GREAT ORMOND STREET HOSPITAL CHARITY

Increasing research capacity in the neuromuscular team at Great Ormond Street Hospital and UCL Great Ormond Street Institute of Child Health

Prepared November 2018

Thank you

Thank you so much for all your support for Professor Franceso Muntoni's neuromuscular research team. As you will read in the following pages, the funding you have given has provided the team with the resources they need to develop, expand and stabilise.

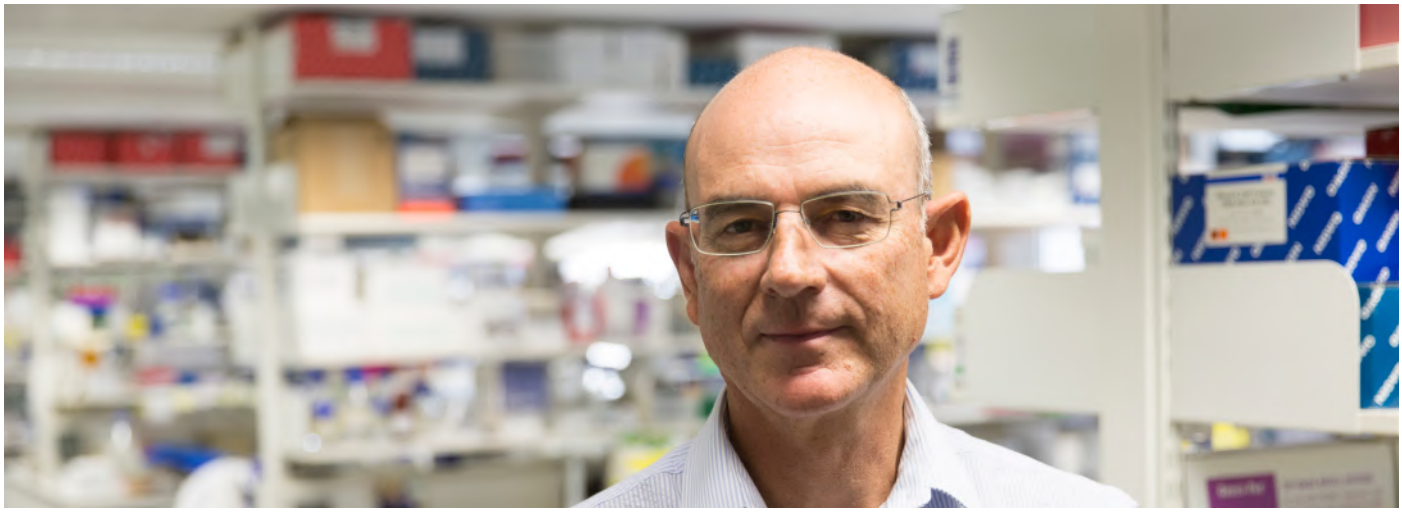
This additional capcacity has allowed the team to increase both the number of clinical trials, and number of children participating. Associated improvements in the organisational, training and administrative process of clinical trials conducted by the team has lead to an improved patient and family experience - assessments take less time, waiting times are minimised and there are fewer cancellations.

The improvements in the team have also given the team the capacity to support and coordinate multicentre trials for potential new therapies, maximising access to these treatments.

Thank you for your continued support for this programme, which is making an enormous difference.

Cover photo: Ten-year-old Jake, was diagnosed with Duchenne muscular dystrophy (DMD) when he was four years old. Jake is taking part in Professor Muntoni's clinical trial to develop a new drug that targets a part of the dystrophin gene which affects about one in ten children with DMD.

