Institution: University of Kent

Unit of Assessment: 4 – Psychology, Psychiatry and Neuroscience

Title of case study: US Clinical Approval for Neurological Treatment

Period when the underpinning research was undertaken: 01/10/2005 to 31/12/2020

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:
Prof. David Wilkinson	Professor of Psychology	01/10/2005 to date

Period when the claimed impact occurred: 01/8/2013 to date

Is this case study continued from a case study submitted in 2014? Yes

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

Professor David Wilkinson's research into the human vestibular system has underpinned the development and clinical approval of the *ThermoNeuro Modulation Device,* a new non-invasive treatment for neurological disease based on vestibular stimulation. In 2018, this device received both *de novo* regulatory approval for episodic migraine prevention from the Food and Drugs Administration (FDA) in the US and a CE mark as a medical device from the British Standards Institution (BSI) in the UK. The former enables the device to enter routine clinical use in the US, while the latter is an important milestone towards clinical approval in the UK. Later that year, the same device gained *Breakthrough Device* designation by the FDA for the clinical management of Parkinson's disease.

2. Underpinning research (indicative maximum 500 words)

This case study is based on a long-standing programme of research by Professor David Wilkinson on the therapeutic value of non-invasive vestibular stimulation, which provides a simple and effective means of altering the signals sent from the balance organs of the inner ear to the brain. This alteration can be achieved by applying low-amplitude electric current to the part of the scalp behind the ears (galvanic vestibular stimulation) or by applying warm/cool thermal current to the external ear canal (caloric vestibular stimulation), which likewise changes the firing rates of the nearby vestibular nerve. These changes modulate metabolic activity and vascular flow in many cortical and subcortical areas of brain.

The programme evolved from initial single-case and small group studies conducted with stroke participants presenting with acquired face blindness, constructional apraxia, aphasia, or hemi-spatial neglect (see 2014 case study). Wilkinson's research then progressed to larger clinical studies funded by the Medical Research Council **[G1]** with further studies supported by the British Academy, Harvard Catalyst, and the East Kent Hospitals University NHS Foundation Trust.

In **2012**, Wilkinson began a collaboration with Scion Neurostim LLC **[G2]**, a US-based medical device company that led to the development of the *ThermoNeuro Modulation Device*. This involved studies on the therapeutic potential of vestibular stimulation in migraine headache and Parkinson's disease, both of which impose considerable unmet clinical needs. According to the American Headache Society, migraine is the third most common disease and the sixth most disabling health condition, affecting around 12% of the worldwide population. Patients often resist prophylactic therapy owing to unpleasant side effects, cost, and perceived low efficacy of the currently available medication. Meanwhile, one in 37 people will be diagnosed with Parkinson's disease at some point in their life. The available medication typically declines in efficacy as the disease progresses and often leads to complications. Non-motor symptoms often become the major determinant of quality of life and care-giver burden. Each patient typically presents with

multiple non-motor symptoms, resulting in multiple prescriptions that can interact unexpectedly and are confusing to manage.

The research funded by Scion enabled Wilkinson et al. to show clinically relevant reductions in the number of migraine headache days, migraine pain, and use of over-the-counter migraine abortive medications in 81 volunteers suffering from 4-14 migraines per month and recruited from headache centres across the UK and US **[R2]**. In Parkinson's disease, following a successful single-case study that established proof of concept, Wilkinson designed and led the definitive clinical trial designed to meet regulatory approval. The results showed compelling reductions in motor (including reduced rigidity, freezing, and tremor) and non-motor (including better memory, sleep, and less depression and anxiety) features **[R1]**. These exceeded the minimal clinically important difference in 87% (14 of the 16) individuals who received active, as opposed to placebo, stimulation and completed the full treatment. Effects were present at one-month follow-up and still partially visible at six months, indicative of long-term plastic change, which is unusual for a neurological treatment **[R2, R4]**.

Publications arising from these studies provide the direct clinical evidence base required for the regulatory approvals described in Section 4 **[b, c]**. Many of the publications are co-authored with collaborators from Scion Neurostim LLC and UK clinicians.

