DEEP BRAIN STIMULATION OR DUODOPA FOR ADVANCED PARKINSON DISEASE IN BRITISH COLUMBIA

Evaluation of safety, effectiveness and cost-effectiveness of Deep Brain Stimulation (DBS) or intestinal DUODOPA for treatment of advanced Parkinson disease in British Columbia and budget impact.

HEALTH TECHNOLOGY ASSESSMENT REPORT

A report for the BC Health Technology Review Office, on behalf of health authorities and the Ministry of Health. Vancouver. December, 2017. Version 2.0

Acknowledgements

Table of Contents

*DUODOPA RCT measured the effect on outcomes when patients were on medication because

if patients were off medication, patients would have been off DUODOPA too. For the

purpose of comparison, all numbers used in this review were measured when patients were

on medication.

List of Tables

List of Figures

List of Abbreviations

BC	British Columbia
BCCSSS	BC Clinical and Support Services Society
BCPSQC	BC Patient Safety & Quality Council
BMT	Best Medical Therapy
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEDEC	Canadian Drug Expert Committee
CUA	Cost Utility Analysis
DBS	Deep Brain Stimulation
FHA	Fraser Health Authority
HCP	Health Care Providers
HTA	Health Technology Assessment
HTR	Health Technology Review
ICER	Incremental Cost-Effectiveness Ratio
IHA	Interior Health Authority
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
PEG-J	Percutaneous Endoscopic Transgastric Jejunostomy
MOH	Ministry of Health
NHA	Northern Health Authority
OR	Odds Ratio
PVN	Patient Voices Network
PD	Parkinson's Disease
PD Drugs	Antiparkinsonian Drugs
PHAC	Public Health Agency of Canada
PHC	Providence Health Care
PHSA	Provincial Health Service Authority
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjust Life-Years
RR	Relative Ratio
SAE	Serious Adverse Event
UPDRS	Unified Parkinson's Disease Rating Scale
VCH	Vancouver Coastal Health
VCHA	Vancouver Coastal Health Authority
VIHA	Vancouver Island Health Authority

Executive Summary

The purpose of this health technology assessment (HTA) is to summarize the available evidence on the effectiveness of DBS surgery and DUODOPA gel therapy, and to analyze the cost-effectiveness of treating advanced PD patients with Duodopa compared to DBS and the budget impact of a policy change in BC to expand access to DBS treatment for advanced PD patients, as compared to maintaining the status quo or supporting treatment with DUODOPA gel therapy.

PD is a progressive neurodegenerative disease. It is caused by a wide metabolic problem in the brain that affects multiple neurochemical systems. One of the results of this pathology is that it causes the dopamine regulating cells to die. Symptoms may include resting tremors, muscle rigidity, stiffness, depression, anxiety, sleep disturbances, and alterations of smell, taste and autonomic function. The symptoms usually start mildly and progress to more severe symptoms in the span of years or even decades. There is no available surgical or pharmacological treatment that has been proven to slow down or stop the progression of PD. Currently, the treatment goals are to relieve symptoms and maintain quality of life.

Patients who have progressed to advanced stages of PD, alongside their caregivers, bear a tremendous burden of disease. They experience a drastic reduction in quality of life due to factors such as loss of autonomy, increased visits to the emergency room and other medical professionals, loss of social interactions and confidence, weakening relationships with family and care providers, depression, feelings of anxiety, physical pain from lack of symptom control, and financial strains related to costs of medical equipment and professional care to manage daily activities

Across Canada, from the provinces that responded to the request for information, DBS has been covered by the provincial public system in Newfoundland and Labrador (NL), Alberta, Quebec, Manitoba, and Saskatchewan. It is the preferred treatment and standard of care in Alberta, Manitoba, Saskatchewan, and Newfoundland and Labrador. DBS surgeries are performed within each respondent province, with the exception of NL. Patients residing in NL must travel to either Toronto or Halifax for surgery. NL provides funding for the primary devices and partially covers travel expenses as per provincial Medical Transportation Assistance Program.

DUODOPA is not on the Quebec "List of Medications". However, this product was reimbursed for a limited number of patients through the "exceptional patient measure" administered by Provincial health insurance. In NL, the practice pattern is to offer DBS before DUODOPA unless other factors such as age, or inability to travel outside province preclude DBS as a treatment option. In Manitoba, to qualify for coverage of DUODOPA by the public health system, patients must meet certain eligibility criteria. In Alberta, DUODOPA is covered under the public system for patients ineligible for DBS, or for those who are likely to be non-compliant with DBS therapy (i.e., lack of ability to comply with programming of DBS at home), or those who refused to have brain surgery.

Worldwide, DBS appears to be the standard of care in the majority of jurisdictions for patients who no longer have a good response to best medical (oral) therapy (BMT) or who have unacceptable motor fluctuations. DUODOPA when compared to BMT in other jurisdictions has not demonstrated acceptable cost-effectiveness thresholds in any context, except Scotland. Canada, Australia and Wales have not recommend to list DUODOPA within their respective

jurisdictions. Scotland is the exception and recommended use of DUODOPA only among those who were not eligible to receive DBS.

Currently in BC, there is only one salaried surgeon who conducts DBS at VGH. Upon referral of potential eligible patients by their primary neurologist, patients will be placed in the first waitlist (W1 list) to have an introductory consultation with the DBS surgeon. During the primary consultation, patients are either approved for surgery, in which case they move on to the second wait list (W2 list), or are deemed to be ineligible for surgery. Patients who are moved to the W2 list must wait approximately an additional 1.5-2 years to receive DBS, with thus an overall wait time of approximately 3-4 years.

The use of DUODOPA in BC is highly restricted. Patients are eligible for DUODOPA if they are deemed ineligible for DBS following strict clinical criteria or if the wait for DBS is longer than 1 year. Patients only become eligible ███████████████████████████████████████ █████████████████████████████████████.

It was unanimously expressed by all stakeholders that patients with advanced stage of PD who are no longer receiving adequate symptom relief by BMT, should be eligible for either DBS or DUODOPA therapy. Moreover, stakeholders were also in unanimous agreement that while some patients may be eligible for only one of the two treatment options, personal choice for therapy should also be taken into consideration.

Health Care providers noted that lack of OR time, staff, lack of training for staff, and physical space would be considerable challenges in expanding access to DBS or DUODOPA in BC. In increasing the number of patients receiving either treatment option, there would need to be a potential increase in both the number of health care providers offering such services, as

well as an increase in the number of specialty clinics that advise and help patients with postoperative care and long-term management.

In discussion of the definition of 'patients with advanced PD', participants recognized themselves as reaching this point when they could feel that they were no longer receiving adequate relief and control over their symptoms from their best-combined oral therapies. This in turn has led patients to feel a very significant decrease in the quality of their lives, in addition to an increased dependency on their caregivers. Patients have reported struggling with feelings of social isolation, resulting from having to stay at home due to the severity of their symptoms, worsening physical conditions demanding the need to discontinue work or previous hobbies, difficulties in maintaining responsibilities within their household, as well as changes in the dynamic of their relationships with caregivers, given the shift in the patient's emotional state and self-confidence. It should be noted that patients have felt great stigmatization by individuals in the community who are not aware of the symptoms of PD.

Patients undergoing DBS have reported that there has been a substantial decrease in symptoms observed post-surgery, with an approximate 70-90% reduction in tremor and dyskinesia, with others reporting the disappearance of dystonia altogether, alongside a major decrease in the frequency and dosage of their required medication, allowing them to maintain their position in the workforce, the ability to travel, and increase in social interactions. It was mentioned that for some patients this surgery has turned back the clock by approximately 5-7 years regarding disease progression. However, it was also mentioned that not all symptoms were relieved by DBS (e.g. difficulty with speech).

HTR Meeting [Jan 2018]
Dec 2017 | Centre for Clinical Epidemiology and Evaluation | Vancouver Coastal Health Research Institute

21

Patients receiving DUDODOPA gel therapy, attest to an approximately 50% increase in managing daily chores and home responsibilities, such as doing laundry, walking the dog, and etc. It was stated by the caregivers that this also lead to a significant decrease in their burden of responsibility, both emotionally, physically, and financially as patient did not require as much informal help and daily use of medical equipment. Regarding the patient's ability to return to work, it was stated by all patients that DUODOPA could allow them to go back to work, at least part time (or in some variation given the support of their employer). It was stated that DUODOPA has allowed the patients' and care providers' previously, "shrinking social lives to increase, and allow them to get out of the bubble that they were living and being forced to stay at home". Patients are now able to travel, visit friends, and even receive company (whereby previously all such activities had proven to be impossible).

For patients who had received either DUODOPA or DBS, caregivers overwhelmingly stated a sense of relief. It was confirmed unanimously by all caregivers that in fact, both treatments had made tremendous changes in the quality of lives of both the patient and the care provider. It was described by some care providers as "being able to get my partner back, she was finally back".

In the clinical assessment of evidence, initially, studies comparing DUODOPA to DBS directly were included. If the evidence for direct comparison was not sufficient, studies comparing DUODOPA to oral levodopa and DBS to BMT were included for indirect comparison of DUODOPA with DBS.

Two retrospective observational studies compared DUODOPA directly to DBS. The 15-month study, which included 40 patients, did not find any differences between DUODOPA and

DBS in all four UPDRS subscales. The 5-year study, which included 60 patients, found that DBS was significantly better than DUODOPA in UPDRS part IV due to the finding that DBS reduced time with troublesome dyskinesia. DUODUOPA and DBS showed similar results in other UPDRS subscales.

Five parallel RCTs were included in the indirect comparison. Patients who received DBS showed significantly better results in UPDRS III, UPDRS IV and daily ON time without troublesome dyskinesia when compared with DUODOPA. While greater reduction indicates greater improvement, on average, DBS patients showed further decreases in both UPDRS III and IV scores as compared with DUODOPA patients (respectively 5.5 and 2.3, measuring motor disability and complications).

Data from the 5-year observational study corroborated with the UPDRS IV result in the RCTs, confirming that the effects observed in the UPDRS IV (motor complication) are likely to be continued in the long term. On the other hand, results from the long-term study showed a similar effect between UPDRS III scores for patients with DBS and Duodopa. This suggests that it might take longer than three months for the DUODOPA therapy to impact UPDRS III scores. In addition, the DUODOPA RCT only lasted for 3 months, which may not have allowed adequate time for the adverse event to occur. Therefore, it is not appropriate to compare the data of complications in the DUODOPA RCT to DBS RCTs in a safety risk analysis.

The quality of evidence from the observational studies is low due to the small sample size and high risk of selection bias. While there is good quality of evidence provided by the RCTs, the quality of the indirect comparison is low due to a linear network and potential of bias in the safety data from DUODOPA RCT; however at present, it is the best available evidence.

In the economic literature review, a single study was identified that enabled a direct comparison of DUODOPA to DBS. Note that the primary purpose of this study was to compare apomorphine to DBS, DUODOPA and BMT. The search returned 5 CEA studies comparing DUODOPA to BMT (where only one study, considering a lifetime time horizon, reported an ICER within acceptable cost-effectiveness thresholds), and 10 CEA studies comparing DBS to BMT. Six studies found DBS compared with BMT was within the acceptable cost-effectiveness thresholds from a variety of perspectives (societal, payer, national health service) and time horizons (1 year, 5 years, 10 years, and lifetime.

Incorporating the best available evidence into a decision-analytic simulation model, we showed that treatment of advanced PD patients in BC with DBS, as compared to DUODOPA, is much more cost-effective in almost every simulated scenario at a wide range of WTP values per QALY. In order for DUODOPA to have a similar cost profile as DBS, a 78% price reduction would be required. However, and critically, this would still not yield the same clinical outcomes as DBS. The results were most sensitive to the cost of the technologies, and the rate of disease progression.

The current capacity for DBS surgery being offered to the advanced PD population in BC is substantially below the current demand for treatment of advanced PD patients in the province, and thus has led to an ever-increasing backlog demand over the years.

In order to manage the existing and future demand for treatment, BC will require to provision health care resources for approximately ▇▇▇▇▇▇ surgeries per year (DBS implants or PEG-J implants) for this patient population, for the ▇▇▇▇▇▇, and maintain a capacity for approximately ▇▇▇▇▇▇ surgeries hereafter in order to keep wait times below ▇▇▇▇▇.

In order to increase access to advanced treatments, the most cost-effective option with the lowest impact seems to be the increase in capacity of DBS surgeries across BC. Health authorities will require an implementation study to assess the current surgical capacity, and health care personnel training (availability of surgeons, specialized nurses, OR time and equipment, etc.) within their regions, and evaluate whether to continue to centralize the advanced treatments within VCHA infrastructure, or whether as to decentralize certain service such as the support from the DBS clinic for pre-operative evaluation and post-operative DBS calibrations, battery changes to minimize travel time for patients to access care, and optimize the VCHA services for highly specialized services (the DBS implant itself). In the next 10 years, this patient population is estimated to require ███████ for health care costs if treated with DBS.

Offering DUODOPA as an alternative treatment for advanced patients who are eligible to DBS for whatever reason (patient preference, lack of available surgical capacity, etc.), even at a small proportion (20%), would result in even higher costs to expand access to treatment, with a different impact to each of the multiple funding sources involved in the health care management of this patient population. Under this scenario, the costs avoided with oral PD drugs, DBS devices and hospital costs, would not offset the incremental cost of DUODOPA ($██ ████ in 10 years).

Chapter 1 Background and Problem

1.1   Purpose of this health technology assessment (HTA)

The purpose of this health technology assessment (HTA) is to summarize the available evidence on two specific therapies available for patients with advanced Parkinson's disease (PD), Deep Brain Stimulation (DBS) and Levodopa-Carbidopa intestinal gel (DUODOPA). This report includes evidence on key stakeholders' perspectives, safety and the efficacy of DBS and DUODOPA in comparison to each other and to the best medical treatment (BMT), defined as the most responsive combination of oral medications specific to each patient. Also, a cost-effectiveness analysis and budget impact of both treatments are included.

1.2   Policy question and research objectives

1.2.1   Primary policy question or decision problem to be answered by this HTA

- Is DBS safe and effective, compared to DUODOPA, in improving specific symptoms (motor fluctuations, tremor, and dyskinesia) in advanced Parkinson patients inadequately controlled by the available oral pharmacological treatments or with unacceptable side effects?

- And if yes, is DBS cost-effective and what would be the budget implications of expanding coverage for this technology in BC?

1.2.2   Primary research questions to be answered by this HTA

- What is the burden of PD in this population?

- How is Parkinson's disease treated in BC (all alternatives)?

- What are the eligibility criteria for DUODOPA and DBS among PD patients in BC?

- How many patients in BC are living with Parkinson's disease that would be eligible for DBS?

- What is the patient experience living with advanced PD?

- What is the advanced PD patient experience on DBS or DUODOPA treatment?

- What is the evidence on clinical effectiveness and cost-effectiveness of DBS compared to DUODOPA?

- How cost-effective is DBS compared to DUODOPA in BC from the public health care system perspective?

- What are the known costs for BC (Ministry, health authorities,) of the drug treatment, DBS and other long term costs to manage this patient population?

- What is the health authority infrastructure (i.e. capital, equipment, HR, etc.) required to provide DBS?

- What is the budget impact for the public health care system of implementing DBS in BC compared to the current standard of care?

- What is the evidence on the societal impact (return to work for caregivers and patients, out-of-pocket costs, psycho-social aspects, etc.)?

- What is the availability of DBS in other publicly funded systems in Canada or other similar health care systems?

1.3 Background information

1.3.1 Description of condition and severity of disease

PD is a progressive neurodegenerative disease where 50% of the patients reach advanced stages in between 6 to 10 years (1) , caused by a wide metabolic problem in the brain that affects multiple neurochemical systems. One of the results of this pathology is that it causes the dopamine regulating cells to die. Patients may show motor symptoms such as resting tremors, muscle rigidity, stiffness and impaired balance. However, other non-motor symptoms, such as depression, anxiety, sleep disturbances, alterations of smell and taste, and autonomic function, may also be present prior to the emergence of motor symptoms. The symptoms usually start mildly and progress to more severe symptoms in the span of years or even decades.

There is no available surgical or pharmacological treatment that has been proven to slow down or stop the progression of PD. Currently, the treatment goals are to relieve symptoms and maintain quality of life. (2)

After about two to five years of medical treatment, roughly 30% to 50% of patients develop motor complications that can be a function of both disease progression and drug side effects. (3) After more than 10 years of medical treatment, these motor complications can potentially be disabling despite best medical therapy. Dyskinesia and motor fluctuations are the two most common motor complications in PD. Dyskinesia is an abnormal involuntary movement that occurs when dopamine treatment is in effect (ON time).(4) Dyskinesia can be very uncomfortable as patients will constantly demonstrate a continuous twitching motion for hours, which may lead to extreme soreness and pain. Dyskinesia may also prevent patients

HTR Meeting [Jan 2018]
Dec 2017 | Centre for Clinical Epidemiology and Evaluation | Vancouver Coastal Health Research Institute

28

from performing some fine motor movements common in daily activities, such as writing or eating. Motor fluctuation is characterized by switching between time in good treatment response (ON time) and poor treatment response (OFF time) due to the effect of the levodopa wearing off. (4) The transition between ON and OFF time can in some cases be sudden and unpredictable. The patient can stay in OFF-time for hours before their next dose of medication. Patients with advanced PD may experience more and more "OFF" times due to disease progression, as well as more time with dyskinesia during "ON" periods.

Other than motor complications, advanced PD patients may also develop non-motor symptoms due to disease progression, such as depression, dementia, psychosis and disruption to the sleep-wake cycle. (3)

1.3.2   Burden of illness, potential size of patient population, and wait time for treatment

PD is unique in that each person may experience different symptoms and even rates of disease progression; however, all patients will progress through the disease because at present no available surgical or pharmacological treatment can reverse or slow down progression.

Patients who have progressed to advanced stages of PD, alongside their caregivers, bear a tremendous burden of disease. They experience a drastic reduction in quality of life due to factors such as loss of autonomy, increased visits to the emergency room and other medical professionals, loss of social interactions and confidence, weakening relationships with family and care providers, depression, feelings of anxiety, physical pain from lack of symptom control, and financial strains related to costs of medical equipment and professional care to manage daily activities. (4)

Cost-of-illness studies have shown that costs of PD are high, mainly due to drug, hospitalization and productivity loss, and tend to increase as the disease progresses.(5) A study from the UK in 2015 showed that PD patients admitted to the hospital over a 4-year period, cost the system in total approximately £907 million. (6) Again in the UK, the total annual per patient cost of PD in 2011 was £28,700 per patient. A large proportion of these costs were attributed to direct non-medical costs (£13,364) and informal care costs (£12,454).(7)

Although slightly out dated, the Canadian Institute for Health Information (CIHI) and the Public Health Agency of Canada (PHAC) estimated that PD accounted for approximately $201 million in direct costs to the health system (including hospital care, physician and drug expenditures), $244 million in indirect costs (including mortality and morbidity costs), and resulted in 52,978 disability-adjusted life years (DALYs) in 2000-2001. (8) DALYs can be thought of as one lost year of healthy life due to a specific disease, disorder or injury. Among neurological conditions, PD is the 3rd leading cause of DALYs in Canada behind stroke and Alzheimer's disease.

In 2014, Statistics Canada (9) published that 61% of individuals with PD reported out-of-pocket expenses in the previous year attributable to PD. Nearly half of them (47%) attributed out of pocket costs to medications, and for approximately 20% of individuals they were in excess of $500. Other out-of-pocket expenses were also reported by PD patients (mobility devices (23%), rehabilitation therapy (18%) and home care and homemaker services (15%), being of $500 or more for 45% of patients who reported those expenses. Although only 15% reported paying out-of-pocket to obtain home assistance, 56% of all individuals with PD reported receiving formal and/or informal assistance. The majority of this assistance is provided

by the individual's spouse (64%). On average, the spouse caregivers were aged 69 (22% employed) and other caregivers were on average 52 years old, with 66% employed.

Statistics Canada estimated that 55,000 Canadians age 18 or older suffered from PD. (9) The BC Parkinson's Society estimated 13,300 individuals are living with PD in BC, however, the proportion of patients with advanced PD has not been estimated. (10) As of August 2017, there are 212 patients with advanced PD who are waiting to have their initial consultation to confirm eligibility for deep brain stimulation (DBS) or are confirmed eligible and are waiting for surgery (Table 1).

Table 1. Advanced PD patients referred to potential DBS treatment still waiting for surgery or consultation (11).

Waiting for	W1			W2			W1 + W2
	F	M	T	F	M	T	T
<1 year	19	29	48	4	3	7	55
1-3 years	38	87	125	4	14	18	143
>3 years	1	1	2	1	11	12	14
Total	58	117	175	9	28	37	212

W1 = waitlist to first consult with DBS surgeon; W2 = waitlist to be submitted to surgery after initial consultation with surgeon and confirmation of eligibility criteria; F = female; M = male; T = total
Source: Personal Communication with DBS Clinic (12)

The BC population has increased and aged over the past five years resulting in an increased demand for DBS. On average, waitlisted patients have been waiting (either for the first consultation with the surgeon or the surgery itself) for 20 months (ranging from 1 to 61 months) (Table 2). More than half of these patients live in the Greater Vancouver area (FHA and VCHA catchment areas). However, a significant proportion of waitlisted patients are from Island Health Authority (VIHA) and Interior Health Authority (IHA) catchment areas (▉▉▉,

Table 3). For such patients, travel costs to and accommodations in Vancouver to access treatment is an additional burden of disease.

Table 2. Advanced PD patients on waitlist for potential DBS treatment by year of first referral to DBS specialist (backlog of patients waiting for DBS) *

		Year when patient was first referred to DBS specialist						
Waitlist	2012	2013	2014	2015	2016	2017	Total	
■	■	■	■	■	■	■	■	
■	■	■	■	■	■	■	■	
■	■	■	■	■	■	■	■	

Source: Personal Communication-DBS Clinic (12)

* Each patient cohort by year and waitlist is mutually exclusive. Patients in W1 are still waiting to consult with the DBS specialist for the first time. Patients in the W2 list have had the initial consultation with the DBS specialist and after been deemed eligible candidates, they are waiting for the surgery to be scheduled. Patients in either waitlist were still waiting to receive surgery to the date when this data was received.

Table 3. PD patients in the waitlist for DBS by HA catchment area

		Year of first referral						
	2012	2013	2014	2015	2016	2017	Total	%
■	■	■	■	■	■	■	■	■
■		■	■	■	■	■	■	■
■		■	■	■	■	■	■	■
■			■	■	■	■	■	■
■			■		■	■	■	■
■					■		■	■
■		■	■	■	■	■	■	

Source: Personal Communication-DBS Clinic (12) and BC Ministry of Health (13)

HA = health authority; *Place of living missing from database.

1.3.3   Treatment options

Dopamine can be produced by neurons in a healthy brain. Patients with PD have a substantial proportion of degenerated dopamine producing neurons. The remaining cells cannot produce sufficient dopamine to maintain a healthy concentration in the brain. Levodopa is the most commonly used drug to treat PD. It is a precursor of dopamine that is used to supplement the brain to maintain a relatively healthy cerebral concentration of dopamine. It is converted into dopamine by an enzyme called DOPA decarboxylase, which is present in the brain and peripheral tissues. (14) Carbidopa or benserazide are DOPA decarboxylase inhibitors with no central nervous system activity. Therefore, by combining carbidopa (Sinemet) or benserazide (Prolopa) with levodopa, the DOPA decarboxylase inhibitors prevent levodopa from being metabolized outside of the brain, thus minimizing the side effects of levodopa. (2)

Early PD may be treated with levodopa; however, monoamine oxidase-B (MAO-B) inhibitor or dopamine agonist are also part of the PD drugs arsenal. (2) Other types of pharmacological treatment options may also be used to manage PD. Such options available in Canada for advanced PD include amantadine, catechol-O-methyltransferase (COMT) inhibitors or anticholinergics. (2) These drugs are used to supplement or complement the effect of levodopa. Just like any drug treatment, PD treatment has a therapeutic window, which is referring to the range of drug concentration (or dose) that relieves symptoms without inducing side effects to the medication. As the disease progresses, the therapeutic window becomes narrower. In advance PD, the therapeutic window is so narrow that a simple variation in the gastric drug absorption rate may lead to fluctuations in the drug concentration, resulting in unacceptable symptoms. Keeping the drug therapy within the limit of the therapeutic window

is the one of the keys components for effective PD management. Fluctuations that rises above the upper boundary of the therapeutic window may lead to troublesome dyskinesia. On the other hand, fluctuation that falls below the lower boundary of the therapeutic window may result in inadequate symptom control. Patients with advanced PD will often have trials with several appropriate pharmacological treatment options, and are thus likely prescribed a combination of these drugs. When patients have tried a combination of all appropriate pharmacological options, but continue to experience intolerable symptoms or motor complications (e.g., troublesome dyskinesia or prolong immobility during OFF-time), DBS or DUODOPA may be considered. DBS improves PD symptoms by interfering with the dopamine signalling in the brain, whereas DUODOPA gets around the problem of narrowing therapeutic windows by providing the brain with a continuous and steady dose of levodopa.

To be eligible for DBS, patients must be identified by a neurologist to have an inadequate level of symptom relief under their best combined oral medication at maximally tolerated doses. With DBS, tremor, dyskinesia, and motor fluctuations (i.e. bradykinesia and rigidity) can be dramatically improved. Patients seeking relief from other motor symptoms, or those struggling mostly with non-motor symptoms of PD, are not eligible for DBS. (12) Advanced age (>70 years of age) may be a contraindication for surgery due to comorbidities. For example, patients with atrial fibrillation are usually on anticoagulation therapy, which may results in ineligibility for surgical procedures. However, eligibility for DBS is largely dependent of the overall health of the individual and at the surgeons' discretion. Dementia and uncontrolled psychiatric diseases are both contraindications for surgery.

