Institution: University of Bristol		
Unit of Assessment: 4) Psychology, Psychiatry and Neuroscience		
Title of case study: Increased competition and innovation in Deep Brain Stimulation technology improves health and quality of life for Parkinson's disease patients		
Period when the underpinning research was undertaken: 2012 - 2015		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Alan Whone	Consultant Senior Lecturer in Movement Disorder Neurology	2012 to present
Steven Gill	Honorary Professor in Neurosurgery	2006 to present
Period when the claimed impact occurred: 2015 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

The VANTAGE trial, a 'first-in-man' premarket clinical study of a novel device to administer Deep Brain Stimulation (DBS) in Parkinson's disease, has transformed the international neuromodulation technology market. Multiple-source, constant current, rechargeable battery, devices developed by Boston Scientific and evaluated for the first time in the multicentre VANTAGE study, pioneered novel features that have opened the market to further advancement. This trial led directly to device approval in Europe, the US and Japan, [text removed for publication]. Over 160,000 patients worldwide have undergone DBS, most commonly for treatment in Parkinson's disease. Boston Scientific has gone from being unknown in this area to market leaders across Europe with the market size in the UK estimated at [text removed for publication]. DBS device innovations have improved health and quality of life in people with Parkinson's disease globally. Confirming the tolerability of rechargeable batteries has reduced the need for costly and potentially dangerous replacement procedures, with cost-savings of USD60,900 per patient.

2. Underpinning research

Applying defined electrical fields to targeted brain regions, Deep Brain Stimulation (DBS), transforms quality of life for people living with treatment resistant tremor or disabling motor fluctuations in Parkinson's disease (PD). Advances in DBS can be achieved through enhanced technology that heightens stimulation related efficacy whilst reducing side effects, improves ease of DBS administration and lengthens device durability. The University of Bristol (UoB) played a major role in developing and delivering on the early phase trial that was key to providing evidence for the clinical and cost benefits of a novel DBS system in PD.

By 2010, the neuromodulation field appeared to be stagnating with a single company dominating the global market, potentially limiting the drive for technological advance and producing a commercial monopoly. Boston Scientific (BSC), though well established as a medical device company, was fledgling in neuromodulation. Utilising engineering know-how from their cardiac and spinal-stimulation business they developed a new DBS system that was novel in several key features including: delivery of direct current rather than direct voltage; individual contact programming, permitting shaping of the stimulation field and therefore potentially improving symptomatic benefit whilst reducing stimulation related side effects, and a novel battery with a

25-year re-chargeable life. The pivotal Vercise™ Implantable Stimulator for Treating Parkinson's disease (VANTAGE) trial, funded by the company [i], was the first clinical study of this non-market authorised device and the first to formally evaluate use of a multiple-source, current-controlled, rechargeable, DBS system.

UoB was selected to be the only UK specialist university centre for the VANTAGE study. Dr Alan Whone, who was the UK PI closely involved in the development of the VANTAGE trial protocol, is a nationally recognised clinical leader in PD and single authored the published clinical criteria for determining eligibility for DBS for Parkinson's disease, which was adopted by both NHS England and NHS Wales in 2013 [3]. North Bristol NHS Trust (NBT) is one of the largest providers of DBS for Parkinson's disease in the UK, and Dr Alan Whone leads the neurology arm of the Movement Disorders programme at the Bristol Brain Centre, a facility combining clinical care with clinical research. Professor Steven Gill leads the neurosurgical arm of the DBS programme at NBT and has pioneered an optimised operative pathway for DBS lead placement. In addition to delivering the Bristol study-site to time and target in terms of patient numbers, Dr Whone was the UK PI for this trial and Professor Gill was involved in DBS lead development that followed observations by the neurosurgeons during the first 10 cases that related to lead coupling or deflection behaviour. Dr Whone was also one of the four investigators in the writing committee that produced the trial study manuscript independently of the funders.

The VANTAGE trial was a multicentre, prospective, open label, non-randomised study, to assess the implantable Vercise™ DBS system. The trial took place across six European centres, of which Bristol was the UK centre led by Dr Whone. This was the first DBS study to prospectively assess multiple-source, current-controlled, stimulation and to determine in such detail the patients' ability to handle/tolerate a rechargeable system. The trial showed that, compared with baseline, use of a multiple-source, constant-current, implantable DBS device improved motor function (primary endpoint), enhanced quality of life ($p<0.0001$), and extended daily "on" time in patients with Parkinson's disease (3.5 hours, SD 6.8 hours, $p<0.0001$) and that battery recharging was well tolerated as measured by study questionnaires [1]. In the 'intention-to-treat' analysis involving all enrolled patients regardless of whether or not the new system was actually employed, the primary outcome demonstrated a motor clinical rating scale improvement from baseline to 26 weeks of 23.8 points (SD 10.6), $p< 0.0001$, which equates to a very large clinically important difference [1].

