Institution: University College London		
Unit of Assessment: 1 - Clinical Medicine		
Title of case study: Development and validation of the first treatments for Duchenne Muscular Dystrophy and Spinal Muscular Atrophy		
Period when the underpinning research was undertaken: 2014-2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): **Francesco Muntoni**	**Role(s) (e.g. job title):** **Chair of Paediatric Neurology**	**Period(s) employed by submitting HEI:** **1993- present**
Period when the claimed impact occurred: 2014-2019		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Research from UCL is transforming the lives of children with two of the most common life-limiting neuromuscular diseases that affect over 2 million children worldwide. It has led to approval of the very first effective treatments for Duchene Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA). Two medicines for DMD - Exondys 51 and Vyondys 53 – which improve quality of life and life expectancy for at least 20% of DMD patients have been approved by the FDA and have already benefitted more than 1500 patients. Spinraza, approved in SMA, has prolonged life in more than 2600 children in the US alone. The UCL team has facilitated Spinraza implementation in the UK and since its NHS adoption in June 2019, 300 patients have already gained access. These medicines have together generated sales of more than USD5.5billion.

2. Underpinning research

Duchene Muscular Dystrophy (DMD) affects 1 in 3,500 young males and Spinal Muscular Atrophy affects 1 in 6,000-10,000 babies and young children. In DMD, genetic mutations in the dystrophin gene cause progressive muscle weakness leading to cardiorespiratory failure in early adulthood. SMA is a motor neuron disease arising from mutations in the survival motor neuron gene (SMN). There are several types of SMA and babies with the most severe form (Type 1) survive for less than a year.

DMD: 65% of boys with DMD have mutations in the DMD gene that prevent production of a crucial muscle protein. Researchers at UCL coordinated a national consortium on muscular dystrophy experimental therapy (UK MDEX) to assess the feasibility of modifying DMD expression in these cases where the gene deletions are 'out-of-frame' and the protein-coding part of the gene is unaffected. They explored use of antisense oligo-nucleotides (ASOs) to correct the gene reading frame and allow the production of a functional protein (**R1**). This original work focused on identifying a medicinal ASO product (eteplirsen) that can rectify gene function in 13% of boys with DMD. Muntoni led successful Phase 1 and Phase 2 studies (**R2**) which both clearly demonstrated target engagement and production of the otherwise absent DMD protein. Subsequent longer, industry-led studies in the US demonstrated clinical efficacy and this, together with proof of DMD protein production, provided by Muntoni's research, led to the FDA conditional approval of the first medicine for DMD, eteplirsen (Exondys 51).

In 2013, UK MDEX, led by Muntoni, developed an ASO to target a different part of the DMD gene (**R3**). This was patented by Sarepta. The drug, golodirsen (Viondys 53) is applicable to 8% of the DMD population. The primary biochemical endpoint of robust restoration of dystrophin (considered a surrogate endpoint by FDA) has been successfully met in the SKIP-NMD international trial (**R4**).

SMA: Research led by Muntoni at UCL identified the role that a deficiency of the protein responsible for SMA has in the brain, and in the peripheral nervous system (**R5**)**.** He went on to demonstrate that ASOs can be used to manipulate gene expression in SMA and augment the production of the deficient SMN protein, identifying an effective ASO that dramatically improves the outcome in mice affected by SMA (**R6**). This work informed development of another AON by Ionis/Biogen that was taken forward as a therapy for SMA. UCL was the UK coordinating centre, with Muntoni as clinical investigator, in an Ionis/Biogen sponsored clinical trial for SMA1 patients to test the therapeutic ASO for SMA. Early beneficial effects of nusinersen were observed, with over 50% of infants on nusinersen meeting at least one motor milestone for their age group, which prompted early termination of the trial. All participants were invited to continue treatment in an extension trial.