Patients with advanced PD who are not eligible for DBS due to contraindications for surgery may be eligible to received DUODOPA, covered by BC PhamaCare, under the Ministry's special authority program. Patients must be assessed and confirmed eligible for DUODOPA by a Movement Disorder Specialist at the UBC clinic, be experiencing at least 25% of their waking hours in the OFF time with severe disability while in this state, receive an adequate trial of maximally tolerated doses of levodopa with a demonstrated clinical response, and have failed an adequate trial of other adjunctive medications. However, patients that have been waiting for ≥1 year for a DBS consultation may also be considered for DUODOPA (given that they meet the other clinical eligibility criteria for DUODOPA). Patients are ineligible to receive DUODOPA if they have contraindications for Percutaneous Endoscopic Gastrostomy tube (PEG-J), severe psychosis, or severe dementia. If third party insurance is available, patients will receive coverage by PharmaCare only when the patient's private insurance can no longer act as the primary payer (reached insurance cap on total lifetime benefits). (15)

1.3.4 Description of technologies under assessment and regulatory status

1.3.4.1 Deep Brain Stimulation

DBS has been used as the only option to treat advanced PD in BC before approval of DUODOPA in February 2017. (16) DBS is described as an implementation of an electrode in the brain, modulating the overactive brain regions responsible for many of the motor symptoms observed in PD. DBS has proven to be effective in decreasing observed symptoms in PD, with two specific advantages over other types of neurosurgery which involve the destruction of brain tissue (i.e., thalamotomy and pallidotomy). (17) Firstly, stimulation can be adjusted

individually to best manage each patients' specific symptoms post surgery. Secondly, DBS also allows for the reversal of treatment as stimulation settings can simply be turned off. (18)

It takes approximately 8 hours of surgery to complete the DBS procedure. The electrodes are positioned in the brain through a small hole drilled into the cranium (burr holes) through which the surgeon will insert the leads, and pinpoint the target site in the brain that offers the best results under stimulation. The patients are kept awake and asked to perform certain tasks during the procedure.

Figure 1 DBS surgery images (19)
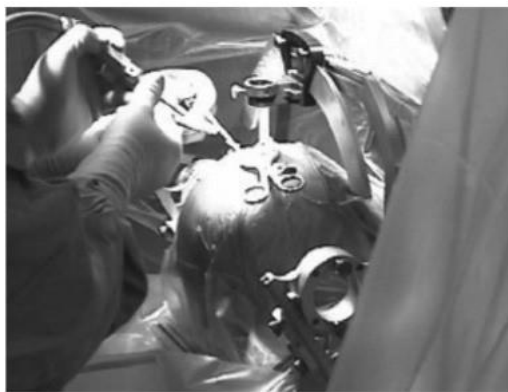
Drilling burr hole — Neurologist examining the patient during a DBS procedure

Source: National Parkinson Foundation information material (20).

Electrodes can be placed in three different sites during the DBS surgery: the thalamic, globus pallidus internus, and subthalamic nucleus regions. Each specific site is targeted to help reduce the most significant specific symptoms experienced by each PD patient. (18) The thalamic region is targeted for those who most prominently suffer from Parkinson's tremor, the globus pallidus internus region is targeted for patients with severe dyskinesia, and the subthalamic nucleus region is targeted for patients who experience motor fluctuation while receiving best medical (oral) treatment. For the purpose of this report, we have assumed there is no different in outcome between subthalamic nuclei and globus pallidus internus DBS in advanced PD, as this subject is still under debate, and not the focus of this report. (21) The electrodes can also be placed in one hemisphere of the brain (unilateral) or in both hemispheres (bilateral). Bilateral patients might be more prone to cognitive side effect from the surgery such as memory or speech problems. (22) Although some patients may only require unilateral stimulation upon first receiving DBS, there is the possibility that with progression of the disease, they may need additional surgery to implant a second lead to manage and control the worsening symptoms of PD. Therefore, to avoid additional brain surgery, almost all patients with advanced PD undergoing DBS surgery in BC have leads implanted for bilateral stimulation, even if they only require a unilateral pulse generator at the time. (12)

There are two identified manufacturers for the DBS devices in use in BC: Medtronic, and Boston Scientific. The DBS system contains an electrode (also called the lead), an extension connecting the electrode to the neural stimulator, and the implantable neural stimulator (often called the pulse generator), which contains a built-in battery that is implanted under the skin on the patient's chest similar to a heart pacemaker (Figure 2). (23) When the battery is depleted,

the pulse generator is replaced in isolation via a relatively simple battery replacement procedure. This procedure does not require an additional brain surgery, but rather a chest incision to disconnect the old pulse generator from the extensions and reconnect to a new one, similar to replacing the battery in a heart pacemaker.

The Medtronic DBS systems are called the Activa SC™ (for unilateral stimulation), Activa PC™ (for bilateral stimulation), and Activa™ RC (rechargeable for bilateral stimulation). The products are registered with Health Canada under the licenses 85709, 81337, and 81338, respectively. The Boston DBS systems are called the Vercise PC™ (for bilateral stimulation), and Vercise™ (rechargeable for bilateral stimulation). The products are registered with Health Canada under the licenses 96822 and 93641, respectively.

Figure 2 DBS system components

Source: Medtronic and Boston websites (2017) (24, 25), UCDavis Health (26)
From top row left: illustrations of the location where the DBS components are implanted and their function; second row from left: one of Boston DBS systems; one of Medtronic DBS systems; Medtronic recharger (belt-type); Boston recharger (collar-type)

While the DBS systems manufactured by Boston Scientific and Medtronic are essentially comprised of the same components with a similar function, there are some differences between these two products. The main difference seems to be related to the life-span of the rechargeable battery and compatibility with magnetic resonance imaging (MRI). The rechargeable model from Boston Scientific has a life-span of 25 years, as compared to the Medtronic rechargeable model which has a 10-year life-span. It is possible to replace the batteries for Medtronic's primary DBS system with a rechargeable battery from Boston Scientific (with the appropriate Boston adaptor), however these patients may no longer receive MRIs because Boston Scientific systems are not yet MRI-compatible. Medtronic does not offer adaptors to connect the Medtronic batteries to Boston extensions/leads. At present, the surgical team for DBS in BC has indicated that a patient would only be considered for a Boston Scientific DBS system, which is incompatible with MRI, if the patient required the directional leads offered by this manufacturer (i.e., the benefit of having directional leads must outweigh the inability to undergo imaging with MRI). Medtronic systems are MRI safe for all body regions (under specific conditions), whereas the DBS device from Boston Scientific is currently only approved for an MRI of the head.

Medtronic has submitted an application to Health Canada (currently under review) for a new model which has a rechargeable battery with a ▮▮▮▮▮ life- span. Boston Scientific has submitted an application to Health Canada (currently under review) for a new model which is MRI-compatible. They are both estimated to enter the market in 2018/19.

Previously, VCHA has cooperated with a third manufacturer, St. Jude's (recently acquired by Abbott), as part of a study trial for this manufacturer's DBS device; however, due to

unsatisfactory results their use was discontinued. Presently, the majority of the DBS equipment is supplied by Medtronic; however, some equipment is also supplied by Boston Scientific. (12) No contract has been set with Abbott but recently they have submitted an application to Health Canada for approval of their new DBS systems (currently under review). With the possible expansion of services, resulting in additional surgical teams performing DBS surgeries in BC, alongside the emergence of new DBS models entering the market in the upcoming years, manufacturer choice and market shares may be affected.

According to the DBS Clinic (12), almost 100% of advanced PD patients receive primary bilateral stimulation starting with a non-rechargeable primary cell implant, with a battery which should last an average of 3.5-5 years (depending on the level of stimulation required by each individual patient). In the first battery replacement procedure, patients will usually receive another non-rechargeable pulse generator. Patients will be offered a rechargeable pulse generator if they require a battery replacement within 2 years of their last procedure (either the initial surgery or the first battery replacement procedure), or in cases where patients are expected to have a long life expectancy (younger patients receiving DBS or those with slow progression), as to avoid multiple battery replacement procedures throughout their lives. The current prices for both Medtronic and Boston Scientific systems are shown in Table 4.

Table 4. Prices of DBS components and system costs for primary implant or battery replacement

Component	Unit price	Primary DBS complete system: bilateral non-rechargeable*	Non-rechargeable battery replacement (bilateral)	Rechargeable battery replacement (bilateral)
Medtronic				
�	▮	▪		
▮	▮	▪		
▮	▮	▪		
▮	▮	▪	▪	
▮	▮			▪
▮				
▮	▮			▪
▮	▮			▪
▮	▮	▮	▮	▮
▮				
▮		▮	▮	▮
▪				
▮	▮	▪		
▮	▮	▪		
▮	▮	▪		
▮	▮	▪		
▮	▮	▪	▪	
▮				
▮	▮	▪		
▮	▮	▪		
▮	▮			▪
▮				
▮	▮			▪
▮	▮			▪
▮	▮			▪
▮	▮			
▮		▮	▮	▮

Source: personal communication with manufacturers, confidential price list; * based on the BC DBS clinic experience that almost a totality of advanced PD patients will receive or be prepared for a bilateral stimulation; # ▬▬ ▬▬▬ ▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬ ¥ rechargeable Boston batteries can be adapted for primary Medtronic DBS system and the total cost including the adaptor would be ▬▬▬▬▬, however, mixed systems are not well accepted due to incompatibility with MRI.

1.3.4.2   DUODOPA

The use of DUODOPA in BC is highly restricted. Patients are only eligible for DUODOPA if they are deemed ineligible for DBS following strict clinical criteria or if the wait for DBS is longer than 1 year (see section 1.3.3). Patients only become eligible ███████████ ██. DUODOPA is commercialized in Canada under the 02292165 Health Canada license, and sold in 100 mL cassettes (each containing 2000 mg levodopa/500 mg carbidopa). These cassettes must be stored in the refrigerator (2 to 8°C) with the outer carton protected from light. Each cassette is for single use only (no product remains can be used the next day), and must only be used for a maximum period of 16 hours from the time that it has been taken out of the refrigerator. Some patients may require more than one cassette over a 16-hour period, depending on the dose necessary for each patient.(27) AbbVie is the only manufacturer that produces intestinal levodopa infusion in Canada.

Patients who are eligible to receive DUODOPA must undergo a Percutaneous Endoscopic Gastrostomy (PEG) to implant a jejunal tube (PEG-J tube) directly in their small intestine. This allows DUODOPA to be continuously released in small and accurate doses via a pump. Doses are titrated to the individual patient. During the 16 hours of continuous infusion, patients must carry the pump attached to their intestinal tube (Figure 3). At present, the PEG procedure for PD patients is only performed at the UBC Hospital. (10)

Figure 3 DUODOPA system
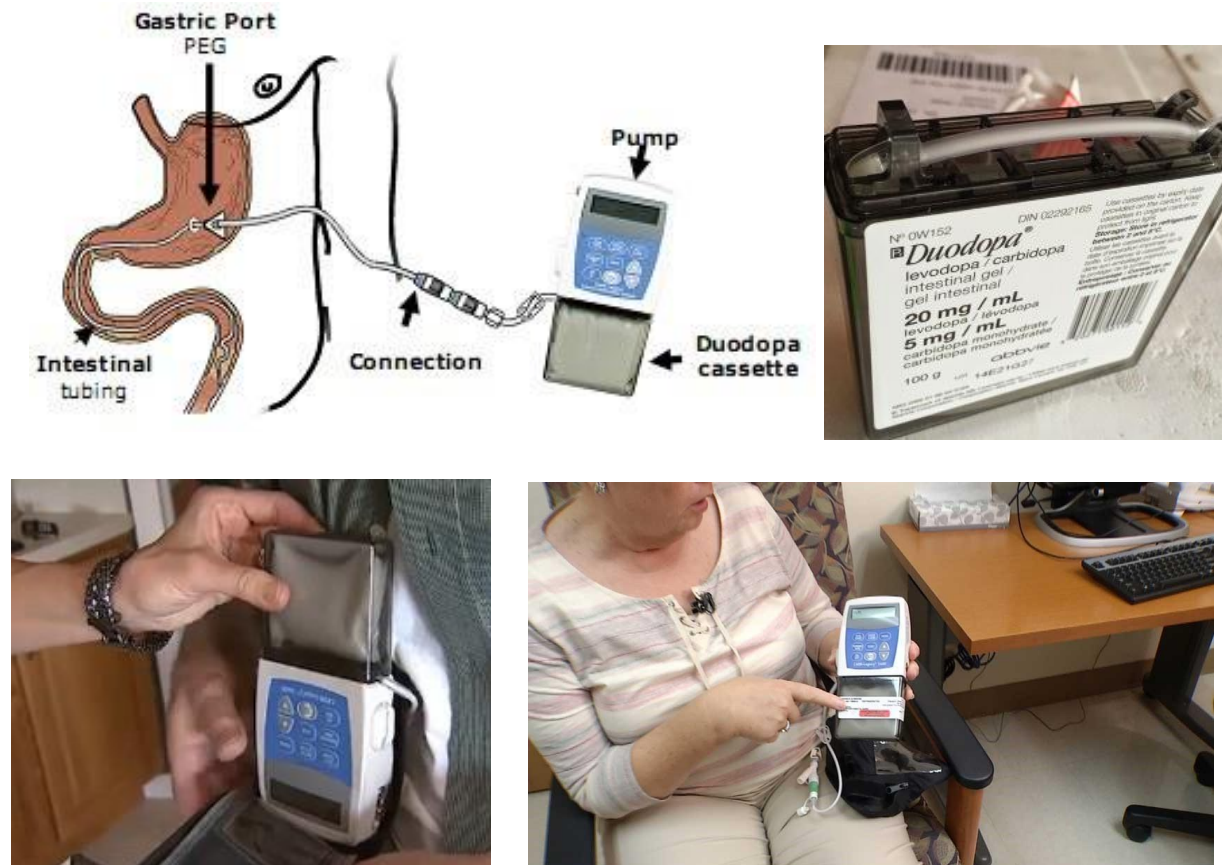
Top-left image: schematic illustration of intestinal tube placement and connection to the DUODOPA; top-right image: DUODOPA cassette; bottom-left image: pump and cassette placed in a bag/belt for patient to carry; bottom-right image: pump in use attached to the patient intestinal tube.
Source: AbbVie commercial material-DUODOPA (2017) (28), Patient blog about DUODOPA (29), Cleveland Clinic information material (30) , KCTV5 news article (31).

DUODOPA costs CAD $████ a year per patient. This price is based on the consumption of one cassette of medication per day, and includes the cost of all the tubes, disposables, pumps and accessories, as well the enrollment of patients in the AbbVie Care program for the duration of time they are on therapy (except wound and skin care products). However, the manufacturer has reported that approximately 8.3% of patients receiving DUODOPA will require a higher dose of the medication. Given that medication remaining in the cassette

cannot be used, such patients will thus require two cassettes of DUODOPA per day, effectively doubling the annual cost of the therapy for those patients to CAD $███████ per year. (32)

1.3.5   Current usage of DBS and DUODOPA in BC

In BC, ███ DBS surgeries in total were performed since 2012 at VGH and the UBC hospital, with an average capacity of ████ surgeries per year, and an average ██% annual growth in the number of surgeries. Currently, only one surgeon is performing DBS implantations. This surgeon also treats patients requiring DBS surgery for reasons other than PD (e.g. tremor, dystonia, pain, etc.). As such, ██% of DBS surgeries were performed on PD patients, resulting in an annual average capacity of ███ surgeries per year for PD, with a similar average annual growth of ██% in the number of surgeries for this indication (Table 5).

The province has spent over $███████ in DBS components for all indications since 2012, including new implants and battery changes (excluding Spinal Cord DBS) (Table 6) which is mostly funded by VCHA (Table 7).

Table 5 DBS surgeries in BC per fiscal year by diagnosis (13)

Diagnosis / Fiscal year	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18*	Total	%
ESSENTIAL TREMOR/DYSTONIA	7	7	8	12	26	4	64	35.56%
NEUROPATHIC PAIN						2	2	1.11%
NEUROSURGERY OTHER P3				2			2	1.11%
PARKINSON'S DISEASE	9	11	17	23	12	2	74	41.11%
PED NEUROSURGERY OTHER - IIA					1		1	0.56%
PED NEUROSURGERY OTHER - IV			1				1	0.56%
REFRACTORY DEPRESSION	5	1		1			7	3.89%
SPASTICITY / PAIN	1	1	1				3	1.67%
UNKNOWN		6	3	11	1	5	26	14.44%
Total	22	26	30	49	40	13	180	
Annual % growth general		0.18	0.15	0.63	-0.18	NA		
Annual % growth PD patients		0.22	0.55	0.35	-0.48	NA		

	All indications	For PD
Average annual # DBS surgeries	33.4	14.4
Average annual growth in # DBS surgeries	0.20	0.20

* 3-month data (up to Jul 31st)

Table 6 Historical spending in DBS components by the calendar year - including new implants and battery changes for all indications (except spinal cord injury) and all manufacturers

Components	2012	2013	2014	2015	2016	2017	2012-17
Volume of Components							

Table 7 Annual spending on DBS equipment for PD by health authority*

	2012	2013	2014	2015	2016	2017**	2012-17
▉	▉	▉	▉	▉	▉	▉	▉	▉
	▉	▉	▉	▉	▉	▉	▉
▉	▉	▉	▉	▉	▉	▉	▉
	▉	▉	▉	▉	▉	▉	▉
▉		▉	▉	▉	▉	▉	▉	▉

* exclude expenses with DBS components used in Spinal cord stimulation; **BCCSS database, transactions up to 15-jul-2017 (33); M = Medtronic components; B = Boston components.

DUODOPA was added to the BC PharmaCare special authority request program in February 2017(16) under an exceptional coverage scheme. Since February 2017, authorization for DUODOPA has been granted to ▉ patients. Patients can become eligible for DUODOPA if they have been waiting for ≥1 year for a DBS consultation, given they meet the other clinical eligibility criteria for receiving this drug. Consequently, 74% of patients on the DBS waitlist are currently potential candidates for DUODOPA as an alternative treatment to DBS (▉, Table 1), and this proportion is likely to increase if there is no expansion in the capacity to conduct DBS surgeries in BC.

1.3.6   Promising treatments on the horizon

An apomorphine injection device (Movapo®) manufactured by Paladin Lab Inc. is being reviewed by CADTH. (34) It is a pen with pre-set dose of apomorphine for intermittent subcutaneous injection. This new technology is indicated for acute, intermittent treatment of hypomobility, "off" episodes in advanced PD. (35) It is not indicated to be used for maintenance treatment of PD, as compared to continuous subcutaneous infusion of apomorphine (CSAI).

CSAI is a technology that continuously infuse apomorphine underneath the skin of the patients through an external pump and a subcutaneous catheter (butterfly needle) that can be inserted and removed. It has been used in Europe for a number of years. CSAI is not available in Canada. Two economic studies comparing CSAI as an alternative for DUODOPA or DBS had mixed results.

A cost analysis in Spain demonstrated that, over a 5-year time horizon, CSAI costs would be higher than DBS, but lower than DUODOPA, among patients with advanced PD. No clinical outcomes were reported. (36)

In another study, examining use of CSAI in the UK and German health systems, when considered over a lifetime horizon, using QALYs and LYs gained, CSAI dominated DBS (i.e., lower cost and better outcomes). When CSAI was compared to DUODOPA, it was found that DUODOPA had better QALY outcomes but due to its higher cost was found to have an incremental-cost per QALY gained (ICER) of £244,684.69 (€72,914.58). (37)

Another non-oral alternative in the market is Rotigotine transdermal patches (Neupro®) manufactured by UCB Canada Inc. and reviewed by CADTH in 2015. (38) The drug was recommended to be listed for the treatment of advanced PD by CEDEC, as an adjuvant to oral levodopa, on condition that the total daily drug plan cost would be comparable to the costs of ropinirole or pramipexole. Rotigotine is still under review in BC.

Levodopa/carbidopa subcutaneous infusion and levodopa/caribidopa/entacapone intestinal gel are two other emerging technologies currently undergoing clinical trials. (39, 40) Regular physical exercise has also been investigated as an alternative treatment to improve patients' quality of life and mobility.

The comparison of DBS or DUODOPA to these other alternative therapies are not under the scope of this HTA, but may be of future interest to the Province.

1.4   Structure of report

A jurisdictional scan and stakeholder perspectives, including patients, are outlined in the next three sections. This is followed by a detailed assessment of the clinical and economic evidence. The economic model is found in the subsequent section and is followed by the budget impact analysis.

Chapter 2 Jurisdictional Scan

Summary

DBS is the standard of care and first choice of therapy for advanced PD patients across Canada and internationally.

DUODOPA is largely reserved for those patients ineligible to DBS, refusing brain surgery or unable to travel when DBS is not offered locally, despite not being found within acceptable cost-effectiveness thresholds in any context.

DBS battery replacements has been offered by service providers other than the original DBS surgery setting. DUODOPA can be provided by trained neurologists.

2.1   Objectives

To outline policies from across Canada regarding the use of these technologies, whether they have been publicly funded, and the current state of technology use internationally.

2.2   Methods

Two methods were used to perform an environmental scan: a search of grey literature using the Centre for Reviews and Dissemination (CRD) database and websites of main HTA agencies (CADTH, NICE, AHRQ, SIGN); and emails to public health contacts in all Canadian provinces and territories.

The emails were sent by The Canadian Agency for Drugs and Technologies in Health (CADTH) liaison officers across Canada, and by the policy analysts from the BC Ministry of Health using the intergovernmental relations network. A snowball sampling scheme was used, with follow up with the responders as necessary. The manufacturers were also contacted by the UBC research team. Individual interviews with facilities that have implemented either technology were conducted by the UBC researchers and incorporated in this report. There were three main questions of interest: [1] Which technologies (DUODOPA, DBS, and DBS types) are

being publicly funded for advanced PD patients, [2] Is there any written policy regulating or limiting the utilization of any specific technology, and [3] which factors influence the decision on the type of treatment to be covered (i.e. cost, patient preference, convenience, availability, other barriers).

For manufacturers of both technologies under consideration the main questions of interest were about their system components, price, battery life-span, logistics related to treatment delivery and patient support after system implantation.

2.3 Results

2.3.1 Jurisdictional Surveys and Interviews

Newfoundland and Labrador (NL), Alberta, Quebec, Manitoba, and Saskatchewan partially responded to a request for information. None of these provinces have a written policy guiding the use of either technology and the choice of technology is guided by clinician judgement.

DBS has been covered by the provincial public system in all five provinces. It is the preferred treatment and standard of care in Alberta, Manitoba, Saskatchewan, and Newfoundland and Labrador. DBS surgeries are performed within each province, with the exception of NL. Patients residing in NL must travel to either Toronto or Halifax for surgery. NL provides funding for the primary devices and partially covers travel expenses as per provincial Medical Transportation Assistance Program. Battery changes are performed locally by the NL neurosurgeons and fully covered by the public system.

Medtronic is the stated choice of device in Alberta, Manitoba and NL. Alberta has reported that patients are resistant to receiving rechargeable batteries in consideration of the

inconvenience of continuous recharging, however, patients who require high voltage settings, are offered rechargeable batteries due to the rapid depletion non-rechargeable batteries (depletion duration of 2-3 years as opposed to the standard 5 years). One Alberta specialist indicated that Ontario has had a better experience with rechargeable batteries. This seems to be due to the use of devices from Boston Scientific, which are considered to be more comfortable to recharge for the patients. In Alberta there are two surgeons (Edmonton and Calgary) implanting DBS in a streamline manner, allowing for a 6 to 12 month wait period from time of referral to the DBS specialist to surgery.

DUODOPA is not on the Quebec "List of Medications". However, this product was reimbursed for a limited number of patients through the "exceptional patient measure" administered by Provincial health insurance. Details of the eligibility criteria were not provided.

In NL, the practice pattern is to offer DBS before DUODOPA unless other factors such as age, or inability to travel outside province preclude DBS as a treatment option. These patients may then access DUODOPA gel if they have 3rd party insurance. Neither option is considered unless the patient is experiencing severe disease with poor symptom control.

In Manitoba, currently there is only one physician trained to administer DUODOPA and the province has approved 2-3 patients for coverage. To qualify for coverage of DUODOPA by the public health system, patients must meet all of the following criteria:

- Experience at least 25 percent of the waking day in the OFF state

- Has severe disability while in the OFF-state as assessed by a Movement Disorder Specialist

▢ Has received an adequate trial of maximally tolerated doses of levodopa, with

 demonstrated clinical response

 ▢ Has failed adequate trials of other adjunctive medications (entacapone,

 dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors) if not

 contraindicated and/or contrary to the clinical judgement of the prescriber.

- Request for coverage must be made by a neurologist who is experienced in the

 treatment of Parkinson's disease and who has completed the education program

 referenced in the Product Monograph.

In Alberta, DUODOPA is covered under the public system for patients ineligible for DBS,

or for those who are likely to be non- compliant with DBS therapy (i.e., lack of ability to comply

with programming of DBS at home), or those who refused to have brain surgery.

ABBVIE stated that there are currently ███ patients on DUODOPA treatment across

Canada (BC, AB, MB, ON, QC, NL) under private or public insurance, or a mix of both. Some have

been using DUODOPA for as long as 8 years.

The key barriers mentioned by the Provinces are availability of specialists to provide

either DBS or DUODOPA treatments, as well as cost or the inability of patients to travel.

2.3.2 Published HTAs

HTA agencies in Canada and countries with similar publicly funded health systems have

evaluated DBS and DUODOPA at different times with focus on different decision problems.

The jurisdictional scan of HTA reports returned 10 HTAs: 5 from Canada (4 DBS, 1

DUODOPA), 2 from Australia (1 DBS, 1 DUODOPA) and 3 from the United Kingdom (1 DBS, 2

DUODOPA). None of the HTAs directly compared DBS to DUODOPA.

