Institution: Plymouth University

Unit of Assessment:
1 (Clinical Medicine)

Title of case study: Multiple Sclerosis: developing treatment and improving outcomes

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

This case study summarises a body of research on Multiple Sclerosis (MS) developed at Plymouth University under the leadership of Professor Zajicek and Professor Hobart. Hobart's work on clinical outcome measurements has directly influenced clinical research, trials and drug licensing, especially in MS and Alzheimer's disease. The MS scales developed by Hobart have been endorsed by the United States FDA and are in demand by commercial organisations in the development and trialling of treatments for MS and have led to the licensing of new drugs. Zajicek has led the topical field in evaluating the potential benefits and risks of cannabis for treating MS, contributing to the evidence base behind the medical use of cannabinoids in general, and pioneering its global potential use to slow neurodegeneration.

2. Underpinning research (indicative maximum 500 words)

This case study presents a body of clinical research into potential new treatments, and clinical outcome measures, for MS with the aim of developing new treatments, not only for modifying the disease course but also in slowing progression. MS is the commonest cause of neurological disability and death among young adults, with over 100,000 people affected in the UK. Although there are an increasing number of treatments for the inflammatory phase of relapsing-remitting MS, there are no treatments that alter the course of progressive MS.

Clinical outcome measures are used to systematically track treatment and they are the central dependent variable on which decisions about people's treatments and the spending of public funds are made. Gait impairment is a key issue in MS and is reported as a main complaint by 85% of patients. Hobart initially undertook research on how to measure the impact of MS on walking ability while at University College London (3). By interviewing patients and clinicians, he developed a set of 12 statements on how MS affected walking ability. He continued to develop and modify this scale while at Plymouth University and produced Version Two, which is based on new and independent rating scale methods. This was developed as part of the wider programme of MS research at Plymouth.

Following a series of publications focussing on empirical examinations of the most widely used clinical outcome measures, in 2007 Hobart re-asserted in *Lancet Neurology* that many instruments used in state-of-the-art clinical trials were not fit for purpose. The implications of this issue was and remains significant; clinical trials are undermined, results are not confident reflections of treatment effects, and patients may be missing out on the opportunity to receive successful treatments.

In response to increasing calls from healthcare researchers and practitioners for an accessible account of the new psychometric methods, the National Institute for Health Research Health Technology Assessment (NIHR HTA) funded Hobart in 2009 to study the advantages of applying advanced level measurement science to clinical outcomes measurement (4). This has enabled this newer version of the scale to be made.

Although there has been considerable anecdotal evidence on the benefits of cannabinoids in symptomatic treatment of MS, there has been a paucity of clinical trial evidence. Professor Zajicek (1995-to present) was the Chief Investigator for an MRC-funded (£1.5m) Cannabinoids in MS (CAMS) study (1). This 15-week on treatment, 33 centre, 667 patient, randomised placebo-controlled trial provided evidence for symptomatic benefit of pain, spasticity and muscle spasms. Based on the findings from CAMS, Zajicek investigated the potential disease modifying benefits in the Cannabinoid Use in Progressive Inflammatory Brain Disease (CUPID) trial (2). Supported by funding from MRC, NIHR, MS Society and MS Trust (£3.5m) the CUPID trial randomised 493 patients with progressive MS to either oral tetrahydrocannabinol (THC) or a placebo treatment. Whilst the main results did not demonstrate overall efficacy, there was a suggestion of effect in

people with lower levels of disability. A further study, MUltiple Sclerosis and Extract of Cannabis (MUSEC) was set up to investigate oral cannabis extract and used an 11 point scale as a more patient orientated measure of efficacy. Cannabis extract was confirmed as a viable treatment option, and an effective form of pain relief, for those experiencing muscle problems associated with MS. These studies and scale represent the largest integrated trials of their kind globally.

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

1. Zajicek* J., Fox* P., Sanders* H., Wright* D., Vickery* J., Nunn A., Thompson A., UK MS Research Group. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet*. 2003 Nov 8;362(9395):1517-26. PMID: 14615106. ISI:000186464500007. 1. All authors contributed to study design and protocol development. Vickery was trial coordinator, Wright was involved in statistical analysis, Zajicek, Vickery, Sanders, and Wright wrote the paper, with revisions and contributions from Fox and others.