This improvement in motor function remained stable up to week 52 and continued to show similar effect in a follow-on investigation that reported outcomes at 3 years post-implantation [2]. In secondary endpoints, the improvement in motor function recorded in the primary outcome was accompanied by improvements in activities of daily living ($p=0.0005$), which again equated to a magnitude representing a large clinically important difference. Furthermore, intake of antiparkinsonian drugs, measured by levodopa equivalent dose, fell substantially from baseline to week 52 (-863.4mg of L-dopa equivalents, $p<0.0001$) [1].

The pioneering DBS developmental programme that is a close collaboration between UoB and NBT led by Whone and Gill is ongoing, with the Bristol team being the first in the world to implant a miniaturised skull-mounted DBS pulse generator in November 2020.

3. References to the research

[1] Timmermann L, Jain R, Chen L, Maarouf M, Barbe MT, Allert N, Brücke T, Kaiser I, Beirer S, Sejio F, Suarez E, Lozano B, Haegelen C, Vérin M, Porta M, Servello D, **Gill S, Whone A**, Van Dyck N, Alesch F. (2015). Multiple-source current steering in subthalamic nucleus deep brain stimulation for Parkinson's disease (the VANTAGE study): a non-randomised, prospective, multicentre, open-label study. *The Lancet Neurology,* 14 (7): 693-701. DOI: 10.1016/S1474-4422(15)00087-3

[2] Timmermann L, Jain R, Chen L, Brucke T, Seijo F, San Martin ES, Haegelen C, Verin M, Visser-Vandewalle V, Barbe MT, **Gill S, Whone A**, Porta M, Servello D, Alesch F. (2016). 134 VANTAGE Trial: Three-Year Outcomes of a Prospective, Multicenter Trial Evaluating Deep Brain Stimulation With a New Multiple-Source, Constant-Current Rechargeable System in Parkinson Disease. *Neurosurgery*, 63, 155–155. DOI:10.1227/01.neu.0000489704.68466.0a

[3] Whone A. (on behalf of NHS Commissioning Board) (2013). Clinical Commissioning Policy: Deep Brain Stimulation (DBS) In Movement Disorders (Parkinson's Disease, Tremor and Dystonia)

Research grants:

[i] **Whone A** (UK-PI), (Timmermann L (CI), University Hospital Cologne). Vercise Implantable Stimulator for Treating Parkinson's Disease (VANTAGE) trial, Boston Scientific, 2010 -2015, study costs provided by BSC (to Bristol).

4. Details of the impact

Parkinson's disease (PD) is the second commonest neurodegenerative disorder world-wide with a prevalence of over 6 million. The global burden of PD has doubled over the last 30 years and is expected to continue to increase as a result of an aging population.

International regulatory approval and market access

The VANTAGE trial was a landmark study for Boston Scientific (BSC), which has since become a market leader in the multi-million neuromodulation sector. Following the VANTAGE investigation [1], the Vercise™ device gained CE marking in Europe (2015) [Bi] and Japan, and study findings were part of the premarket approval submission in North America resulting in FDA approval in the US (2017) [Bii]. The pioneering work to launch the Vercise™ DBS system in Europe has been the model for BSC to expand its activities both within Europe and outside. BSC is now operating in [text removed for publication] [A]. The Vercise™ DBS System also has regulatory approval in Latin America and Asia Pacific [C] and is available in [text removed for publication] [A], making the device available in 83 countries globally.

Commercial growth of Boston Scientific

After the VANTAGE study [1], Boston Scientific has gone from being unknown in the DBS field to a market leader. The company 2019 Annual Report states, '*Neuromodulation net sales increased USD94 million, or 12.0 percent, in 2019, as compared to 2018'* and *'This year-over-year increase was primarily driven by strong performance of our deep brain stimulation (DBS) systems'* [C]. Since launching in Europe, BSC has rapidly gained market share and is now the leader for new implants across the EMEA region, with sales estimated to account for [text removed for publication] [A]. In the UK in particular, BSC now accounts for [text removed for publication] [A].

Increased market competition and device innovation

One of the main differentiators of the BSC platform explored in the VANTAGE study [1] is the rechargeable battery technology that can last the lifetime of the patient and removes the need for costly and potentially dangerous battery replacement procedures. While the competing DBS companies did offer a rechargeable battery, the more formal evaluation of patient tolerability regarding recharging technology assessed in the VANTAGE investigation [1] had a significantly large impact on the UK market, and likewise in much of Europe. This resulted in a change in the replacement market from [text removed for publication] [A, C]. This dramatic shift is largely driven by the adoption of BSC technology, where VANTAGE was the landmark study for BSC launching a rechargeable cell into this market. In addition to the original Vercise™ device (2015), in 2019 BSC launched the Vercise™ Primary Cell (PC) and Vercise Gevia™ DBS systems [C].