Deep Brain Stimulation

Four Canadian DBS HTAs were identified (Table 8). (37-40) Of these, 3 HTAs broadly

aimed to determine the costs and cost-effectiveness of DBS compared to best medical therapy

(BMT). The other HTA aimed to determine the cost-effectiveness of rechargeable compared

with non-rechargeable DBS devices. (41) The most recent HTA from CADTH, published in 2011,

included a systematic review. (42) This report concluded that "limited evidence regarding the

cost-effectiveness of DBS compared with BMT was identified" and that the identified evidence

was "inconsistent" and therefore no clear conclusion could be made. (42) The estimated cost

per DBS procedure at McGill's University Health Centre (UHC) was $27,444. (43) A similar cost

was reported in Ontario ($24,420-$28,420). (44) The Ontario HTA provided the only

incremental cost-effectiveness ratio: $11,650 per 10-point improvement of the UPDRS motor

function score (part III). (44) The HTA from McGill was the only report that indicated support for

the expansion of the DBS program. (43) The remaining 3 reports did not provide specific

recommendations to adopt or reject DBS. (41, 42, 44)

One Australian DBS HTA was identified. (45) The purpose of this HTA was to estimate

the costs of DBS surgery compared with ablative surgery. The report concluded that the

estimated cost of DBS surgery was AUS$ 26,245 and recommended that "interim public funding

should be supported for patients where their response to medical therapy is not sustained and

is accompanied by unacceptable motor fluctuations AND subject to the patients' participation

in a controlled trial". (45)

One UK DBS HTA was identified. (46) The purpose of this HTA was to determine the

costs and resource requirements to provide DBS in Ireland compared with providing DBS

abroad (the scenario in 2012). The median cost over 10 years to deliver a DBS service in Ireland was estimated to be €65,600 (compared with €44,700 for treatment provided abroad).

As can be seen, the DBS HTAs conducted in Canada, Australia and the United Kingdom had different objectives. Generally, the DBS HTAs conducted in the Canadian setting did not provide a specific recommendation to either adopt or reject DBS, except in Quebec where the expansion of DBS treatment was recommended. In Australia, DBS was recommended for funding. In Ireland, no specific recommendation was made to either continue to support DBS treatment abroad or to establish a DBS service in Ireland.

Table 8 Economic outcomes and recommendations from HTA reports of DBS

Jurisdiction	Year	Objective	Method	Time horizon	Outcomes	Recommendation
Canada						
CADTH (42)	2011	To determine the cost-effectiveness of DBS compared with BMT for patients with Parkinson's disease or neurological movement disorders	Systematic review	n/a	n/a	• Limited evidence regarding the cost-effectiveness of DBS compared with BMT was identified • The evidence identified was inconsistent, no clear conclusion can be made
CADTH (41)	2010	To determine the cost-effectiveness of rechargeable versus non-rechargeable deep brain stimulation devise for patients with Parkinson's disease or neurological movement disorder	n/a	n/a	n/a	• No specific recommendation • The search did not identify any literature on the cost-effectiveness of rechargeable versus non-rechargeable DBS devices.
McGill University Health Centre (43)	2009	To systematically review the literature on effectiveness and safety of DBS since 2005, as well as estimate the budget required to meet the shortfall at the McGill University Health Centre	Costing	1 year	Cost / DBS procedure (including 1-yr follow up): $27,444	• "The McGill University Health Centre should support and expand the DBS program at the Montreal Neurological Hospital and Institute to the extent possible."
Ontario (44)	2005	To provide an economic analysis of DBS	• Costs ◻ Cost-effectiveness	1 year, 10 years	DBS cost / case: $24,420 - $28,420 Potential downstream cost savings / offsets due to reduction in L-dopa: $2,800 / patient over 10 years (discounted of 5% is included) DBS costs (including predicted offset): $25,620 $11,650 per 10-point improvement on UPDRS motor function score	• No specific recommendation • "The cost per procedure to institutions with the expertise to undertake DBS and the human resource considerations are likely to be limiting factors in the further diffusion of DBS."

Australia						
Medical Services Advisory Committee (45)	2001	To determine whether DBS is more effective than ablative surgery (thalamotomy or pallidotomy).	Costing	None, cost components of DBS surgery	Cost DBS: AUS$ 26,245	• "MSAC recommends that, based on the strength of evidence pertaining to deep brain stimulation for Parkinson's disease (MSAC Application No. 1031), interim public funding should be supported: o for patients where their response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; and o Subject to the patients' participation in an appropriate controlled trial to obtain information on adverse events, longer-term patient outcomes and costs in the Australian setting. This should be carried out in consultation with appropriate groups and States, and should be limited to centres with necessary expertise."
United Kingdom						•
Ireland (46)	2012	To compare the resource requirements and costs of providing DBS in Ireland compared with DBS abroad (current scenario)	Model (unspecified) • Cost minimization analysis	10 years	Median cost over 10 years: Abroad: €44,700 Ireland: €65,600	• no specific recommendation to fund national DBS service or to continue with DBS service provision abroad • national DBS will cost more per patient compared with current service (offered abroad) • cost difference significantly influenced by any changes to the relative contribution by private health insurance companies to DBS care for patients with private insurance • national DBS service may cost more but may improve access to DBS for patients otherwise eligible but unable to travel

DUODOPA

In Canada, DUODOPA was reviewed by CADTH's Common Drug Review in 2009 (47). DUODOPA was compared to the oral levodopa / carbidopa therapy. DUODOPA was estimated to cost $166 / day and the oral levodopa / carbidopa therapy was estimated to cost <$3/day. On the basis of costs relative to benefits, DUODOPA received a "do not list" recommendation (Table 9). (47)

In Australia, DUODOPA was reviewed by the Pharmaceutical Benefits Advisory Committee (PBAC) in 2008. (48) The ICER provided by the submitter was AUS $45,000-75,000 (including carer burden) and AUS $130,000–150,000 (excluding carer burden). The time horizon was not specified. PBAC concluded that DUODOPA "not be recommended for listing" (Table 9). (48)

In the United Kingdom, 2 DUODOPA HTAs were undertaken (1 in Scotland (49), and 1 in Wales (50)). The Scottish Medicines Consortium recommended in 2016 that DUODOPA be "…accepted for restricted use within NHS Scotland. Use is restricted to those patients who are not eligible for DBS" (Table 9). (49) Over a 20 year time horizon, the manufacturer estimated the ICER to be £58,250. The All Wales Medicines Strategy Group recommended in 2007 that DUODOPA "…should not be recommended for use within NHS Wales". (50) Over a 5 year time horizon, the manufacturer estimated the ICER to be £84,198. (50)

Overall, Canada, Australia and Wales did not recommend to list DUODOPA within their respective jurisdictions. Scotland was the exception and recommended use of DUODOPA only among those who were not eligible to receive DBS (Table 9).

Table 9 Economic outcomes and recommendations from HTA reports of DUODOPA

Jurisdiction/ Author Agency	Year	Objective	Method	Time horizon	Outcomes	Recommendation
Canada						
CADTH (47)	2009	To determine the cost-utility of DUODOPA compared with BMT	Method not stated • Cost-utility •	5 years	QALY estimate was redacted Cost (DUODOPA): $166 / day Cost (oral form levodopa/carbidopa): <$3 / day	• Do not list
Australia						
Pharmaceutical Benefits Advisory Committee (48)	2008	To determine the cost-effectiveness of DUODOPA compared with BMT	Model (unspecified) • Manufacturer submitted • H&Y stage	Not specified	ICER: AUS$ 45,000 – 75,000 (including carer burden); AUS$ 130,000 – 150,000 (excluding carer burden)	Reject: not recommended for listing
United Kingdom						
Scotland (Scottish Medicines Consortium (SMC)) (49)	2016	Not stated	Markov model • manufacturer submitted • 25 health states plus death • States a combination of H&Y score and "off" time	20 years	ICER: £58,250 Incremental cost: £73,291 Incremental QALY: 1.26	• Co-careldopa (DUODOPA) intestinal gel is accepted for restricted use within NHS Scotland. Use is restricted to those patients who are not eligible for DBS. • SMC decision reflects a discount to the list price of co-careldopa intestinal gel. However, the ICER presented in the report does not include this discount as the discount is

						considered "commercial in confidence".
Wales (All Wales Medicines Strategy Group (AWMSG)) (50)	2007	To determine 1. Whether the additional benefits offered by co-careldopa intestinal gel (DUODOPA®) over relevant comparators justify the associated costs, and if so, 2. Whether the total budgetary impact of supporting the use of co-careldopa intestinal gel (DUODOPA®) is acceptable.	Model (unspecified) • Cost-utility • submitted by manufacturer • hypothetical cohort of 100 patients	5 years	ICER: £84,198 / QALY Incremental drug costs: £73,842 Incremental AE costs: £1,740 Non-drug conventional care:- £8,640 Incremental QALY: 0.877	• Not recommended • "Co-careldopa intestinal gel (DUODOPA®) should not be recommended for use within NHS Wales for the treatment of advanced levodopa-responsive Parkinson's disease. The clinical and cost effectiveness data presented was not sufficient for AWMSG to recommend its use."

2.4   Summary of jurisdictional scan

DBS appears to be the standard of care in the majority of jurisdictions for patients who no longer have a good response to best medical (oral) therapy (BMT) or who have unacceptable motor fluctuations. DUODOPA when compared to BMT in other jurisdictions has not demonstrated acceptable cost-effectiveness thresholds in any context, except Scotland. Despite the lack of evidence for cost-effectiveness of DUODOPA, a number of jurisdictions in Canada are offering DUODOPA therapy for patients who are ineligible or cannot access DBS. We were unable to identify a direct comparison of DBS with DUODOPA for patients deemed eligible for either therapy.

In Canada, DBS is the first choice of treatment for patients with advanced PD when they are no longer achieving a good response to oral BMT. DBS is the first choice of treatment even if patients are required to travel out of province to receive DBS. DUODOPA appears to be an exceptional, last alternative treatment for patients not deemed eligible for DBS, those refusing surgery, or those unable to travel to access surgery elsewhere. However, public coverage is not standardized across Provinces.

Chapter 3 BC context and other stakeholders perspectives

Summary

There seems to be mutual agreement from all stakeholders that both DBS and DUODOPA have a profound impact in increasing patient quality of life. Although neither therapy is considered to be curative or combating the underlying advancement of the disease, they are both considered to significantly support, control, or alleviate symptoms and maintain general quality of life.

Moreover, it was also clearly stated that while some patients may be eligible for only one of the two treatment options, personal choice for therapy should also be taken into consideration. In the possibility of an increase in resources, multiple stakeholders (such as neurologists and administrators) have indicated the need for expansion of these services at other centres across the Province.

3.1 Objective

To understand the BC experiences with therapies available for patients with advanced PD, and determine the burden of illness, patterns of care, and capacity in BC as it relates to the management of PD.

3.2 Methods

During July and August 2017, we conducted phone and email interviews with 14 key stakeholders identified to provide a particular perspective on the policy question. The participants were recruited via snowball sampling, and included stakeholders working in the Greater Vancouver area with varying expertise and health care experience:

- 5 Representatives
  - Department of Drug Intelligence and Optimization
  - Parkinson Society of BC
  - Medtronic, Boston Scientific, and AbbVie
- 9 HCPs with experience of care management for patients with PD

- o Surgeons and neurologists with expertise on DBS and DUODOPA therapy

- o DBS Clinic at VGH

- o UBC Parkinson's Research Centre

Feedback was made anonymous so no personally identifiable information was included. A semi structured interview guide was developed to guide the interviews. This guide evolved over the course of the interviews, as questions were refined to reflect what had been learned through the previous interview(s).

3.3 Findings

3.3.1 Clinical experience with the technology in BC

In BC, DBS is only conducted at UBC and VGH. The neurosurgery team at VGH has performed over ███ cases so far. (23) Most surgeries conducted at VGH used DBS systems from Medtronic; however, devices made by Boston Scientific have also been used. Previously, VGH has cooperated with St. Jude (now Abbott) as part of a trial for their device, but there is no contract with this manufacturer at present. (12) Although patients with DBS are given a remote that enables them to make small adjustments within a pre-determined voltage range (established by the DBS clinic to be at a safe level for the patient), other changes to the stimulator setting to account for disease progression must occur through the DBS clinic. At present, neurologists across BC are not able to adjust the stimulation level for patients, and thus, all patients must refer to the DBS clinic for any required adjustments.

DUODOPA is provided by a single manufacturer, AbbVie. At present, DUODOPA is only reimbursed in BC under special authority. ███ patients per year receive funding for this treatment through this program. The UBC Movement Disorder Clinic is currently coordinating

the care for those deemed eligible to receive DUODOPA, primarily in cooperation with a specialized nurse who is funded and trained by AbbVie, to provide support and care for post-operative and long-term management and care required for DUODOPA therapy.

Upon patient eligibility for DUODOPA (confirmed by the UBC Movement disorder clinic), AbbVie enrolls patients into the AbbVie Care Program. Through this program, a nurse trained by AbbVie to specialize in the care and management of DUODOPA (also referred to as the DUODOPA nurse), aids in coordinating the delivery of DUODOPA with the Specialty Health Network (the distributor of DUODOPA) to the patients' homes. The PEG procedure takes place at the UBC Hospital. The titrations required postsurgery are usually done over a span of 2-3 days at the UBC movement disorder clinic during the day. After establishing the clinical need (dosage of medication required), coordination of coverage with insurance providers for each patient, and the primary titration process, patients may receive support for future maintenance of stoma and adjustments in dosage by the DUODOPA nurse. This can be achieved via technological platforms, home visits, or visits to the DUODOPA Clinic at the UBC Parkinson's Research Centre. Future adjustments in medication can also either be directly executed by the patient, or by the patients' primary neurology team with support from the DUODOPA nurse.

AbbVie also provides the jejunal tubes used for the PEG procedure at the UBC Hospital (both the tubes used for the primary procedure and replacement tubes if necessary), the pump, accessories (except wound care products), as well as support from a reimbursement specialist from AbbVie to maximize insurance coverage for each patient. In addition, within the contract set out by the UBC Parkinson's Research Centre with AbbVie, funds are provided to the centre

to allow for the DUODOPA nurse (███████) to train other nurses, doctors, lead titration sessions, and provide support to patients for long-term care and management.

3.3.2   Access to treatment

Currently in BC, there is only one salaried surgeon who conducts DBS at VGH. Upon referral of potential eligible patients by their primary neurologist, patients will be placed in the first waitlist (W1 list) to have an introductory consultation with the DBS surgeon. At present, patients are usually in the W1 list for a period of approximately 1.5-2 years. During the primary consultation, patients are either approved for surgery, in which case they move on to the second wait list (W2 list), or are deemed to be ineligible for surgery. Criteria for ineligibility may include contraindications for the surgery (age, physical status, comorbidities, etc.), displaying symptoms of PD that cannot be targeted by DBS, lack of social or familial support systems to manage the necessary post-operative follow-up and care, displaying symptoms of PD that cannot be targeted by DBS, or for some patients, not qualifying for the surgery due to the extent of disease progression based on severity of symptoms (not as advanced as other patients).

Patients who are moved to the W2 list must wait approximately an additional 1.5-2 years to receive DBS, with thus an overall wait time of approximately 3-4 years. According to the DBS clinic, only patients who are deemed eligible for surgery, subsequent to a thorough examination in the first consultation with the lead surgeon, are referred to the DBS clinic. However, there still exists a possibility that patients may become ineligible for DBS, due to changes in their disease status, while waiting in the W2 list to receive the surgery.

Moreover, due to the funding structure for DBS, battery replacement procedures are now performed by the DBS neurosurgery team at UBC (and previously at VGH). Although, it has been reported by various stakeholders that under the circumstance that a provincial funding program should be implemented, this procedure could also be performed by other trained neurosurgeons closer to each catchment area.

3.3.3 Cost for patients

Patients undergoing DBS do not have any direct costs related to the surgery. The fees for surgical consultation, work-up prior to surgery at the DBS Clinic, surgery, discharge, and post-discharge and follow-up visits to the DBS Clinic are all covered under the provincial health plan, with funds allocated to VCH to provide such services. However, there are high out of pocket costs for patients, mostly related to transportation, accommodation fees, parking fees, and time away from work for recovery and follow-up visits. More than 50% of the patients receiving DBS are from outside of the VCH catchment.

Patients with DBS, on average, will make two visits to VGH prior to the surgery. On the day of the surgery, patients will come in on the morning and are discharged within 1-2 days. This translates to 3-4 nights of accommodation fees for some patients. Post-discharge, a follow-up appointment is made with the DBS at 6-8 weeks from the time of surgery, where the stimulator is turned on. The number of appointments made from this point on is dependent on each individual patient. Some patients will only require one or two more appointments to ensure that their stimulator is fully adjusted. However, most other patients will require more frequent and continuous follow-up appointments up to six months postoperatively, with approximately 60% or patients coming back prior to their scheduled six month follow-up.

Patients will also require another follow-up visit at the one year mark. Given that patients are feeling comfortable with their adjustments at the one year mark, the follow-up visits are then scheduled annually. It is again estimated that about 60% of patients require a follow-up visits at least twice a year. This is most prominently due to the fact that disease progression for PD is not affected by DBS, as surgery only alleviates the motor symptoms of this condition.

With varying speeds of disease progression specific to each patient, many patients will require adjustments in their stimulation settings to maintain the effectiveness of DBS, and to also correspond with changes in dose or frequency of other medications over time. Further, although the battery used for DBS has an approximately four to five year lifespan, depending on the progression of disease and severity of symptoms, patients with higher stimulation settings will 'burn through' the battery much faster, and thus will require more frequent visits to the DBS clinic. This will inevitably require the patient to receive a battery replacement surgery earlier than the five year mark.

The current guidelines of DUODOPA funding is such that patients are only deemed eligible ██ ███████. Within the AbbVie Care program the support of a reimbursement specialist is provided to patients, who in cooperation with the patients, determine method of payment through ██

██

██

██

██████████████████████ (32).

As compared to DBS, it is reported that patients with DUODOPA will require less frequent follow-up visits. Similar to DBS, patients will require a surgical consultation; however, the surgery itself is an outpatient procedure which allows patients to be discharged on the same day. Upon recovering from the surgery (with a recovery period of approximately 1-2 weeks), patients must go to UBC for dose titration sessions (to adjust the dose of DUODOPA as appropriate for each patient), which are usually conducted over 2-3 days. Following the initial titration, additional adjustments to medication are not commonly required. More so, with specific instructions from the nurse coordinating the post-operative care for DUODOPA, such adjustments can also be carried out by patients, caregivers, or the regular neurology team. In contrast to DBS, patients receiving DUODOPA will have monthly out of pocket expenses for care and management of the stoma, alongside cleaning and washing out the tubes connected to the pump for delivery of DUODOPA (usually done by simply using soap and water). Moreover, it has been reported that while the expectation of complication is fairly low, there may be some complications requiring use of antibiotics, and in severe cases, a tube replacement.

3.3.4   Technology potential for illness and injury prevention

There seems to be mutual agreement from all stakeholders that in fact, both DBS and DUODOPA have a profound impact in increasing the patients' quality of life. Although neither therapy is considered to be curative or combating the underlying advancement of the disease, they are both considered to significantly support, control, or alleviate symptoms and maintain the patient's general quality of life. These therapies are considered to increase the motor function of the patient; thereby, not only increasing the patient's and care provider(s)' quality of lives through decreased dependency and physical limitations, but also, reducing harm and

preventing injuries by decreasing the likelihood of falls and other injuries leading to frequent

visits to the ER or various other HCPs. Moreover, the overall enhancement of the patient's

physical ability will lead to the patient regaining a sense of control, and thus significantly

improving patient and care provider emotional and psychological well-being.

3.3.5 Technology potential for improving marginalized and disadvantaged populations

Both DBS and DUODOPA are therapies which are only considered in the circumstance

that BMT is insufficient in providing adequate symptom relief for the patient. Therefore,

patients assessed for these treatments are typically patients with advanced PD that reach the

maximum tolerated dose of oral therapy with Antiparkinsonian drugs (PD drugs). With disease

progression, such patients can be described as displaying frequent and severe symptoms, thus

making patients vulnerable through the increasing inability to care for themselves, to work, to

partake in social events, and loss of overall physical and cognitive ability, thus leading to both

potential social exclusion and economic marginalization. In regards to this, DBS and DUODOPA

have the potential to significantly enhance the patient's physical ability and psychological well-

being, to such a degree as to return the patient's sense of autonomy and control, enabling the

patient to be socially engaged and return to their role as an active member of society.

3.3.6 Perspective on patients experience (reported by clinicians or service providers)

It was unanimously expressed by all stakeholders that patients with advanced stage of

PD who are no longer receiving adequate symptom relief by BMT, should be eligible for either

DBS or DUODOPA therapy. This conclusion was derived from the understanding that patients,

as well as their respective care providers, experience a very poor quality of life due to not only

physical pain and loss of motor skills or cognitive abilities, but also in terms of other stresses

such as emotional burden of disease and influence on the patients' relationships and sense of self. In addition to this, it was also reported that in their professional experience, the vast majority of patients receiving either DBS or DUODOPA have shown dramatic increases in both physical capabilities and quality of life. Moreover, stakeholders were also in unanimous agreement that while some patients may be eligible for only one of the two treatment options, personal choice for therapy should also be taken into consideration. In the possibility of an increase in resources, multiple stakeholders (such as neurologists and administrators) have indicated the need for expansion of these services at other centres.

3.3.7 Non-health benefits (autonomy, convenience, comfort and confidence)

For patients with advanced PD, both the frequency and severity of symptoms increase to the point where patients often lose some or all sense of autonomy in their daily lives, as well as decreased confidence to engage in social interactions. This in turn has a very negative impact on the patient's quality of life and happiness. Thus, advanced therapies for PD have the potential for great non-health benefits, allowing patients to regain autonomy, confidence, social interactions, strengthening of relationships, and an overall increase in psychological well-being. It should be noted that the caregiver's quality of life may also be dramatically increased, as they will not only regain more time to engage in their own lives, but also, regain a sense of a partnership within their relationship with the patient.

3.3.8 Environmental impact

Some aspects of both treatment options with regards to perceived environmental impact should be noted. For DBS, the frequency of battery replacements and the appropriate waste management should be considered. Regular batteries last an average of 4-5 years, at

which time the patient requires a battery replacement procedure for a new battery, and

disposal of the battery by the hospital. For patients with higher stimulation levels, rechargeable

batteries are considered. BC performs more than █ battery replacements a year for DBS for all

indications. (12) Medtronic stated that batteries should be collected in batches from the

hospital and shipped to a safe disposal facility via Medtronic with no cost to the hospital.

For DUODOPA, the disposal of used cassettes with drug remaining should be

considered. The majority of patients use █ cassettes per month, and about █% will use █

cassettes per month. The volume of waste produced is relevant when added to the ice packs

and delivery boxes.

Figure 4 DUODOPA waste for disposal

Source: Parkinson patient blog (29)

As advised by AbbVie, special precautions are necessary for disposal and other handling:

ensuring that cassettes are for single use only and that opened cassettes cannot be reused at a

later time, that any left-over product should be disposed in accordance to the patients'

geographic region and environmental regulations, and that all empty and used cassettes must be returned to the pharmacy for disposal. (28) Currently, DUODOPA is distributed to patients by the Specialty Health Network, owned by Shoppers Drug Mart, which also collects used cassettes for recycling purposes upon delivery of the medication.

3.3.9   Sector cost

███

███

███████████████████████████████   ████████████████████████████

███████████████████████████

3.3.10   Capacity for providing the technology in BC

Health Care providers noted that lack of OR time, staff, lack of training for staff, and physical space would be considerable challenges in expanding access to DBS OR DUODOPA in BC. ██

██ has been conducting the respective procedures for these therapies. In increasing the number of patients receiving either treatment option, there would need to be a potential increase in both the number of health care providers offering such services, as well as an increase in the number of specialty clinics that advise and help patients with postoperative care and long-term management.

Considering the backlogged demand of PD patients waiting for DBS (W1 + W2 lists) and their geographical location, BC would require another 3-4 surgeons in Greater Vancouver (between VCHA and FHA), 1 in the VIHA area, and 1 in the IHA area to clear the waitlist in

approximately 1 year, assuming they are given the same OR time and resources from the DBS clinic team as the current surgeon, and assuming they would be completely dedicated to treat advanced PD patients (i.e., not performing DBS implants for other indications). NHA does not have a number of patients in the wait list equivalent to the current yearly capacity for one DBS surgeon in the same *modus operandi*, however, other funding modes and economy of scale should be explored by this health authority to assess whether to provide DBS within their region.

3.3.11   Cost of implementation

This could include costs of "hiring" and training a number of other surgeons for the primary implant and deciding on the funding mode for battery replacement with the same surgeons or referring these simpler procedures to other surgeons (neurosurgeons, general surgeons, etc.). Also, costs of creating other clinics across the Province, and training other HCPs such as those available in the DBS clinic at VGH to provide pre- and post-operative care to DBS implanted patients, as the DBS clinic at VGH reaches maximum capacity.

3.3.12   Perspectives on providing the technology as an insured service in BC

It is mutually agreed upon by stakeholders that patient preference for either treatment is an important ethical factor to be considered. Furthermore, given the significant debilitating outcomes of advanced stage PD, and in consideration of significant impact of these therapies and increase on the quality of lives of both patients with advanced PD, and their respective care providers, these services should be insured services in BC. However, at present DBS is still seen as the standard of care for patients who are good candidates for the surgery.

3.3.13 Risk for successful implementation (financial, human resource, stakeholders, others)

Some apparent risk for successful implementation seems to be the need for additional infrastructure (space, logistics such as OR booking time, staff, training of both front-line staff, as well additional surgeons for both treatment options) in additional hospitals, specifically in consideration of establishing these facilities and resources within FHA, IHA and VIHA. Alternatively, if such services are not provided in these regions, another risk for implementation in ensuring equal access would be the added travel costs associated for receiving care.

As mentioned in the interviews with multiple stakeholders, ███████████████ ██████████████████████████████ low MSP fees associated with the procedure. DBS implant is a long surgery (8-9 hours) with a billing fee that is relatively speaking much lower as compared to other procedures. Therefore, should expansion be considered, the province may need to renegotiate the fee schedule or salary agreements, minimum number of surgeries performed per year, and other factors as pertained to this specific procedure.

