Institution: University of Plymouth		
Unit of Assessment: UoA3		
Title of case study: Improved measurement in clinical trials resulting in increased commercial revenue and patient benefits		
Period when the underpinning research was undertaken: 2007-2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Professor Jeremy Hobart	**Role(s) (e.g. job title):** Professor of Clinical Neurology and Health Measurement and Consultant Neurologist	**Period(s) employed by submitting HEI:** 10.01.2005 - present
Period when the claimed impact occurred: Aug 2013 – Dec 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Patient care is most greatly influenced by clinical research, whose accuracy is determined by the quality of measurement and analyses. Hobart's expertise in Patient Reported Outcome (PRO) measurement and analysis directly influenced FDA policy and, through use in commercial and academic clinical trials, created patient and commercial benefits. Global pharmaceutical companies use Hobart's PROs in clinical trials of, and/or labelling claims for, new treatments. These treatments have benefited over one million patients worldwide and generated £80 Billion commercial income. Hobart's collaboration with the global initiative, Brain Health Matters in Multiple Sclerosis, has improved clinical services and patient knowledge and resulted in patients playing a proactive part in managing their own disease.

2. Underpinning research (indicative maximum 500 words)

3.

This case study is underpinned by research into Patient Reported Outcomes (PROs), especially for Multiple Sclerosis (MS), and the development of international consensus guidelines for MS care.

Research into the development and analysis of PROs

PROs measure how people feel and function, determining disease impact and treatment efficacy in clinical trials and practice. Consequently, they are central dependent variables guiding people's treatments and public expenditure.

Following publications reporting on empirical examinations of widely used PROs, Hobart explained why many instruments used in clinical trials were not fit for purpose [3.1]. In response to calls from healthcare researchers for accessible accounts of new psychometric methods, the National Institute for Health Research Health Technology Assessment funded Hobart to study the advantages of applying advanced level measurement science to PROs. This advanced Hobart's skills for developing "well-defined and reliable" PROs and led to revisions of his MS PROs [3.2]. The work highlighted the importance of ensuring clinical trial PROs are developed, and evaluated, using appropriate methods. Hobart developed particular expertise in Rasch Measurement Theory (RMT), a hypothesis-testing analytical statistical tool, to guide PRO development and evaluation by identifying limitations and highlighting areas for refinement [3.3]. An exemplar of measurement advances associated with Hobart's work was the ENHANCE global clinical trial which used a Hobart PRO as a primary outcome measure [3.4]. This was the

first study to use an *a priori* determined meaningful change estimate of a PRO as its primary endpoint. Hobart also evaluated existing PROs' strengths and weaknesses, and their ability to meet FDA requirements. This analysis has utilised a combination of qualitative and quantitative methods, including RMT, to assess whether the developmental approach meets best practice and the reliability of data generated. The underpinning research and capability demonstrated within these projects has created opportunities for further impact in PRO analyses within clinical trials.

Hobart has worked commercially with LORA group LLC in the U.S to develop new PROs for dermatology (primary axillary hyperhidrosis, Brickell Biotech) [3.5], haematology (sickle cell disease, Global Blood Therapeutics) and urology (prostatic hypertrophy, Vantia). These projects, which demonstrate the near ubiquitous applicability and value of these methods, have further advanced methods for developing PROs as fit-for-purpose measures of well-defined constructs in specific clinical contexts.

Advancing Care in MS through Research

Hobart is a founder member of the Brain Health Initiative (BHI), which aims to maximise the brain health of people with MS. The initiative has been endorsed by over 50 international groups and its outputs are frequently used by clinicians, industry, charities and patients to influence clinical practice and services. In 2018, the BHI published an internationally applicable policy statement report on MS care. Subsequently, Hobart led the development of the first international consensus guidelines for MS care articulating the core message, "time matters in MS", in a clinically applicable format. The work involved a panel of international specialist MS neurologists participating in an iterative, online, modified Delphi process to define 'core', 'achievable' and 'aspirational' time frames reflecting minimum, good and high care standards, respectively. In a second step, a multidisciplinary Reviewing Group (MS nurses, people with MS, allied healthcare professionals) provided insights, ensuring that recommendations reflected perspectives from multiple stakeholders. The third step was the development of a clinical audit tool. This has been deployed in MS centres in 14 countries with Hobart as the clinical lead for audit [3.6].

