Institution: University of Birmingham

Unit of Assessment: 2 – Public Health, Health Services and Primary Care

Title of case study: Improving quality of life for patients with Parkinson's disease

Period when the underpinning research was undertaken: 2000 – July 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:
Carl E. Clarke	Professor of Clinical Neurology	1999-present
Claire L. Smith (nee Tomlinson)	Honorary Research Associate Systematic Reviewer	2008-2009 2009-present
Natalie Ives	Reader in Clinical Trials	2001-present
Smitaa Patel	Senior Medical Statistician	2005-present
Keith Wheatley	Professor of Clinical Trials	1998-present
Adrian Williams	Chair of Clinical Neurology Honorary Chair of Neurology Honorary Professor	1989-1999 1999-2004 2004-2011
Caroline Rick	Trials Management Team Leader	2005-2019

Period when the claimed impact occurred: 2014 – July 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Our work has **improved care for people with Parkinson's disease (PD)**, an incurable neurological condition that is affecting an increasing number of people. Specifically, we have:

1. **Changed UK National Institute for Health and Care Excellence (NICE) and Canadian guidelines for the treatment of PD**. Levodopa is now recommended as initial therapy, subthalamic deep brain stimulation (DBS) is advised for people with advanced disease, and provision of physiotherapy and occupational therapy in early disease is downgraded.
2. **Changed care practices** such that levodopa is used as first line therapy in 90% of UK patients compared to 75% in 2013 and the number of patients with advanced disease who receive DBS has increased by 27%. These changes will substantially improve patient outcomes and have resulted in **decreased NHS treatment costs.**

2. Underpinning research

Parkinson's disease (PD) is an incurable neurological condition affecting 2% of men and 1.3% of women, with numbers expected to double by 2050 as the population ages. PD results from the loss of nerves in the brain that produce **dopamine**. Initial symptoms include tremor, slowness, stiffness, and fine movement difficulties, but over 10 to 20 years it progresses to imbalance, resulting in falls/fractures, and non-movement complications of dementia, depression, anxiety, and sleep disturbance. No therapies are available to stop disease progression and treatment is limited to improving symptoms using dopaminergic agents including the dopamine precursor, **levodopa**, **dopamine agonists** that mimic dopamine's effects, or enzyme inhibitors such as **monoamine oxidase type B inhibitors (MAOBI)** that stop dopamine breakdown in the brain. Later in the disease, patients less than 70 years with no dementia or depression may benefit from **subthalamic deep brain stimulation surgery (DBS)**

as well as rehabilitation therapies including **physiotherapy, occupational therapy, and speech therapy**. However, the optimal combination of treatments for particular patients at different disease stages is still unknown.

Levodopa has been the main initial treatment for PD for many years but prolonged use leads to involuntary movements (dyskinesia) and a shorter duration of response. To delay the use of levodopa, dopamine agonists and MAOBIs were proposed for initial treatment. However, this approach had not undergone clinical assessment and is more costly. Furthermore, the roles of DBS and rehabilitation therapies were uncertain.

In order to provide evidence for the optimal clinical management of patients with PD, Professor Clarke at the University of Birmingham (UoB) led a large portfolio of work assessing drug, surgical, and rehabilitation therapies to identify the most suitable and cost-effective treatment and management strategies for PD patients. This has produced 3 Key Findings [KF1–KF3] that have informed directly on the development of the optimal PD patient pathway.

Establishing appropriate drug treatment pathways for patients with Parkinson's disease

An analysis of available evidence by Clarke and the UoB Clinical Trials Unit (BCTU) [R1], identified that it was unclear which drugs were the most suitable for early and later stages of PD. Therefore, the team established **PD MED**, a large, long-term comparative trial designed to assess the risks versus benefits of initially treating PD patients with dopamine agonists and MAOBI compared to levodopa. Between 2000 and 2009, 1,620 patients were allocated to levodopa, dopamine agonist, or MAOBI therapy and their quality of life assessed during follow-up for at least 10 years until trial closure in 2019. An interim analysis in 2014 [R2] showed **a significant benefit in quality of life for patients initiated on levodopa compared to levodopa-sparing therapies [KF1]**, indicated by a higher mobility score (PDQ-39) and higher overall health assessment score (EQ-5D) in levodopa-treated patients**.** Discontinuation of treatment due to side effects was also significantly less common in levodopa patients whilst indicators of disease progression did not differ between the groups.