The *Lancet* has an impact factor of 38·28. The journal is currently ranked second out of 153 journals in the general medicine category.

2. John Zajicek*, Susan Ball*, David Wright*, Jane Vickery*, Andrew Nunn, David Miller, Mayam Gomez Cano*, David McManus, Sharukh Mallik, Jeremy Hobart*, on behalf of the CUPID investigator group. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. *Lancet Neurology* 2013 Jul 13 [Epub ahead of print] Zajicek contributed to the study concept and design and participated in study conduct, patient enrolment, and interpretation of data, Wright contributed to the study design, planned and supervised the statistical analysis, and participated in the interpretation of data, Ball and Cano did the statistical analysis and contributed to the interpretation of data, Hobart contributed to the study design, conduct, patient enrolment, data analysis and interpretation, Vickery coordinated the study.

Lancet Neurology has an impact factor of 23.92 and ranks highest among the world's leading clinical neurology journals.

3. John Zajicek*, Jeremy C Hobart*, Anita Slade*, David Barnes, Paul G Mattison, on behalf of the MUSEC Research Group. MUltiple Sclerosis and Extract of Cannabis: results of the MUSEC trial *J Neurol Neurosurg Psychiatry 2012;**83**:11 1125-1132*. Zajicek was the chief investigator, and led the design, conduct and interpretation of the study, Hobart and Slade conducted several analyses and reviewed the paper in preparation.

This international peer-reviewed journal for health professionals and researchers publishes the most ground-breaking and cutting-edge research in neurological sciences and has an impact factor of 4.7.

4. Hobart*, JC.; Riazi, A.; Lamping, DL.; et al (2003) Measuring the impact of MS on walking ability: the 12-item MS walking scale (MSWS-12), *Neurology*, Vol 60, pp 31-36, Lippincott, Williams and Wilkins, USA

The leading clinical neurology journal worldwide, Neurology is directed to physicians concerned with diseases and conditions of the nervous system. Impact factor 8.31

5. 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.).

Peer-reviewed journal published by NIHR. Impact factor 6.91.

6. 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. *MS Journal* Online publication ahead of print Apr 10, 2013.

International, peer-reviewed journal that leads within its specialism. Impact factor 4.472.

*Current and former Plymouth University staff. Other institutional affiliations at time of publication as follows:
University College Hospital: Mallik, McManus, Miller, Riazi, Thompson.
Oxfords University: Fitzpatrick
London School of Hygiene: Lampling
University of Western Australia: Andrich
Rochester university, NY: Schwid
MRC: Nunn,
NHS Trusts: Barnes, Mattison

4. Details of the impact (indicative maximum 750 words)

Hobart's work on scales has impacted internationally on MS trial based research. As a result of the MS walking scale (MSWS-12) research, developed by Hobart, a new diagnostic technology has been developed. This has subsequently been translated throughout the world and has undergone adaptation and validation. The scales have been translated into over 60 different languages including French, Dutch, Russian and Spanish and evaluated for cross country validation. The MSWS-12 questionnaire has been used around 9,200+ times and the longer MSIS-29 questionnaire has been used around 30,000+ times (www.clinictrials.gov).

Since 2007, Plymouth University's trading company, UoPEL has received £437,000 of license income for sales of measurement scales developed by Hobart and targeted specifically at patients with Multiple Sclerosis (MS) and Parkinson's disease. The University has received £135,000 of this in the current financial year (2012/13) and is projecting a total income this year of c£200k (a further £65,000). This income is based on a range of 6 Scales developed by Hobart, derived via licenses established with Plymouth University, University College London and the Plymouth Hospitals NHS Trust. Commercial organisations such as Biogen Idec, TEVA Pharma, Novartis, Ipsen and Merck continue to demand the use of the Scales in the development and trialling of treatments for MS.