Financial risk is moderate since there is interest and support to increase resources from all stakeholders (Physicians, Patients, Care providers, and advocacy groups such as BC Parkinson Society), with a general recognition of the positive outcomes and high efficacy of both treatment options.

Chapter 4 Patient Experience

Summary

In comparison of DBS versus DUODOPA, patients reported that both treatments are viewed as invasive procedures. Patients understood the substantial benefits of DBS; however, they also identified major risks associated with this surgery to include possible changes to personality and speech. Despite this, the patients felt that "the decision [to receive DBS] was made by their physical state and the lack of response to medications, so that they had no other choice but to undergo DBS surgery," with hopes that this procedure would decrease "their dependency on the medication that was driving their lives", and increase both their physical capabilities, as well as their quality of life. (pg. 7)

It was described that prior to receiving DUODOPA, patients were quite reliant on their care providers, with no control of when symptoms would present themselves. It was stated by one care provider that before DUODOPA, there was a constant fear of not knowing when she would need help, and therefore always being attentive to her need, every minute of the day. However, after DUODOPA therapy, there is the possibility of scheduling a routine for care, and most importantly, the ability to not fear for the patient's safety at other times.

4.1   Objective

To gain an understanding of the outcomes important to patients, in order to guide the evaluation of the clinical literature and inform the economic modeling and interpretations of findings presented in this report.

4.2   Patient experience from literature

4.2.1   Method

A rapid review of qualitative studies was conducted by Canadian Agency for Drugs and Technologies in Health (CADTH) (51) on behalf of the Health Technology Review (HTR) Office from the BC Ministry of Health to aid in meeting the overall objectives of this HTA. The research question guiding this review was:

- What are the perspectives of individuals, and their non-clinical caregivers, with advanced PD regarding their experiences with either deep brain stimulation or levodopa-carbidopa intestinal gel (DUODOPA) interventions?

4.2.2   Results

CADTH found 495 citations in a preliminary literature search. Of these studies, 458 were excluded based on first-level screening of titles and abstracts. Upon full-text review, an additional 23 articles were excluded, with 14 articles, alongside relevant associated publications, meeting the inclusion criteria established by the above declared research questions. (51)

4.2.3   Summary of findings

This review provided rich qualitative data on patient experiences. In comparison of DBS versus DUODOPA, patients reported that both treatments are viewed as invasive procedures. Patients understood the substantial benefits of DBS; however, they also identified major risks associated with this surgery to include possible changes to personality and speech. Despite this, the patients felt that "the decision [to receive DBS] was made by their physical state and the lack of response to medications, so that they had no other choice but to undergo DBS surgery," with hopes that this procedure would decrease "their dependency on the medication that was driving their lives", and increase both their physical capabilities, as well as their quality of life. (pg. 7)

DUODOPA was believed to have more modest benefits, mainly the ability to decrease oral medication; however, this procedure was also identified to be rather invasive with the limitation of dependency on a pump. Overall, to many patients DBS and DUODOPA "are not

mutually exclusive; rather the decision is about order and sequence of treatment that best navigates the benefits and the risks, including the side effects of available options". (pg. 7)

No studies were found reflecting the patients' experiences from DUODOPA. For patients who had undergone DBS surgery, many reported a positive experience from DBS, including fewer "off" periods and improved motor skills. However, despite the relative success from the surgery, patients reported feelings of anxiety and distress in transitioning after the DBS surgery. "As one male patient put it: 'before stimulation, every day was a struggle. Now, I miss the time when I used to fight. Nowadays, I'm like a soldier when the war is over, there's no longer anything to fight against. My life seems empty. I get up in the morning without any aim or prospects.' " (pg. 8). Moreover, some patients have reported the emergence of new symptoms after DBS which were not previously experience, mainly concerning issues with balance and speech. This can be a difficult period as "patients again come to face that they have PD," and must therefore develop mechanisms to cope with the reality of their situation. "This integration and reconciliation is likely key with patients' and their caregivers' ability to come to terms with DBS." (pg. 10)

Regarding Caregivers, some "were relieved by DBS, stating that they felt '[…] I am probably the one who is most happy. It is a paradox, but I think so. In some ways, I have gotten my husband back' ". (pg. 9) On the other hand, some caregivers and patients reported difficulties in adjusting expectations to match the patient's new physical state, or more so, a higher perceived level of ability by the caregivers as compared to the reality of the patient's condition, " 'My wife cannot tell when I am feeling bad, and then she thinks I am lazy. She starts

fussing, telling me to get my act together…and I try, but when I am in pain or in some other way cannot function, then there is nothing to do about it.' " (pg. 9).

4.3   Patient experience specific to BC

4.3.1   Methods

Patient recruitment was initiated via 2 sources: the Patient Voices Network (PVN), which is administered by the [BC Patient Safety & Quality Council](#) (BCPSQC) Patient & Public Engagement network, and Parkinson Society of BC. The PVN invitation was published on the BCPSQC website for a period of approximately 1.5 months; however, there was no expressed interest in participating in this patient engagement initiative from any patients partnering with this network. Therefore, all participants were recruited via support from the Parkinson Society of BC. This was achieved via referrals of interested participants, or by direct contact by patients who had become aware of this initiative via the Parkinson Society BC official website and newsletter.

4.3.2   Participants

A total of 39 participants were interviewed. Of these 39 interviews, 16 interviews were conducted with patient caregivers, and 23 interviews with patients who are identified to have advanced PD. Patients were identified to be advanced based on symptom classifications derived from the Hoehn and Yahr Scale. (52)

From the 16 interviews with caregivers, there was an even 50% split of males versus females. From the 23 patients interviewed, 62% were male and 38% were female. The average age for patients with advanced PD (patients directly interviewed or those discussed during caregiver interviews) was approximately 68 years.

Most interviews were conducted via phone interviews. This was done to ensure that patients from all geographic regions within BC (e.g., patients from Vancouver Island and northern/interior of BC) were provided with the opportunity to participate in these interviews, as well, in consideration of the physical ability of patients with advanced PD. For participants who showed interest, and confirmed ability to travel comfortably to the VGH Research Pavilion, a focus group interview was conducted. Therefore, two patients with experience with DBS, three patients with experience with DUODOPA, and 2 caregivers with experience with DUODOPA were interviewed in-person.

4.3.3   Summary of interviews

Patients with advanced PD included a subpopulation of naïve patients (those who had not received either DBS or DUODOPA, either due to ineligibility or being on the waitlist to receive therapy), patients who had experience with DBS, and patients with experience with DUODOPA. Similarly, caregivers to patients in the three different classifications listed above were also interviewed.

4.3.3.1   Advanced Patients with PD (experiences before receiving DBS or DUODOPA, OR patients who have never received either DBS or DUODOPA)

In discussion of the definition of 'patients with advanced PD', participants recognized themselves as reaching this point when they could feel that they were no longer receiving adequate relief and control over their symptoms from their best-combined oral therapies. This in turn has led patients to feel a very significant decrease in the quality of their lives, in addition to an increased dependency on their caregivers. Patients have reported struggling with feelings of social isolation, resulting from having to stay at home due to the severity of their symptoms,

worsening physical conditions demanding the need to discontinue work or previous hobbies, difficulties in maintaining responsibilities within their household, as well as changes in the dynamic of their relationships with caregivers, given the shift in the patient's emotional state and self-confidence. It should be noted that patients have felt great stigmatization by individuals in the community who are not aware of the symptoms of PD, and therefore, have often jumped to the conclusion that patients are displaying involuntary movements due to being "drunk or out of my mind".

In consideration of the therapies available or patients with advanced PD, some patients have indicated that they are not eligible to receive either DBS or DUODOPA, due to contraindications for either or both treatment. Patients in this classification have expressed their frustrations in having limited access to other therapies, which have not yet been approved in Canada as compared to the United States. For such patients, there is a great deal of anxiety and fear about longitudinal prospect of managing their condition with their diminishing physical and cognitive abilities, and ultimately, the understanding that with the progression of their disease, they will likely have to transfer management of their condition to long-term care and palliative care facilities. This sentiment was more pronounced for patients and caregivers of those living further away from Vancouver, due to difficulties with access to specialists (such as a neurologist) to manage the long-term care required for patients with advanced PD. It should be noted that in regards to the long-term care and management required for such patients, there was an emphasis on the patient's concern about the monetary and financial implications of requiring continuous care, as well as increased dependency on medical equipment and home adjustments required to navigate changes in the patient's physical ability.

For patients who have been put on the waitlist for DBS or are currently under consideration to received DUODOPA, their personal decision to consider either treatment is solely based on their critical need for this therapy. Patients reported significant burden of treatment as both treatments are considered by patients to be rather invasive. However, there is a common and shared sentiment amongst the patients that given their progression of their disease and physical ability, there really is no choice but to go for the therapy. In this regard, when asked whether patients considered either treatment as preferred given the risk factors associated with either option (neurosurgery for DBS and a Percutaneous Endoscopic Gastrostomy (PEG) to implant a jejunal tube (PEG-J tube for DUODOPA), patients indicated that while they had considered the risks of treatment, the risks as compared to the potential benefit (given their overall diminishing physical and cognitive abilities) was considered to be "worth the risk".

In consideration of a hypothetical thought experiment where patients were asked the question to identify either DBS or DUODOPA as their preferred treatment, given that they would be eligible for both options, patients reported mixed results. Many patients indicated that DBS was more favorable given that they understood the surgery to be a rather "simple surgery, as far as brain surgeries go", and as well the convenience of limited long-term care and management required by the patient. In addition, patients who preferred DBS were also aware that in receiving DUODOPA therapy, they would be required to carry around a pump with them at all times, alongside increased follow-up care and management required; therefore, such patients indicated that these limitations would be too hard on a daily basis, and so they would rather prefer DBS to DUODOPA. Conversely, other patients indicated DUODOPA to be their

preferred option. The reason for this choice is mainly centered around the perceived fear of neurosurgery and the possible negative outcomes (i.e., changes in personality, loss of personality, tampering with their mind and thoughts, and etc.), in addition to the idea that neurosurgery is a non-reversible treatment option, whereas DUODOPA therapy can be terminated at any point. Moreover, several patients indicated that they really didn't have a preferred option, and that the main priority for them was to receive any therapy that would increase both their physical and mental capabilities, as well as their overall quality of life.

4.3.3.2   Patients with experience with DBS

It was mutually expressed that at the time of decision-making, despite being aware of the risks and possible downstream repercussions, the degree of dyskinesia, tremor, and other PD symptoms, alongside the inconvenience of frequent dosage of medications which were not very effective in providing symptom relief, the decision was made to receive DBS. It was mentioned by many participants that a major goal of the surgery was to discontinue oral medications as it is a constant reminder of PD.

Post-surgery

Patients reported that there was a substantial decrease in symptoms observed post-surgery, with an approximate 70-90% reduction in tremor and dyskinesia, with others reporting the disappearance of dystonia altogether. However, it was also mentioned by certain patients that some symptoms such as rigidity, slowness of movement, walking, freezing, and tone control were not relieved by DBS. It was stated by patients that it took approximately 2-3 months to arrive at a point where they were comfortable with their stimulation settings. Within

this period, patients were required to go to the DBS clinic every week for the first few appointments, then every second week.

Many patients have reported difficulties in having to make frequent trips to the DBS clinic, specifically those who are currently working and those who are travelling from areas such as Vancouver Island, and Northern and Interior regions in BC. For patients who are travelling longer distances, a substantial increase in out of pocket costs have been described in regards to both transportation and accommodation. It has been reported that although there is the possibility of partial provincial coverage for these patients, restrictions on eligibility (having to prove eligibility and only being covered for procedures, thus exempting follow-up appointments at the DBS clinic or with specialists), combined with the reality of available transportation payment options and schedules, inevitably results in the majority of costs being transferred to patients. This has been reported to lead to a reduced number of scheduled follow-up appointments, despite of the patient's health status and need to adjust either their medication or stimulation settings.

Patients have reported a 75% improvement in UPDRS scores, alongside a major decrease in the frequency and dosage of their required medication, and that DBS has allowed them to maintain their position in the workforce, the ability to travel, and increase in social interactions. It was mentioned that for some patients this surgery has turned back the clock by approximately 5-7 years regarding disease progression. It is the patients' belief that the effects of this surgery will last approximately 10 years.

It should be mentioned that despite the positive outcomes experienced by DBS, some patients reported negative experiences due being awake throughout the surgery. It was

reported by these patients that they were not very well informed about the reality of what it would feel like to be awake during the surgery, and as well, no real support was provided to patients after this experience. These patients described feelings of anxiety and stress from having undergone this experience, with continuous nightmares and "flashbacks".

Retrospective comment

Patients confirmed that the surgical team had explained that DBS is potentially great for symptom relief at the extremities, tremor and fine motor movement; and that this did not encompass all motor symptoms such as balance and other non-motor symptoms such as mood, tone of voice, and degeneration of the areas of the brain affecting behavior and memory. It was mentioned that perhaps the risk of surgery was in fact a little higher than was originally lead to believe by the surgical team, specifically in regards to the risk of post-surgical infections. This conclusion is in part due to hearing about the experiences of other patients who have had post-surgical complications with DBS, many months after the initial surgery. It was the patients' understanding that if you had not developed an infection after the initial 6-week recovery period post-surgery, you were in the clear. Patients could not comment on the specific circumstances leading to infections for such patients.

Considerations for battery replacement

It was stated by patents that on average, patients required a battery replacement operation approximately every 3 to 3.5 years. When asked about preference for a rechargeable 10-year battery, some patients stated that this would be a possibility if they found that they needed a battery replacement operation sooner than the 3 to 3.5-year mark. However, one patient mentioned that they would not opt for the rechargeable battery, with reasons being

that: (A) they would have to be reminded on a daily basis to recharge the battery, causing both anxiety and serving as a reminder of their disease status, and (B) that you would need a surgery after 10 years anyway; therefore, it did not make sense to receive a battery replacement surgery with the added burden of being responsible for recharging the battery. Moreover, it was mutually agreed by all patients that rechargeable batteries are not often considered due to the fact that the battery replacement procedure is quite simple, with a quick recovery period of approximately 10 days. Therefore, given the minimal risk for patients, the burden of undergoing this procedure does not outweigh the annoyance of regularly recharging the DBS battery. It was emphasized that the battle with PD is to have as normal a life as possible, and therefore, the responsibility of recharging the battery would interfere with this, serving as a constant reminder of the patient's disease status.

Considerations for DUODOPA

Although patients who had received DBS had not been offered DUODOPA therapy in any formal capacity, it was mentioned that if given the choice, DBS would still be preferred to DUODOPA. The main reason for this was again the idea that carrying around a pump, which requires daily management and cleansing, would not only be an extra burden, but also serve as a daily reminder of the patient's disease status. In addition, patients would be tempted to 'fiddle around' with the device, whereas with DBS, they only require minor changes in stimulation setting, and a battery replacement procedure every 3.5 years following the initial period of attaining the right level of stimulation.

<u>Out of pocket costs</u>

Maintenance of DBS is not considered to be a direct out of pocket cost to patients, as adjustments in stimulation and battery replacements are coordinated via the DBS clinic. However, there are other substantial costs for patients, including oral medication, frequent absence from work (due to the initial surgery and recovery period, as well as multiple visits to the DBS clinic for required adjustments to the stimulation settings), travel expenses to the DBS clinic, and cost of exercise. Patients are highly encouraged to try a wide scope of physical activities and exercise classes (such as swimming, boxing, etc.), often lead by physiotherapist or coaches, essential in helping patients with PD maintain their physical ability. Unfortunately, however, there are no subsidies provided to cover the high cost of such activities, leaving many patients unable to afford these services. Detailed information about out-of-pocket costs can be found in Appendix Q.

<u>Comments/additional information</u>

Patients have stated that the long wait time to receive DBS is something that they worry about in the long-term. For some patients, the wait time for surgery was simply too long and thus unacceptable given their condition, therefore compelling them to seek treatment in other centres abroad (mainly in the United States). This proved to be quite a significant financial burden given travel expenses and the cost of the treatment (including difficulties coordinating coverage by insurance companies and third-party payers), as well as complications in coordinating care and follow-up appointments with the BC DBS clinic upon their return to adjust stimulation settings.

Furthermore, patients shared knowledge of a research study, pointing out that it may be beneficial for patients to adjust the stimulation settings based on what activity they were partaking in, for example: a certain setting may decrease motor symptoms but affect the patient's ability to speak (voice and tone); therefore, in time of public speaking, the patient could adjust the stimulation to account for this.

It was reported that as patients require increases in stimulation settings due to disease progression, they are concerned as to whether the BC surgeon will have intimate knowledge of their case and history. However, patients have indicated that they are provided with exemplary support from nurses at the BC DBS clinic, who are very diligent in helping patients with any required adjustments. In addition, despite the growing cohort of DBS patients and need for continuous follow-up, the DBS clinic has been very accessible. Patients have reported that the DBS clinic has increased staff to accommodate for this, and that they are provided with great suggestions for how to best adjust to life with DBS. Patients feel that they now have much more flexibility as to when they must take their medication (mostly due to a decrease in frequency and not having to worry about complications with nutrition uptake), and can simply call the DBS clinic to change their stimulation as needed. This is described to provide patients with a sense of control, an asset lost throughout the progression of PD.

Moreover, it was reported that it would be very beneficial to have more education about PD and DBS. Patients are often congratulated for how much better they are doing since DBS; however, there are comments from individuals stating that they are sad to hear that the surgery did not help them get 'cured'. People need to be educated that at present, this disease

does not have a cure, and thus, patients can only hope to improve management of symptoms and prolong time in which they feel more in control.

4.3.3.3   Patients with experience with DUODOPA

Dec 2017 | Centre for Clinical Epidemiology and Evaluation | Vancouver Coastal Health Research Institute

[redacted]

[redacted]

[redacted]

[redacted] .

Decision to receive DUODOPA and considerations for DBS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

███

███

██

██

████████████

Post-surgery

██

███

██

██

██

███

██

███

███

██

███

██

██

███

██

Dec 2017 | Centre for Clinical Epidemiology and Evaluation | Vancouver Coastal Health Research Institute

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Experience with DUODOPA in management of PD

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Comments/additional information

██

███

██

███

██

██

███

██

███

██

███

██

███

████████████████████████████████

4.4   Caregiver Input

For patients who had received either DUODOPA or DBS, caregivers overwhelmingly stated a sense of relief. It was confirmed unanimously by all caregivers that in fact, both treatments had made tremendous changes in the quality of lives of both the patient and the care provider. It was described by some care providers as ████████████████████ ████████████. It was stated by a care provider that if their partner (the patient) is limited, they are limited. In contrast, the patient described the fact that the caregiver would never leave their side as weighing heavy on their shoulders. It has been tremendous for both the patient and the care provider to not only be able to do more things together, but to also have time for activities individually.

In contrast, caregivers of patients' on the wait list for either treatment, or in the case of non-eligibility for both treatments options, reported a very progressive deterioration of their quality of lives, in addition to severe anxiety and stress in managing the ever-increasing burden of care placed on their shoulders. It was reported that the anticipated financial burden to provide continuous care for such patients, meant that many caregivers had already been forced to leave their positions at work, or conversely, that they could not afford to stop working because they could not financially afford the costs of care if they were to retire.

Moreover, it was reported that the shift in responsibility and burden of disease has greatly altered the dynamic of their relationship with the patient ██████████████████ ██ ██

Chapter 5 Assessment of Evidence

Summary

    Clinical Effectiveness: No RCT directly comparing DUODOPA with DBS was identified. Two retrospective observational studies compared DUODOPA directly to DBS. The 15-month study, which included 40 patients, did not find any differences between DUODOPA and DBS in all four UPDRS subscales. The 5-year study, which included 60 patients, found that DBS was significantly better than DUODOPA in UPDRS part IV due to the finding that DBS reduced time with troublesome dyskinesia. DUODUOPA and DBS showed similar results in other UPDRS subscales.

    Five parallel RCTs were included in the indirect comparison. In total, 483 patients were randomized to DBS, 430 patients to BMT in the DBS RCTs, 37 patients received DUODOPA and 34 patients received oral levodopa. Patients who received DBS showed significantly better results in UPDRS III, UPDRS IV and daily ON time without troublesome dyskinesia when compared with DUODOPA. While greater reduction indicates greater improvement, on average, DBS patients showed further decreases in both UPDRS III and IV scores as compared with DUODOPA patients (respectively 5.5 and 2.3, measuring motor disability and complications). Although the UPDRS III estimate was statistically significant, the 95% CI spanned across nearly 10 points. The imprecision suggested that UPDRS III estimate contained a fairly high degree of uncertainty.

    The quality of evidence from the observational studies is low due to the small sample size and high risk in selection bias. While there is good quality of evidence provided by the RCTs, the quality of the indirect comparison is low due to a linear network and potential of bias in the safety data from DUODOPA RCT.

    Economic Literature Review: A single study was identified that enabled a direct comparison of DUODOPA to DBS. Note that the primary purpose of this study was to compare apomorphine to DBS, DUODOPA and BMT. From the NHS perspective the ICER was £136,390 per QALY and from the German healthcare perspective the ICER was €209,900 per QALY.

5.1   Objectives

To assess the clinical effectiveness, safety and cost-effectiveness of levodopa/carbidopa

intestinal gel (DUODOPA) compared with deep brain stimulation (DBS) in advanced PD.

5.2 Clinical effectiveness

5.2.1 Methods

5.2.1.1 Inclusion criteria

Table 10 defines the patient population, inclusion criteria and outcomes of interest.

Table 10 Inclusion criteria

Patient Population	Intervention	Appropriate Comparators	Outcomes
Patients suffering from advanced Parkinson's disease with symptoms or side effect cannot be adequately relieved by BMT	Direct comparison		Clinical outcomes
	Levodopa/carbidopa intestinal gel (DUODOPA)	Deep brain stimulation	All-cause mortality Serious adverse events Quality of life
	Indirect comparison		Change of UPDRS subscales (Part I to IV)
	DUODOPA or DBS	Oral levodopa or BMT	Change in on-time without troublesome dyskinesia Adverse effects

Note: BMT: best medical treatment; CEAC: cost-effectiveness acceptability curve; ICER: incremental cost-effectiveness ratio; LOS: length-of-stay; WTP: willingness-to-pay.

Study design

For the purposes of this project, we followed the 2011 report on the hierarchy of evidence from the Centre for Evidence-based Medicine at University of Oxford. (53) We first searched for any systematic review of randomized controlled trials (RCTs) (level 1). If the amount of evidence was deemed insufficient at this level, we searched for randomized trials (level 2). If again the amount of evidence was deemed insufficient at this level, we searched for nonrandomized studies (level 3). Lower levels of evidence were considered hypothesis-generating and determined to be insufficient for policy decision-making.

Initially, studies comparing DUODOPA to DBS directly were included. If the evidence for direct comparison was not sufficient, studies comparing DUODOPA to oral levodopa and DBS to BMT were included for indirect comparison of DUODOPA with DBS.

5.2.1.2   Exclusion criteria

- Non-English-language publications

- Abstract/conference proceedings

- Letters and commentaries

- Early Parkinson's disease

- Studies without an appropriate comparator group

- Studies published before 2000

5.2.1.3   Literature search overview

Initial scoping searches were done in June 2017 using Medline (Ovid) to assess the volume and type of literature relating to the objectives. The scoping search also informed the development of the final search strategies. The search strategies were developed by an information specialist, with input from the reviewers. The strategies were designed to capture generic terms for DBS, DUODOPA and Parkinson's disease. We searched relevant citations from 2000 to 2017. Published articles were identified in Medline, Embase and the Cochrane Central Register of Controlled Trials via Ovid. Search results were imported into Endnote and Microsoft Excel for screening. The search is considered up to date as of June 23, 2017.

Relevant articles were identified during screening. Articles retrieved for full-text reading were separated by the type of publication (i.e., systematic reviews, randomized trials, and nonrandomized comparative studies). Economic studies were also sorted out for detailed reading at this point in the process. Search filters for the various study designs were incorporated into the searches to increase the sensitivity of the searches. (54, 55)

5.2.1.4 Study selection and data extraction

One reviewer screened titles and abstracts and then full texts following a specified protocol. A second reviewer confirmed the relevance of included studies. The study flow was summarized using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

A reviewer extracted all the data for clinical outcomes, while another reviewer extracted all the data from economic analyses. Data were cross-checked for errors by the two reviewers. Any discrepancy was resolved by discussion.

5.2.1.5 Quality assessment

The systematic reviews and RCTs were critically appraised using an adapted Cochrane checklist for critical appraisal.(56) A risk of bias table for included RCTs was generated. Nonrandomized studies were critically appraised with the Downs and Black checklist recommended by the Cochrane Collaboration. (57)

5.2.1.6 Data synthesis

Cochrane Review Manager software, RevMan 5.3.5, was used to synthesize data for clinical outcomes. (58) Dichotomous outcomes were analyzed by using risk ratio (RR) or odds ratio (OR). When we found a statistically significant RR or OR we also calculated risk difference (RD) and number needed to treat for the outcome (NNT) when possible. The results from economic studies were presented in descriptive tables.

The indirect comparison results were synthesized by ITC program from CADTH. (59)

5.2.1.7 Subgroup analysis

No subgroup analysis was planned.

5.2.2   Search results

5.2.2.1   Search for studies comparing DUODOPA to DBS directly

We first performed a search for studies directly comparing DBS to DUODOPA in MEDLINE and Embase (Search strategies in A.1 and A.1). A total of 188 citations were identified in this search, eight of which were found to be duplicates. At this stage, all 180 titles and abstracts were screened, resulting in 12 records identified as economic studies and exclusion of another 80 articles.

Eighty-eight articles were established to be reviewed and assessed at the level of full text, from which two systematic review and two observational studies met the inclusion criteria. No RCT directly comparing DUODOPA with DBS was identified. Twelve records were identified as economic studies. The PRISMA diagram of the direct comparison search can be found in Figure 4.