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

[R1] Wilkinson, D., Podlewska, A., Banducci, S., Pellatt-Higgins, T., Slade, M., Bodani, M., Sakel, M., Smith, L., LeWitt, P., & Ade, K. (**2019**). Caloric vestibular stimulation for the management of motor and non-motor symptoms in Parkinson's disease. *Parkinsonism and Related Disorders*, 65, 261-266. doi: 10.1016/j.parkreldis.2019.05.031 (project duration: 2014-19) Caloric vestibular stimulation for the management of motor and non-motor symptoms in Parkinson's disease - Kent Academic Repository

[R2] Wilkinson, D., Ade, K., Rogers, L., Attix, D., Kuchibhatla, M., Slade, M., Smith, L., Poynter, K., Laskowitz, D., Freeman, M., Hoffer, M., Saper, J., Scott, D., Sakel, M., Calhoun, A., & Black, R. (**2017**). Preventing episodic migraine with caloric vestibular stimulation: a randomized controlled trial. *Headache: The Journal of Head and Face Pain*, 57, 1065-1087. doi: 10.1111/head.13120. (project duration: 2012-2018) Preventing episodic migraine with caloric vestibular stimulation: a randomized controlled trial - Kent Academic Repository

[R3] Wilkinson, D., Podlewska, A., & Sakel, M. (**2016**). A durable gain in motor and non-motor symptoms of Parkinson's Disease following repeated caloric vestibular stimulation: A single-case study. *NeuroRehabilitation*, 38, 179-182. doi: 10.3233/NRE-161308 (project duration: 2014-19) A durable gain in motor and non-motor symptoms of Parkinson's Disease following repeated caloric vestibular stimulation: A single-case study - Kent Academic Repository

[R4] Wilkinson, D., Podlewska, A., Banducci, S. E., Pellat-Higgins, T., Slade, M., Bodani, M., ... & Ade, K. (**2019**). Caloric vestibular stimulation for the management of motor and non-motor symptoms in Parkinson's Disease: Intention-to-treat data. *Data in brief*, 25, 104228. doi: 10.1016/j.dib.2019.104228 Caloric Vestibular Stimulation for the Management of Motor and Non-MotorSymptoms in Parkinson's Disease: Intention-to-Treat Data - Kent Academic Repository

Grants and Awards

[G1] Research grant: MRC Developmental Clinical Studies – Does repeated vestibular stimulation induce lasting recovery from hemi-spatial neglect? (MRC Ref: G1001222). Project duration: 2011-13. Value: £251,001.

[G2] Scion Neurostim LLC: five research and innovation grants awarded to David Wilkinson from August 2013 to date, with a total financial investment of £209,055, coupled with the free provision and maintenance of stimulation units.

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

This case study details how the *ThermoNeuro Modulation Device*, a novel non-invasive device for treating migraine and Parkinson's disease, gained regulatory approval for clinical use in the US (**26/3/2018**) and a CE mark in the UK (**7/8/2018**), as well as how the underpinning research also helped develop new generations of the device itself. All the activity detailed below results from a partnership between Wilkinson and the US medical device company, Scion Neurostim LLC, and continues a 2014 case study with activity from **1/8/2013** onwards.

The outstanding impact to date from this collaboration is regulatory approval for the device in the US for the treatment of episodic migraine. In **2018**, the US Food and Drug Administration (FDA) issued a *de novo* classification of the *ThermoNeuro Modulation Device* developed by Scion Neurostim LLC as a 'prophylactic treatment of episodic migraine in adolescent and adult patients 12 years or older' **[a]**. The award of *de novo* status allows for clinical use and reimbursement codes to be generated by healthcare providers. The application for this approval **[b]** names Wilkinson as an investigator and cites five of his studies between 2005 and 2016 (including **[R3]**).

Also in **2018**, the FDA subsequently awarded the same device *Breakthrough* status for the treatment of Parkinson's disease **[c]**. The application **[d]** draws exclusively on the safety and efficacy data generated by Wilkinson's group **[R1, R2, R3, R4]**. The *Breakthrough* designation is assigned by the FDA to devices that are deemed to address serious diseases with unmet needs. This ensures easier access to FDA staff and a reduced timeline for final device clearance for in-clinic use.