The scales have been used widely in MS clinical trials. For example, the scale was used in two phase 3 clinical trials with the resulting data demonstrating that the treatment effect was clinically significant for people with MS leading to Fampridine being granted a conditional licence by the European Medicines Agency (EMA) for MS. Fampridine is licensed to improve walking ability for patients with MS. Hobart was asked to provide evidence (2009) from this research that the treatment effect was clinically significant at both the US and European regulatory deliberates (FDA, EMA 2009).

This body of research has also recently influenced the decisions of the United States Food and Drug Administration (FDA) in introducing new regulatory guidelines and stimulated debate about the appropriateness of a wide range of existing clinical outcome measures for a range of conditions. These guidelines (2013) advise pharmaceutical companies conducting trials on the outcome measures and approaches that FDA will give credence to in terms of deciding on the labelling of drugs.

As stated by Laurie Burke, Associate Director for Study Endpoints and Labeling, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, "Jeremy Hobart and Stefan Cano have had a substantial impact at FDA. They have helped to make a complex science that is fundamental to our work, accessible to us, and advance our understanding and abilities to a higher level. This has enabled us to appraise better the work we review such that our evaluations are as accurate as we can make them, and our advice to industry is maximized. … They have also helped us to develop and ground our thinking in terms of producing guidance to industry in the production of clinical outcomes assessment instruments (patient, clinician, and observer-reported outcome measurement instruments) for use in clinical trials. These documents

are very influential because they provide industry with roadmaps, guiding the efficient modification and scientific upgrading of existing instruments, and guiding development of the next generation of clinical outcomes assessment instruments to assess interventions for patients."

The cannabinoids studies led by Zajicek have had clear impact on health and welfare through the provision of clinical trial evidence. The results have contributed to an overall understanding of clinical cannabinoid use, and contributed to the weight of evidence for symptomatic and potential neuroprotective action. A drug company is in the process of applying for licensing of the cannabis extract used in CAMS and MUSEC studies, and looking for larger pharmaceutical partners. Two patents have been granted on the basis of this work.

The clinical trials have been the largest and longest studies of clinical cannabinoid exposure, and the original CAMS study now has over 450 citations (~1 per week). These studies have received considerable media coverage including the BBC, ITV News, New York Daily News, Nature, Guardian. This is beyond the normal coverage for clinical trials, and the results have been presented at major international MS meetings (most recently in 2012 at 28th Congress of European Committee for Treatment and Research in MS, ECTRIMS, in Lyon, France: http://ectrims2012.eventresult.com/), as well as national and local patient meetings. They have been summarised on the MS Society website and are used as providing evidence on the search for therapy in the disease's secondary progressive stage, when patients have few treatment options. The results have demonstrated clearly the difficulties of both conducting long-term clinical trials and neurodegenerative disorders, but also the problems of side-effects often leading to non-compliance. In addition these studies have provided more data on the long term risks with cannabinoids which has global importance for drug legislators.

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

Statement from United States Food and Drug Administration on the impact of Hobart's work.

Fampridine FDA advisory committee meeting where Hobart presents his case, using his scale data, that the effect of the drug on walking is clinically meaningful for people with MS. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm126190.htm

Commercial Information can be provided on a confidential basis from Plymouth University's Trading Arm stating overall income, demand and translations.

Report of Good Measurement Principles Task Force at the FDA
http://www.ispor.org/TaskForces/Good-Measurement-Practices-Clinician-Reported-Outcomes.asp

Review and Qualification Clinical Outcomes Assessment open workshop organised by FDA, 19 October 2011 with presentation from Hobart
http://www.fda.gov/Drugs/NewsEvents/ucm276110.htm

Summary of Cannabinoids research carried out by Zajicek on the Multiple Sclerosis Society website:
http://www.ms-uk.org/index.cfm/cannabisresearch Cannabis fails to slow progress in Multiple Sclerosis

Example of international media coverage and debate of the cannabinoids research:
http://www.nydailynews.com/life-style/health/cannabis-eases-multiple-sclerosis-ms-stiffness-study-article-1.1179450