Outcome measures: For successful clinical trials, robust and responsive outcome measures are required. The UCL team developed two functional outcome measures, the North Star Ambulatory Assessment (NSAA) scale for DMD; and the Revised Hammersmith Scale (RHMS) for SMA (**R7**). Since 2010 these scales have become primary or secondary outcome measures in more than 10 DMD and SMA global clinical trials, in addition to the investigator initiated clinical studies at UCL (**R2, R4**)**.**

3. References to the research

R1. Kinali M, Arechavala-Gomeza V, Feng L, Cirak S, Hunt D, Adkin C, Guglieri M, Ashton E, Abbs S, Nihoyannopoulos P, Garralda ME, Rutherford E, McCulley C, Poppwell L, Graham I, Dickson G, Wood M, Wells DJ, Wilton S, Holt T, Kole R, Straub V, Bushby K, Sewry CA, Morgan JE, **Muntoni F** (2009). Local Restoration of Dystrophin Expression in Duchenne Muscular Dystrophy: A Single Blind, Placebo-controlled Dose Escalation Study Using Morpholino Antisense Oligomer AVI-4658. *Lancet Neurol*; 8:918-28. 10.1016/S1474-4422(09)70211-X

R2. Cirak S, Arechavala-Gomeza V, Guglieri M, Feng L, Torelli S, Anthony K, Abbs S, Garralda E, Bourke J, Wells DJ, Dickson G, Wood MJA Wilton SD, Straub V, Kole R, Shrewsbury S, Sewry C, Morgan J, Bushby K, **Muntoni F** (2011). Exon skipping and dystrophin restoration in Duchenne Muscular Dystrophy patients after systemic phosphorodiamidate morpholino oligomer treatment. *Lancet*; 378:595-605. DOI: 10.1016/S0140-6736(11)60756-3

R3 Popplewell LJ, Adkin C, Arechavala-Gomeza V, Aartsma-Rus A , de Winter CL, Wilton SD, Morgan JE, **Muntoni F**, Graham IR, Dickson G (2010). Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human DMD gene: Implications for future clinical trials. *Neuromuscul Disord* Feb;20(2):102-10.doi: 10.1016/j.nmd.2009.10.013.

R4. Frank D, Schnell F, Akana C, El-Husayni S, BS[1]; Desjardins C, Morgan J, Charleston J, Sardone, V, Domingos J, Dickson G, Straub V, Guglieri M; Mercuri E, Servais L, **Muntoni F**, on behalf of the SKIP-NMD Study Group*. (2020) Increased Dystrophin Production With Golodirsen in Patients with Duchenne Muscular Dystrophy. *Neurology*. May 26;94(21):e2270-e2282 DOI: 10.1212/WNL.0000000000009233

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R6 Zhou H, Meng J, Marrosu E, Janghra N, Morgan J, **Muntoni F** (2015). Repeated low doses of morpholino antisense oligomer: an intermediate mouse model of spinal muscular atrophy to explore the window of therapeutic response. *Hum Mol Genet.* Nov 15;24(22):6265-77 DOI: 10.1093/hmg/ddv329

R7 Ramsey D, Scoto M, Mayhew A, Main M, Mazzone ES, Montes J, de Sanctis R, Dunaway Young S, Salazar R, Glanzman AM, Pasternak A, Quigley J, Mirek E, Duong T, Gee R, Civitello M, Tennekoon G, Pane M, Pera MC, Bushby K, Day J, Darras BT, De Vivo D, Finkel R, Mercuri

E, **Muntoni F** (2017) Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. PLOS ONE https://doi.org/10.1371/journal.pone.0172346

4. Details of the impact

Research at UCL has identified antisense oligonucleotides (ASOs) that restore function of genes associated with the most common neurodegenerative diseases affecting children (DMD and SMA). This work has been instrumental in developing effective novel interventions that are the first to be licenced to treat these life-limiting conditions which affect over 2 million children worldwide. The medicines are transforming the lives of thousands of affected children, allowing them to live active lives for longer; maintaining the ability to walk and avoiding respiratory failure. The medicines have also had significant economic benefits for the companies manufacturing them.