Health economic benefit

Over 160,000 patients worldwide have undergone DBS, most commonly for treatment in Parkinson's disease. A US study estimated that a rechargeable implantation has a cost-savings of USD60,900 per patient over the course of nine years [Ei]. A pilot cost-effectiveness evaluation of the Vercise™ DBS system in the Japanese health system in 2018, estimated a cost reduction of JPY3,181,844 (c. USD30,000) per patient over 10 years, which more than doubled to JPY8,030,314 (c. USD75,800) over a 20-year period [Eii].

Benefits for health and quality of life

Quality of life was a secondary outcome of the VANTAGE study [1] and showed an approximately 30% improvement in PDQ-39 scores (questionnaire assessment of how often people affected by Parkinson's experience difficulties across 8 dimensions of daily living), which equates to a very large clinical effect. In addition, the patient motor diary showed increases in good quality "on" time as well as sleep, while decreasing the amount of time spent in a motor 'off' state or in a state of troublesome dyskinesia [1]. BSC have subsequently set up a registry of patients with the Vercise™ DBS system [Fii] to enable ongoing and long-term monitoring of patient outcomes, and Bristol patients formed part of that registry. Recent data, gathered up to three years post-implant, from 283 patients, report improvements in Quality of Life including bodily discomfort as well as benefits to motor function [Fi]. Feedback from a patient who switched to the Vercise™ DBS described the benefit to their quality of life; *'With [my previous DBS] system I felt limited… But with Vercise, this system has given me more time that I can spend with the grandkids.'* [J].

DBS was an established therapy for PD; however, the VANTAGE study led to the launch of several innovations, including multiple independent current control, short pulse widths, and the ability to program multiple frequencies. Each of these options independently improves patient outcomes by offering increased programming flexibility to optimize post-operative management. In addition, a single rechargeable implant can last the lifetime of the patient, removing the need for costly and potentially dangerous battery replacement procedures. Together these innovations represent a sophisticated DBS system with health benefits that have been, and are being explored, in 14 clinical trials involving Parkson's patients [G].

Shortly after the VANTAGE study, BSC released a directional lead on the same stimulator platform. The benefits of direct current stimulation and field-shaping, first explored in the VANTAGE study [1], have since become accepted across the movement disorders community for the benefit they bring to symptom control, side effect minimisation and quality of life improvement for people with Parkinson's [H].

The core technology of the stimulator itself has a demonstrable improvement on various clinical sequelae, the best example being gait improvement. Gait-related disorders frequently lead to falls, which represent a significant economic burden, with an estimated 27% of PD patients suffering from a hip fracture in the first 10 years of diagnoses and annual fall risk of 55-68% among all PD patients. A study of patients with severe gait disorders implanted with the Vercise™ DBS system reported improvement (no, or slight problems) sustained over three years following intervention [I].

5. Sources to corroborate the impact

[A] Boston Scientific (2021). Supporting Letter – Director International Clinical Operations

[B] i) Boston Scientific (2015). Boston Scientific Announces CE Mark for the Vercise™ Primary Cell Deep Brain Stimulation System
ii) Boston Scientific (2017). Boston Scientific Receives U.S. FDA Approval for the Vercise™ Deep Brain Stimulation System

[C] Boston Scientific (2019). 2019 Annual Report

[D] open PR (2020). Deep Brain Stimulation Devices Market 2020 | Industry Insights by Top Players Medtronic, Boston Scientific, St Jude Medical, Beijing Pins, SceneRay

[E] i) Hitti *et al.* (2018). Reduced long-term cost and increased patient satisfaction with rechargeable implantable pulse generators for deep brain stimulation. *Journal of Neurosurgery*, 131, 799–806. DOI:10.3171/2018.4.JNS172995
ii) Kitamura *et al.* (2018). Cost-Minimization Analysis of Vercise DBS System for Parkinson's Disease in Japan. *Value in Health,* 21, S71. DOI:10.1016/j.jval.2018.07.537

[F] i) Deuschl *et al.* (2020). Real-World Clinical Outcomes Using a Novel Directional Lead from a DBS Registry for Parkinson's Disease (1385). *Neurology,* 94 (15).
ii) ClinicalTrials.gov (2014). NCT02071134 Vercise DBS Registry

[G] ClinicalTrials.gov (2020). Search, Other terms: "Boston Scientific Vercise"

[H] Steigerwald *et al.* (2019). Directional Deep Brain Stimulation. *Neurotherapeutics*, 16, 100–104. DOI:10.1007/s13311-018-0667-7

[I] Valldeoriola *et al.* (2019). Simultaneous low-frequency deep brain stimulation of the substantia nigra pars reticulata and high-frequency stimulation of the subthalamic nucleus to treat levodopa unresponsive freezing of gait in Parkinson's disease: A pilot study. *Parkinsonism & Related Disorders*, 60, 153–157. DOI:10.1016/j.parkreldis.2018.09.008

[J] YouTube (2019). Boston Scientific DBS: Bill D.'s DBS Upgrade: A Joy That's Indescribable