Increasing research capacity in the neuromuscular team



Above: Professor Francesco Muntoni

Part 1: Personnel funded by this grant

Position	Name	Start Date	End Date	% FTE	Notes
Clinical Research Fellow 0.5	Kate Maresh*	01/02/2018	31/01/2020	60	Replacement for Jacqueline Pitchforth.
Clinical Research Fellow 0.8	Federica Trucco*	05/04/2018	04/08/2019	80	
Physiotherapy Assistant 0.5	Evelin Milev	01/04/2016	31/03/2019	50	
Physiotherapist 1.0 (G6)	Mario Iodice	01/06/2016	28/02/2019	50 but 100 from 01/11/2018	Currently split between Mario Iodice and Efthymia Papagiotopoulou.
	Efthymia Papagiotopoulou*	03/07/2018	02/07/2019	50	
Research Physiotherapist 1.0 (G7)	Vacant*		31/05/2020 (Subject to start date)	100	Replacement post to be advertised through GOSH. Expected start date: 12/2018
Clinical Trial Co-ordinator 1.0	Manju Agarwal*	11/10/2016	10/10/2019	100	

**The team have been successful in securing funding from other sources which have required them to be used in this financial year. We have been flexible with the funds issued under this award and such there is underspend on a number of posts. Therefore these posts will be extended beyond the original due date and the end dates shown are inclusive of these extensions.*

A reminder of all previous personnel who have been employed on this grant during the course of this programme

Position	Name	Start Date	End Date	% FTE
Research Physiotherapist	Aleksandra Pietrusz	22/04/2016	08/11/2016	100
Research Physiotherapist	Ricarda Tilmann	24/07/2016	31/03/2017	50
Research Physiotherapist	Jackie Reznik	01/06/2017	31/05/2018	100
Clinical Research Fellow	Jacqueline Pitchforth	01/07/2016	08/08/2018	50

Part 2: Progress

A. Trial capacity

The number of trials within the neuromuscular programme is increasing year on year and, prior to having the funding available, capacity was a huge problem and a very limiting factor to how many studies we could participate in as well as the number of patients within each study. The nature of the studies and the patient group mean that studies are highly resource intensive requiring support for the clinical, physiotherapy, research nursing, study coordination and data management teams. In the last year, we have turned down two studies due to lack of capacity, as we lost two fellows in a short space of time where previously the number of studies was in the region of eight to ten.

A multidisciplinary team is essential to support research including clinical leads, specialty doctors and clinical research fellows, research nurses, physiotherapists, radiographers, study coordinators and data managers. Funding has been used to develop, expand and stabilise the neuromuscular research team so that we can increase the total number of trials and participants within those trials.

The clinical research fellows are in charge of all the preparatory aspects of a study: from reviewing IRAS (Integrated Research Application System) applications, parents/patients Information leaflets to looking at the databases for potential candidates, networking with other centres and contacting families ahead of any start of the study. In particular, Dr Pitchforth has been crucial in helping other sites to be involved in Rare Diseases study **13DN27** with protocol amendments and protocol understanding by other colleagues. The same colleague has also been in charge of recruiting and following-up patients in the Esperare study (**15NM11**) which has recruited the total target number of patients and is now closed. Dr Trucco only started with us in April 2018 but since then has taken a lead role for two the Sarepta studies with patients receiving weekly dosing, streamlined processes in place to ensure no prescriptions are missed, and all bloods and safety related queries answered in a timely manner. In addition to this, she has also taken responsibility for the Audentes studies (Inceptus and Aspiro) for MTM (myotubular myopathy) patients as well as being a back-up for all the other clinical trials.

The ability to have a lead physiotherapist and at least one back-up for each study has improved the organisational process (in particular study cover when someone is on leave or sick) with no need to re-schedule or cancel appointments, which can represent a protocol deviation and also cause frustration for families, especially when changes are made at a very short notice. The role of the physiotherapy assistant has been crucial in organising the assessments by having the assessment tools in place and set-up before the patient arrives,

reducing time consuming for each assessment and, therefore, being able to carry out more assessments per day (which has consequently freed up the space and consultation rooms needed to see more patients, including from different trials).

The trial coordinator Manju Agarwal has been essential to this team, as she has taken over lead of many studies from a colleague who was trying to manage a portfolio of studies and didn't have enough capacity. Manju has now taken the lead for over seven studies and ensures that the set-up, costing, contracts and approvals for the study is in place in a timely manner ensuring all relevant staff are trained prior to performing assessments for any particular study. She has also helped to archive some of the older studies, which needed completion post closeout visits.

