

London Newcastle
**MRC Centre for Translational Research in
Neuromuscular Diseases**

A Strategic Partnership of National Importance

Mid term report

October 2016

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1. Executive Summary

Serious muscle wasting neuromuscular diseases (NMD) are individually rare, but collectively represent an important unmet health need affecting over 150,000 children and adults in the UK, and more than 17m people globally. They are devastating diseases, and cause death in childhood or in prime adult life, or cause life-long disability. The focus of the Centre's founding clinical and basic science investigators from UCL and Newcastle has been to work together to overcome barriers to translational research. The MRC investment in the Centre has been transformative in enabling the UK to become a world leader in addressing some of the key bottlenecks in progressing science to patient benefit. The platforms, expertise, and collaborative multi-partner translational culture the Centre has developed means the UK is now poised to lead the world in developing disease modifying therapies to improve the lives of patients. We would not have been in this position had it not been for the pivotal MRC investment. Effective disease modifying therapies remains the central goal, and thanks to our work building translational platforms over the past 8 years, this is now achievable. We are now in a position to make exceptional progress towards therapy by maximising the full potential of the MRC Centre expertise and platforms. We are uniquely placed internationally to harness brand new disease modelling iPSC techniques, drug discovery opportunities and new biomarker technologies, combined with innovative bioinformatic and early phase trial methodologies, to make major progress and deliver disease modifying therapies over the next 10 years.

The MRC Centre investigators created six brand-new core translational research activities which have had an important impact in progressing experimental personalised medicine across the entire NMD field in the UK: 1) We built the world's largest stratified adult and paediatric patient cohorts, now exceeding 9500 patients, and these are an unrivalled resource for experimental medicine, trials, genetics and biomarker studies. 2) We developed bespoke experimental trials expertise, support and coordination that underpinned delivery of over 100 natural history studies and experimental trials in children and adult patients. 3) We lead internationally in developing innovative, valid, sensitive MRI biomarkers in patients to track disease progression; now adopted widely including by industry. 4) We developed a national neuromuscular biobank of NMD patient-derived primary human muscle and fibroblast cell lines for preclinical science and therapy studies, now exceeding 11,500 samples and shared extensively nationally and internationally, and also with industry. 5) We linked basic and clinical scientists to assess clinical validity and relevance of 15 preclinical NMD mouse models. 6) We established the UK's major NMD translational research education, training and networking programme which has trained 37 clinical and non-clinical PhDs, has enabled us to host an annual national translational research conference in collaboration with the major patient advocacy group in the UK, attended by over 2500 delegates since 2008. This has allowed us to effectively connect and network the UK clinical, scientific and patient NMD communities. All milestones and objectives set by the MRC were exceeded in the first phase of the Centre 2008-2013; all the 2013-2018 milestones/objectives are achieved or on target.

The Centre's core translational activities have added major value to separately funded NMD science programmes, currently >£70m, lead by investigators across the Centre. This has directly resulted in significant advances in both preclinical scientific understanding and early therapy development including both proof-of-concept and phase IIa studies in a number of NM diseases. However, since renewal, rapid genetic discovery advances, in which we have played a major role, highlight the major opportunity Centre investigators now have to develop therapies for a much wider range of NMD targets. Together, the Centre PIs have generated over 800 peer reviewed publications since 2013 including in Nature journals, Lancet journals, Cell, Science, JAMA and New England Journal of Medicine. Some highlights include: **Genetics**; we discovered 41 new NMD disease-causing genes and uncovered new pathophysiological mechanisms and therapy targets. **Muscular Dystrophy**: we delivered ground-breaking experimental medicine proof of principle trials of antisense oligonucleotide therapy in Duchenne muscular dystrophy (DMD published in *Lancet*^{1, 2}) and in spinal muscular atrophy³. The FDA has just approved the DMD antisense therapy for clinical use after considering MRC Centre generated data (September 2016), and this represents the only DMD drug in the USA [<http://www.fda.gov/NewsEvents/Newsroom>]. Our DMD Trial design is underpinned by the first rare disease care guidelines to achieve UK NICE accreditation published in *Lancet Neurology*⁴. **Neuromuscular Channelopathies**: we delivered the first phase II experimental trial and showed clear efficacy of reprofiled mexiletine in genetic myotonia allowing us to obtain European orphan drug status, and published in *JAMA*⁵. We developed new in vivo clinical electrophysiological tools for channelopathy

diagnosis & genetic stratification published in *Annals of Neurology*⁶. We provided genetic evidence supporting a gating pore current as a new pathophysiological mechanism and target for muscle degeneration in channelopathies published in *Neurology and Journal of Physiology*⁷⁻⁹. We discovered the first loss of function sodium channel mutations and showed they cause previously unrecognised, and potentially treatable, fatal neonatal myopathies¹⁰. We completed a phase II trial in periodic paralysis demonstrating efficacy of repurposed dichlorphenamide directly resulting in FDA licensing and European orphan status to aid EU licensing; published in *Neurology*. **Inherited Neuropathies:** we undertook the first international phase II experimental trial in the commonest genetic neuropathy (CMT1A) and published in *Lancet Neurology*¹¹. We identified a new disease mechanism linked to accumulation of neurotoxic deoxysphingolipids causing sensory neuropathy published in *Journal of Biological Chemistry*¹². We showed that 3 prime cryptic mutations in the neurofilament protein gene caused axonal protein accumulation as a new mechanism in human neuropathy, published in *American Journal of Human Genetics*¹³. We identified a gene responsible for folic acid transport and showed high dose folinic acid improved a severe neuropathy in patients published in *Brain*¹⁴. **Inclusion Body Myositis:** we translated findings in our IBM VCP mouse model into patients and undertook the first safety and tolerability study of a non-licensed experimental compound to upregulate the cell's heat shock protein response published in *Science Translational Medicine*¹⁵. This led directly to successful funding of a full efficacy trial (\$3m) led by the MRC Centre which commences in 2017. **Mitochondrial Diseases:** we demonstrated that resistance and aerobic exercise therapy is safe and effective in mtDNA deletion muscle disease published in *Brain*¹⁶, that mitochondrial disease can be mitigated by idebenone therapy in an experimental medicine trial published in *Brain*¹⁷, and we showed mitochondrial DNA diseases are potentially preventable by mitochondrial donation published in *Nature*^{18, 19}. The MRC Centre has attracted excellent students (on average 10 applicants per position) and has recruited world leading scientists including in the last 3 years: Thomas Voit (formerly Director of Institute of Myology Paris), Gipi Schiavo (from Cancer Research UK), Michael Lunn (Editor in Chief neuromuscular Cochrane collaboration), Paul Whiting (from Pfizer), and Avan Sayer (from Southampton University). Over the lifetime of the Centre the MRC investment of £6m has supported and enabled investigators to leverage over £100m in external funding.

Our international scientific advisory board recently concluded that we have created one of “*the world's leading translational neuroscience centres for NMDs*” and advised that by fully consolidating and harnessing our unique core translational capabilities we are poised to make exceptional advances towards disease modifying therapies. The MRC support to date means the UK now has an opportunity to lead the world in developing disease modifying therapies by creating a new radical experimental therapy centre building on the proven UCL-Newcastle partnership axis. Furthermore, we can extend our proven “know-how” to a wider group of NMD targets, and use our expertise to back translate our deep disease phenotype knowledge and genetic discovery to evaluate targets and understand disease mechanisms, so that the impact of our findings can be of benefit to a wider community of NMD patients. Furthermore, the systematic interdisciplinary approach we will take will be relevant as a model system not only for rare diseases (there are 20,000) but also for translational neuroscience efforts more broadly.