Figure 4: PRISMA diagram of direct comparison search
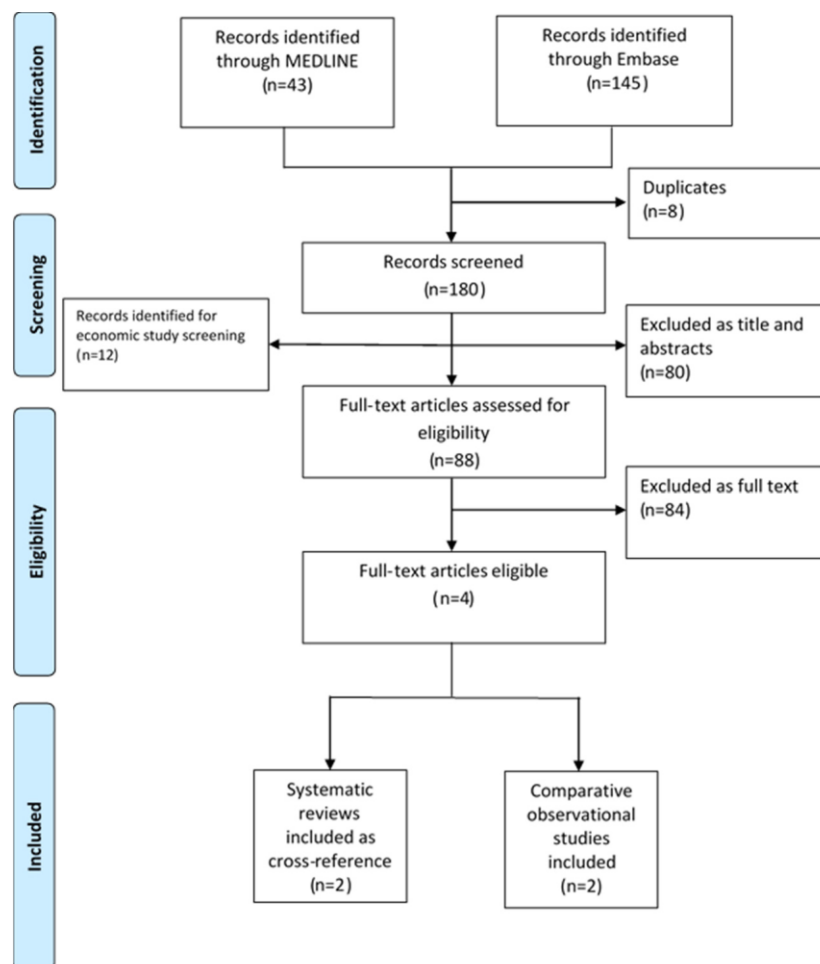
5.2.2.2 Search for studies comparing DUODOPA or DBS to BMT

Since no RCT comparing DUODOPA directly with DBS was found, search strategies were

developed to search for studies comparing DBS to best medical treatment (BMT) or DUODOPA

to BMT in MEDLINE, Embase, and CENTRAL (A.2 to A.7). The purpose of this search was to

identify RCTs that would provide data for indirect comparison. First, the most updated

systematic reviews comparing DBS or DUODOPA to BMT were identified from our search and

RCTs were extracted from the reviews. Then RCTs published after the latest search dates of the

systematic reviews were searched and screened. A total of three RCTs met the inclusion criteria

for DUODOPA; however, two of which were crossover RCTs and as such, not suitable for indirect comparison. Overall, one RCT comparing DUODOPA to BMT and four RCTs comparing DBS to BMT were included. Other than the 12 records identified in the direct comparison search, an additional 16 records were identified as economic studies. In total, 28 records were identified as economic studies. The PRISMA diagram of the search for indirect comparison RCTs can be found in Figure 5.

Figure 5: PRISMA diagram for RCTs comparing DUODOPA or DBS to BMT
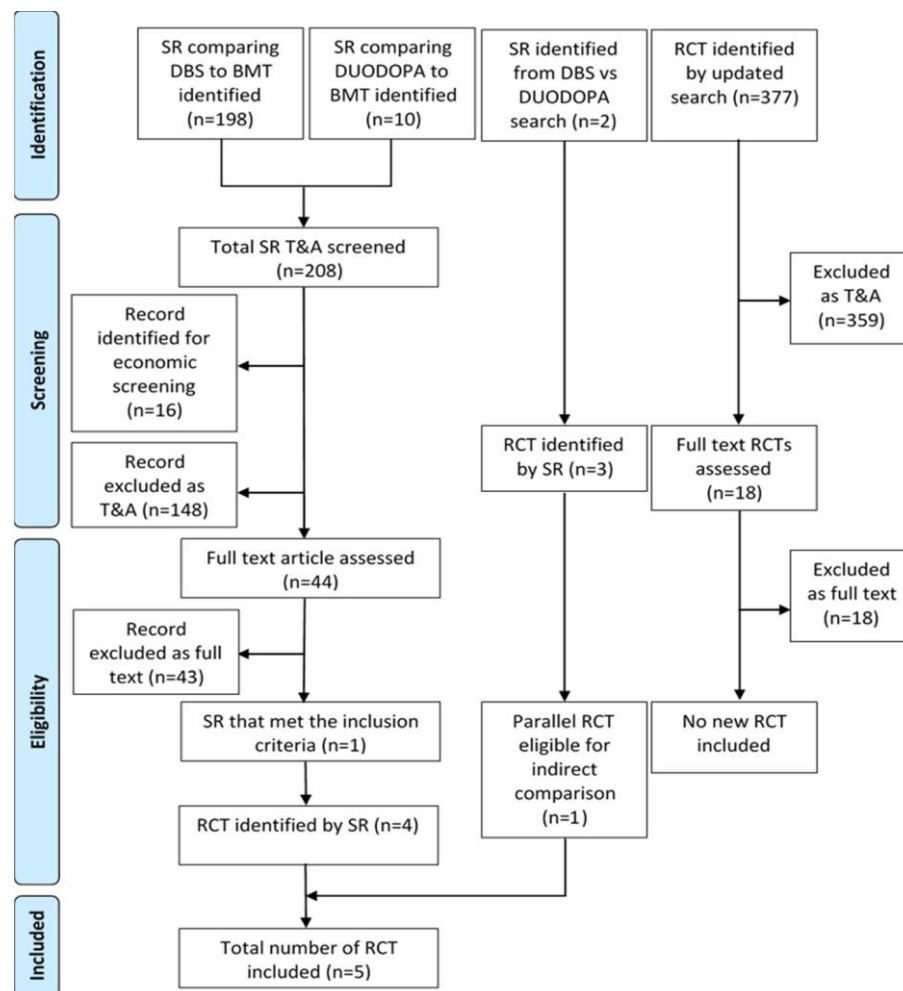
5.2.3   Description of included studies

All three systematic reviews identified were used for cross-reference only (17, 60, 61).

Clarke 2009 (60) included both DUODOPA and DBS. However, the authors did not perform any

direct or indirect comparison of DUODOPA and DBS. Wirdefeldt 2016 (61) only included studies

comparing DUODOPA to BMT. Perestelo-Perez 2014 (17) only included studies comparing DBS

to BMT. Therefore, the systematic reviews did not provide very useful information other than

references of RCTs included within their review.

Two comparative observational studies comparing DUODOPA to DBS were included (62,

63), both identified to be retrospective studies. Merola 2011 examined 20 DUODOPA patients

and 20 DBS patients from baseline, and at 15-month median follow-up. (63) Merola 2016

examined 20 DUODOPA patients, 20 DBS patients and 20 BMT patients at baseline and at the 5-

year follow-up. (62) Merola 2011 matched patients with similar baseline characteristics such as

the age of onset, duration of disease and level of disability. Merola 2016 selected patients with

similar disability. Both observational studies compared the level of disability between

treatment groups using the Unified PD rating scale (UPDRS). UPDRS is a validated questionnaire

used to measure the level of disability caused by PD. (64) It contains four subscales: part I

measures non-motor aspects of experiences of daily living (i.e., cognitive impairment, mental

illness), part II measures daily activities, part III measures motor disabilities and part IV

measures motor complications. It is one of the most commonly measured outcomes in PD

studies.

Four parallel RCT comparing DBS to BMT, one parallel RCT comparing DUODOPA to oral

levodopa and two crossover RCT comparing DUODOPA to oral levodopa were found (65-71).

RCTs with crossover design were not suitable for indirect comparison, therefore they were excluded from the indirect comparison. (70, 71) A total of five RCTs were included in the indirect comparison. In the RCTs, 483 patients were randomized to DBS, 430 patients to BMT in the DBS RCTs. Thirty-seven patients were randomized to receive DUODOPA in the DUODOPA RCT, while 34 patients were randomized to oral levodopa. In our indirect comparison, we considered oral levodopa to be the same as BMT because patients in the oral levodopa arm are prescribed a similar set of medications. All RCTs measured UPDRS and reported adverse events. The characteristics of included studies and the baseline characteristics of patients can be found in Appendix B.

5.2.4 Description of excluded studies

Two crossover RCT that meet our inclusion criteria were excluded because crossover studies were not suitable for indirect comparison. Some studies suggested by the clinical advisors and AbbVie did not meet our inclusion criteria. They are listed in the table of excluded studies.

5.2.5 Quality assessment

The observational studies that directly compared DUODOPA to DBS were critically appraised by a modified Downs and Black checklist. (57) The detail of the appraisal can be found in Appendix D.1. The two observational studies shared the same limitation as all other retrospective studies. Due to the fact that these studies were non-randomized and unblinded, they had a high risk of selection bias, detection bias and performance bias. This aside, the sample size of 20 per intervention arm was small.

The RCTs included for indirect comparison were critically appraisal by the Cochrane risk of bias tools. (56) The detail of the appraisal can be found in Appendix D.2. The RCTs generally had a high risk of detection bias and performance bias because most of them were not blinded. It was common to find that patients and surgeons were not blinded in the surgical studies as this was not logistically possible. However, although feasible within the study design, outcome assessors were also not blinded, thus leading to an increase in risk for detection bias. Other than blinding, the RCTs had a low risk of selection and attrition bias due to computerized randomization and a low dropout rate, respectively, and also reported all relevant outcomes.

Although the included RCT was of good quality, the network that allowed the indirect comparison was a linear network, with only one linked intervention (BMT) between DBS and DUODOPA. In a linear network, it is not possible to test for inconsistency like a closed loop network. In addition, there was only one RCT included in the DUODOPA side of the network, therefore not allowing testing for heterogeneity. The absence of inconsistency and heterogeneity would have shown the strength of the evidence presented by the indirect comparison. Since these tests were not possible with the current evidence, the quality of evidence presented by the indirect comparison was low; however, it is still considered to be the best available evidence at present.

5.2.6   Direct comparison results

Two small retrospective observational studies compared DUODOPA to DBS. In Merola 2011 (63), a significant improvement from baseline was observed in UPDRS part II, III and IV in both DUODOPA and DBS arm. However, the treatment effect was not significantly different between DUODOPA and DBS. The main outcomes of these studies are summarized in Table 11.

Table 11: Summary of results in Merola 2011

Study Name	Merola 2011		
Duration	Median follow-up 15 months		
Intervention	DUODOPA	DBS	
Number of patients	20	20	
End of study outcome	Medication on	Stimulation on/med off	p-value
UPDRS I*†	4.3±2.2	2.0±1.8	NR
UPDRS II*†	18.3±7.6	13.7±6.2	0.547
UPDRS III*†	29.1±15.9	30.3±17	0.206
UPDRS IV*†	5.6±3.4	3.0±2.9	0.776

Note: DBS=deep brain stimulation; NR=not reported; UPDRS=Unified Parkinson's Disease Rating Scale.
*Higher UPDRS score indicates more disabled. †Absolute value at the end of the study was shown.

Merola 2016 employed the similar method as Merola 2011. (62, 63) In addition to DBS and DUODOPA, Merola 2016 also reported outcomes from the BMT arm. Merola 2016 reported no significant difference in UPDRS I and III between all three arms. UPDRS II was significantly better in both DBS and DUODOPA arm when compared with BMT. UPDRS IV was also shown to have significant improvement in DBS and DUODOPA arms when compared with BMT. In addition, patients in the DBS arm also showed a significant improvement compared to the DUODOPA arm due to the greater improvement in score from the dyskinesia items in UPDRS IV. The summary of result from Merola 2016 can be found in Table 12.

Table 12: Summary of outcome from Merola 2016

Study Name	Merola 2016			
Duration	Median follow-up 5 years			
Intervention	DUODOPA	DBS	BMT	p-value
Number of patients	20	20	20	
End of study outcome	Medication on	Stim ON/med ON	Medication on	
UPDRS I*†	3.4±3.7	2.7±2.1	4.2±3.0	0.372
UPDRS II*†	13.5±9.8	13.1±4.7	20.8 ±7.6	0.005
UPDRS III*†	23.9±10.1	23.6±9.2	24.4±10.1	0.345
UPDRS IV*†	6.2±2.1	2.8±2.2	10.9±3.6	<0.001

Note: BMT=best medical treatment; DBS=deep brain stimulation; UPDRS=Unified Parkinson's Disease Rating Scale.
*Higher UPDRS score indicates more disabled.†Absolute value at the end of the study was shown.

5.2.7   Indirect comparison results

Since direct comparison only provided a limited amount of low-quality evidence, we performed an indirect comparison using RCTs comparing DUODOPA to DBS through BMT. Five parallel RCTs were included in this indirect comparison. (65-69) One RCT examined compared DUODOPA to oral levodopa, while allowing all other appropriate medications for 3 months. The four other RCTs compared DBS to BMT for 3 to 12 months.

5.2.7.1   UPDRS

UPDRS was reported by subscales in the RCTs. DUODOPA significantly improved UPDRS scores in part II and IV, while DBS significantly improved UPDRS scores in all subscales. While DUODOPA was compared to DBS, DBS showed greater improvement in UPDRS part III and IV, no significant differences were observed in part I and II. The summary of UPDRS results can be found in Table 13.

Table 13: DUODOPA vs. DBS indirect comparison in UPDRS

	DUODOPA vs. BMT (3 months)		DBS vs. BMT (3-12 months)		ITC DUODOPA vs. DBS	
	Difference in change from baseline (95% CI)	P value	Difference in change from baseline	P value		P value
UPDRS I*	0.3 (-0.4,1)	0.4	-0.3 (-0.5, 0.0)	0.08	0.6 (-0.2, 1.3) †	0.15
UPDRS II*	-3.0 (-5.3, -0.8)	0.0086	-2.3 (-4.4, -0.3)	0.03	-0.7 (-3.7, 2.3) †	0.66
UPDRS III*	1.4 (-2.8, 5.6)	0.5	-4.1 (-6.1, -2.1)	<0.001	5.5 (0.8, 10.1) †	0.02
UPDRS IV*	-1.2 (-2.4, -0.1)	0.036	-3.5 (-4.58, -2.6)	<0.001	2.3 (0.8, 3.8) †	0.002

Note: BMT=best medical treatment; DBS=deep brain stimulation; ITC=indirect treatment comparison; UPDRS= Unified Parkinson's Disease Rating Scale.
*Negative change indicates improvement.
†Positive difference between DUODOPA and DBS indicates DUODOPA performed worse than DBS.

5.2.7.2 Quality of life

Quality of life was measured by The Parkinson's Disease Questionnaire -39 (PDQ-39) in four RCTs. (65, 67-69) A decrease in PDQ-39 score indicated an improvement in quality of life. Both DUODOPA and DBS significantly improved the quality of life in advanced PD patients when compared with oral levodopa or BMT (PDQ-39 score weighted mean difference (WMD) -7.0 [95% CI -8.6, -5.4] and -6.8 [95% CI -9.0, -4.6] respectively). DUODOPA and DBS provided a similar effect on PDQ-39 when compared indirectly to each other (-0.2 [95%CI -2.8, 2.5], p=0.89).

5.2.7.3 Daily ON time without troublesome dyskinesia

The number of daily waking hours spent in ON time without troublesome dyskinesia was reported in four RCTs. (65-68) This measurement is the result of time spent within the therapeutic window, allowing patients to experience adequate relief of symptoms with minimum side effects. Both DUODOPA and DBS significantly increased the daily ON time without troublesome dyskinesia in advanced PD patients (WMD 1.9 hours [0.6, 3.2] and 4.2 hours [2.9, 5.4] respectively). DBS patients on average gained an additional 2.3 hours of ON time (without troublesome dyskinesia) as compared with DUODOPA patients (WMD 2.3 [0.5, 4.1], p=0.01).

5.2.7.4 Withdrawal from study

The odds ratio of patients withdrawing from the study was lower in the DBS arm than compared with the BMT arm (OR 0.56 [95% CI 0.32, 0.98], p=0.04). The odds ratio of withdrawal in the DUODOPA arm was also lower than the oral levodopa arm; however, due to the small sample size, this resulted in a wide 95% CI (OR 0.44 [0.04, 5.14], p=0.52). Since the

95% CI of the DUODOPA RCT odds ratio covered the entire 95% CI of the odds ratio of DBS

RCTs, no indirect comparison was performed in this outcome.

5.2.7.5   Complications

Indirect comparisons were not performed in any of the complications because oral

levodopa patients in the DUODOPA RCT also received a Percutaneous Endoscopic Gastrostomy

(PEG) tube, exposing them to additional risk as compared to regular BMT patients. We discuss

this important limitation in the limitation section below (section 5.2.7.5).

5.2.7.5.1   All-cause mortality

No death was reported in the DUODOPA RCT. The odds ratio of death in DBS RCTs were

not different between DBS and BMT (OR 3.13 [0.74, 13.19], p=0.87). Since there were no cases

of death in the DUODOPA RCT, indirect comparison was not performed.

5.2.7.5.2   Serious adverse event

The percentage of patients experienced a serious adverse event was 30.6% (117/382)

and 10.6% (42/385) in DBS and BMT group respectively (65, 68, 69). The risk ratio (RR) of

patients experiencing at least one serious adverse event was significantly higher in DBS as

compared with BMT (RR 2.90 [2.11, 3.98], p<0.0001, Appendix E.7). In the DUODOPA RCT, 14%

of the patients in the DUODOPA arm had a serious adverse event in the first three months.

DUODOPA patients did not show a difference in risk for serious adverse events when compared

with patients on oral levodopa (RR 0.66 [0.23, 1.87], p=0.43).(67) The risk ratio of serious

adverse event of DUODOPA and DBS should not be compared directly or indirectly, because the

comparator arm in DBS and DUODOPA are not equivalent in the context of this outcome. In the

DUODOPA RCT, patients in the oral levodopa group also received a PEG tube plus placebo,

therefore, they were also exposed to the surgical risk of serious adverse event from having a PEG tube. Thus, not necessarily having an equivalent risk of serious adverse events as in the BMT arms from the DBS studies.

A single arm 12-month extension of the DUODOPA RCT showed that within the 12 months observational period, 23% of patients experienced a serious adverse event. (72)

5.2.7.5.3 Total adverse event

The risk ratio of patients experiencing at least one adverse event was not significantly different between DBS and BMT, or DUODOPA and oral levodopa (RR 1.38 [0.41, 4.64], p=0.6 and 0.95 [0.86, 1.04], p=0.26 respectively).

5.2.8 Limitations

The clinical effectiveness analysis was limited by lack of high-quality evidence directly comparing DUODOPA to DBS. Only two small retrospective observational studies examining the effects of DUODOPA and DBS were identified. These two studies were limited by the risk of bias common in retrospective observational studies. Due to the fact that only patients surviving for a long period of time were included under the intervention, this posed a risk that patients with poor outcomes may be excluded, indicating selection bias. In addition to the risk of bias, the two studies were fairly small in sample size, thus not providing enough power to show a statistical difference in most outcomes.

Because of the limited evidence identified in direct comparison, RCTs that would allow indirect comparison of DUODOPA to DBS through BMT were identified. A limitation for these RCTs was determined to be the high risk of detection and performance bias due to the lack of blinding. Other than that, the RCTs provided good quality data with large sample sizes. Despite

this however, the network in the indirect comparison included only three interventions, making the network linear. A linear network presented many limitations that could affect the quality of the indirect comparison. The major limitation in a linear network was that a consistency test between direct and indirect comparison was not possible. Moreover, there was only one RCT identified that examined DUODOPA, making testing for heterogeneity on the DUODOPA side of the network impossible.

Other than the limitation within the network, the DUODOPA RCT also presented some limitation of its own. Some of the outcomes measured in the PD trial may need up to 12 months to fully reflect the efficacy of the intervention. The DUODOPA RCT was a short-term study which lasted for only three months. This might not give enough time for the effects of DUODOPA to be displayed in the UPDRS part III. This might help explain the reason why the RCT data showed that DBS produces a greater effect than DUODOPA in UPDRS III, while the 15-month observational study showed the two interventions had similar scores in the subscale. However, results were consistent with the fact that DBS produced a greater improvement in UPDRS IV than DUODOPA in both RCT and observational studies. A shorter duration may also explain why the DUODOPA RCT observed no deaths. Therefore, three months may not be enough time for these outcomes to occur.

In addition, in the DUODOPA RCT, patients using oral levodopa also received PEG. Under normal circumstances, patients not receiving DUODOPA would not be exposed to the risk of having a PEG tube. Having a PEG tube might be the reason why the DUODOPA study observed a similar rate of serious adverse event in both arms.

5.2.9   Summary of clinical effectiveness

- Two retrospective observational studies compared DUODOPA directly to DBS. The 15-month study, which included 40 patients, did not find any differences between DUODOPA and DBS in all four UPDRS subscales. The 5-year study, which included 60 patients, found that DBS was significantly better than DUODOPA in UPDRS part IV due to the finding that DBS reduced time with troublesome dyskinesia. DUODUOPA and DBS showed similar results in other UPDRS subscales.

- Five parallel RCTs were included in the indirect comparison. In total, 483 patients were randomized to DBS, 430 patients to BMT in the DBS RCTs, 37 patients received DUODOPA and 34 patients received oral levodopa.

- Patients who received DBS showed significantly better results in UPDRS III, UPDRS IV and daily ON time without troublesome dyskinesia when compared with DUODOPA. While greater reduction indicates greater improvement, on average, DBS patients showed further decreases in both UPDRS III and IV scores as compared with DUODOPA patients (respectively 5.5 and 2.3, measuring motor disability and complications). Although the UPDRS III estimate was statistically significant, the 95% CI spanned across nearly 10 points. This imprecision suggested that the UPDRS III estimate contained a fairly high degree of uncertainty.

- DBS patients gained on average an additional 2.3 hours of ON time without troublesome dyskinesia when compared with DUODOPA. This finding

corroborated with the UPDRS IV results, showing that DBS provided more relief in troublesome dyskinesia when compared with DUODOPA.

- Data from the 5-year observational study corroborated with the UPDRS IV result in the RCTs, confirming that the effects observed in the UPDRS IV (motor complication) are likely to be continued in the long term.

- On the other hand, results from the long-term study showed a similar effect between UPDRS III scores for patients with DBS and Duodopa. This suggests that it might take longer than three months for the DUODOPA therapy to impact UPDRS III scores.

- In the DUODOPA RCT, patients in the oral levodopa arm also received a PEG tube. For such patients, this additional intervention potentially introduces a risk for adverse events not present for regular BMT patients. In addition, the DUODOPA RCT only lasted for 3 months, which may not have allowed adequate time for the adverse event to occur. Therefore, it is not appropriate to compare the data of complications in the DUODOPA RCT to DBS RCTs in a safety risk analysis.

- The quality of evidence from the observational studies is low due to the small sample size and high risk in selection bias. While there is good quality of evidence provided by the RCTs, the quality of the indirect comparison is low due to a linear network and potential of bias in the safety data from DUODOPA RCT.

5.2.10   Other studies that provided data for the economic model

Since studies included in the clinical effectiveness analysis did not provide high-quality long-term data, data from other long-term single-arm studies were used to fill this information gap. These studies were not under the scope of the research question for inclusion in the clinical effectiveness evaluation; however, they provided data for parameters in the economic model. The parameters and the studies that provided the data can be found in Appendix E.

5.3   Economic literature review

The purpose of the economic literature review was to:

1) Determine the cost-effectiveness of levodopa/carbidopa intestinal gel (DUODOPA) compared to DBS.

2) Determine the societal impact of DUODOPA and DBS (e.g., return to work for caregivers and patients, out-of-pocket costs psycho-social aspects, etc.)

5.3.1   Methods

5.3.1.1   Inclusion criteria

The inclusion criteria are detailed in Table 14.

Table 14: Inclusion criteria for health economics studies

Study Design	Patient Population	Intervention	Comparator	Outcomes
Systematic reviews HTA CEA: Simulation model CEA: Trial-based economic analysis Comparative studies Resource utilization studies	Patients with advanced Parkinson's disease with symptoms or side effect that cannot be adequately controlled with BMT	Levodopa/carbidopa intestinal gel (Duodopa)	Deep brain stimulation	Cost QALY ICER Resource utilization

Note: BMT: best medical treatment; CEA: cost-effectiveness analysis; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

5.3.1.2   Exclusion criteria

The following exclusion criteria were applied: non-English language, abstract

/conference proceedings letters and commentaries, early Parkinson's disease, and studies

published before 2000.

5.3.1.3   Literature search overview

Published articles were identified using the search strategy in Medline and Embase via

Ovid using filters for economic studies (Appendix A). A grey literature search was also

performed in the University of York's Centre for Reviews and Dissemination (CRD) database and

five HTA databases (CADTH, NICE, AHRQ, BC Guideline, SIGN). Manual searches were

performed in the references of systematic reviews identified during screening. Search results

were imported into

Endnote® and Microsoft® Excel for screening. The search is considered up to date as of June 2017.

We screened for systematic reviews of economic analyses and HTA reports that were returned in the search for systematic reviews of clinical effectiveness (n=28), grey literature (n=17) and economic studies filtered in Medline and Embase (n=215). Additional word search with economic terms were performed among the RCTs and observational studies to ensure we capture all relevant economic studies (n= 275).

The following terms were used: "econ", "cost", "fundin", "price", "expen", "model", "markov", "monte carlo", "finan". We expanded the inclusion criteria to include primary economic studies to update the results from the most recent systematic reviews found, and to investigate other existing models used to compare the Duodopa or DBS to BMT to support disease progression modeling.