New antisense oligonucleotide therapies for Duchenne Muscular Dystrophy (DMD)
As a direct result of Muntoni's research to identify effective ASOs that allow production of dystrophin protein in affected children, Sarepta Therapeutics Inc has brought the first genetic treatments to market, which in total can treat one in five boys with DMD. **Exondys 51® (eteplirsen)** was granted approval by the FDA in December 2016. As part of the approval process, Muntoni presented a dossier to the FDA panel that included the data from the original UCL-led phase 1 and 2 trials in the UK. The Sarepta FDA document states, "Based on promising results observed in the Phase 1 proof of concept study (Study 33) and a 12 week dose-ranging study (Study 28) conducted in the United Kingdom from 2007 to 2010, Sarepta conducted a 28-week double-blind, placebo-controlled Phase 2 study (Study 201) in July 2011" (**S1**). Exondys 51® is applicable to 13% of the male DMD population and is now regularly given to some 1500 DMD patients in the US, significantly delaying the onset of disability. Trials showed that the group treated with eteplirsen showed no increase in the proportion of patients losing the ability to walk (as measured by a 6 minute walking test) over 4 years (17%) while the percentage of those who lost the ability to walk in the untreated group increased exponentially over the same period (**S2**). This benefit, and the subsequent reduction of respiratory decline (**S3**) is now felt by over 1500 DMD patients who are regularly receiving EXONDYS 51®, as well as their families and carers.

In December 2019, **Vyondys 53™ (golodirsen)** became Sarepta's second RNA therapy when it was approved by the FDA and made commercially available immediately. This drug can be used in a further 8% of the male DMD population (a further 18,000 patients worldwide). Long term follow-up of children in the original SKIP NMD EU trial showed that golodirsen also reduced the risk of loss of ambulation, and improved respiratory outcomes, in treated patients. In particular, patients treated for 3 years showed a less severe annual decline in walking abilities and of respiratory function compared to untreated patients (**S4**).

New Antisense oligonucleotide therapy for Spinal Muscular Atrophy
Research from UCL to identify an effective ASO for SMA contributed to the development of **Spinraza® (nusinersen)** by Biogen, which was granted approval in December 2016 by the FDA and May 2017 by the EMA. By the end of 2018, it had been used to treat more than 2600 people in the US alone, with >95% of those remaining on treatment and >80% reaching the maintenance dosing phase. The efficacy of Nusinersen was demonstrated in SMA1 children and in less severe variants and led to rapid EMA and FDA approval. The impact of Spinraza on the lives of affected families has been dramatic. A couple, whose daughter was diagnosed with SMA Type 3 at three years old and treated with nusinersen said, "She loves painting, and each one of those minor movements has been monumental… we still have challenges to face, but we now have this tool to fight back with" (**S5**). A recent Phase 2 trial involving 25 children with SMA1 or SMA2 treated with nusinersen found that over 80% of the children were able to sit, stand and walk independently at three year follow up (**S6**). Biogen then initiated an extended access program (EAP) for all infants affected by SMA1.

Ensuring access to nusinersen treatment for SMA in the UK

Nusinersen (Spinraza) received NICE approval in June 2019 (**S7**) and the NHS adopted it for use in infants with SMA. Since then, the UCL team has played a key role in developing a co-ordinated approach and the up-skilling necessary to deliver this treatment throughout the UK and 300 patients are already receiving treatment.

In the UK, the SMA Research and Clinical Hub UK consortium (SMA REACH UK), led by Muntoni, is collecting data on all the SMA1 children recruited nationally on the EAP. These children can expect to enjoy significantly longer life. Clinical studies show that only around 15% of untreated SMA sufferers were still alive after 24 months of a study, while 50% of patients treated after onset of symptoms could still be alive after 36 months if treatment began early enough. All patients who received nusinersen before symptoms appeared were still alive after 36 months (**S8**).