In order to realise the genuine potential **for our research to change patient lives** we seek further MRC strategic support to enable us to construct a multi-partnership approach to funding. We aim to fully embed the core translational activities by seeking support from our host organisations and NIHR. However, we can only realise this unique opportunity, and the full potential of this platform, by seeking support from MRC as a partner to establish a radically new preclinical experimental therapy centre. A new centre will have state of the art essential core preclinical capabilities including: 1) Disease modelling (including iPSC and gene editing technology) 2) Drug discovery 3) Gene therapy innovation 4) Innovative next generation biomarker development 5) New integrative bioinformatic capability and 6) A new translational PhD training programme. This new preclinical centre will enable a nationally important strategy that will support and align with MRC strategy. It will advance proof of concept studies at scale and it will be the world's “go-to” centre for industry partnering.

Such a UK Centre will lead internationally, and will advance disease-modifying therapies with the realistic prospect of research changing the lives of patients. Partnership with the MRC is essential to realise this vision.

2. Background: establishing a national strategic partnership to drive

progress: The Centre was established in 2008 following the first five year MRC award of ~£3m and was renewed in 2013 with matching host and MRC contributions from UCL and Newcastle producing a total funding envelope of ~£6m. This resource has been split equally by the Director between the two Centre partner sites in London UCL and Newcastle. ***The mission of the Centre is to translate science into experimental medicine and new treatments for children and adults with disabling fatal neuromuscular diseases.***

A strategic research partnership of national importance: the MRC Centre is a translational research partnership that builds on clinical and research links and complimentary expertise. It initially connected colleagues at the UCL Institutes of Neurology and Child Health with those at the Institute of Genetic Medicine and the Wellcome Centre for Mitochondrial Research at Newcastle University. In the second phase of the Centre we have also built links with Oxford, Manchester, and, most recently, Cambridge. Many of the Centre's PIs lead major specialised clinical NMD child and adult patient services which assess over 15000 adult and paediatric patients from across the UK, cared for at major co-located NHS Foundation Trust Hospitals. The Centre's PI expertise is truly interdisciplinary and spans discovery science right through to a deep understanding of the clinical diseases.

Dr Robert C Griggs (NY USA) Chair of the MRC Centre SAB since 2008 wrote in September 2016 "the investigators have clearly met or exceeded all milestones and objectives. They have demonstrated international leadership and are clearly poised to do much more. We consider that a national strategic therapy centre would have few if any international rivals" (see appendix 5)

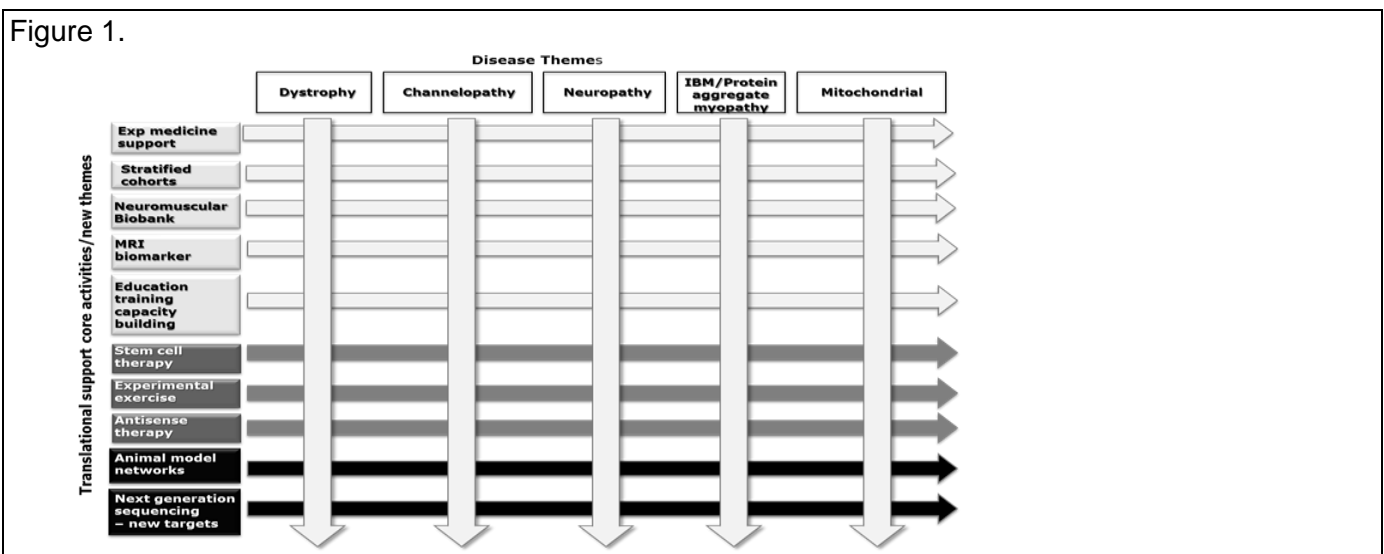
Overcoming obstacles translating science into patient benefit: in establishing the Centre we recognised the significant gap between scientific advances in genetic and acquired neuromuscular diseases and the absence of effective treatments for patients. Centre PIs lead separately funded research groups with critical mass focussed on five broad disease areas which are the main **"disease themes"** of the MRC Centre: muscular dystrophies, channelopathies, peripheral neuropathies, inclusion body myositis and mitochondrial diseases. The Centre adds value to these separately funded disease orientated research programmes by addressing key gaps in the translation of science into experimental medicine. We established a strategic multidisciplinary translational research framework that addressed the following key obstacles to effective translation 1) lack of stratified patient cohorts for personalised medicine 2) insufficient support to deliver experimental medicine trials 3) insufficient availability of human patient neuromuscular tissues for preclinical science 4) lack of sensitive biomarkers and limited application of MRI biomarkers 5) lack of scientific translational research training programmes for scientists and clinicians in neuromuscular diseases 6) lack of linkage and collaboration between expert clinical and animal scientists to assess validity and translatability of findings in animal models to humans. Specific collaborative core activities in each of these areas were established and we have delivered and exceeded all milestones which were set by the MRC. Core activities of the Centre:

- **Core-1 Stratified cohorts for personalised medicine:** development of highly phenotyped genetically stratified patient cohorts as an essential prerequisite for personalised medicine.
- **Core-2 Experimental trials support:** a system of coordination and support to link discovery science to innovative experimental trials in the five neuromuscular disease themes.
- **Core-3 Neuromuscular human cell biobank:** a resource of human fibroblasts/muscle cells for preclinical testing and discovery science linked to routine NHS diagnostic biopsy procedures.
- **Core-4 MRI biomarker outcome measure development:** physics development and systematic application of quantitative MRI as a biomarker and NMD outcome measure.
- **Core-5 Capacity building for future NMD translational research:** education and capacity building PhD programmes in NMD translational medicine.
- **Core-6 Animal NMD models:** improved linkage and collaboration between expert NMD clinical and animal scientists to evaluate validity & translatability of findings in animal models to humans.

The core activities have been critical in adding value to discovery science and enabling successful delivery of experimental medicine studies in each disease theme for example: i) Dystrophin restoration in DMD¹, ii) Mexiletine or dichlorphenamide in muscle channelopathies⁵, iii) Vitamin C in Charcot Marie Tooth 1A¹¹,

iv) Heat shock protein upregulation in inclusion body myositis¹⁵, v) Resistance and aerobic exercise in mitochondrial disease¹⁶, vi) Idefenone in mitochondrial disease¹⁷. **Figure 1** illustrates the Centre's five vertical disease themes and the interdependence of disease themes and core support areas: each theme has critical mass of discovery science supported by major programmes of separate funding (>£70m) that underpin the Centre's translational activities. The ten left-hand column boxes represent cross-cutting themes that are the key tools of the Centre designed to add value by aiding and informing translation of discovery science into experimental patient studies. The top five light grey boxes on the left indicate the **core activities that are supported by MRC funding (matched by host support)** and that cut across the vertical disease themes overcoming obstacles to translation into man. Also shown in this diagram are the Centre experimental therapy directions from 2013 in which the Centre has developed critical mass (three light grey boxes represent new therapy themes: stem cell therapy, experimental exercise therapy and antisense therapy). These therapy themes are separately funded, but major added value is achieved by linking with the Centre core activities. Finally, there are major independently funded programmes of next generation sequencing (NGS) and animal model research (shown as left hand column black boxes). NGS in the Centre had already lead to the discovery of new genes and new therapy targets by Centre PI's and since 2013 we have discovered >40 new genes (see genetic report).