B. Number of studies

The table below provides details of commercial research contracts over the last five years; this indicates the increase in income which is associated with an increase in activity (patients recruited). At least 10 new commercial studies have started since the award, and this funding has allowed the team to increase recruitment to open more commercial studies.

Below is a list of all trials we are participating in where we receive funding for taking part (commercial and non-commercial).*

R&D No	Actual End Date	Actual Start Date	Site Study Status	Principal Investigator
09DN05	23/03/2018	23/06/2011	Approved	Professor Francesco Muntoni
09DN11	31/01/2019	07/05/2010	Approved	Professor Francesco Muntoni
12DN09	01/04/2017	04/06/2013	Approved	Dr Adnan Manzur
12DN20	03/07/2017	27/02/2013	Approved	Professor Francesco Muntoni
12DN33	22/09/2016	15/08/2013	Completed	Professor Francesco Muntoni
13DN11	14/10/2016	01/11/2013	Completed	Professor Francesco Muntoni
13DN31	31/10/2018	02/12/2014	Approved	Professor Francesco Muntoni
14DN06	31/12/2016	02/02/2015	Approved	Professor Francesco Muntoni
14NM09	30/03/2018	05/11/2014	Approved	Professor Francesco Muntoni
14NM14	23/08/2017	16/01/2015	Completed	Professor Francesco Muntoni
15NM07	29/03/2019	12/05/2015	Approved	Professor Francesco Muntoni
15NM11	30/04/2018	12/08/2016	Completed	Professor Francesco Muntoni
15NM15	01/06/2020	18/09/2015	Approved	Professor Francesco Muntoni
15NM22	31/12/2019	14/01/2016	Approved	Professor Francesco Muntoni
15NM23	29/07/2016	17/12/2015	Approved	Professor Francesco Muntoni
15NM30	31/10/2018	24/10/2016	Approved	Professor Francesco Muntoni
15NM33	31/03/2020	22/04/2016	Approved	Professor Francesco Muntoni
16NM06	31/12/2018	07/02/2017	Approved	Professor Francesco Muntoni
16NM17	15/04/2019	13/03/2017	Approved	Dr Pinki Munot
16NM22	11/03/2019	10/03/2017	Approved	Professor Francesco Muntoni
16NM23	31/03/2020	09/02/2018	Approved	Dr Mariacristina Scoto
17NM01	30/06/2020	29/06/2017	Approved	Professor Francesco Muntoni
17NM07	31/03/2021	06/09/2017	Approved	Professor Francesco Muntoni
17NM18	31/01/2020	12/01/2018	Approved	Dr Mariacristina Scoto
18NM01	30/08/2019	21/06/2018	Approved	Professor Francesco Muntoni

**See appendix for legend to study codes*

C. Number of patients

The number of patients recruited has increased from 139 in 2016/17 to 351 in 2017/18.

One stucy (13DN27 - see appendix for list of studies) is a study entitled "the Neuromuscular Rare Disease Translational Research in patients with Duchenne Muscular Dystrophy". The study's primary aim is to investigate the possible correlation between multiple SNPs (single-nucleotide polymorphisms) in genes other than dystrophin and the severity of clinical manifestations (especially motor function and cardiac function) in children and adults with DMD by using next generation sequencing. This study started initially in two centres (London and Newcastle) and has since been expanded to other centres that are part of the neuromuscular Northstar network (currently 25 centres); therefore the number of participants has significantly increased in the last year with the aim to have 400 recruited by the end of this year (December 2018).

In addition, since the start of the award the team has supported the highly resource intense extended access program for Nusinersen in patients with spinal muscular atrophy, which has included the participation of 27 patients at GOSH and coordination of the other 15 centres in UK and one centre in Ireland.

Going forwards the team will support extended access programmes for Eteplirsen for patients with Duchenne muscular dystrophy (two patients have already been recruited at GOSH). Our centre has been working with Pharmaceutical companies, advocacy groups and the hospitals involved to provide access to the treatment to patients who were originally involved in the trial prior to potential regulatory approval. Six patients are starting treatment at GOSH and NHNN (National Hospital for Neurology and Neurosurgery).