Assessing the relative effectiveness of surgery for Parkinson's disease

Through a systematic review of PD surgery trials since 1990 [R3], Clarke and BCTU identified the need for much larger, randomised controlled trials (RCT) to assess the cost-effectiveness and long-term effects of surgery on patient-rated quality of life. To do this they conducted **PD SURG** [R4], the largest RCT of surgery in PD. 366 patients with advanced PD were randomised to DBS surgery with best medical therapy (BMT) or BMT alone. At 1 year, the combination of **surgery and BMT improved quality of life for patients with advanced PD compared to BMT alone [KF2]**, indicated by significantly higher mobility scores (PDQ-39) in the surgery group.

Assessing the effectiveness of Physiotherapy and Occupational Therapy in Parkinson's Disease

The team carried out a systematic review of the effectiveness of physiotherapy in PD. This showed that although there was evidence of short-term symptomatic relief, the effect of physiotherapy on a patient's quality of life was unclear, and there was no evidence of cost-effectiveness [R5]. This highlighted a need for a large RCT with improved methodology and reporting to assess the cost-effectiveness of physiotherapy and its effect on QoL in the longer-term. **PD REHAB** [R6] was the largest rehabilitation trial ever performed in PD. 762 patients with mild to moderate PD were randomised to receive either immediate physiotherapy and occupational therapy or therapy deferred for 12 months. **Therapy had no effect on patient-rated quality of life at 12 months [KF3]**.

3. References to the research

R1. Wheatley, K., Stowe, R.L., **Clarke, C.E.**, Hills, R.K., **Williams, A.C.**, Gray, R. Evaluating drug treatments for Parkinson's disease: how good are the trials? BMJ 2002; 324(7352): 1508–11. doi: 10.1136/bmj.324.7352.1508

R2. PD MED Collaborative Group, Gray, R., **Ives, N.**, Rick, C., **Patel, S.**, Gray, A., Jenkinson, C., McIntosh, E., **Wheatley, K.**, **Williams, A.**, **Clarke, C.E.** Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. Lancet 2014; 384(9949): 1196–205. doi: 10.1016/S0140-6736(14)60683-8. Epub 11 June 2014.

R3. Stowe, R.L., **Wheatley, K.**, **Clarke, C.E.**, **Ives, N.J.**, Hills, R.K., **Williams, A.C.**, Daniels, J.P., Gray, R. Surgery for Parkinson's disease: lack of reliable clinical trial evidence. J Neurol Neurosurg Psychiatry. 2003 Apr; 74(4): 519–21. doi: 10.1136/jnnp.74.4.519.

R4. Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R. *et al*. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurology 2010; 9(6): 581–91. doi:10.1016/S1474-4422(10)70093-4

R5. Tomlinson, C.L., **Patel, S.**, Meek, C., **Clarke, C.E.**, Stowe, R., Shah, L., Sackley, C.M., Deane, K.H., Herd, C.P., **Wheatley, K.**, **Ives, N**. Physiotherapy versus placebo or no intervention in Parkinson's disease. Cochrane Database Syst Rev. 2012 Aug 15; 8: CD002817. doi: 10.1002/14651858.CD002817.pub3.

R6. Clarke, C.E., **Patel, S.**, **Ives, N.**, Rick, C.E., Dowling, F., Woolley, R., **Wheatley, K.**, Walker, M.F., Sackley, C.M.; PD REHAB Collaborative Group. Physiotherapy and occupational therapy versus no therapy in mild to moderate Parkinson's disease: a randomized clinical trial. JAMA Neurol. 2016 Mar 1;73(3):291–9. doi: 10.1001/jamaneurol.2015.4452.