Figure 1.



3. Progress against milestones in six core translational activities

Delivery in the first phase of the Centre 2008-2013

We exceeded all objectives in the first phase of the Centre as assessed at the QQR and listed here:

- New **critical mass** Francesco Muntoni, Jenny Morgan, Hanns Lochmüller, Rita Horvath, Richard Hughes (& entire Cochrane Neuromuscular Unit), Ros Quinlivan all relocated to the Centre.
- We discovered **new genes, new pathophysiological mechanisms** and identified potential new targets and novel preventative measures in NMD (*Nature*^{18, 19} & *Nature Genetics*²⁰).
- We established the **national MRC neuromuscular biobank** with >1800 human cell lines used in >20 science projects and linked to international rare disease biobanks via EuroBioBank.
- We delivered a step change in **UK natural history/experimental personalised medicine studies** rising from just 3 to >30 with an increase in patients entered into experimental studies from 29 to >200 (*Lancet, Lancet Neurology & Brain*)^{1, 5, 11, 14, 15}. We lead international experimental medicine initiatives in the NMD field.
- We **utilised animal models** in imaging studies, to understand pathophysiology and as **preclinical models for potential therapeutics for a number of NMD**. These include novel generation antisense for modification of splicing in Duchenne and spinal muscular atrophy mouse models, and assessment of hyperglycosylation strategies in dystroglycanopathies. We used cell cultures from patients with muscular dystrophy and IBM to explore compound libraries for therapeutic potential.
- We developed a major **education and training** translational research programme and trained ten MRC funded PhD students (two clinical, eight non-clinical). We attracted additional PhD students.
- We established world-leading nationally coordinated **stratified experimental medicine patient cohorts** (>9,500 patients) in target NMD: these cohorts are a critical prerequisite for experimental

medicine trials/personalised medicine. We provided highly visible, outward looking, collaborative, **nationally coordinated translational leadership** including web-seminars, PhD student retreats, workshops and a high profile MRC translational research annual meeting jointly with major UK Muscular Dystrophy UK charity attracting >200 scientists (as well as developing new patient partnerships [http://www.cnmd.ac.uk]).

- The Centre is an internationally recognised focal point for NMD research with **national and global collaborations** (Oxford Neuroscience and Cambridge MRC Mitochondrial Biology Unit, Europe, Japan, USA, Australia). We developed **industry partnerships** that delivered new experimental trials and MRI biomarker development (e.g. GSK, Senexis, Prosensa, Sarepta, and Shire). We leveraged MRC Centre status to attract additional funding from grant organisations, host institutions & NHS Biomedical Research Centres >£70million.

Delivery in current phase of the Centre 2013-2018 (See appendix 7 for detailed core activity reports).

At renewal in 2013 we set out our ten-year vision (2008-2018) to consolidate the expertise and core translational activities of the Centre in order to maximise the potential for the UK to become the world leading place to translate science into early phase experimental medicine in NMDs. We aimed to deliver new experimental medicine studies in each of the five disease themes to show this was possible. We argued that our continued leadership would change UK NMD clinical practice and embed an experimental trials culture so that, like UK cancer care, all UK NMD patients would either have the option to enter national stratified cohorts & experimental medicine trials, or would have effective treatments. We aimed to build on effective academic, industry, funder and patient partnerships.

We now provide evidence that the activities of the Centre has delivered this vision and there is now a clear UK translational research culture. We show there has been a 1000% increase in patients in research cohorts and clinical trials that can be directly linked to the MRC Centre.

The strategic partnership we created is of national importance and means the UK is uniquely poised to make exceptional progress to take full advantage of brand new preclinical technologies and lead the word in delivering disease modifying therapies to improve the lives of patients. This unique opportunity can only be realised with continued focussed MRC support to enable a multi-partner funding approach.

In 2013 we set the seven specific objectives listed below. Here, we briefly summarise the evidence showing that we have delivered against these objectives and in subsequent sections and in the appendices we provide full details:

1. Objective: People to deliver translational research: *we said:* to build on critical mass and aim to recruit new world-class colleagues. We will train more students in unrivalled and inspiring educational environments, and prioritise mentoring best young scientists. **Evidence demonstrating delivery:** Since renewal Professors Avan Sayer from Southampton, Thomas Voit from the Institute of Myology Paris (and previously an MRC Centre SAB board member) and Gipi Schiavo from CRUK London all moved to join the Centre as PIs. Dr James Miller (NCL), Dr Mike Lunn (UCL) and Professor Paul Whiting UCL Drug Discovery Institute CSO (ex-Pfizer) also became Centre PIs. Our annual UK national translational research conference exceeded 200 delegates per annum. Our PhD programmes, which have trained / are training > 37 students are extremely popular (10 applicants for each place) and we created a vibrant translational science educational culture with many innovations e.g. clinical and non-clinical supervision, exposure of non clinical students to patients and clinical pathological meetings, students meet patient organisations and student retreats. *Quote from PhD student 2015 annual conference - "this meeting is amazing and inspiring, I can really see how my lab research links with patients and their diseases"*.

2. Objective: Maximising added value of core areas to achieve "pull through" from discovery science into experimental medicine: *we said:* core translational activities will continue to add value to discovery science and we will deliver new experimental medicine and natural history studies in each target disease. We will develop and refine stratified cohorts, biobanks, MRI biomarkers and additional outcome measures as essential platforms for experimental therapy studies. We will refine our use of preclinical cell and animal models to inform study design of novel experimental therapies. We will extend experimental trial culture to more UK clinicians and NMD patients. **Evidence demonstrating delivery:** since renewal we used cohorts, biobank, MRI biomarkers and knowledge from preclinical animal models to enable us to

deliver world leading experimental trials in muscular dystrophies, neuropathies, channelopathies, inclusion body myositis and mitochondrial diseases. We use a range of approaches including antisense oligonucleotides, small molecules, repurposing and exercise interventions. MRC Centre experimental medicine has lead directly to Orphan status and FDA licencing.

3. Objective: Advancing neuromuscular gene discovery to identify new therapy targets and new biomarkers: *we said:* Centre PI programmes of next generation DNA sequencing will enable further genetic stratification of cohorts, identify new therapy targets & enhance diagnostics. Biobanked stratified patient material will be key to advance understanding of new gene disease pathophysiology & preclinical therapy development. **Evidence demonstrating delivery:** since renewal MRC Centre PIs discovered 41 new genes and took full advantage of biobank cell lines to generate preclinical cell models to understand disease mechanisms.

4. Objective: Antisense strategies to treat NMD: *we said:* we will target other dystrophin gene exons using different antisense oligonucleotide (ASO) chemistries in collaboration with industry (AVI BioPharma and GSK/Prosensa). We will study a new generation of peptide conjugated antisense oligomers. We aim to develop applications of antisense technology to new NMD such as spinal muscular atrophy. **Evidence demonstrating delivery:** since renewal we delivered 6 new antisense experimental trials in partnerships with industry in Duchenne and in spinal muscular atrophy. The MRC Centre PI Duchenne trial data has very recently lead to FDA approval of the first antisense therapy- September 2016 [<http://www.cnmd.ac.uk/News>].

5. Objective: Stem cell therapies: *we said:* we are developing strategies to correct autologous DMD stem cells with a lentiviral vector. We will assess safety and efficacy using myogenic stem cells injected into a single human muscle. We will develop a safe, efficient method to transduce stem cells for systemic delivery. **Evidence demonstrating delivery:** we have significantly advanced preclinical work and established stems cells with a dystrophin gene carrying lentiviral vector.