As a result of these approvals, the following stages are now underway at Scion, as confirmed by Dr Robert Black, Chief Operating Officer of Scion Neurostim LLC **[e]**:

- Discussions have taken place with CMS (Medicare & Medicaid) and the FDA about the further Parkinson's disease studies required for full FDA approval, to make sure that expectations for eventual product reimbursement by CMS are met.
- Preparations for commercialisation in the durable medical equipment (DME) category and ongoing discussions with medical device and pharmaceutical companies on marketing the device.
- Raising external capital (for the first time in Scion's history) with commitment now in place from a lead investor that manages a multibillion-dollar endowment and has now completed due diligence. Further early follow-on investors have taken the project 50% to the investment target for full rollout of the device.

Scion Neurostim also received a CE mark for its devices in **2018** from the British Standards Institution (BSI), in respect to 'the design and manufacture of a caloric vestibular system stimulator device for the prevention of episodic migraine in adults' **[f]**. A submission for this device is now in preparation for the UK Medical and Healthcare Products Regulatory Agency.

As with all CE submissions, one of the key elements in preparing the portfolio was the conduct of Usability studies. As the original application shows, Wilkinson's lab made a major contribution to this aspect of the submission **[g]**. This is based on practical-use scenario protocols aimed at the target patient populations, in particular the design of the earpiece and the simplification of the control panel implemented in the Gen 4.0 version. Wilkinson is named as an investigator in the application, which includes one of his published studies **[R2]** in the Final Clinical Report.

Scion Neurostim LLC's Chief Operating Officer confirms:

'Our new neuromodulation device has been completely redesigned to improve reliability and robustness and to simplify operation. Based largely on the feedback from PD subjects in Dr. Wilkinson's pilot study, the control interfaces were reworked to make it easier for PD patients to operate the device' **[e]**.

The latest technical development of the *ThermoNeuro Modulation Device* also benefits from Wilkinson's input, based on his long history of galvanic vestibular stimulation research (see section

2). This played a significant role in Scion's decision to add an electrical (galvanic) stimulator to the existing thermal device, which delivers the modulation signal without the need for skin electrodes, preparation, and gels. The Chief Operating Officer adds:

'Our plan is to work with Dr. Wilkinson on the development and testing of a GVS device that works through the same headset-based Gen 4 platform. This new GVS device is designed with home-use in mind, which enables an expanded approach to clinical applications of GVS, beyond the laboratory' **[e]**.

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

[a] US Food & Drug Administration, *De Novo Classification (Migraine)* (26/3/2018). Evidence for clinical approval for the ThermoNeuroModulation device.

[b] Scion Neurostim to US Food & Drug Administration, *De Novo Application (Migraine)* (14/4/2017). Evidence that Wilkinson's research was instrumental in the development of the ThermoNeuroModulation device (see pp. B18, E105).

[c] U.S. Food & Drug Administration, *Breakthrough Device Designation (Parkinson's Disease)* – (8/11/2018). Evidence for designation of ThermoNeuroModulation device.

[d] Scion Neurostim to US Food & Drug Administration, *Breakthrough Device Application (Parkinson's Disease)* (9/10/2018). Evidence that Wilkinson's research was instrumental in the development of the ThermoNeuroModulation device (e.g. pp. 52, 59, 79, 179-87, 189, 195, 213).

[e] Email from Chief Operating Officer, Scion neurostim LLC, to Prof. David Wilkinson (25/6/2020) detailing plans for the commercialisation process and Generation 4 ThermoNeuroModulation device.

[f] Bristish Standards Institution letter to Scion Neurostim confirming CE Mark for calorific vestibular stimulation device (7/8/2018).

[g] Scion Neurostim application to BSI for CE Mark for calorific vestibular stimulation device (1/3/2018). Evidence that Wilkinson's research was instrumental in the development of the device (e.g. pp. 793, 804, 805, 812).