3. References to the research (indicative maximum of six references)

3.1 **Jeremy C Hobart**, Stefan J Cano, John P Zajicek, Alan J Thompson. *Rating scales as outcome measures for clinical trials in neurology: problems, solutions, and recommendations* Lancet Neurol 2007; 6: 1094–105

3.2 **Hobart J**, Cano S, Baron R, Thompson A, Schwid S, Zajicek J, Andrich D. *Achieving valid patient-reported outcomes measurement: A lesson from fatigue in multiple sclerosis.* Multiple Sclerosis Journal 2013 19(13) 1773–1783. 2009

3.3 **Hobart J,** Cano S. *Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods*. Health Technology Assessment, 13(12):1-200. 2009

3.4 **Hobart J**, Ziemssen T, Feys P, Linnebank M, Goodman AD, Farrell R, Hupperts R, Englishby V, McNeill M, Chang I, Lima G, Elkins J, on behalf of the ENHANCE study investigators. *Prolonged-release fampridine treatment results in clinically meaningful improvements in patient-reported walking ability in people with multiple sclerosis: results from the Phase 3 ENHANCE trial.* 2018
CNS Drugs (published online 10 Dec 2018; https://doi.org/10.1007/s40263-018-0586-5)

*3.5 Kirsch BM, Burke L, **Hobart J**, Angulo D, Walker PS. The Hyperhidrosis Disease Severity Measure-Axillary: Conceptualization and Development of Item Content. Journal of Drugs in Dermatology 2018; 17(7): 611-618.*

3.6 **Hobart J**, Bowen A, Pepper G, Crofts H, Eberhard L, Berger T, Boyko A, Boz C, Butzhueven H, Gulowsen Celius E, Drulovic J, Flores J, Horakova D, Lebrun-Freney R, Overell J, Piehl F, Rasmussen P, Jose Sa M, Sirbu C-A, Skromne E, Torkildsen O, van Pesch V, Vollmer T, Zakaria M, Ziemssen T, Giovannoni G. *International consensus on quality standards for brain health-focused care in multiple sclerosis.* Multiple Sclerosis Journal (published online 30 Oct 2018, DOI: 10.1177/1352458518809326).

4. Details of the impact (indicative maximum 750 words)
Success in basic science rarely leads to effective treatments, as those that are shown to work in controlled laboratory conditions can be worthless when studied in human beings. Hobart demonstrated that many of the PROs used to test the efficacy of treatments in controlled conditions were not fit for purpose and consequently hindered advances in basic science. His research has increased the chances of reaching the correct conclusions about the effectiveness of treatments, which influence decisions on patient care and guide future research.

PROs supporting treatment developments, licensing approvals and clinical adoption
Hobart's research influenced FDA (U.S Food and Drug Administration) policy (last REF period). which created an increased focus from regulatory bodies on the quality of clinical outcome measures within licensing decisions. Hobart's PROs are referenced in the FDA compendium of clinical outcome assessments, which endorsed their global position as Gold Standard measures. Consequently, they have been deployed in clinical research of MS treatments in over 85 countries [5.1].

Between 1 August 2013 and 30 November 2020, five Hobart PROs have been licensed a total of 136 times including with global pharmaceuticals such as Roche, Merck, Sanofi, Novartis and Biogen [5.1]. The importance of the PROs informing clinical research and licensing decisions is reflected by the price companies are willing to pay, with charges up to £32,000 per clinical trial license and total fees in this period of over £1.26M [5.1]. Many of the trials have been of Disease Modifying Therapies which are now core treatments; particularly in MS, an incurable chronic disease currently affecting 2.3 million people worldwide. Since 1 August 2013, Hobart's PROs have been directly involved in the clinical trials of 36 treatments, mostly in MS but also in other areas [5.1]. The global sales value of 11 of the most widely adopted MS treatments (using just the figures available between 2013 and 2020) equates to £80 Billion [5.2]. Moreover, we have evidence that they have reached over one million patients [5.2]. Novartis MS Global Brand Medical Directors Thomas Hach and Dee Stoneman stated that *'The scales were used because of their scientific value and recognition in the clinical and regulatory community. The evidence generated from these studies help to inform clinical opinion and ultimately allow eligible patients to benefit from these treatments… [this demonstrates] the significant impact and value of the work Professor Hobart and his team at the University of Plymouth have in the area of MS research through the development and licensing of high quality Patient Reported Outcome Measures'* [5.3]

For example, the MS medicines Lemtrada (alemtuzumab) and Aubagio (teriflunomide) demonstrate the financial value of Hobart PROs in supporting licensing and clinical adoption. Hobart PROs played a key role in developing the evidence of the clinical benefits of these medications. Lemtrada secured market authorisation in Europe on 12/09/2013 and Aubagio on 26/08/2013. Data supplied by Sanofi highlights both the patient and commercial impact of these medicines:

- Lemtrada [text removed for publication].
- Aubagio [text removed for publication].