6. Objective: Experimental medicine exercise physiology/therapy: *we said:* we will exploit the critical mass of expertise and new experimental exercise facilities we established with £2m host investment support across UCL and NCL. We will address key experimental questions in relation to molecular basis of exercise benefit and identify genetically stratified NMD groups for whom exercise is safe and effective. **Evidence demonstrating delivery:** since renewal we completed exercise trials in mitochondrial disease and the largest exercise trial conducted in inherited neuropathy and inclusion body myositis demonstrating efficacy.

7. Objective: Industry partnerships *we said:* continuing strong industry partnerships will enable us to i) Develop and apply new experimental therapies e.g. i) antisense ii) Reprofile licensed drugs e.g. bezafibrate in mitochondrial disease and retigabine in channel disease iii) Develop MRI biomarkers iv) Use industry compound libraries to screen preclinical NMD models. Successful partnerships already exist with GSK; Prosensa; Sarepta, Shire, Senexis; Santhera, Trophos. **Evidence demonstrating delivery:** We have worked with 15 different industry partners on 24 different experimental trials, natural history studies and MRI biomarker studies all listed in trials appendix to this report.

Detailed evidence of outputs against agreed targets for core activities 2013-2018: The MRC Centre has already met or exceeded all the agreed 2013-2018 objectives/metrics in relation to each of the core areas (see metrics summary table): **i) MRC Centre stratified cohorts and experimental medicine trials:** A major success of the MRC Centre has been the dramatic increase (1000%) in clinical trial activity across a large number of different NMDs. In addition the Centre investigators worked together to build the world's largest stratified cohorts of NMD patients for research. Shown in Table 2, we had 10 drug or exercise trials in process before February 2013 and currently have 27 open drug and exercise trials. We had 507 patients enrolled in experimental trials before February 2013 and currently have 1148 patients enrolled in trials and 9527 in stratified patient cohorts (Table 1, Figure 1).

Table 1: MRC Centre Experimental Medicine Trials and Stratified Cohorts

	Jan-13	Nov-14	Jul-16
Trials	507	772	1148
NH/Cohorts	2896	5423	9527

Figure 1: MRC Centre Trials and Stratified Cohorts Recruitment Numbers Chart

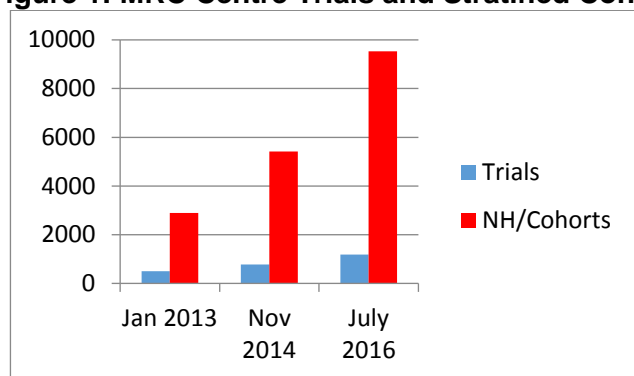


Table 2: MRC Centre Experimental Medicine Trials and Stratified Cohorts

	Pre Feb 2013		July 2016	
	Open	Closed	Open	Closed
Drug Trials	5	12	23	23
Exercise trials	5	3	4	5
MRI studies	5	0	5	4
NH/Cohort	12	5	28	15

Added value: Fully characterized patient cohorts have transformed our ability to undertake natural history studies and interventional studies working together across the two sites. **ii) MRC Centre Neuromuscular biobank:** our established national MRC biobank of nerve, muscle and skin derived tissues continues to grow and to be available to scientists and continues to add value to discovery science and preclinical testing of therapies (e.g. antisense in DMD). At September 2016 we have more than 11,500 samples. We successfully extended sample collection to other UK centres and are introducing a range of new activities.

Added value: the MRC Centre biobank has benefited >200 basic, translational research and research & development projects within the centre and generated high-profile publications (Appendix 7). **iii) MRI**

Biomarker studies: Development of NMD MRI biomarkers was a completely new initiative established by the MRC Centre. We have applied qualitative and developed quantitative MRI methodology to develop MRC Centre MRI protocols that have been adopted by other academic groups and by industry. We have exceeded all milestones since renewal; **Validated MR Clinical Endpoints for Trials:** we have validated more than 9 new putative MRI readouts in published studies; A further 9 new MRI readouts are under development in ongoing centre-led studies. The **numbers of patients enrolled in MR studies of clinical outcomes has markedly increased;** studies we completed since renewal enrolled more than 200 patients and 100 control participants; 200 patients and 50 controls are currently enrolled in active centre MRI studies. **Impact and International standing:** Our MRI outcome measures development has been key to a number of international multi-centre MRI natural history studies and treatment trials led by Centre investigators including LGMD2I (Straub, Hollingsworth); Clinical Outcome Study in Dysferlinopathy (Bushby, Straub, Blamire, Hollingsworth); BIOIMAGE-NMD (Blamire, Straub, Clark, Muntoni), SKIP-NMD (Muntoni), SCOPE-DMD (Straub)). Centre PIs lead international patient-group/pharma/academic initiatives to promote the standardization and acceptance of MRI outcome measures in NMD (e.g. Action Duchenne imaging consortium; SCOPE-DMD / BIOIMAGE-NMD “Making outcomes work” Stakeholder Workshop May 2016) with the objective of driving regulatory acceptance of MRI trial endpoints. **Added**

Value: Centre-funded infrastructure (MRI Physics posts) has enabled both novel biomarker technical development and provided core support (data analysis) to enable our patient imaging studies. Cross-centre collaboration, working created a critical mass of pooled expertise to effectively propagate standardized neuromuscular MRI developments between our sites, and streamline cross-centre MRI studies. This has facilitated successful EU FP7 funding applications (BIOIMAGE-NMD; SKIP-NMD), and Centre support has part-leveraged a clinical infrastructure grant to upgrade the MRI facility (MRC CIF award £1.2M). **iv) Animal models:** Although the MRC Centre does not directly fund animal research, animal models continue to be of importance to the Centre and several Centre PI’s have significant programmes of research that involve NMD animal models. The MRC Centre does support a series of translational PhD projects in the Centre which utilise preclinical animal models in each of the major disease themes (details of MRC Centre animal projects are in appendix 7). We developed strong links with MRC

Harwell and PIs are members of the MRC Mouse Network. **Added value:** the MRC Centre enables human clinical scientists with human cohorts to link with animal scientists working with animal models to work projects towards translation. **v) Education and training:** At renewal we were awarded (MRC and host funded) 16 four-year non clinical, 4 three-year clinical and 13 one-year clinical pump priming posts and we have appointed to all posts. **MRC Centre PhD programme:** The cornerstone of our training are the 4 year non-clinical and 3 year clinical PhD programmes. Full details of our PhD programmes are given in appendix 6. PhD programmes are embedded in a translational environment where all students become knowledgeable in all aspects of their target disease. Highlights of the programme include i) first year of the non clinical programme has rotating lab rotations (UCL) or students do an MRes (NCL), ii) attending Centre annual 4 day neuromuscular disease update course iii) presenting work at annual MRC Centre Translational Conference iv) annual student organised scientific retreat. **Metrics;** at renewal the site visit team advised we appointed clinical fellows for one year (pump priming posts) that we then encouraged them to apply for competitive MRC training fellowship. Four of our appointed clinical PhD students (Maiya Kugathanan, Karen Suetterlin, Helen Devine and Claire Wood) obtained MRC 3 year MRC fellowships following this initial pump-priming (appendix 6). A further training aim in the MRC Centre renewal was to work with industry to develop joint MRC Centre / industry PhD studentships (CASE studentships). We have successfully appointed two CASE PHD studentships with GSK. **Other MRC Centre educational activities:** monthly invited seminar series and yearly MRC Centre UK Translational Research Conference (over 200 delegates annually).