We are also working on providing expanded access programme treatment with Ibedenone for boys with DMD not on steroids and with a declining respiratory function. Finally, the team is also supporting the research team of Professor Thomas Voit who has a study of assistive devices in DMD and is planning an AAV gene therapy trial for boys with DMD.

D. Details of studies turned away

Having the staff in place has allowed us to expedite many preparatory processes of assessing new studies for adoption where as in the preceding two years the team had turned down 10 novel experimental approaches. Since these posts have been funded the number of trials turned down has reduced dramatically to only two in the past three years. The reason for turning these down was due to capacity as we have lost a few clinical fellows and not been able to replace them as swiftly as we had hoped.

E. Sustainability

The GOSH Research and Innovation Team working with the GOSH Executive and Finance Team has developed a transparent funding model where the direct costs from commercial research income are returned to the research / clinical areas undertaking the research. We are currently working with the UCL finance team and the GOSH team to have this allocated funding moved to a grant at UCL. The aim is that this will ensure that research posts will become sustainable over time. This works well for research nurses, therapists and data managers and provides a contribution to clinical fellow / consultant time. To ensure the two Clinical Research Fellows become sustainable their time has also been included in non-commercial research grant applications. The time of study/trial coordinators is harder to fund, but, working with the NIHR Clinical Research Facility Team the time of study / trial coordinators is being add to commercial contracts going forward. This has allowed the employment of a new trial coordinator, who started in June 2018, and enabled the recruitment of a trial assistant to support the smooth running of the coordination of the studies from an administrative perspective. Being crucial for each of the current trials, the role of the physiotherapist is consistently attracting funders and sponsors who express willingness to add sustainability contribution to the costs for physiotherapists not only to remain but also to increase their time on the projects.

Due to the successful neuromuscular networks, both in SMA and DMD, we have attracted the attention of commercial companies that are interested in natural history data and data on patients treated with innovative therapies with substantial investment in these network for supporting the work of trial coordination, physiotherapists and clinical research fellows. With one company we are now able to advertise for a trial coordinator and physiotherapist. With the clinical fellow, we are in the process of applying for funding from the company. We are hoping that soon we will also be able to apply this model to Sarepta and Avexis as well helping us to cover these posts in the future.

Consequently, because of the revised funding model described above and in view of the increased capacity and adoption of more studies, the commercial income for the neuromuscular team has increased steadily over the years with some funding still to come for 2017/18.

Post	**Plans for sustainability and progress so far** (you may wish to include information on commercial income, non-commercial grant funding here)
Physiotherapy Assistant	Investigating continued funding for this post
Physiotherapist	Application for a 0.5 Physiotherapist for 3 years sent to DMD Charity
Clinical Research Fellow	A clinical fellow post has successfully been advertised and recruited to with the candidate starting soon (1.0 WTE). The funding is through the commercial funding we have obtained over the last few years coming back to UCL. A second post is also available through this route and is currently going through advertisement (1.0 WTE).
Clinical Research Fellow	
Clinical Trial Coordinator	Application to the EU for a new grant (0.5 WTE) as well as through applications to a commercial company as we have many SMA trials on going so need to cover this (0.5 WTE).
Research Physiotherapist	Application to commercial company for support with the SMA studies and partial cover for DMD trials.
Clinical Trials Assistant	From June this year we have been fortunate to have a CTA working with us helping with administrative tasks related to clinical trials where he takes care of any GCP/CV/training related matters and manages site files and assists with patient expenses. The funding is from commercial income we have sitting at GOSH. This has helped the team focus more on other tasks that require more attention

F. Additional benefits of this funding

In the last year, we have managed to continue recruiting patients to studies as we have had staff in posts. This has meant that the team has felt more positive as increased capacity has reduced the pressure felt by existing team members. We have had regular meetings with the whole team so that progress of trials can be discussed and have introduced a letter for patients to ensure families have regular updates with studies which has come from the clinical fellow and trial coordinator.