4. Details of the impact

We have **improved care for people with early and advanced Parkinson's disease (PD)** by defining a first line drug that improves the mobility and overall health of patients with early PD, demonstrating that surgical intervention can improve mobility for patients with advanced disease and downgrading guidance on use of rehabilitation therapies in early PD. We have achieved this through: (1) **changing national guidelines for PD in the UK and Canada** and by (2) **changing practitioner best practice**. As a result of these changes in therapy, **NHS treatment costs for PD patients have been reduced**.

1. UK and Canadian guidelines for PD have changed resulting in improved care practices for patients

In 2017, the **UK National Institute for Health and Care Excellence (NICE) guidelines for the treatment of PD** were **changed**. The key findings [KF1, KF2, KF3] from UoB trials were instrumental in underpinning many of these changes [S1]. NICE now recommends that clinicians:

1. "Offer levodopa to people in the early stages of Parkinson's disease whose motor symptoms impact on their quality of life." [S1. Recommendation 26. p. 74; from KF1].
2. "Consider deep brain stimulation for people with advanced Parkinson's disease whose symptoms are not adequately controlled by best medical therapy." [S1. Recommendation 89. p. 215; from KF2].
3. "Consider referring people who are in the early stages of Parkinson's disease to
    (1) a physiotherapist with experience of Parkinson's disease for assessment, education and advice, including information about physical activity." [S1. Recommendation 69. p. 161; from KF3].
    (2) an occupational therapist with experience of Parkinson's disease for assessment, education and advice on motor and non-motor symptoms." [S1. Recommendation 72. p. 168; from KF3].

Prior to 2017, NICE did not specify which therapy to use as the first line treatment for PD patients with early disease. The Guideline Development Group (GDG) stated that when reaching their decision to recommend offering levodopa (Recommendation 26), they gave particular attention to KF1 from PD MED as "it was a long-term independently-funded study conducted in the UK" [S1. p. 64]. Similarly, PD SURG [R4] contributed significantly to NICE decisions regarding surgery guidelines as it was 1 of only 4 surgical studies considered [S1. p. 200]. UoB was also asked to provide additional data from PD SURG beyond the 1-year follow up reported in R4, which were used, along with R4, to determine guidance on use of surgery for early [S1. p. 217] and advanced PD [S1. p. 201] as well as to assess the cost–utility of surgery [S1. p. 204–5], which is an important factor in governing recommendation changes. UoB's Professor Adrian Williams and Dr Caroline Rick, who had been involved in the design and conduct of PD SURG, were also invited as 'Expert Witnesses' to answer questions about the trial to assist the GDG in their review of evidence for DBS and subsequent decision to recommend DBS [S1. p. 198]. The provision of individual patient data from the PD SURG trial allowed NICE to perform their own health economics analysis which found the provision of DBS favourable.

PD REHAB [R6] was also deemed "of particular importance" by the GDG, as it was "a large, recent UK-based study" [S1. p. 159]. Based on KF3, NICE changed the 2006 guidance that physiotherapy and occupational therapy *should* be available to people with PD (CG35), to instead advise clinicians to '*consider*' rather than '*recommend*' physiotherapy and occupational therapy and stated that if offered, therapy should be given by therapists with experience of PD.

These UoB-driven changes to the NICE guidelines have been acknowledged as life changing for PD patients, as stated by the CEO for Parkinson's UK, the world's largest patient-led organisation for PD. Patients believe that through the changes to NICE guidelines in response to Birmingham's research: "the quality of care for everyone affected by Parkinson's disease in the UK has improved." [S2]

The 2017 NICE guidelines [S1] have also underpinned subsequent **changes to guidelines in Canada** [S3 Ref 103], providing downstream impact of the influence of our research [KF1–KF3] in the UK. In 2019, the Canadian Guidelines for PD were modified to recommend that:

1. "Levodopa may be used as a symptomatic treatment for people with early Parkinson disease (Grade A)." [S3. Recommendation C31; from KF1].
2. "Deep brain stimulation of the subthalamic nucleus or the globus pallidus interna is effective against motor fluctuations and dyskinesia (grade A)." [S3. Recommendation C49; from KF2].
3. "Consideration should be given to referring people who are in the early stages of Parkinson disease to:
   (1) a physiotherapist with experience of the disease for assessment, education and advice, including information about physical activity (grade B)." [S3. Recommendation C56; from KF3].