4. Progress and added value in Centre key disease themes

(i) Neuromuscular Genetics UCL Lead Henry Houlden (HH), NCL Lead Rob Taylor (RT): the Centre established well characterized disease patients cohorts (>9500) with DNA, myoblasts, lymphoblasts and fibroblasts collected through the Centre biobank. The cohorts have been critical in supporting genetics programmes and many functional genomic projects. We have fully equipped genetics, functional and iPSC laboratories in Newcastle and London with the latest next generation sequencers and analysis pipeline. Centre investigators discovered 41 new NMD disease-causing genes that have uncovered new pathophysiological mechanisms and targets. Our cohorts enabled us to submit the largest number of neuromuscular patients to the Genomics England (GEL) genome sequencing program. Centre PI Henry Houlden leads the GEL neurology clinical interpretation partnership (GeCIP). (Funding and publication lists see appendices 3 and 4).

(ii) Muscular Dystrophy: UCL Lead Francesco Muntoni (FM), NCL Lead Volker Straub (VS). There has been significant progress in all areas supported by the MRC centre. Here we highlight progress in 3 areas: **a) New genes:** we identified the following new genes responsible for different muscular dystrophies: *B3GALNT2*, *GMPPB*, *SGK196*, *ISPD*, *CAPN3*. We assessed the therapeutic potential of the overexpression of LARGE, a glycosyltransferases involved in the glycosylation of alpha-dystroglycan that we have previously identified and we were able to induce increased glycosylation even in cells from patients with dystroglycanopathies. (FM, Hum Mol Genet 2014) **b) stem cell work:** there has been progress in the characterisation of different subpopulations of human derived cells in their capacity to contribute to muscle regeneration and satellite cell formation following intramuscular transplantation into mouse muscle (FM, Mol Ther. 2014). We characterised the effect that the pathological environment has on muscle regeneration (FM, Skelet Muscle. 2015). We optimised viral gene correction of autologous stem cells (FM, Curr Gene Ther. 2014). We engineered a novel shortened dystrophin to exploit the full capacity of lentiviral vector carriers (FM, Sci Rep. 2016). A similar viral vector will be used by Prof Cossu in a first in man autologous mesoangioblast transplantation study in Manchester, with involvement of the MRC Centre PIs both in study design and biochemical outcome measure assessment. We identified specific defects in glycosylated dystroglycan deficient cells in satellite stem cell function which are very important for the pathological features which characterise the dystroglycanopathies (FM, Stem Cells. 2012). **c) progress in experimental medicine trials:** in both London and Newcastle we initiated phase I-IIa-IIb clinical trials in DMD exploring the safety and feasibility of a new morpholino and a new 2' O-Methyl antisense oligonucleotide designed to skip exon 53 and 45 of the *DMD* gene respectively. These are EU FP7 funded (www.skip-nmd.eu/) (www.scope-dmd.eu/). We developed improved techniques for quantifying dystrophin and explored the biological significance of its reduced expression in pathology (FM, VS, Neurology 2014; FM, VS, JAMA Neurol. 2014). Our trials benefitted from new MRC Centre protocols in muscle imaging. The SCOPE-DMD study led to two stakeholder workshops coordinated by MRC Centre

PIs to discuss challenges in orphan medicine and attended and hosted by the European Medicines Agency and published in Lancet Neurology (VS, FM, Lancet Neurol. 2016). UCL and NCL were trial sites in a Phase IIb study on drisapersen, a 2'OMe antisense oligonucleotide developed by Prosensa, which met the primary endpoint (FM, VS, Lancet Neurol. 2014). We co-lead several phase I trials for assessing the safety and PK of a novel compound to upregulate utrophin production, sponsored by Summit (FM, PLoS One. 2016).

(iii) Neuromuscular Channelopathies; UCL Lead Michael Hanna (MH), NCL lead Hanns Lochmuller (HL) The Centre core activities have transformed our ability to define genetics, understand disease mechanisms and deliver experimental medicine trials. **Muscle channelopathy genetics:** we established the world's largest genetically stratified muscle channelopathy cohort (>1600 patients) linked to our nationally commissioned diagnostic patient service. This invaluable tool allowed us to accurately define the minimum prevalence of muscle channelopathies in England (MH, Neurology 2013). **New channel gene mutations and new phenotypes:** we identified new sodium channel gene SCN4A mutations that cause fatal and potentially treatable childhood disorders (MH, Pediatrics 2014). We identified the first bi-allelic recessive mutations affecting the sodium channel Nav1.4 causing congenital myopathy. (MH, Brain 2016). We identified new SCN4A mutations in congenital myasthenic syndrome (MH, Neurology 2016). We described cases of stridor and episodic life threatening respiratory crises due to laryngeal myotonia linked to SCN4A mutations and showed that functionally deleterious SCN4A rare variants are over represented in SIDS (submitted). **Muscle channelopathy pathophysiological mechanisms:** we tested the bi-allelic mutations we identified in the congenital myopathy patients and determined that these produced loss of Nav1.4 channel function either by complete lack of sodium current or reduced sodium current (MH, Brain 2016). We expressed the rare variants we identified associated with SIDs and showed they altered channel function including gain and loss of function mechanisms (MH submitted). We pursued understanding of the molecular pathophysiology of diseases caused by gating pore currents in muscle channelopathies (MH, Curr Opin 2014). **Animal models:** we worked with MRC Harwell and identified and characterised a new mouse model of human SCN4A disease with a novel potential therapeutic target (MH, Brain 2014). **Clinical translational activities in the MRC Centre;** i) we completed a large multicentre natural history study (NIH funded) in almost 100 non-dystrophic myotonia patients (MH, Brain 2013). ii) We completed a large multicentre international randomised controlled experimental trial (NIH funded) in periodic paralysis showing that dichlorphenamide reduced the median attack rate of participants with hypokalaemic periodic paralysis (0.3 vs 2.4, $p = 0.02$). This resulted in the first licensed treatment for periodic paralysis in 2015 when the FDA approved it. iii) Inhibiting intramuscular chloride accumulation was shown to reduce muscle membrane depolarisation and muscle paralysis in hypokalaemic periodic paralysis in two mouse preclinical studies using bumetanide. We are therefore currently conducting a pilot safety study using intravenous repurposed bumetanide in hypoPP patients. iv) We established long-term safety and efficacy and developed treatment guidelines for use of mexiletine in non-dystrophic myotonia. (MH, JAMA Neurology 2015). v) We developed MRI as a diagnostic technique (MH, Neuromusc Dis 2013).

(iv) Inherited Neuropathies UCL Lead Mary Reilly (MR), NCL Lead Rita Horvarth (RH)

MRC Neuropathy stratified cohorts, natural history and biomarker studies: since 2013 we extended our inherited neuropathy natural history study and now have 3768 patients. We completed a natural history study of HSN1 secondary to SPTCL1 mutations recruiting 35 patients. We developed the MRC Centre MRI neuromuscular protocol as the first responsive outcome measure over 12 months in CMT1A (MR, Lancet Neurol 2016) and have shown this protocol is responsive in hereditary sensory neuropathy, HSN1 (MR). We studied NEFH as a potential biomarker for CMT1A in a longitudinal study (MR, Musc & Ner 2016). **New genes:** We recruited 200 neuropathy patients to our exome study and have identified 7 new genes: three genes for autosomal dominant CMT2, *NEFH* (MR, AJHG 2016), *MARS* (MR, JNNP 2013) and *IGHMBP2* (MR, AJHG 2014), two genes for hereditary motor neuropathy, *BICD2* (MR, AJHG 2013) and *FBOX38* (MR, AJHG 2013) and two genes for complex neuropathies *EXOSC8* (RH, Nat Comm 2014) and *SYT2* (RH, AJHG 2014). We identified multiple new mutations/phenotypes/mechanisms in our cohort in known inherited neuropathy genes including *DYNC1H1*, *DNMT1*, *MPZ*, *MFN2*, *FIG4*, *C12orf65*, *ADCK3*, *COX10*, *FIG4*, *SPTLC2* and *TRPV4* (MR, RH publications) and published on the usefulness of the presence of peripheral neuropathy to predict the genotype in mitochondrial ophthalmoplegia (MR, Brain 2014). We published a guide to the use of next generation sequencing in inherited neuropathies (MR, Nat Reviews Neurol 2013). **Understanding Molecular Pathophysiology:** we showed that *BICD2*