5.3.1.4   Study selection and data abstraction

Titles and abstracts were screened by two reviewers. Records identified for full text review were screened by the one reviewer and those meeting the inclusion criteria were identified for data abstraction. Data from the full text records were abstracted by a second reviewer. If systematic reviews were identified, these were used to cross-reference the included studies.

5.3.1.5   Quality of reporting

The International Society for Pharmacoeconomics and Outcomes Research "Consolidated Health Economic Evaluation Reporting Standards (CHEERS)" (73) was applied to

assess the quality of reporting. CHEERS was applied to all records identified as cost-effectiveness studies. CHEERS criteria were not applied to the title, abstract or background & objectives, resulting in a maximum score of 21.

5.3.1.6   Data abstraction and synthesis

The following data were abstracted (as relevant): authors, year of publication, country, currency, time horizon, model type, costs, QALYs, ICERs, and items relevant to resource utilization. Data were qualitatively synthesized.

5.3.2   Search results

Records (n=520) were screened of which 2 met the inclusion criteria: 1 cost-effectiveness analysis (37) and 1 costing study. (74) The flow of studies is illustrated in Figure 6. Furthermore, 25 additional studies were identified to support disease progression modeling: 4 CEA studies comparing DUODUOPA to BMT, 10 CEA studies comparing DBS to BMT, 1 HTA comparing two DBS service-provision strategies, 1 costing study comparing DUODOPA to BMT, 4 DBS costing studies, and 5 studies describing aspects of resource utilization.

All studies identified as model-based cost-effectiveness studies were reviewed to elicit the model structure. Records identified in the screening process as cost-effectiveness studies in patients with early PD were reviewed to identify model structures not previously used in advanced PD. One additional study (75) was identified. Model structure is further described in 6.2.7. Please see Appendix F for study details regarding model structure.

Figure 6: PRISMA Economics literature review

Figure 1: PRISMA diagram

Identification

| Medline and EMBASE Econ Studies (n= 215) | CRD (n = 17) | Medline and EMBASE SR screening (n = 28) | Medline and EMBASE RCT/OBS cost terms search word (n = 275) | Manual reference searches (n = 3) |

Screening

Duplicates removed (n = 18)

Records screened (n = 520)

Records excluded (n = 471)

Eligibility

Full-text articles assessed for eligibility (n = 49)

Full-text articles excluded, with reasons (n = 21)

Primary studies already included in the SR reviews (n=4)
Abstracts (n= 7)
Clinical outcomes (n=4)
Early stage medication cost projection (n=1)
Model in early stages, previously used in advanced stages and already included (n=1)
Non-english (n=2)
Do not meet PICO – early vs advanced stage DBS (n=2)

Included

DUODOPA vs DBS (direct comparison)
CEA (n=1)
Costing study (n=1)

Other literature identified
CEA
DBS vs BMT (n=10)
DUODOPA vs BMT (n=4)

CMA
DBS in-house vs abroad (n=1)

Costing
DBS vs BMT (n=4)
DUODOPA vs BMT (n=1)

Resource utilization
DBS (n=5)

New disease progression model
Early PD (n=1)

Studies identified during validation with stakeholders (n = 2)

Included
CEA DUODOPA vs BMT (n=1)

Excluded
n=1

Notes: BMT=Best Medical Therapy; CEA= Cost-Effectiveness Analysis

5.3.3 Stakeholder validation of included studies

Stakeholders were invited to review the list of included studies provide additional references that were not identified and included in the literature review. Stakeholders identified two additional articles: one was included and one was excluded. The reason for exclusion is provided in Appendix G.

5.3.4 Quality of reporting

Quality of reporting using CHEERS was applied to all studies (n=17) that reported CEA (model-based and study-based). Please see Appendix H for further details. Overall, the quality of reporting was acceptable. Walter & Odin, the only CEA study we identified comparing DUODOPA to DBS, appropriately reported 19 of the 21 items. The authors did not sufficiently justify their choice of study to model "measurement of effectiveness" and they did not report the sources of funding for the study. The CHEERS scores ranged from 8/21 to 21/21. The criterion least frequently reported was the "measurement of effectiveness" (n=8). These studies failed to provide a rationale for the choice of study (or studies) that provided evidence for the effectiveness of the interventions under consideration.

5.3.5 Results of the economic literature review

5.3.5.1 Cost-effectiveness of levodopa/carbidopa intestinal gel (DUODOPA) compared to DBS.

The search strategy did not return any studies that directly compared DUODOPA to DBS. However, the search strategy returned one study, Walter and Odin 2015, which provided estimates of costs and QALYs for DUODOPA and DBS. (37) Therefore, the cost-effectiveness of DUODOPA compared to DBS was calculated.

Briefly, Walter and Odin developed a Markov model with 15 states: Hoehn & Yahr stages 3-5 (each further subdivided into 4 categories of proportion of "OFF" time), complications, adverse events and death. The primary purpose of this study was to estimate the cost-effectiveness of continuous subcutaneous apomorphine compared with DBS, levodopa/carbidopa intestinal gel (i.e., DUODOPA) and BMT over a lifetime time horizon. The data are presented from the perspective of both the UK healthcare system (NHS) and the German healthcare system, both of which are publically funded. This study was funded by EVER Neuro Pharama (manufacturer of apomorphine). All costs are 2014 £ (UK) or 2014 € (Germany).

Costs and QALYs were presented for all 4 treatments and therefore we used data from this study to calculate the incremental cost-effectiveness ratio (ICER) of DUODUOPA compared to DBS. From the NHS perspective, over a lifetime time horizon, the ICER was £136,390 per QALY. (37) From the German health care system perspective, over a lifetime time horizon, the ICER per QALY was €209,900. Please see Appendix F and Appendix I for further details. Regardless of perspective, the ICER per QALY comparing DUODOPA to DBS was not within generally acceptable cost-effectiveness thresholds.

The search strategy identified one cost study, Valldeoriola 2013, which directly compared the costs of Duodopa, DBS, and continuous subcutaneous apomorphine. (74) Briefly, Valldeoriola and colleagues convened an expert panel: the investigators (n=3) in addition to 11 experts from 9 centres in 5 Spanish regions. All panel members completed the Health Resource Questionnaires (HRQ) designed to capture healthcare resources associated with DBS, Duodopa and apomorphine from the Spanish National Health Service perspective. Unit costs were obtained from the Spanish Cost Database. This study was funded by Medtronic (manufacturer

of a DBS unit). Costs are reported in € (2010). For DBS, over a 5 year time horizon, the mean annual cost was €17,603 and the mean cumulative cost was €88,041. For Duodopa, over a 5 year time horizon, the mean annual cost was €46,797 and the mean cumulative cost was €233,986. Please see Appendix F and Appendix I for further details. The authors conclude: "The initial DBS investment was offset at year 2 by reductions in the ongoing consumption of oral PD drugs. For every patient treated annually with CDLCI [Duodopa] or CSAI [apomorphine], substantial cost savings could be made with DBS."

5.3.5.2   Literature to support disease progression modeling

CEA of DUODOPA vs. BMT: The search identified 5 CEA studies directly comparing DUODOPA to BMT. Three studies were model-based (76-78) and two studies were study-based. (79, 80) Details regarding study characteristics and results can be found in Appendix F and Appendix I, respectively. All studies reported costs, 4 studies reported ICERs per QALY (76-78, 80) and 1 study reported an ICER per unit improvement in UPDRS. (79) All studies adopted different time horizons (1 year, 2 years, 20 years and lifetime) and perspectives (societal, payer and 2 national health services). Both the 15D and EQ-5D were used to measure quality of life. Four of the five studies were funded by the manufacturer of DUODOPA. (76-78, 80) Please see Appendix L for a summary of the analytic approach. The ICERs were estimated to be €26,944 per QALY (2017, 20 year horizon), £36,024 per QALY (2011, lifetime horizon), SEK 6.1 M per QALY (2004, 2 year horizon) and NOK 9.2 M per QALY (2008, 1 year horizon) compared to BMT. Two studies, one considering a lifetime time horizon and one considering a 20 year time horizon, reported ICERs within acceptable cost-effectiveness thresholds. (77) (78)

CEA of DBS vs. BMT: The search identified 10 CEA studies directly comparing DBS to BMT. Four studies were model-based (81-84) and six studies were study-based. (44, 85-89) Details regarding study characteristics and results can be found in Appendix F and Appendix I. Heterogeneity in time horizon (1 year, 2 years, 5 years, 10 years, lifetime) and perspective (societal, payer, national health service) was observed. Two instruments were used to measure quality of life: EQ-5D and PDQ-39. Three studies were funded by Medtronic (DBS device manufacturer). Please see Appendix L for a summary of the analytic approach. The ICER ranged from €6,677 per QALY (2010, lifetime time horizon) (90) to £468,528 per QALY (2010, 1 year time horizon). (85) Six studies found DBS compared with BMT was within acceptable cost-effectiveness thresholds from a variety of perspectives (societal, payer, national health service) and time horizons (1 year, 5 years, 10 years, and lifetime). (81-85, 88)

Costing studies of DUODOPA: The search identified two studies reporting the costs associated with DUODOPA. (74, 91) Details regarding study characteristics and results can be found in Appendix F and Appendix J respectively. (74, 91) Valldeoriola and colleagues estimated that the mean cost of DUODOPA was €46,797/year and the mean cumulative cost (over 5 years) was €233,986. (74) Palhagen and colleagues, considering a 3 year time horizon, estimated the mean total cost per month of DUODOPA was €8,226: ~€4,000 drug costs, ~€400 direct medical cost, ~€2,000 direct non-medical costs and ~€1,500 in indirect costs. (91) The 1 year costs estimated by Valldeoriola et al. are similar to the drug and direct medical costs (~€4,400/month; ~€52,800/year) estimated by Palhagen et al.

Costing studies of DBS: The search identified five studies reporting the costs associated with DBS. Details regarding study characteristics and results can be found in in Appendix F and

Appendix J, respectively. (43, 74, 92-94) The time horizon varied across studies (cost of surgical procedure, 1 year, and 5 years). The highest cost for DBS (surgical procedure only), $69,329, was reported by Lad and colleagues from a US perspective. (93) The lowest mean cost per year of DBS, €17,603 was reported by Valldeoriola and colleagues, from a Spanish health care system perspective. (74) The estimated mean cumulative 5 year cost was €88,014. (74)

The search returned one study, an HTA commissioned by the Health Information and Quality Authority in Ireland, which applied a cost-minimization analysis to compare the costs of offering DBS within Ireland compared with the costs of DBS via the Treatment Abroad Scheme (TAS), the current method of accessing DBS for patients in Ireland. Considering a 10-year time horizon, offering DBS within Ireland was estimated to cost an additional €20,900 per patient compared to DBS offered via TAS (€65,600 in-house, €44,700 TAS). (46) The report did not explicitly recommend or reject the implementation of a within-Ireland DBS program.

Resource utilization: The search returned 5 studies which provided data regarding resource utilization associated with DBS. (41, 95-98) The search did not return any studies that specifically provided resource utilization associated with DUODOPA. These studies provided additional information regarding medication costs before and after DBS surgery, estimate of the lifespan of DBS implantable pulse generator and nursing time required to program and assess DBS devices. These studies are summarized in Appendix K.

5.3.5.3   Literature regarding the societal impact of DUODOPA and DBS

Only one CEA study identified in our search, Lundqvist and colleagues (DUODOPA compared with BMT), included indirect costs. (80) Several indirect costs were included in this study: travel costs by car/taxi, pay loss for relative staying at home (using the average wage in

Norway) and physiotherapy. Indirect costs (except travel costs) were collapsed into a single category, "health-related costs". Travel costs represented 0.7% of total costs (mean NOK 1,400 over first 12 months with DUODOPA) and "health-related costs" accounted for 22.1% of costs (mean NOK 53,500 over first 12 months with DUODOPA). Estimates of the individual components of "health-related costs" were not reported.

A recent systematic review by Rodriguez-Blazquez estimated the direct and indirect costs associated with Parkinson's disease. (5) The search strategy for this systematic review was not specific to advanced Parkinson's disease or to a specific treatment (e.g., DBS, DUODOPA). Overall, the authors noted that less than half of all cost of illness studies identified included indirect costs (please see Table 1 contained within Rodriguez-Blazquez for further details). The authors broadly categorized indirect costs into "productivity losses" and "informal care". Productivity losses include costs due to "premature retirement, reduction of working hours, sick and disability leave". (5) A range of yearly productivity losses were reported: €1,700 (Portugal), €8,780 - €14,280 (Germany) and $10,046 (United States). In addition, the authors cite a US study which quantified earning losses (to age 79 years) of $569,393 if diagnosed at 45 years of age and $2,451 if diagnosed at 75 years of age. (5, 99)

The authors operationalize informal care as the "costs of unpaid help from others for everyday activities…can be estimated as the productivity loss when the persons take work leaves or give-up employment to take care of the patient". (5) The authors cite two UK-based studies that estimate the cost of informal care. (7, 100) Findley and colleagues reported that "those who lived at home received on average 6.4 hours professional care and 34.04 hours informal care per week". (7) The mean annual cost per year of informal care was £12,454. (7)

The authors note that informal care accounts for 43% of all costs: "... the direct non-medical costs of professional care accounted for 50% of all costs, indirect informal care 43%, while only 7% of costs were attributed to direct medical costs". Note, that the reported in Findley et al are heterogeneous in terms of patient treatment (i.e., not specific to DBS, DUODOPA, other). McCrone estimated that the cost of informal care was ~£11,000 per year (100), similar to the cost reported by Findley.

5.3.6   Limitations

The search returned limited literature regarding the cost-effectiveness of DUODOPA compared with DBS. The search returned 1 CEA study which enabled a direct comparison of DUODOPA to DBS. In addition, only 1 costing study which directly compared the costs of DUODOPA to DBS was identified. Lack of additional literature does not allow for comparison of ICERS across various time horizons or perspectives.

5.3.7   Summary of economic literature review

- A single study was identified that enabled a direct comparison of DUODOPA to DBS. Note that the primary purpose of this study was to compare apomorphine to DBS, DUODOPA and BMT. From the NHS perspective the ICER was £136,390 per QALY and from the German healthcare perspective the ICER was €209,900 per QALY. This study was adequately reported according to CHEERS criteria. This study was funded by EVERNeopharma, manufacturer of apomorphine and found that apomorphine dominated DBS and DUODOPA.

- The search returned one costing study, from the Spanish National Health Service perspective, which directly compared the costs of DUODOPA to DBS. The 5-year mean cumulative cost of DBS and DUODOPA respectively was €88,041 and €233,986. This study was funded by Medtronic (manufacturer of a DBS device).

- The search returned 5 CEA studies comparing DUODOPA to BMT. The ICERs were estimated to be £36,024 per QALY (2011, lifetime horizon), SEK 6.1 M per QALY (2004, 2 year horizon) and NOK 9.2 M per QALY (2008, 1 year horizon) compared to BMT. One study, considering a lifetime time horizon, reported an ICER within acceptable cost-effectiveness thresholds. (77)

- The search returned 10 CEA studies comparing DBS to BMT. The ICER ranged from €6,677 per QALY (2010, lifetime time horizon) (90) to £468,528 per QALY (2010, 1 year time horizon). (85) Six studies found DBS compared with BMT was within acceptable cost-effectiveness thresholds from a variety of perspectives (societal, payer, national health service) and time horizons (1 year, 5 years, 10 years, and lifetime). (81-85, 88)

- Overall, the quality of reporting (CHEERS) was adequate. Many (7/16) were missing information to justify the measurement of effectiveness utilized.

- Only one CEA study identified in our search, Lundqvist and colleagues (DUODOPA compared with BMT), included indirect costs. (80) The indirect "health-related costs" accounted for 22.1% of costs (mean NOK 53,500 over first 12 months with DUODOPA).

- A recent systematic review by Rodriguez-Blazquez provided estimates of the direct and indirect costs associated with Parkinson's disease. (5) A range of yearly productivity losses were reported: €1,700 (Portugal), €8,780 - €14,280 (Germany) and $10,046 (United States). In addition, the authors cite a US study which quantified earning losses of $569,393 at 45 years and $2,451 at 75 years old. (5) Two UK studies estimated the mean annual cost per year of informal care was £12,454 (7) and ~£11,000. (100)

- The search returned a model-structure in a CEA study of early PD that was not utilized in the CEA studies of late PD literature. This study, Fundament and colleagues, utilized UPDRS to model disease progression rather than Hoehn & Yahr stages. Further details regarding choice of model structure are discussed in Chapter 6.

Chapter 6 Economic Analysis for British Columbia

Summary

    For the treatment of advanced PD patients eligible for either DBS or DUODOPA treatment, the best available evidence suggests that DBS is the more cost-effective alternative in most scenarios. Results were most sensitive to the cost of the technologies, and the rate of disease progression. There is a moderate degree of uncertainty in the model. The effectiveness estimates were generated from indirect comparison (DBS and DUODOPA compared to BMT) and adaptation of costs of treating patients with DUODOPA from international data. DBS has more robust evidence on the effects of treatment in the different UPDRS domains, as well as for local cost data. Adoption of DUODOPA under controlled trial circumstances (or for patients who are not eligible for DBS) ideally would be monitored to confirm if the real-life benefits of the technology fall under the parameters used in the simulation model in order to confirm cost-effectiveness estimates reported herein.

6.1   Objectives

To evaluate the cost-effectiveness of treating advanced PD patients with Duodopa compared to DBS.

6.2   Methods

We created a decision-analytic model for outcomes of treating advanced PD patients to estimate the costs, health outcomes, and QALYs associated with DBS and Duodopa over a 10-year time horizon in BC.

6.2.1   Target population and subgroups

We stratified the BC population into three age subgroups (45-64 years, 65-79 years, and over 80 years). The analysis was performed separately for males and females and within each age subgroup. To generate population-based results, subgroup-specific results were weighted-averaged, with the weights being the distribution of PD patients waiting for potential DBS surgery in BC within each subgroup.

6.2.2 Setting, location and time horizon

The period for which the complete local DBS cost data were available for this analysis was 2012/2013 to 2016/2017. The projections were made for the same population for the years 2018/2019 to 2026/2027. We used a 10-year time horizon in the base-case analysis given that the evidence shows a mean life expectancy for PD patients with onset between 40 and 65 years of age is 21 years. (101) Furthermore, clinical trials have reported that patients have been diagnosed with PD for approximately 10-12 years before receiving either DBS or DUODOPA therapy. Additionally, 5-year and 15-year time horizons were investigated in the sensitivity analyses.

6.2.3 Study perspective

We chose a publicly funded health system perspective. Out-of-pocket expenses and productivity loss were not included in the reference case.

6.2.4 Comparators

We compared Duodopa with DBS surgery, the latter being the current standard of care.

6.2.5 Discount rate

A 1.5% discount rate was applied to both costs and outcomes in alignment with CADTH guidelines.(102) Alternative values were explored in sensitivity analyses.

6.2.6 Choice of health outcomes

The main outcome of interest was quality-adjusted life years (QALYs), which captures both the length and quality of life associated with different outcomes from DBS surgery, Duodopa (and PEG-J surgery), BMT after withdrawal, and the impact of complications and adverse events. The secondary outcomes were the number of life-years gained, probability of

withdrawal, rate of adverse events, and falls. Secondary outcomes were chosen based on the perceived importance to patients and relevance to the health system.

6.2.7   Model structure

In 2004 the Movement Disorder Society recommended moving away from the H&Y stage classification to a broader measurement that captures factors beyond motor disability of the disease (UPDRS - Part III). In response clinical studies investigating the effect of PD treatments have increasingly reported the effects on the different dimensions of the UPDRS score, as well as daily life activity level (UPDRS - Part II), mental symptoms (UPDRS - Part I), and the quality of the patient's treatment management, including motor complication (UPDRS - Part IV).(103)

To date, previous economic models in DBS and Duodopa (37, 75-77, 81-84, 104) have mostly relied on simulating PD progression and treatment effects by H&Y stage, with very few incorporating UPDRS scores. (75, 81, 104) In general, models have mostly assumed that disease progression has a linear trend. Our model was built from the ground-up, based on a more recently published economic analysis, which fully incorporated individual sections for UPDRS scores (I, II, III, IV). (75) In our model, UPDRS scores were then mapped to pay-offs such as costs and utilities. This approach provides considerable improvement to previous models in several important aspects. First, modeling disease progression in a non-linear way allows for accommodating realistic aspects such as the flattening of progression towards the end of life. Second, full incorporation of UPDRS scores by its dimensions enables comparison of treatments that have different effects on different UPDRS dimensions. Third, the model realistically simulates withdrawal from treatment with adjustments to account for disease progression after

withdrawal and its effects on mortality. Finally, the analysis robustly simulates heterogeneity in the PD population, allowing for patients to start the model at different ages, disease progression trajectories, and disability levels.

After evaluating the available clinical evidence, consulting with clinicians, surgeons and other stakeholders, and assessing other published economic models comparing DBS or Duodopa to BMT or against each other, we decided to use a hybrid Markov model (developed in Microsoft Excel) alongside a microsimulation modeling framework (using R version 3.3.1)..

Figure 7 provides the overall structure of the Markov model. The cycle length was one year. Only three states (treatment, no treatment, death) were required as the nuances of disease progression were considered in the microsimulation component (Figure 8 Microsimulation of UPDRS progression by patient

At baseline (cycle 0), UPDRS values reflect patients' scores before DBS surgery or before initiation of Duodopa via a PEG-J catheter. The patients receiving surgery (either DBS or PEG-J implantation) and those who have survived the procedure (30-day mortality was modeled from the literature) are immediately moved to the treatment stage. At each cycle, patients stay in the treatment stage ('DBS+BMT' or 'Duodopa+BMT') until they either withdraw from advanced treatment (remaining under BMT only) or die.

In this model, individual patients' underlying UPDRS progression (before the implementation of the interventions under evaluation) was estimated under BMT (dashed line in Figure 8 Microsimulation of UPDRS progression by patient

Figure 7 Microsimulation model health states
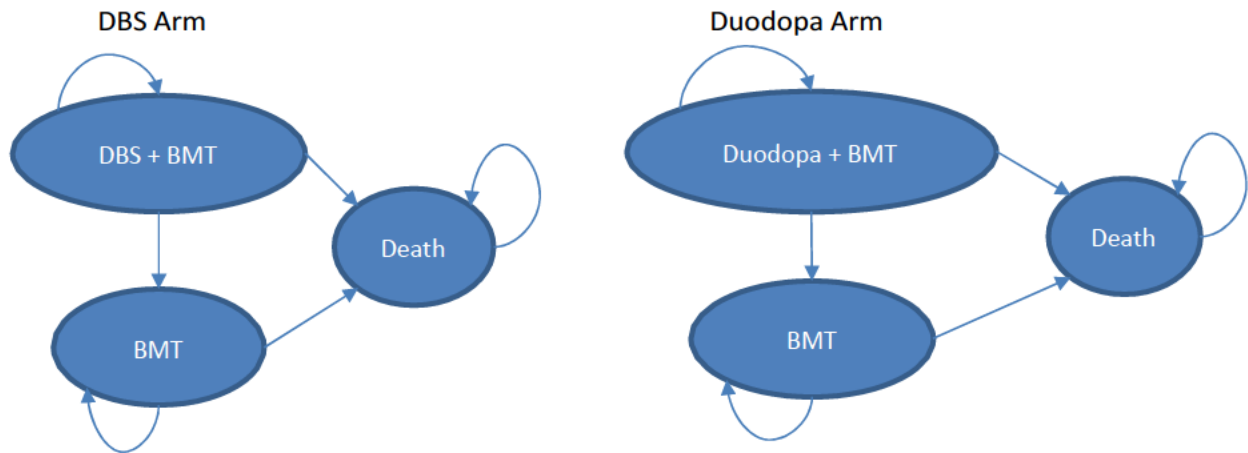
Figure 8 Microsimulation of UPDRS progression by patient
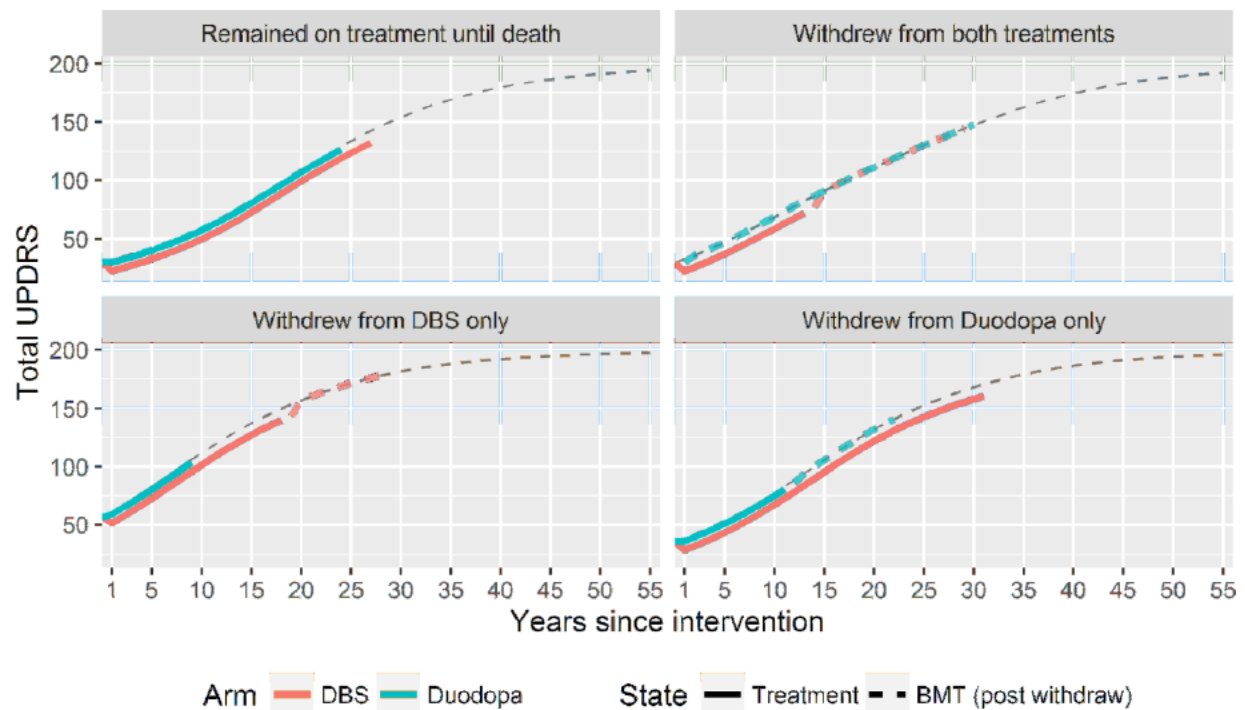
Footnotes: These are exemplary trajectories of UPDRS progression for 4 patients in the model. The dashed lines represent underlying total UPDRS (sum of all four dimensions) if the patient had only received BMT. Each patient was assigned a random starting score at time 0, and then UPDRS trajectory until death was simulated under DBS and Duodopa. The figure illustrates four exemplary scenarios in our model. For example, the bottom right quadrant shows a patient who remained on DBS for 31 years until death. This same patient would have withdrew from treatment after 11 years and died after only 22 years if treated with Duodopa.

