, T.A. Yousry, M.G. Hanna Accepted for UK Neuromuscular Translational Research Conference, London, 2011

*Skeletal Muscle MRI-Determined Fat Fraction and Myometric Strength in Inclusion Body Myositis and Charcot-Marie-Tooth Disease Type 1a* CDJ Sinclair, JM Morrow, A Fischmann, MG Hanna, MM Reilly, TA Yousry, X Golay, JS Thornton Accepted for UK Neuromuscular Translational Research Conference, London, 2011

*Improved Magnetization Transfer MRI of Skeletal Muscle in Myopathy and Neuropathy* CDJ Sinclair, JM Morrow, MG Hanna, MM Reilly, TA Yousry, X Golay, JS Thornton Accepted for UK Neuromuscular Translational Research Conference, London, 2011

**Core Activity – Education and Training**

As outlined in the original MRC grant application, milestones were set for each of the five main themes (clinical trials, MRI, biobank, animal models, education and training). The milestones for education and training are below. In italics are the details of how each of these milestones have been addressed to date. All milestones have been met or are on course to be met.

<p><b>Added value</b></p>	<ul style="list-style-type: none"> <li>• Integration of neuromuscular training module into existing training courses permitting specialised training of basic science and clinical PhD students in a broad neuroscience setting. <i>The week-long neuromuscular course in the six week introduction of the non clinical PHD programme is an integration of the existing neuromuscular module for the Institute of Neurology MSc in Neurosciences and the newly developed MRC Centre Neuromuscular PhD programme. This course has been run in 2007 and 2008 during the first years of the 4 year non clinical PhD programme.</i></li> <li>• Centre PIs will attract further funding for students that can participate in the teaching activities <i>As detailed above we have obtained funding through the “UCL Impact Scheme” for four further non clinical PhD students who have started a bespoke 3 year non clinical PhD programme in Oct 2010. The centre PIs have also attracted through new grants (since October 2007) funding for more than 30 other non-clinical students and clinical research fellows who are availing of all the teaching activities within the MRC Centre.</i></li> <li>• Organisation of UK-wide neuromuscular meeting <i>We have had four UK wide neuromuscular meetings as detailed in appendix 4. These have been very successful and attract more than 250 attendees each</i></li> </ul>
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	<p><i>year. To be truly UK wide we have rotated the meeting geographically (London 2008, Newcastle 2009, Oxford 2010, London 2011). The next meeting will be in Newcastle in March 2012.</i></p>
<b>Deliverables</b>	<ul style="list-style-type: none"> <li>• A minimum of 6 PhD students trained in neuromuscular disease</li> </ul> <p><i>Four of our non-clinical students and one clinical student have now submitted their theses.</i></p>
<b>Milestones</b>	<p>Recruitment of 4 students in 2007</p> <p><i>We successfully recruited 4 non clinical PhD students in 2007 (listed appendix 1).</i></p> <ul style="list-style-type: none"> <li>• Recruitment of 4 students in 2008</li> </ul> <p><i>We exceeded our 2008 target by obtaining funding from our host universities and successfully recruited 4 non clinical and 1 clinical PhD student in 2008.</i></p> <p><i>Furthermore since 2009, by getting further support from our host universities and also by successfully recruiting 4 UCL Impact studentships, we have recruited 1 further clinical PhD student (2009) and 4 further non –clinical PhD students (2010)..</i></p>
<b>Success criteria</b>	<ul style="list-style-type: none"> <li>• Completion rate of students within 4 years of entering the program</li> </ul> <p><i>All 5 students due to finish in 2011 have submitted their thesis.</i></p>
<b>Responsibilities</b>	<ul style="list-style-type: none"> <li>• Reilly and Chinnery to report to Steering Committee on behalf of Training Committee</li> </ul> <p><i>Mary Reilly and Patrick Chinnery (or delegate) have reported to the monthly Steering Committee since January 2007. All meetings are minuted.</i></p> <ul style="list-style-type: none"> <li>• Two supervisors per student, monitored by Training Committee</li> </ul> <p><i>In UCL, for the 1<sup>st</sup> year of the 4 year non clinical PhD programme, Prof Greensmith has supervised each student in association with the PI in charge of each three-month attachment.</i></p> <p><i>For years 2-4, each student has two supervisors as detailed in appendix 1. For the UCL students, Profs Reilly and Greensmith from the training committee receive 6 monthly reports from the students and meet the students regularly.</i></p> <p><i>The two UCL clinical PhD students also have two supervisors as detailed in appendix III</i></p> <p><i>For Newcastle, all students have two supervisors as detailed in appendix III.</i></p> <ul style="list-style-type: none"> <li>• <b>Prof Reilly ultimately responsible</b></li> </ul> <p><i>Prof Reilly has remained in charge and ultimately responsible for education and training.</i></p>