   (2) an occupational therapist with experience of Parkinson disease for assessment, education and advice on motor and nonmotor symptoms (grade B)." [S3. Recommendation C58; from KF3].

2. <u>Care practices for PD patients have changed, resulting in cost savings to the NHS</u>

Use of levodopa as first line treatment for PD patients in the UK has increased. During this REF period, the use of levodopa has increased by 11.5% from 78.5% in 2013 to 90% in 2019, whilst the combined use of dopamine agonists and MAOBIs has decreased by 12% [S4]. Based on national estimates for new incident PD patients (18,461 in 2018), this means that 2,210 more PD patients are now treated initially with levodopa each year compared to in 2013 and should experience the improved quality of life that comes with this treatment. KF1 clearly drove these changes in treatment since use of levodopa first started to increase when Clarke first disseminated the results of PD MED at congress meetings around 2011 [S5]. Subsequently, during this REF period, publication of KF1 in 2014 [R2] and its incorporation in NICE guidelines in 2017 [S1] has supported a continuing rise in use of levodopa, which has increased by 7.5%

since 2014, as in the year following each landmark, the percentage of PD patients in the UK who received levodopa increased.

International **clinician awareness of levodopa as the best initial treatment for PD patients has been raised**, through its inclusion in 2016 in Bradley's Neurology in Clinical Practice [S6] — the main US textbook on Neurology — and by its inclusion along with KF2 and KF3 in the Birmingham Movement Disorders Course [S7] that is held bi-annually for 200 international specialist registrars in neurology and geriatrics.

Use of Deep Brain Stimulation surgery for patients with advanced PD has increased. More than 200 patients in the UK now receive DBS each year — an increase of 44% compared with 2013/2014. This increase in DBS was driven directly by KF2 and DBS usage has doubled since publication of PD SURG in 2010. It would be expected that this change in practice would substantially improve quality of life and mobility for these patients [S8].

Taken together, these research-led changes in treatment practice have also resulted in **reduced treatment costs for PD patients, resulting in savings for the NHS**. This is demonstrated by a cost-effectiveness analysis of PD MED which showed that initial treatment with levodopa, instead of levodopa-sparing therapies, would save the NHS an average of £3,390 per patient over 4 years [S9]. Based on 2,120 more PD patients now receiving levodopa as initial treatment each year, this represents an annual saving of £1.8m for the NHS [S7]. Furthermore, extrapolation of the PD SURG data, combined with assumptions concerning future costs and Quality Associated Life Years, suggests that use of deep brain stimulation surgery would be **cost-effective for the NHS** over 5 years [S10].

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

[S1] Parkinson's disease in adults; NICE guideline [NG71]. Published: 19 July 2017

[S2] Testimonial: CEO for Parkinson's UK

[S3] Canadian Guideline for Parkinson disease, 2nd Edition, Parkinson Canada, 2018

[S4] Thin database of medication for initial treatment of PD patients from 2005–2019

[S5] Congress abstract and poster for WFN XIX World Congress on Parkinson's Disease and Related Disorders 2011

[S6] Bradley's Neurology in Clinical Practice Seventh Edition, 2016, Elsevier

[S7] Training material from Birmingham Movement Disorders Course

[S8] HES data on subthalamic nucleus implantations between 2001 and 2019

[S9] PD MED cost effectiveness study: Cost-effectiveness analysis of levodopa versus levodopa sparing therapies as initial treatment for Parkinson's disease: a large, open-label, pragmatic randomised trial.

[S10] Cost effectiveness evidence for DBS McIntosh, E., Gray, A., Daniels, J., Gill, S., Ives, N., Jenkinson, C., Mitchell, R., Pall, H., Patel, S., Quinn, N., Rick, C., Wheatley, K., Williams, A.; PD SURG Collaborators Group. Cost-utility analysis of deep brain stimulation surgery plus best medical therapy versus best medical therapy in patients with Parkinson's: Economic evaluation alongside the PD SURG trial. Mov Disord. 2016 Aug; 31(8): 1173–82. doi: 10.1002/mds.26423. Epub 2016 Feb 5. PMID: 26846185.