is likely to cause HMN due to perturbation of BICD2-dynein-dynactin-mediated trafficking and impair neurite outgrowth (MR, AJHG 2013) and that FBXO38, needed for regulation of genes required for neuronal axon outgrowth and repair is likely to cause HMN by transcriptional dysregulation with an associated impairment of neurite outgrowth (MR). In HSN1 secondary to SPTLC1/SPTLC2 mutations, we showed that the deoxysphingolipids (DSBs) which are produced when a mutation alters the substrate specificity of the SPT enzyme, are toxic to both sensory and motor neurones and have an ongoing project studying IPS cells from patients and looking at the potential of both serine and antisense oligonucleotide therapy for this group of patients (MR). In the complex neuropathies, we developed a zebrafish model to investigate the major disease mechanisms in the complex spinal muscular atrophy, pontocerebellar hypoplasia and hypomyelination syndrome and identified EXOSC8 mutations, and showed that the neurodegeneration was caused by a defect in mRNA metabolism (RH, Nat Comm 2014). Based on the disease mechanisms of 2 novel disease genes we have identified, EXOSC8 (RH, Nat Comm 2014) and SYT2 (RH, AJHG 2014), we identified a potential novel approach for therapy, targeting the neuromuscular junction in motor neuropathies (RH, Neurology 2015). **Clinical trials:** we completed a prospective biomarker study as part of an international study in CMT1A. We completed a trial of aerobic exercise for CMT1A and are analysing the results. (MR). Our UCL study is part of the first antisense oligonucleotide trial in an inherited neuropathy i.e. TTR-related Familial Amyloid Polyneuropathy being run by IONIS.

v) Inclusion Body Myositis (IBM) UCL lead: Michael Hanna (MH), NCL lead: Hanns Lochmüller (HL)

We aim to understand the causes of IBM and identify novel therapeutic strategies. **1) IBM Natural History:** a prospective IBM patient cohort >90 (UCL/NCL); has been deeply phenotyped at the clinical, serologic, histopathological and MRI level and outcome measures/MRI biomarkers for experimental trials are being developed. (MH, Neuromusc Dis 2013). **2) Development of in vitro models of IBM:** we established two cell culture systems modelling “degenerative” or “inflammatory” components of IBM. In both models cells recapitulated pathological characteristics of IBM (MH, Sci Trans Med 2016). **3) Screening novel compounds:** using this in vitro model we examined effects of pharmacological manipulation of the Heat Shock Response (HSR), an endogenous cellular defence pathway on IBM-like pathology. We found that Arimoclomol, a co-inducer of the transcription factor HSF-1 ameliorated several IBM-relevant features. We established a new collaboration with a small drug discovery company, Senexis (Cambridge), and identified new amyloid targeting agents (MH, Sci Trans Med 2016). **7) Assessing Arimoclomol in the VCP mouse.** We characterised the Valosin Containing Protein (VCP) mouse. VCP is intimately related to TDP-43 function & is implicated in conditions such as motor neuron disease. The VCP mouse recapitulates the pathology of human IBM in which muscle shares key pathological features. We showed upregulation of HSP with arimoclomol significantly improves the mouse phenotype (MH, Sci Trans Med 2016). This study may have wider implications for NMD & treatments, e.g. the sarcopenia of ageing shares several characteristics with IBM, several muscular dystrophies also display an inflammatory component that is driven by NFκB activation, which we hypothesize will be inhibited in vivo by Arimoclomol treatment, as it is in vitro. **6) MRC Centre-First in IBM man experimental safety study:** We undertook an investigator-lead placebo controlled safety and tolerability study of Arimoclomol in 24 IBM patients with pre and post treatment muscle biopsy. Data confirms safety and tolerability and an efficacy study is currently being planned. This project represents a fundamental step in a translational research programme in IBM that we established in the MRC Centre (MH, Sci Trans Med 2016). **7) MRI Biomarkers:** we showed that qMRI parameters in muscles in IBM patients prospectively show consistent significant reductions that correlate with reduced power (MH, Lancet Neurol 2016). **8) Genetics:** with separate MRC funding we undertook a whole exome study in IBM and identified associations with immune system and protein homeostasis genes (MH, Neurobiol Aging 2016). **9) Exercise physiology:** we completed a study investigating aerobic training in IBM on fitness levels, muscle strength and function using a randomised crossover design with training and control periods. **10) Links with industry and new clinical trials:** we established links with industry; we completed a phase IIb/III multicentre IBM clinical trial with Novartis in December 2016. This study tested a monoclonal antibody against the myostatin receptor. Following an award (\$1.7m) from the FDA Office of Orphan Products Development Grant Program and support from Orphazyme we will lead a RCT efficacy trial from 2017.

(v) Mitochondrial Diseases UCL lead Michael Hanna (MH) NCL lead Doug Turnbull (DT)

Experimental clinical studies; single, large-scale deletions of mitochondrial DNA are a common cause of mitochondrial disease and cause a broad phenotypic spectrum ranging from mild myopathy to devastating multi-system syndromes. Using the MRC cohort of 87 patients with single, large-scale mitochondrial DNA deletions we demonstrated that patient outcomes are significantly ($p < 0.05$) correlated

with the size of the deletion, the deletion heteroplasmy level in skeletal muscle, and the location of the deletion. We used mixed modelling techniques to model the progression of disease according to these predictors, allowing a better understanding of the progression over time. ***m.3243A>G mitochondrial DNA mutation*** is the most common genetic cause of mitochondrial disease. Utilising the MRC cohort of 156 subjects, we showed that *m.3243A>G* heteroplasmy and age strongly associate with overall disease burden progression ($p < 0.0001$), and demonstrate that genetic familial lineage is a significant modulator of disease burden ($p < 0.0001$) (DT, MH, JNNP 2013) ***Peripheral neuropathy in patients with progressive external ophthalmoplegia (PEO)***. We observed in a study of 116 patients that the prevalence of peripheral neuropathy is a rare clinical feature in patients with a single mitochondrial DNA deletion and that peripheral neuropathy is an independent predictor of a nuclear DNA defect (odds ratio 8.43, 95% CI 2.24-31.76, $p = 0.002$) (MH, Brain 2014). **New diagnostic tools.** We developed a new diagnostic procedure using fluorescent immunocytochemistry using four different antibodies on the same section. This technique can be automated and has the potential to play a major role in the investigation of mitochondrial dysfunction in the future (DT, Sci Rep 2015). **Mitochondrial gene discovery and molecular mechanisms: mtDNA-related mitochondrial disease:** our studies have identified novel mitochondrial DNA (mtDNA) mutations associated with multisystem and myopathic presentations of paediatric and adult-onset mitochondrial disease, delineating the mechanisms leading to molecular pathology in muscle and the central nervous system. We extended these studies to delineate and model disease progression (see above), the nature of mtDNA mutations within muscle satellite cells and mechanisms underlying mtDNA mutation accumulation for a sub-group of pathogenic mtDNA mutations, single, large-scale mtDNA deletions (DT, Hum Mol Genet 2013, DT, Hum Mol Genet 2014). **Nuclear mitochondrial disease:** Using NGS in a cohort of ~60 patients with biochemical evidence of multiple respiratory chain complex abnormalities, we have identified an unprecedented high rate of disease gene discovery (approximately 70% of the individuals); confirmatory functional studies have been completed for some of these genes including *ELAC2*, *FBXL4*, *TRIT1* and *APOPT1*. Mechanistic studies have led to the identification of the molecular mechanisms underlying reversible infantile respiratory chain deficiency and to the reassignment of the *NDUFA4* protein to mitochondrial respiratory chain complex IV. We have also used WES to delineate the molecular basis of undiagnosed adult-onset mitochondrial PEO with multiple mtDNA deletions, identifying *SPG7* mutations as an important cause and describing new clinical phenotypes (RH, In J Biochem Cell Biol 2015, MH, Cell Rep 2013, DT, Brain 2014).