6.2.8 Parameter sources and assumptions

Input parameters for the model came from the literature review (reported in Chapter 5), analysis of administrative data from multiple databases within the Ministry of Health (Discharge Abstract Database [DAD], Medical Services Plan [MSP], PharmaCare), and the DBS clinic database. By using local health service resource use data and cost, analysis of the administrative data allowed, as much as possible, to tailor the cost-effectiveness analysis to the BC context.

6.2.8.1 Baseline UPDRS scores distribution and UPDRS trajectories over time under BMT

The initial baseline distribution of UPDRS scores by individual sections was extracted by a meta-analysis aggregating the scores of patients in all treatment arms (DBS, Duodopa, and BMT) from different RCTS. This initial distribution was assumed to be the same for all three age groups, because regardless of age, all patients are already at an advanced stage to be referred to either DBS or Duodopa (Table 15).

Table 15 UPDRS parameter values

Initial distribution of UPDRS scores under BMT when being referred to advanced treatment - absolute values					
	mean	sd	upper range	dist	Source
UPDRS 1	2.2000	3.2854	16	normal	Meta-analysis of included RCTs
UPDRS 2	9.7200	10.2278	52	normal	(65-69) See Appendixes.
UPDRS 3	19.7800	2105875	108	normal	
UPDRS 4	9.1300	3.2620	23	normal	
Annual progression of UPDRS scores under BMT - logit regression estimates					
	Beta	SE		dist	Source
UPDRS 1	0.1055	0.0264		logit	(105-111) See Appendixes.
UPDRS 2	0.1788	0.0447		logit	(112)
UPDRS 3	0.0999	0.0250		logit	See Appendixes.
UPDRS 4	0.0900	0.0225		logit	(105-111) See Appendixes.

| source not found. | | | | |

Annual progression of UPDRS scores under DBS compared to BMT – absolute values – year 1 versus baseline				
	mean	SE	dist	Source
UPDRS 1	-0.2500	0.1429	normal	Meta-analysis of included RCTs
UPDRS 2	-2.3000	1.0408	normal	(65, 66, 68, 69)
UPDRS 3	-4.0900	1.0102	normal	
UPDRS 4	-3.4900	0.4541	normal	

Annual progression of UPDRS scores under Duodopa compared to BMT – absolute values – year 1 versus baseline				
	mean	SE	dist	Source
UPDRS 1	0.3000	0.3571	normal	(67)
UPDRS 2	-3.0000	1.1224	normal	
UPDRS 3	1.4000	2.1429	normal	
UPDRS 4	-1.2000	0.5612	normal	

Note: UPDRS= Unified Parkinson's Disease Rating Scale; sd- standard deviation; dist= distribution; SE= Standard Error

The natural progression of different UPDRS domains, under the condition that advanced patients do not have access to further treatments (thus remaining under oral BMT only), was estimated from pooled results from a number of longitudinal studies (Figure 9). These studies provided the mean and standard deviation of UPDRS domain scores at different follow-up times. These values were combined into a single dataset. A number of regression models (linear, log-linear, logit-linear) were tested on the longitudinal data. The logit-linear model was chosen as the best option, as it showed the second-best goodness of fit (e.g. low mean of residuals) in all UPDRS score subsections in addition to being more in agreement with the clinical expert opinion that motor disability progression (reflected in UPDRS domain 3) is most probably nonlinear and likely to plateau over time.

Figure 9 Overall UPDRS score progression under BMT only – longitudinal studies and logit model fitting
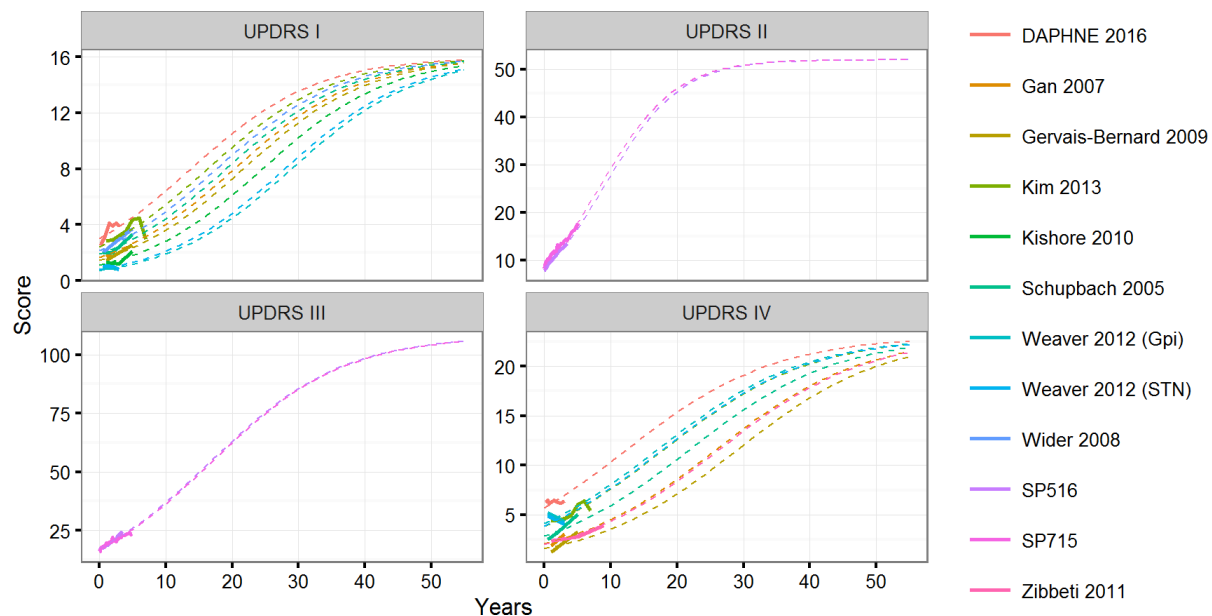
Studies reported different UPDRS parts and were aggregated accordingly. Part 1: DAPHNE 2016(105), Gervais-Bernard 2009(107), Kishore 2010(113), Weaver 2012(110), Gan 2007(106), Kim 2013(108), Schupbach 2005(109), Weaver 2012(110); Part 2 and 3: SP516(112), SP715(112). Part 4: DAPHNE 2016(105), Gervais-Bernard 2009(107), Schupbach 2005(109), Weaver 2012(110), Gan 2007(106), Kim 2013(108), Weaver 2012(110), Zibbeti 2011(111)

Therefore, UPDRS score progression was forecasted using separate models for each category, with a logit-transformed response [logit(updrs) = intercept + beta*time + beta2*study]. Here, beta represents the coefficient on the predictor for annual time trend. The mean UPDRS score was allowed to vary at time 0 for each study, but the annual time trend was constrained to be the same for all studies. Random- effect terms that capture between-study variation were not modeled because of limitations in the data (amount of data). This analysis was performed using R version 3.3.1. (114)l

6.2.8.2   Mortality

Surgery risks and immediate complications after DBS or Duodopa PEG-J surgery (30-day mortality) were assumed to occur at baseline, before patients entered cycle 1 to receive the

benefits of either treatment. In addition, one-year mortality was applied to the end of cycle 1,

which captured the effect of complications related to each treatment (Table 16). Surgical

mortality and 1- year mortality for DBS were extracted from a meta-analysis of three RCTs (65,

68, 69); for Duodopa they were calculated from a 1-year observational study. (115). Background

mortality rate was extracted from Canadian life tables for BC (2011–2013) published by

Statistics Canada (Table 17). (116) A study reporting the relationship between UPDRS Part III

score and mortality in advanced patients reported an increase in the risk of death (HR 1.25, 95%

CI 1.15-1.36) for each 10-point increase in the UPDRS Part III score. (117) Correspondingly,

background mortality was inflated according to the UPDRS II score of each patient to

incorporate the increase in mortality due to disease progression. In this model, patients were

assumed to be dead upon reaching a maximum age of 100.

Table 16 Mortality parameter values

	mean	sd	Dist	Source
Probability of death under DBS				
mortality_surgical	0.0100	0.0051	Beta	See Appendixes. (65, 68, 69);
mortality_y1	0.0100	0.0102	Beta	
Probability of death under Duodopa				
mortality_surgical	0.0000	0.0000	Beta	(115)
mortality_y1	0.0247	0.0086	Beta	
PD mortality per 10-point increase in UPDRS 3				
	HR	mean	sd	
Hazard ratio	1.25	0.2231	0.0425	lognormal	(117)

Note: sd- standard deviation; dist= distribution

Table 17 Probability of death by age and sex in British Columbia

Age	Male	Female	Age	Male	Female	Source
45	0.0020	0.0013	73	0.0231	0.0150	(116)
46	0.0022	0.0014	74	0.0256	0.0166	
47	0.0023	0.0015	75	0.0283	0.0185	

48	0.0025	0.0017	76	0.0313	0.0207
49	0.0028	0.0018	77	0.0347	0.0231
50	0.0030	0.0019	78	0.0385	0.0259
51	0.0032	0.0021	79	0.0428	0.0290
52	0.0035	0.0022	80	0.0476	0.0326
53	0.0038	0.0024	81	0.0529	0.0367
54	0.0041	0.0026	82	0.0589	0.0413
55	0.0045	0.0028	83	0.0657	0.0466
56	0.0049	0.0031	84	0.0732	0.0526
57	0.0053	0.0033	85	0.0818	0.0595
58	0.0058	0.0036	86	0.0914	0.0674
59	0.0063	0.0039	87	0.1023	0.0765
60	0.0068	0.0043	88	0.1145	0.0869
61	0.0075	0.0047	89	0.1283	0.0989
62	0.0082	0.0051	90	0.1439	0.1127
63	0.0089	0.0056	91	0.1612	0.1282
64	0.0098	0.0061	92	0.1795	0.1450
65	0.0107	0.0067	93	0.1991	0.1633
66	0.0118	0.0074	94	0.2196	0.1828
67	0.0129	0.0081	95	0.2451	0.2082
68	0.0142	0.0090	96	0.2670	0.2306
69	0.0156	0.0099	97	0.2896	0.2541
70	0.0172	0.0109	98	0.3126	0.2784
71	0.0190	0.0121	99	0.3357	0.3034
72	0.0210	0.0135			

6.2.8.3   Withdrawal

For the first year of DBS, the probability of withdrawal was calculated by a meta-analysis of four RCTs. (65, 66, 68, 69) For Duodopa, withdrawal rates were available for month 1 to 3 from an RCT (67), and from month 4 to 15 from an observational study that followed the previously-mentioned RCT patients for an additional year. (72) To estimate the 1 year withdrawal, we interpolated the 3 and 15-month rates. The probability of withdrawal was assumed constant from year 2 and onwards for both treatment arms. For DBS data, this probability was extracted from a 24-month observational study (118), and for Duodopa, a 34-month observational study. (36) The probabilities and standard errors from these studies with different lengths of follow-up were adjusted to derive annual probabilities (Table 18).

Table 18 Probability of withdraw from advanced treatments

	mean	sd	Dist	Source
Probability of withdraw from DBS				
Year 1	0.0500	0.0255	Beta	See Appendixes. (65, 66, 68, 69);
Year 2+	0.0209	0.0029	Beta	(118)
Probability of death under Duodopa				
Year 1	0.0995	0.0521	Beta	(67, 72)
Year 2+	0.0762	0.0069	Beta	(36)

Note: sd=standard deviation; dist= distribution; RCTs= Randomized Control Studies

6.2.8.4   The effectiveness of technologies

Treatment effect was estimated by pooling the results from head-to-head RCTs comparing Duodopa and BMT, or DBS and BMT. No strong evidence was found that either intervention would change the slope of UPDRS trajectories. Supported by clinical experts involved in this project, the evidence indicates that while use of these technologies will result in an immediate reduction in UPDRS scores, they will continue to progress at the same rates as observed under the BMT intervention. Upon withdrawal, this absolute change in UPDRS is negated and the UPDRS will revert back to its original value under BMT (Figure 8).

To estimate such an absolute treatment effect, we meta-analyzed data from the available RCTs to calculate the mean 1-year absolute difference in each UPDRS domain or category, between either DBS or Duodopa compared to BMT (Table 15). These absolute differences were applied to each individual patient UPDR scores at baseline in the microsimulation model.

Another effect of the interventions is the decrease in the use of oral PD drugs. For the DBS arm, the treatment effect on this outcome was estimated by pooling the results from head-to-head RCTs comparing DBS and BMT, to calculate the maximum tolerated dose of levodopa-equivalent oral drugs received by patients at baseline (before surgery), and the average decrease in consumption after the first year. However, the use of oral drugs gradually increases with disease progression. To estimate oral drug use beyond the first year, the treatment effect was estimated by pooling the results from long term longitudinal studies on DBS patients (up to 5 years) in a mixed-effects logistic regression as a log-linear function of time (Data available in Appendixes). We included a random

intercept and a random linear time trend in the model for each individual study. We used this model to forecast the decrease in oral drug use due to DBS in future years, relative to the maximum tolerated dose overtime (Table 19). This analysis was performed using R version 3.3.1. (114)

Table 19 Decrease in oral PD drugs (levodopa equivalent drugs)

DBS effect			
Regression estimates		LEDD	Source
Maximum tolerated dose before DBS (mg)		1262.04	See Appendixes.
% decrease in dosage			Meta-analysis of RCTs (65, 66, 68, 69)
Estimate		-0.34	
SE		0.03	
Baseline (% of max)		0.6620	
b0 (log odds)		0.6721	(107, 109, 110, 119, 120)
SE(b0) (delta method)		0.1312	
b1		0.0956	
Decrease in oral PD drugs overtime due to DBS			
Time	Proportional decrease relative to the maximum tolerated dose of oral drugs	On the logit scale	Distribution
		Estimate* SE**	
0	0.3380	0.6721 0.1312	Normal
1	0.3170	0.7677 0.1375	
2	0.2966	0.8633 0.1551	Calculated
3	0.2771	0.9589 0.1807	from the
4	0.2584	1.0545 0.2113	regression
5	0.2405	1.1501 0.2451	estimates
6	0.2234	1.2457 0.2809	above
7	0.2073	1.3413 0.3181	
8	0.1920	1.4369 0.3563	
9	0.1776	1.5324 0.3951	
10	0.1641	1.6280 0.4343	
11	0.1514	1.7236 0.4740	
12	0.1395	1.8192 0.5139	
13	0.1284	1.9148 0.5540	
14	0.1181	2.0104 0.5944	
15	0.1085	2.1060 0.6348	
16	0.0996	2.2016 0.6754	
17	0.0914	2.2972 0.7160	
18	0.0837	2.3928 0.7568	
19	0.0767	2.4883 0.7976	
20	0.0702	2.5839 0.8385	

21	0.0642	2.6795	0.8794
22	0.0587	2.7751	0.9203
23	0.0536	2.8707	0.9613
24	0.0490	2.9663	1.0024
25	0.0447	3.0619	1.0435
26	0.0408	3.1575	1.0845
27	0.0372	3.2531	1.1257
28	0.0339	3.3486	1.1668
29	0.0309	3.4442	1.2079
30	0.0282	3.5398	1.2491
31	0.0257	3.6354	1.2903
32	0.0234	3.7310	1.3315
33	0.0213	3.8266	1.3727
34	0.0194	3.9222	1.4139
35	0.0177	4.0178	1.4552
36	0.0161	4.1134	1.4964
37	0.0146	4.2089	1.5377
38	0.0133	4.3045	1.5789
39	0.0121	4.4001	1.6202
40	0.0110	4.4957	1.6615
41	0.0100	4.5913	1.7027
42	0.0091	4.6869	1.7440
43	0.0083	4.7825	1.7853
44	0.0076	4.8781	1.8266
45	0.0069	4.9737	1.8679
46	0.0062	5.0692	1.9092
47	0.0057	5.1648	1.9505
48	0.0052	5.2604	1.9919
49	0.0047	5.3560	2.0332
50	0.0043	5.4516	2.0745
51	0.0039	5.5472	2.1158
52	0.0035	5.6428	2.1572
53	0.0032	5.7384	2.1985
54	0.0029	5.8340	2.2398

Duodopa effect						
Drug class	Proportional decrease relative to the maximum tolerated dose of oral drugs				Distribution	Source
	mean	sd	alpha	beta		
Levodopa	0.7000	0.1750	0.140	0.0600	Beta	Clinician assumption
Other PD drugs	1.0000	0.2500	-1.000	0.0000		Constant overtime

LEDD =: levodopa equivalent drug dose; SE= Standard Error

*logit(p) = b0+b1*time, where p = proportion of maximum dosage

** SE(b0+b1*time) = sqrt(Var(b0) + Var(b1)*time^2) (treat b0 and b1 as independent (different studies))

For the Duodopa arm, patients should no longer require any oral levodopa except for when the pump is turned off at night. Given that Duodopa is continuously infused for 16 hours per day, a constant 70% decrease in oral levodopa compared to the maximum tolerated dose was assumed, and 100% decrease in use of other Drugs. If symptoms progress, the pump infusion is adjusted accordingly and oral medication are not expected to be increased.

6.2.8.5 Adverse events

Patients under oral BMT can experience serious adverse events (SAE); we used the baseline incidence of SAEs from the BMT arm of a randomized trial comparing DBS to BMT (PD SURG trial) (69) as the baseline risk of SAEs.

To estimate the occurrence of SAE under DBS treatment in the first year, we applied the risk ratio of SAE from the metanalysis presented in chapter 5 to this baseline risk of SAE. A proportion of those SAE were assumed to require replacement of the DBS system. These propositions were calculated from the ratio of device-related SAEs and infections among all SAEs from Weaver et al 2009.(68) Only half of the infections were assumed to lead to a system replacement, similar to another published model. (82) For the subsequent years, we assume a constant rate of SAE for DBS, as the same baseline rates of SAE under BMT, but maintaining the ratio of SAE leading to system replacement as in year 1 for cost purposes.

To estimate the occurrence of SAE under Duodopa treatment, however, we could not apply the same method since the only trial published on Duodopa does not compare Duodopa to BMT, but to sham-Duodopa (with patients having a PEG-J implanted in their abdomen for placebo infusion, inflating the rates of SAE in the placebo arm due to the catheter complications). Therefore, for the first year, we assumed the Duodopa-related rates of SAE

from a 1-year single arm observational study (72), and for the subsequent years, a constant rate

of SAE from a 3-year single arm observational study (DAPHNE trial). (105) Details of these

parameters can be seen in Table 20 and Appendixes).

Table 20 Adverse events

Probability of SAE Year 1									
					RR			dist	Source
	P_SAE	alpha	beta	mean	lb	ub	sd		
BMT	0.1366	25	158					Beta	(69)
DBS	0.3962			2.9	2.11	3.98	0.1615	log-normal	Meta-analysis of RCTs (65, 68, 69);
Duodopa	0.2258	14	48					Beta	(72)
Probability of SAE Year 2+									
BMT	0.1366							Beta	(69)
DBS	0.1366							Beta	(69)
Duodopa	0.2583	31	9					log-normal	Daphne trial (105)
Ratio of Infections and device related complications among SAE									
		alpha	beta	% SAE	Ratio among SAEs				
total sample	121								(68)
N. SAEs	49	49	72	0.4050				beta	
N. infections among SAEs	12	12	109	0.0992	0.1224			beta	
N. device-related among SAEs	8	8	113	0.0661	0.1633			beta	
Proportion of infections leading to system exchange	0.5								Assumption from previous model (82)

Note: sd- standard deviation; lb= lower bound; ub= upper bound; dist= distribution; SAE= Serious Adverse Events; BMT= Best Medical Therapy

6.2.8.6   Falls

To estimate the number of falls and the impact of treatments on this outcome, we

started with the initial probability of falls with injury found in the BMT arm of an RCT(69), then

applied the odds ratio of falling for each point increase in UPDRS III score (Table 1. Advanced PD

patients referred to potential DBS treatment still waiting for surgery or consultation (11). (121)

The different effect of DBS or Duodopa on the risk of falling was a combination of withdrawal

rates and effect of the individual interventions on the UPDRS III scores.

Table 21 Incidence of falls

	mean	alpha	Beta	dist	Source
Probability of fall with injury (baseline value based on patients with average UPDRS III score of 21 points)	0.0507	11	206	beta	See Appendixes. (67, 69)
Odds ratio for risk of fall – per 1-point increase in UPDRS III score	1.06	0.0583	0.0142	Log-normal	(121)

Note: dist=distribution; UPDRS= Unified Parkinson's Disease Rating Scale

6.2.8.7   Troublesome dyskinesia

To estimate the effect of each treatment option in improving time 'ON' without

troublesome dyskinesia, the average number of hours per day without troublesome dyskinesia,

derived from a metanalysis of BMT arms from RCTs, was assumed as the baseline in the model

(See Appendixes). As disease progresses and the therapeutic window narrows, patients are

expected to experience less hours of 'ON' time without troublesome dyskinesia per day. To

adjust the baseline number of hours for disease progression, the yearly rate of decrease in 'ON'

time without troublesome dyskinesia was applied to each cycle. To estimate the effects of DBS

and Duodopa on this outcome, we added the additional number of hours of ON time without

troublesome dyskinesia in each cycle.

Parameter input values are displayed in Table 22.

Table 22 Time ON without troublesome dyskinesia – baseline parameters, progression and effect of DBS or DUODOPA

	Mean	sd	dist	Source
The baseline ON time without troublesome dyskinesia in BMT group is (in hours/day)	7.24	0.1939	Normal	See Appendixes. (66-68)
Yearly rate of decrease in ON time without troublesome dyskinesia - per year - BMT progression	-0.03301			(122)
Increase of time ON without troublesome dyskinesia from advanced treatments (in hours/day)				
DBS	4.12	0.64	normal	(65, 66, 68)
DUODOPA	1.86	0.67	normal	(67)

Note: sd- standard deviation; dist= distribution; BMT= Best Medical Therapy;

6.2.8.8   Utilities

Health-state utility values (utilities) were calculated using a published algorithm that links UPDRS scores to the Euroqol-5D (EQ-5D) (75, 123):

$$EQ-5D = 1.59 * e^{(0.01721*Male+0.001448*Age-0.0198*UPDRS\ I-0.00049*(UPDRS\ II)^2-0.0178*UPDRS\ IV-0.2468)} - 0.594$$

According to the original study, the algorithm was developed using a beta regression approach. After a number of models were tested, a log link function was considered to be the most appropriate because it resulted in small errors, covered the full range of utility values possible with the EQ-5D, and did not produce illogical results (e.g. worse UPDRS scores leading to higher utilities). The model was derived from patient-level data from the EARLYSTIM trial, which included patients with early motor complications. (75, 123) An assumption was made that the model can be generalizable to advanced PD patients; however, we included alternatives in the sensitivity analyses.

To account for the uncertainty around the mean utility scores, we assumed a normal distribution of the utility values based on the standard errors of each regression coefficient included in the algorithm (Table 23).

Table 23 Parameters of mapping algorithm from UPDRS scores to EQ-5D utilities scores

Parameter	Mean	SE	Source
Intercept	-0.2468	0.03202	(75, 123)
Age	0.001488	0.0005514	
Male	0.01721	0.007913	
UPDRS I	-0.0198	0.002827	
(UPDRS II)2	-0.0004902	0.00006756	
UPDRS IV	-0.0178	0.00121	

Note: UPDRS= Unified Parkinson's Disease Rating Scale; SE= Standard Error

We did not use the adverse event rates to discount the quality of life scores generated by the mapping algorithm (from UPDRS scores to EQ-5D scores) due to the risk for double counting the effect of adverse events The algorithm was created with average UPDRS scores after treatment, which in theory also accounts for the effect of adverse events resulting in cognitive impairment or mental illness (UPDRS - Part I), daily life activity level (UPDRS - Part II), and motor disability (UPDRS - Part III). However, a sensitivity analysis with utility decrement from adverse events was included.

6.2.8.9   Costs

6.2.8.9.1   DBS Costs (MSP and Hospital costs)

Costs estimates are reported in Table 24. The average annual MSP, PharmaCare and hospital costs for PD patients receiving DBS in BC were available from fiscal years 2011/2012 to 2015/2016. Costs were extracted, aggregated, and analyzed by the HTRO of the Ministry of Health and presented as average yearly costs in the year prior to initial surgery (T-1), costs associated with the initial surgical procedure (T0), costs incurred after the primary procedure in the first year (T+1), second year (T+2), third year (T+3) and fourth year (T+4) (Appendix M). The cost of surgical procedure was removed from first year costs to avoid double counting. The cost of surgical procedure and year 1 were also estimated separately for patients who did not experience a complication, and patients who experienced a complication in the first year after undergoing DBS. Surgical costs and year 1 costs from patients with complications were applied to the incidence of SAEs in the model. All SAEs occurring in the model (regardless of year of occurrence) were assumed to have similar costs to the complications occurring in year 1. Additionally, a proportion of patients with SAEs were assumed to require DBS system

replacements (Table 20) and, therefore, incurred the added costs of a new DBS system. Patients who died from surgery (30-day mortality) were assumed to incur 1/12 of the first year's costs of patients with complications. Hospital and MSP costs from year 5 and onwards were assumed to be the same as costs from year 4.