Appendix

Legend to study codes:

09DN05: The DMD Heart Protection Study

09DN11: CMT: A Natural History Study

12DN09: FOR-DMD

12DN20: PTC019: AN OPEN-LABEL STUDY FOR PREVIOUSLY TREATED ATALUREN (PTC124®) PATIENTS WITH NONSENSE MUTATION DYSTROPHINOPATHY

12DN33: PRO045: A phase IIb, open-label study to assess the efficacy, safety, pharmacodynamics and pharmacokinetics of multiple doses of PRO045 in subjects with Duchenne muscular dystrophy

13DN10: Phase III PTC20 : MCRN2409 (PTC124-GD-020-DMD): A phase 3 efficacy and safety study of ataluren (ptc124) in patients with nonsense mutation dystrophinopathy

13DN11:PRO 053: A Phase I/II, open-label, dose escalating with 48-week treatment study to assess the safety and tolerability, pharmacokinetics, pharmacodynamics and efficacy of PRO053 in subjects with Duchenne muscular dystrophy

14DN06: ENDEAR: A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Infantile-onset Spinal Muscular Atrophy

14NM09: PTC20e: A PHASE 3 EXTENSION STUDY OF ATALUREN (PTC124) IN PATIENTS WITH NONSENSE MUTATION DYSTROPHINOPATHY

14NM19: Summit c1103: A Phase 1b placebo-controlled, multi-centre, randomized, double-blind 3-period dose escalation study to evaluate the pharmacokinetics (PK) and safety of SMT C1100 in paediatric patients with Duchenne Muscular Dystrophy (DMD) who follow a balanced diet.

15NM06: RECENSUS – A MEDICAL CHART REVIEW OF APTIENTS WITH X-LINKED MTM (Myotubular Myopathy)

15NM07: Pfizer B5161002 : A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, EFFICACY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-06252616 IN AMBULATORY BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

15NM15: Nurture: An Open-Label Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Subjects With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy

15NM22: OLEOS: MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE LONG-TERM SAFETY,TOLERABILITY, AND EFFECTIVENESS OF10 MG/KG OLESOXIME IN PATIENTS WITH SMA

15NM23: Summit 004: A Phase I, 2-Part, Open-label, Multiple Oral Dose Study of the Safety, Tolerability and Pharmacokinetics of up to 2 Formulations of SMT C1100 in Healthy Adult Male Subjects and a Selected Formulation of SMT C1100 in Paediatric Subjects with Duchenne Muscular Dystrophy (DMD)

15NM24: INCEPTUS - A Prospective, Non-Interventional Clinical Assessment Study in X-Linked Myotubular Myopathy (XLMTM) Subjects Aged 3 Years and Younger

15NM30: SHINE: An Open-label Extension Study for Patients with Spinal Muscular Atrophy who Previously Participated in Investigational Studies of ISIS 396443

15NM33: Summit 005: A Phase 2 Clinical Study to Assess the Activity and Safety of Utrophin Modulation with SMT C1100 in Ambulatory Paediatric Male Subjects with Duchenne Muscular Dystrophy (C11005)

16NM17: SIDEROS - A Phase III Double-blind, Randomized, Placebo-Controlled Study assessing the Efficacy, Safety and Tolerability of Idebenone in Patients with Duchenne Muscular Dystrophy Receiving Glucocorticoid Steroids

16NM22: ESSENCE - A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy

16NM23: ITALPHARAMACO - Randomised, double blind, placebo controlled, multicentre study to evaluate the efficacy and safety of givinostat in ambulant patients with Duchenne Muscular Dystrophy

17BB22: STRIDE – TRANSLARNA UNUSUAL CARE

17NM01: PFIZER EXT - A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG TERM SAFETY OF PF-06252616 IN BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

17NM07: An Open-Label Safety, Tolerability, and Pharmacokinetics Study of Eteplirsen in Young Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping

17NM18: SPITFIRE - A RANDOMIZED, DOUBLE BLIND, PLACEBOCONTROLLED, STUDY TO ASSESS THE EFFICACY, SAFETY, AND TOLERABILITY OF RO7239361 (BMS-986089) IN AMBULATORY BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

17NM40: BIOGEN SMA GLOBAL REGISTRY

18NM01: Phase 1 Study of WVE-210201 Administered Intravenously to Patients with Duchenne Muscular Dystrophy

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