5. Added value overview

How has the centre evolved/developed new opportunities, identified new programmes, intra university and external? The Centre has added major value to Centre PI research programmes resulting in mission delivery, significant leveraged funding (£100m) and a dramatic increased profile of NMDs both within our institutions, nationally and internationally. Within our universities: at UCL a new Department of Neuromuscular Diseases is being established and in NCL the John Walton Muscular Dystrophy Research Centre opened. Nationally; Centre PIs lead the national NIHR rare NMD disease programme and internationally Centre PIs lead and co-lead many of the large European FP7 and NIH funded rare disease consortia (see grants appendix). The core translational activities of the Centre has enabled PIs to leverage additional funding totalling >£70 million since 2013 and >£100m since 2008 from many sources, both within our own institutions (see matched BRC funding in our 2013 MRC centre renewal and multiple other BRC funded research programmes), nationally (major new MRC and Wellcome grants since centre started in 2008) and through an active collaborative international strategy with successful international collaborative applications (e.g. FP7, AFM, NIH). The Centre has enabled us to be nimble and responsive to new developments (e.g. we responded to the advances in NGS by leading on applying the new technology in NMDs with the subsequent identification of 41 new genes and in antisense therapy development by leading the early phase trials in DMD and SMA). The ***MRC centre core funding and status has been critical*** in allowing us to take full advantage of these local, national and international opportunities to drive forward our research agenda to change patients lives. **What mechanisms are being used to make decisions about the Centre's evolution and what role is the university playing?** Within the Centre we have an active UCL/NCL steering committee with monthly meetings and a yearly meeting of all PIs to develop our ongoing and future strategy. Decision making is transparent and the Director works hard to achieve consensus. Based on the increased profile and success of NMD research in both our host universities we have senior engagement to help develop and implement our strategy beyond 2018. In 2013, at renewal, our university engagement helped us to

develop our strategy to obtain matched funding. Following a PI meeting in 2014 devoted to our future strategy post 2018 and with engagement and discussion from our host universities, and our SAB, we determined a strategy to develop a new preclinical experimental therapy centre with a multipartnership approach to funding including embedding our current MRC activities with host and NIHR funding. *The MRC Centre has dramatically increased the visibility of neuromuscular diseases and put it at the centre of the research agenda for both universities. We have no doubt that having the MRC as a partner in a future centre will be essential to maintain this position and enable successful conclusions to our university negotiations*

Training and capacity and what evaluation mechanisms? The added value the MRC Centre has provided to enable us to train the next generation of neuromuscular clinician and basic scientists has been transformational. There was no UK training scheme for neuromuscular researchers before the MRC Centre and we now have a very popular, vibrant and successful programme. Our success is reflected by the ~10 applications for each post, by the 100% thesis completion rate, by the future successful careers of our graduates (90% have undertaken post-doctoral research or gone back to clinical training and 10% have moved into industry-see training appendix 6). We have increased UK NMD clinical academic capacity and three of our trainees are now clinical academic consultants (appendix 6). We have outlined our programme in detail in appendix 6. We consider that a critical element in our training success is the true translational nature of the programme where every student, whether clinical or non clinical, is trained in a truly translational environment in which developing treatments for patients is the ever present central mission. Evaluation of our programme continues beyond the studentships with a tracking system of future careers to ensure we are capacity building as intended. Table 2 in appendix 6 shows that we are successful in this respect. We are now seeing the first group of our trainees develop as independent PIs in neuromuscular diseases both within our own Centre and at other centres. **How is the Centre promoting its translational agenda / knowledge transfer?** The fundamental concept behind establishing the Centre was to overcome gaps and obstacles to translation hence we formed and fully delivered the six core translational activities. We fully recognize translation is a complex interdisciplinary and expertise is often fragmented. We promote our translational agenda by taking every opportunity to increase the profile of neuromuscular disease translational research in our universities, host hospitals, nationally and internationally. We are fully aware of the power of major grant awards / high profile publications and presentations at international meetings to ensure both knowledge transfer and future success. We have had a specific strategy since the Centre commenced to engage and work with our partner patient organisations; this is exemplified by hosting our yearly national translational neuromuscular conference in partnership with MDUK- the largest UK neuromuscular disease patient organisation and advocacy group. To date over 2500 delegates have attended this conference. We use this and many other roles our PIs have with patient and national bodies to deliver our knowledge transfer agenda. We have built major successful partnerships with industry; for example there are currently 15 different industry partners linked to 24 different experimental trials, natural history studies and MRI biomarker studies (all listed in trials appendix). Internally we liaise closely with appropriate university bodies (eg. UCL translational research office, UCL Business Plc) in developing partnerships and preparing patents.

6. Future Plans

Vision for the Centre beyond 2018

Our vision by 2018 is an embedded experimental medicine platform linked to specialist clinical practice and this will be achieved.

From 2018 we propose a new radical centre focused on experimental therapy of National strategic importance which will lead the world in developing new therapies across many NMDs

By 2018 our Centre will have established a mature nationally connected patient cohort and experimental medicine platform that is easily accessible from specialist clinical practice throughout the UK. We will have realised the vision we set out in 2013; i.e. that *for NMDs where there is no standard treatment, all patients in specialist NMD clinics will have the option to enter a national cohort and/or enter an experimental trial.* We are actively pursuing host support in Newcastle and UCL to firmly embed our core translational activities. Our efforts have addressed significant roadblocks to translating science into experimental trials and therapies. We have shown through pilot studies in a few specific diseases that we can use this platform to translate science into early stage experimental trials and in two cases even achieve FDA approval (eg DMD, channelopathies). Furthermore, we have shown that we can overcome regulatory

obstacles to undertaking trials in rare diseases. However, we can dramatically accelerate the progress made by taking full advantage of brand new technological developments and by establishing new core facilities to develop therapies for the much wider range of NMD targets, revealed by the unprecedented increase in gene discoveries. The platform we have created, and from which we will work to secure host support from 2018, means we are critically poised to lead internationally and make exceptional progress toward therapies across a wider range of NMDs.

The radical new centre proposed will be entirely different to the current Centre but will be completely synergistic with the platforms already created. Unlike the current Centre it will be predominantly **preclinical** and will allow us to establish new core capabilities including robotic iPSC capability (linked to our >9000 human patient fibroblast biobank), embedded drug discovery capability and deep cell and animal phenotyping facility including state of the art cell imaging and animal in vivo tissue imaging. It will also include new core capabilities in next generation biomarker development, advanced bioinformatics development and translational PhD training (including in for e.g. in drug discovery, innovative trial methodology, regulatory framework, and industry partnerships). The proposed new Neuromuscular Experimental Therapy Centre (NEXT Centre) will transform our ability to pursue two broad programmes: 1. A new preclinical therapy development programme and 2. An experimental therapy innovation programme. The proposed Centre will enable genuine bidirectional translational research. Traditional translational research has been linear from bench to bedside and has frequently been disappointing. For example, when treatments that are successful in animal models are trialled in human patients (e.g. multiple MND trials). The unprecedented patient gene discoveries in just the last three years means that the genes for virtually all NMDs have been identified. This has revealed new targets and potential new disease mechanisms. These discoveries have produced a remarkable opportunity to back translate our discoveries in patients by developing a new pre-clinical programme focussed on addressing these pathways and targets. This represents an unprecedented opportunity for drug discovery and therapy development; provided we establish a new Centre with the required capabilities harnessing brand new disease modelling capabilities.