Muntoni is a member of the International Standard of Care group for SMA. He and others in the SMA REACH UK consortium are training medical and treatment staff to ensure optimal care is delivered, including respiratory care, such as physiotherapy and supportive ventilation (**S9**). More than 200 health care professionals attended training workshops in 2019. The clinical and research network is collecting high quality longitudinal data on SMA that is providing a robust national database to ensure a standardised approach to the assessment of SMA is implemented to help improve the standards of care for people with SMA in the UK (**S10**).

SMA REACH UK links all paediatric centres involved in delivery of clinical care for SMA and is funded by advocacy groups and Biogen. NICE has designated SMA REACH UK as the group to manage the access program for nusinersen in England and monitor patient progress, with Muntoni representing the group on the NICE clinical panel which oversees the access programme (**S11**).

Economic impact of novel treatments for DMD and SMA

Exondys 51®, marketed by Sarepta, has registered a rapid rise in demand, with revenues rising from USD155,600,000 in 2017 to USD301,000,000 in 2018 and USD381,000,000 in 2019. Based on the success of Exondys and Vyondys 53, Sarepta continues to invest in further therapies for the treatment of DMD. In the case of Spinraza,(sold by Biogen), sales have shown rapid growth from USD884,000,000 in 2017 to USD1,700,000,000 in 2018 and USD2,097,000,000 in 2019. Revenues for the first half of 2020 were USD1,060,000,000 (**S12**).

5. Sources to corroborate the impact

S1 FDA Advisory Committee Briefing Materials: Peripheral and central nervous system drugs advisory committee 25 April 2016 ETEPLIRSEN Briefing Document 206488 Sarepta Inc. https://www.fda.gov/media/121644/download

S2 Mendell JR, Rodino-Klapac LR, Sahenk Z, Roush K, Bird L, Lowes LP, Alfano L, Gomez AM, LewisS, Kota J, Malik V, Shontz K, Walker CM, Flanigan KM, Corridore M, Kean JR, Allen HD, Shilling C, Melia KR, Sazani P, Saoud JB, Kaye EM; Eteplirsen Study Group. (2013) Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. Nov;74(5):637-47.

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S4 Muntoni F. (2020). Long-term Safety and Efficacy of Golodirsen in Male Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping. Muscle Study Group Annual Meeting, 23, 25th September 2020 (p.73).

S5 https://www.spinraza.com/

S6 De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, Kirschner J, Kuntz NL, Parsons JA, Ryan MM, Butterfield RJ, Topaloglu H, Ben-Omran T, Sansone VA, Jong YJ, Shu F, Staropoli JF, Kerr D, Sandrock AW, Stebbins C, Petrillo M, Braley G, Johnson K, Foster R, Gheuens S, Bhan I, Reyna SP, Fradette S, Farwell W; NURTURE Study Group. (2019). Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul Disord*. Nov;29(11):842-856.

S7 NICE Technology Appraisal Guidance: Nusinersen for treating spinal muscular atrophy (2019): https://www.nice.org.uk/guidance/ta588

S8 Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Qian Y, Sejersen T; SMA Care Group.Neuromuscul Disord. (2018) Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Feb;28(2):103-115.

S9 Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Qian Y, Sejersen T; SMA Care group.Neuromuscul Disord. (2018) Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Mar;28(3):197-207.

S10 Mercuri E, Finkel R, Scoto M, Hall S, Eaton S, Rashid A, Balashkina J, Coratti G, Pera MC, Samsuddin S, Civitello M, Muntoni F; iSMAC Group. (2019) Development of an academic disease registry for spinal muscular atrophy. *Neuromuscul Disord*. Oct;29(10):794-799.

S11 NICE Final appraisal document for Nusinersen for treating spinal muscular atrophy https://www.nice.org.uk/guidance/ta588/documents/final-appraisal-determination-document

S12. Sarepta and Biogen press releases detailing annual sales (2018, 2019 and Q1/Q2 2020 [for Biogen])