'The data [above] is from the Sanofi annual investor report which outlines both the patient and commercial impact of these medicines… [this] demonstrates the… value of the work [of] Professor Hobart.' Dr Eddie Guzdar, Head of Medical Affairs for the Neurology Franchise at Sanofi Genzyme UK and Ireland [5.4]

Similarly, Biogen have used Hobart's PROs in the clinical trials of fampridine prolonged release (Fampyra) to evaluate the effect on improvement of walking in adult patients with multiple sclerosis with walking disability. Up to April 2020, this medicine has been used in over 50 countries and has treated 386,528 people treated worldwide [5.5]. In addition, Hobart's PROs were used in clinical phase 4 trials of Ocrelizumab to treat relapsing and progressive multiple sclerosis. Paul Byrne, Life-cycle leader Ocrevus and James Overell, Principal Global Medical Director, Neuroscience at Roche said that *'The data… is linked to increased clinical recognition*

of the benefit of Ocrelizumab, especially in early MS disease and in targeting progression which is the cause of long-term disability… The rigorous scientific development of the Hobart PROs gives us and the community confidence that we are measuring what is clinically important.' [5.6]

Advising global companies on measurement strategies and data analysis for clinical trials

Hobart's specialist knowledge and skills in health measurement have been used to support global companies with measurement strategies and data analysis. These have informed the companies' decision making as they develop, trial and seek to license new treatments. For example, Since 2019, Hobarts guidance to Roche shaped measurement strategies in four clinical studies in MS. [text removed for publication]. *'Professor Hobarts expertise has been important to us as a company in informing our measurement strategies in relation to Patient Reported Outcome Measures… These clinical studies are key components in assessing the safety and efficacy of our companies [sic] treatments in MS… It is anticipated this will improve the quality of clinical research and support the development, evidence and adoption of high-quality treatments that will ultimately improve outcomes for people with MS.'* Licinio Craveiro, Senior Global Medical Director, Roche.[5.7]

In addition to licensing the PROs within clinical trials, Professor Hobart collaborates with Novartis in the analysis of PRO data and strategic projects focussed on the improvement/development of PROs. He has been contracted in projects seeking to further analyse the PRO data from clinical studies, which have a combined total of over 3500 participants, to maximise the value of interpretations. He was engaged by Novartis to be co-chair of their global Patient Relevant Outcomes Steering Committee in Multiple Sclerosis (PROMPT-MS). This strategic forum seeks to empower people living with MS to communicate relevant outcomes to healthcare practitioners in order to enable shared decision-making and ultimately improve clinical outcomes of MS. These contracts, worth £141,000, demonstrate Hobart's position as a global leader [5.3].

Advancing Care in Multiple Sclerosis (MS)

Time to a diagnosis of MS is often protracted, delaying access to specialist healthcare advice and treatment initiation which results in physical and cognitive decline, fatigue and reduced quality of life. Hobart worked alongside MS specialist neurologists to develop internationally applicable quality standards for timely, brain health focused MS care [5.9]. These became a key component of the Brain Health Matters in MS initiative, which has been endorsed by over 50 influential groups in MS care with champions in 55 countries.

The Brain Health Time Matters project team evaluated the success of this initiative through a survey which received 100 responses from 20 countries across four continents. Due to the MS Brain Health initiative recommendations and consensus standards, 84% of respondents said that they had made changes in their practice, services and/or management of MS. The recommendations and consensus standards had:

- In the case of health care organisation, changed their practices or services.
- In the case of people with MS or their carers, influenced how they managed their MS or the MS of the person they cared for, or
- In the case of respondents from commercial or patient support organisations, influenced how they, or their company, supported the MS community.

Of respondents from Health Care Organisations, 75% identified improvements in information given to people living with MS, whilst 65% felt the initiative had improved their knowledge of preserving brain heath. People with MS who responded to the survey noted multiple benefits. 80% identified that they had improved their knowledge of preserving brain health in MS and over 50% felt that as a result of the initiative they had taken a more proactive part in managing their own disease [5.9]. Case studies highlighting Global Impact on the MS Brain Health time matters website in seven countries include a doubling of treatments used for people with MS in

Serbia and a parliamentary debate agreeing to increase funding for MS research in Australia [5.10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 [text removed for publication]
5.2 Report by Stratified Solutions Ltd highlighting commercial revenue and patient use of treatments that have used Hobart PROs
5.3 Testimonial from Novartis Global Brand Medical Director's Thomas Hach and Dee Stoneman, MS.
5.4 [text removed for publication]
5.5 Testimonial from Thijs Koster, Biogen MS Global Medical
5.6 Testimonial from Roche: Paul Byrne, Life-cycle leader Ocrevus and James Overell, Principal Global Medical Director, Neuroscience
5.7 [text removed for publication]
5.8 Statement from Laurie Burke, LORA Group LLC and ex-Director of the FDA (U.S Food and Drug Administration) Study Endpoints and Labelling Division
5.9 Steering Committee members Brain Health Matters https://www.msbrainhealth.org/about
5.10 Evaluation of the Brain Health Matters in MS initiative and case studies of Global impact of Brain Health Initiative compiled by Oxford Pharmagenesis. https://www.msbrainhealth.org/global-impact