Our current position as international leaders is a direct result of the MRC Centre investment of £6m over 10 years which has leveraged £70m since 2013 alone and well over £100m since the Centre's inception in 2008. MRC Centre status and the MRC investment has been pivotal to the dramatic progress we have made and the national translational research culture we have enabled. It is very likely that the Centre we now propose will be a magnet for industry partners and will leverage an even higher return on MRC investment, thereby contributing to both the health and wealth of the national. We believe this is of national strategic importance for NMDs but potentially for translational neuroscience more broadly including cross learning for the way a proposed Dementia Research Institute could function.

How the Centre's research agenda will be supported/embedded within the universities:

Experimental medicine that results in patient impact is a major part of the biomedical strategy of UCL and Newcastle University. In addition, UCL has a major focus on rare diseases while Newcastle has recently developed critical mass in sarcopenia (Avan Sayer). The MRC Centre activities are therefore aligned with University strategy. We are in discussion with our hosts to support the six translational core activities we have built in order to embed them with secure host support by 2018. (See letter of support from host universities appendix 5). Both Universities recognise the major progress made; in UCL there is agreement a new Department of Neuromuscular Diseases will be established and in NCL the John Walton Muscular Dystrophy Research Centre has opened. Both universities made major financial commitments at renewal (together matching the MRC award) and committed to onward support. Our NIHR BRCs (UCLH, GOSH, Newcastle) have recently been refunded (2016) and we are in discussion with BRC Directors. However, MRC support for new preclinical core facilities in a new Centre would dramatically enhance our position to maximise our leverage and assist in negotiations.

Shape of transformation of the centre for new MRC Centre bid. We envisage our new Neuromuscular Experimental Therapy Centre (NEXT Centre) as a radically new centre focused specifically on preclinical development of experimental therapies across a wide range of NMD targets now revealed by recent patient gene discoveries. It will also encompass biomarker development and bioinformatics. The new preclinical centre would enable partnering with industry and would move therapies towards the host supported experimental medicine platform previously created by the MRC award. Broadly the activities of the new centre would fall into two themes: 1. A new core preclinical therapy development programme and 2. An experimental therapy innovation programme. There will also be a translational PhD programme for clinicians and basic scientists. 1. **Core preclinical development programme:** Gene discoveries since 2013 have revealed overlapping disease mechanisms in clinically diverse NMDs including disruption of RNA dynamics, organelle transport, protein homeostasis, ion channel dysfunction and mitochondrial dysfunction. A deeper understanding of these processes at the molecular, cellular and organismic level

has significant potential to elucidate mechanisms and develop new therapies applicable to multiple neuromuscular diseases. Our core programme would include: **a. Robotic stem cell facility to maximise the potential of our human patient biobank;** a robotic quality controlled facility to enable us to use human iPSCs from patient fibroblasts (harbouring mutations of interest) to derive neurons, muscle and glia as model systems to understand disease mechanisms and undertake drug discovery primary and secondary screens. **b. In-depth deep Phenotyping Facility:** this will allow integration of molecular, cellular and organismic data. It will include cell, tissue and in vivo imaging. It will also provide full neuromuscular phenotyping capability for mouse models to enable more reliable correlation with human disease; this will include mouse nerve and muscle histopathology, neurophysiology, and imaging. **c. Embedded Drug Discovery Capability:** UCL recently established an £8.8m ARUK UCL Drug Discovery Institute to exploit UCL/Institute of Neurology neuroscience “know-how” to develop new therapies for neurodegeneration. Led by Paul Whiting (ex Pfizer) and a team with >70 years drug discovery experience, it provides drug discovery capability, including medicinal chemistry, drug screening, and target validation. It includes high-throughput screening and high content imaging and liquid handling. There is an unrivalled opportunity for the NEXT Centre to embed new postdoctoral staff to expand the capacity of the DDI to enable a full programme of NMD drug discovery. A new centre could potentially provide staff to create this bridge to drug discovery.

2. Experimental therapy innovation programme: This programme will be the core centre programme to deliver innovative new therapy trials and will include: **a. Next generation Antisense Oligonucleotide (AON) / RNA therapy / Gene Therapy applications:** Having successfully delivered AON pilot therapy trials in patients with DMD and SMA, we will target new genes and generic pathological processes [eg fibrosis/atrophy] across NMDs, assess the efficacy and bio-distribution of novel AONs modified for improved targeting of skeletal and cardiac muscle as well as nerve and perform de-risking preclinical toxicology of the most promising AONs. Building on our ongoing AAV therapy initiatives in SMA and DMD, we will pursue preclinical and clinical trials in gene therapy with AAV vectors in these disease and expand to other NMDs including initially Myotubular Myopathy. **b. Repurposing and combinatorial therapy approaches:** We have successfully repurposed mexiletine (achieved orphan drug status) and dichlorphenamide (achieved FDA licensing status) in muscle channelopathies and will pursue further repurposing opportunities. We will assess combinatorial approaches in NMDs building on recent observations of additive benefits of AON plus myostatin in the SMA mouse. We will work with industry partners and use our model systems including human derived hiPSC lines combined with high throughput screening to pursue repurposing and combinatorial opportunities. **c. “Big data platform”** With the development of high throughput technologies that deliver ever increasing amounts of data there arises the challenge not only of analysis and interpretation of this data but also its integration across multiple repositories at UK and global level. Integrated analysis over multiple data sources has the unprecedented potential to enable reuse of data and biosamples beyond the original purpose of their collection and to harness machine-assisted knowledge discovery for the identification of new drug targets and development of novel therapies. This activity will enable the neuromuscular community and the neurology GeCIP to link up their data repositories, patient registries and bioresources into the resources provided by the international community and to give them the expertise to make their data Findable, Accessible, Interoperable and Reusable (FAIR). **d. Responsive biomarker development:** A programme to develop new and evolving sensitive MRI, proteomic, RNA and metabolomic biomarkers building on our successful MRI biomarker development in a number of neuromuscular disease (CMT, IBM, DMD). **We envisage the proposed centre to be supported by several partners but critically the MRC will trigger this partnership through funding of selected aspects of the new Centre.**

Aspects of Centre’s current activity that fulfill a national need; We are at a pivotal point in the development of therapies for NMDs. MRC funding to date has created an experimental medicine platform and core translational tools that are internationally recognised. MRC investment has embedded a neuromuscular experimental network as part of specialist clinical practice in the UK and we have driven a change in clinical practice increasing patients in trial and cohorts and biobanked cells by >1000%. **None of this progress would have happened without the initial MRC investment and its renewal.** This MRC investment has produced a 15:1 (£100m: £6m) return on investment i.e. external leveraged grants and industry support; £100m vs MRC investment; £6M (original award and renewal). This return only happened because of the original MRC recognition through a Centre grant, the profile it provided and the ensuing leveraging potential. **It is only because of MRC investment that the UK is now poised to be a world leader in NMD therapy development.** We argue this is of genuine national importance as we are now extremely well placed to make significant progress towards therapy (see report from SAB appendix 5) in these fatal or disabling diseases which remain an unmet health need. It is only with further MRC investment and recognition that we believe we will have the leverage to generate the multipartner

funding to create the NEXT centre and change patients' lives. **Requirement for a 2-year transition period:** Our ambition is to seek approval to make a detailed case for a new preclinical Centre that we are sure will result in similar 15-1 financial leverage we have shown we can deliver. A new MRC Centre award will be pivotal. We would like to stress that relatively modest MRC investment and MRC Centre recognition will catalyse exceptional return on investment and major progress towards therapies. If this is not possible, having MRC Centre status for a further 2-year transition period will enable us to pursue the multipartner funding required for sustainability and to create the NEXT Centre. Continued Centre status will have major benefit in enabling leverage from our respective NIHR BRCs and will greatly strengthen our position in forming critical pharmaceutical and patient organisation partnerships. We plan new senior positions to bring new preclinical capabilities in translational NMDs and continued MRC status will attract the highest calibre researchers. We will also seek ongoing support for our extremely successful training programme.

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