Table 24 Hospital and MSP costs for DBS

Note: sd- standard deviation; dist= distribution; BMT: Best Medical Therapy; MSP= Medical Service Plan; BC DAD= British Columbia Discharge Abstract Database Metadata

6.2.8.9.2   Duodopa Costs (MSP and Hospital costs)

Due the lack of local cost data for patients under Duodopa treatment in the Province, we used a

published micro-costing study from Europe (Appendix N)(74) to estimate the hospital and MSP

costs for these patients in BC. This study provided estimates of costs for patients under both

DBS and Duodopa treatment. Since the European costs for DBS were generally higher than their

Canadian counterparts, we adjusted the Duodopa costs according to the cost ratio between

DBS costs in BC and in this European study (Appendix N). Next, to distribute the overall

Duodopa costs between MSP and hospital expenses, we took the following approach: the

European study had reported that patients under Duodopa had 14% lower utilization of medical

services than patients in the DBS group. We adjusted the ratio of MSP to hospital costs from

DBS patients in BC (Appendix O) to reflect the European lower utilization of medical services.

The adjusted ratios were applied to the overall Duodopa costs, to estimate the MSP and

hospital costs for Duodopa treatment in the Province.

Lastly, to adjust the hospital and MSP costs in the Duodopa arm for patients with and

without complications, we used the corresponding ratio for DBS from BC, adjusted according to

the expert opinion (Appendix O). The hospital and MSP costs for the DBS surgical procedure for

patients with complications were on average between 1.3 and 1.2 times higher than those

without complications. These ratios were used to determine surgical complication costs for

Duodopa. On the other hand, in the first year of receiving DBS, patients with complications had

hospital costs 20.6 times higher than those without complications. Since the complications from

Duodopa treatment (e.g. PEG-J catheter requiring replacement, peritonitis, skin complications,

etc.) are less invasively treated than the device-related complications under DBS (infections

leading to change of the entire DBS system requiring additional neurosurgery, cerebral

hemorrhage, stroke, etc.), based on expert opinion, we assumed the cost ratio for Duodopa

patients with complications to be 2 times the costs of those without complications. The final

cost parameters used in the model for Duodopa patients are described in Table 25. Thirty-day

mortality costs and costs after year 5 were modeled in the same way as explained for DBS.

Table 25 Hospital and MSP costs for Duodopa

Note: dist= distribution; MSP= Medical Service Plan; BC DAD= British Columbia Discharge Abstract Database
Metadata

6.2.8.9.3   Relationship between costs, withdrawal, and disease progression

Patients withdrawing from Duodopa or DBS, thus remaining under BMT only, were assumed to incur the same costs of BMT observed in BC prior to receiving DBS treatment (T-1).

Hospital and MSP costs under BMT post withdrawal at any cycle, or under DBS or Duodopa after year 4, were adjusted according to the UPDRS progression. The adjustment of costs according to disease progression was based on two published models comparing DBS or Duodopa to BMT (78, 81), presenting the average cost by HY stages (Appendix P). Then the progression according to HY stages was mapped to progression of UPDRS scores.

We used a linear regression model to determine the slope of the average increase in hospital and MSP costs when patients move from one HY stage to another. To link the HY stages to the UPDRS scores, we used a published study cross-tabulating average UPDRS scores per HY stage. (125) The coefficients for the slope of cost progression estimated using this method can be found in Table 26.

Table 26 Coefficient of adjustment of costs according to disease progression (between HY states)

	Slope coefficient	Method	Source
BMT	0.9035	Calculate based on linear regression	Dams et al (81)
DBS	0.9035		
DUODOPA	0.5787	Appendix P (81)	Lowin et al (78)

Note: BMT=Best Medical Therapy

6.2.8.9.4   Drug Costs

To estimate the PD drug costs incurred in this population and the effects of DBS or Duodopa, we separated the expenses associated with Drugs into 2 categories:

- Oral levodopa (all preparations),

- Other PD drugs (catechol-O-methyl transferase Inhibitors, Anticholinergic Agents, Dopamine Agonists, MAO-B Inhibitors, N-methyl-D-aspartate (NMDA) Receptor Antagonists).

In order to be referred to either DBS or Duodopa, PD patients must have received an adequate trial of maximally tolerated doses of levodopa with demonstrated clinical response, and have failed adequate trials of other adjunctive medications. Therefore, it was assumed that the maximum average yearly costs of PD drugs for patients undergoing DBS or Duodopa treatment is the same as the costs observed in year 1 prior to surgery in BC (T-1 in Appendix M) (Table 27). These costs where then prorated according to the expected decrease in oral drug dose due to the introduction to either DBS or Duodopa (Table 19). It was assumed that the observed decrease in the dosage of oral drug doses from clinical studies would proportionately affect the decrease in costs (e.g. if the decrease in oral drug dose in year 1 was 33% we would expect a 33% decrease in costs), and that if patients withdrew from treatment, their costs would go back to the costs of maximally tolerate disease of oral PD drugs before receiving DBS or Duodopa (baseline).

Table 27 Costs of PD drugs – maximum tolerated dose in use before advance treatment

	mean	sd	alpha	beta	dist	Source
██████ ██████	████	████	██	███	███	███████
██████████	███	████	██	███	███	██████ -
						██████
						██
						██████
						███████
						██████

Note: sd- standard deviation; dist= distribution

6.2.8.9.5   DBS devices and Duodopa package

DBS system costs include a pulse generator/battery, leads, device extensions, charger (for rechargeable batteries), tunneling tool, and a patient personal programmer (which is taken home for minor reprogramming changes as needed). The cost for DBS parts acquisition was based on the manufacturer's price list. Adaptors and spare parts (quantities and costs) used in eventual contaminations or battery replacement for old DBS models were extracted from the BC Clinical and Support Services Society (BCCSSS) database. (33) The price of devices and disposables were assumed to be known, because price is subject to negotiation (Table 28).

In the base case, we assumed patients would require battery changes every 4 years, except for ▇% of patients requiring a second battery change less than 3 years after the first replacement (year 6), in which case they will be switched over to a rechargeable battery, extending the time for required replacement to every 9 years (assuming a 100% use of Medtronic devices). Sensitivity analysis assuming other market shares with Boston implants with rechargeable batteries requiring replacement every ▇ years was also included.

Duodopa costs were obtained from the Drug Intelligence and Optimization branch in the BC Ministry of Health(126) and confirmed with the manufacturer. The established fee encompasses the PEG-J tube (primary and replacements), disposables, pump, patient training, and inclusion on the ABBVIE care program support (reimbursement specialist support, ABBVIE nurse, phone central support, and if necessary, home visits for wound and tube care training, drug use training and education). We assumed a proportion of patients under Duodopa treatment will require higher doses that will exceed the use of ▇ cassette per day, requiring ▇

cassettes per day, according to the manufacturer's data on Canadian patients currently receiving Duodopa therapy (Table 28).

Table 28 Cost of DBS devices and Duodopa gel

Source: Personal communication with manufacturers. (32, 127, 128)

6.2.9 Currency, price date, and conversion

All costs were inflated to 2016 Canadian dollars using the annual health and personal care component of the Consumer Price Index for BC. (129)

6.2.10 Analytic methods

For the base-case analysis, we calculated a single set of outcomes for DBS and Duodopa treatments, by weighted-averaging outcomes within each sex and age subgroup. Weights represented the sex and age distribution of patients currently on the waitlist for DBS in BC. Base case results and all subgroup-specific results were calculated from a deterministic analysis (using mean parameter values) from the average results of a microsimulation of 10,000 patients. We also performed a probabilistic analysis using Monte Carlo simulation with 2,000 iterations (with 10,000 patients in each iteration in the microsimulation component) to evaluate the degree of uncertainty in the results. Results of the probabilistic analysis are reported as the cost-effectiveness (CE) plane and the cost-effectiveness acceptability curve

(CEAC). For the probabilistic analysis, probability distributions were assigned to each uncertain model parameter, as follows:

- Beta distribution for the majority of transition probabilities (e.g., withdrawal, mortality, falls, adverse events), representing the degree of uncertainty in the original studies.

- Lognormal distribution for baseline UPDRS distribution in the patient population, hazard ratio of adverse events, hazard ratio of mortality due to increase in UPDRS 3, and odds ratio of falls due to increase in UPDRS 3.

- Normal distribution for UPDRS progression under BMT, effect of treatments in UPDRS scores, and oral drug use overtime.

- We assigned beta normal distribution for utilities since the variance found in the data was small and distribution was reasonably contained in the (-1, 1) interval.

- Gamma distribution was used for all cost parameters.

- In the absence of the reports on variance or standard errors in the original studies and reports, parameter uncertainty (e.g. costs, utility decrements) was modeled based on coefficient of variation of 0.25.

The choice of parameters for the above-mentioned distribution was based on the degree of uncertainty reported in the original studies (representing the sampling variability due to the finite size of the studies, as well as between-study heterogeneity when results were pooled estimates from a meta-analysis of individual studies). The price of devices and disposables were assumed to be known (i.e., no uncertainty), because price is subject to negotiation.

We conducted univariate deterministic sensitivity analyses to evaluate the effect of changes in key assumptions on the results. Among others, we evaluated changes in time horizon, discount, probability of SAEs after first year, cost of Duodopa gel, medical and hospital costs for patients treated with Duodopa, effect of Duodopa in changing UPDRS scores, lasting effect of both treatments in changing UPDRS IV, rate of natural disease progression, effect of DBS in changing oral drug use, and frequency of battery changes (Table 32).

In determining the most efficient strategy, we compared the incremental cost-effectiveness ratio (ICER) against a willingness-to-pay (WTP) of $50,000 per QALY gained.

6.3   Results

6.3.1   Total costs and outcomes – population level

The microsimulation model estimated disease progression in terms of UPDRS scores,

survival, and quality of life (as a result of UPDRS progression and mortality after both

treatments) for the BC advanced PD population (

Figure 10).

In over 10 years, for each 100 patients undergoing DBS treatment, 20 are estimated to withdraw from treatment, and 39 falls causing injury are estimated to occur. Regarding the number of devices over the 10-year time horizon, the same 100 patients are estimated to use ███ complete DBS systems, ███ conventional batteries, and █ rechargeable batteries. On average, during this 10-year period each patient is estimated to live on average for 8.57 years, have 3.45 QALYs, and experience 32,588 hours of 'ON' time without troublesome dyskinesia (equivalent to 1,357 days, 45.3 months, or 3.8 years of near normal motor function)(Table 29).

DBS treatment, over 10 years, is estimated to have a total cost of $228,053 per patient. The total costs include $█████ in DBS system and battery replacements, $█████ in hospital expenses, $█████ in MSP costs, and $████ in PD oral drugs (PharmaCare paid portion) (Table 30).

Figure 10 Estimated average progression of Total UPDRS, EQ-5D and survival under DBS or Duodopa over a 10-year time horizon (discounted values)

Dec 2017 | Centre for Clinical Epidemiology and Evaluation | Vancouver Coastal Health Research Institute

Survival
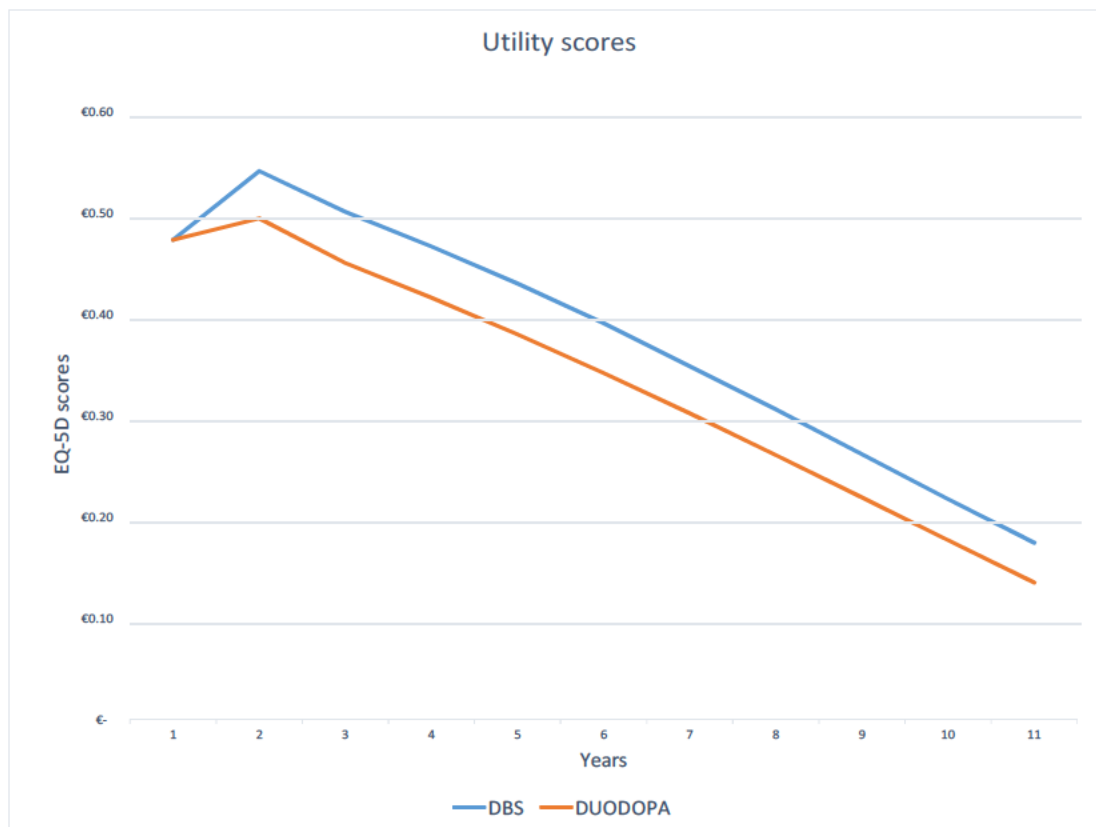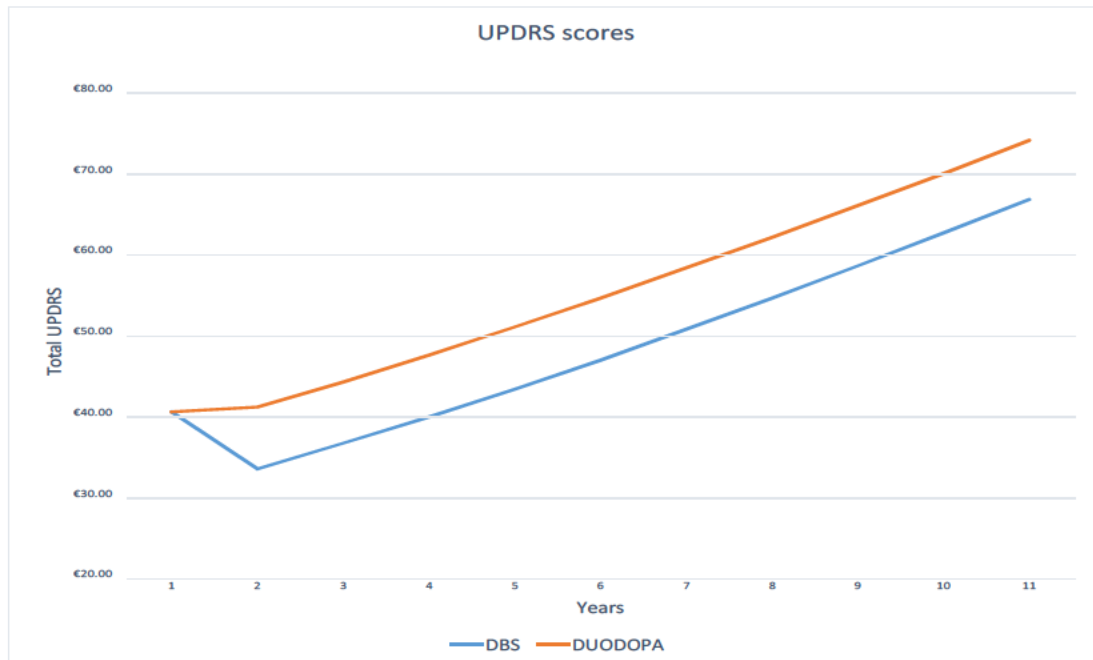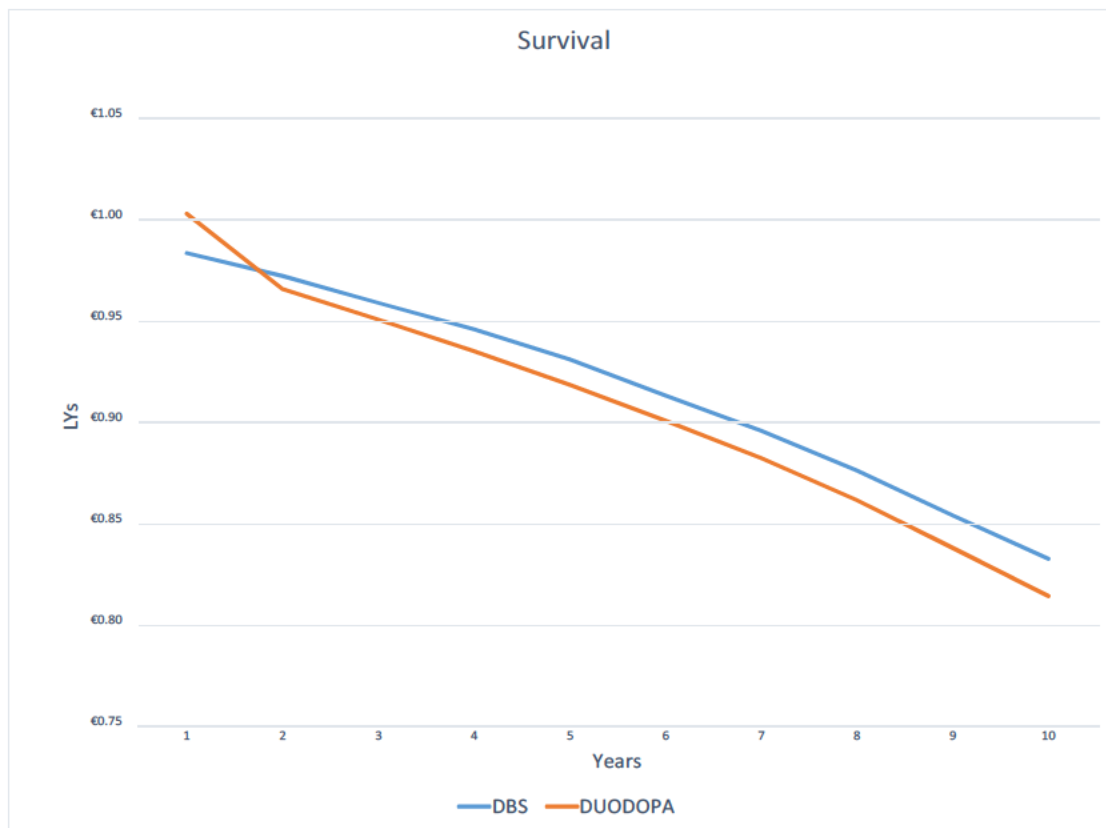
Alternatively, if in this 10-year time horizon the same 100 patients receive DUODOPA therapy, 50 patients are estimated to withdraw from treatment, and 49 falls causing injury are estimated to occur. On average, during this period, each patient is estimated to live on average for 8.49 years, have 3.02 QALYs, and experience 24,517 hours of 'ON' time without troublesome dyskinesia (which is equivalent to 1,021 days, 34.1 months, or 2.8 years of near normal motor function) (Table 29).

DUODOPA treatment, over 10 years, is estimated to have a total cost of $537,208 per patient. The total costs include ███████ in DUODOPA alone, ██████ in hospital costs, ██████ in MSP costs and ██████ in PD oral drugs (PharmaCare paid portion) (Table 30).

Table 29 Clinical outcomes at the population level – deterministic analysis under a 10-year time horizon (results are expressed per patient).

	Undiscounted Outcomes						Discounted Outcomes	
	Withdraw	ON time without troublesome dyskinesia (in hours)	Falls with injury	N. DBS systems	N. batteries non-rechargeable	N. batteries rechargeable	Total QALYs	LY
DBS	0.20	32,588	0.39	■	■	■	3.45	8.57
Duodopa	0.50	24,517	0.49	■	■	■	3.02	8.49

Note: QALY= Quality Adjusted Life-Years; LY= Life-years;

Table 30 Cost outcomes at the population level – deterministic analysis under a 10-year time horizon (results are expressed per patient).

	Discounted Outcomes				
	Cost of Treatment	Cost of Oral PD Drugs	Hospital Costs	MSP Costs	Total Costs
DBS	■	■	■	■	■
Duodopa	■	■	■	■	■

6.3.2   Incremental costs and outcomes – population level

Over a 10-year time horizon, for patients with advanced PD receiving DUODOPA treatment as opposed to DBS, there is an estimated average incremental cost of $309,155 per patient treated, as well as proving to be less effective in terms of survival, QALYs and increase in time 'ON' without troublesome dyskinesia (Table 31).

Table 31 Cost-effectiveness of DUODOPA for advanced PD patients in BC compared to DBS over a 10-year time horizon (results are expressed per patient).

	DUODOPA vs. DBS
ICER / QALY	dominated
ICER / LY	dominated
ICER / Day without troublesome dyskinesia	dominated
Incremental costs	309,155
Incremental QALY	-0.43
Incremental LY	-0.08
Incremental n. hours of time ON without troublesome dyskinesia	-8,071

Note: ICER = incremental cost-effectiveness ratio; QALY = quality –adjusted life years; LY = life years
Dominated = the intervention costs more and is no more effective than the comparator.

This means that in the base case scenario, noting the assumptions discussed above, DBS is the unequivocally preferred treatment in comparison to Duodopa (i.e., lower incremental cost and greater incremental benefit).

6.3.3   Characterizing uncertainty

The probabilistic model for a 10-year time horizon showed some degree of uncertainty. The cloud in the cost-effectiveness plane spread over two quadrants, but the majority fell into the upper left quadrant, showing DUODOPA therapy in comparison to DBS to be generally less beneficial, and to result in higher overall costs (Figure 11). The cost-effectiveness acceptability curve (CEAC) quantifies the uncertainty by demonstrating the probability of DUODPA being cost-effective at a given WTP. For the entire plausible range of WTP, the probability of DUODOPA being cost-effective was very close to zero (not shown).

Figure 11 Cost-effectiveness plane of probabilistic analysis over a 10-year time horizon.

Several deterministic sensitivity analyses were conducted (Table 32),with results being very similar to those from the base-case analysis (DBS being dominant in almost every scenario). For DUODOPA to not add any incremental costs for the treatment of advanced PD patients eligible to DBS, this therapy would have to cost approximately $████ per year. However, despite this, it would still not provide the same effectiveness as compared to DBS in terms of UPDRS scores, and, consequently, QALYs and LYs gained. The only sensitivity analysis in which DUODOPA had a lower cost than DBS was when the underlying disease progression was twice as fast as the average progression reported in the BMT arms of clinical trials. However, in this analysis, despite DUODOPA resulting in lower total costs as compared to DBS (-$█████), this therapy would still yield worse clinical outcomes.

The last sensitivity analysis simulated the current wait time for DBS (4 years) compared to giving immediate access to Duodopa. Even with a 4 year advantage in effect on clinical outcomes, DUODOPA still resulted in lower QALYs over the 10-year time horizon and an associated incremental cost of $292,755.

Table 32 Deterministic sensitivity analysis

	ICER/QALY gained	ICER/LY gained	ICER/Day without troublesome dyskinesia	Incremental Costs	Incremental QALY	Incremental LY	Incremental hours without troublesome dyskinesia
Base-case	dominated	dominated	dominated	309,155	-0.43	-0.08	-8071
Time Horizon - 5 years	dominated	dominated	dominated	209,389	-0.24	-0.02	-4072
Time Horizon - 15 years	dominated	dominated	dominated	257,642	-0.56	-0.16	-11534
Discount 0%	dominated	dominated	dominated	325,475	-0.460	-0.09	-8071
Discount 3%	dominated	dominated	dominated	294,280	-0.41	-0.08	-8071
Equal probability of SAEs after year 1 for DBS and Duodopa	dominated	dominated	dominated	282,940	-0.43	-0.08	-8071
Annual costs of Duodopa reduced by 20%	dominated	dominated	dominated	229,661	-0.43	-0.08	-8071
Annual costs of Duodopa reduced by 50%	dominated	dominated	dominated	110,421	-0.43	-0.08	-8071
MSP and Hospital costs to follow-up patients with Duodopa decreased by 50%	dominated	dominated	dominated	261,981	-0.43	-0.08	-8071
Effect of DBS decrease in 45% the use of oral drugs	dominated	dominated	dominated	309,173	-0.43	-0.08	-8071
DBS battery change every 3 years	dominated	dominated	dominated	297,844	-0.43	-0.08	-8071
PharmaCare billed portions (instead of paid portions	dominated	dominated	dominated	300,770	-0.43	-0.08	-8071
Inflating the QALY`s generated by the algorithm by 30%	dominated	dominated	dominated	309,155	-0.56	-0.08	-8071

Including disutility due SAEs	dominated	dominated	dominated	309,155	-0.35	-0.08	-8071
DUODOPA at ▮▮▮/year (1 cassette/day)	dominated	dominated	dominated	57	-0.43	-0.08	-8071
Dams 2013 algorithm for mapping QALY to UPDRS scores (130)	dominated	dominated	dominated	309,155	-0.35	-0.08	-8071
Double the rate of UPDRS progression under BMT only (patients with rapid disease progression)	251,667	139,270	70	-21,442	-0.09	-0.15	-7307
DUODOPA with equal effect on UPDRS progression as DBS	dominated	dominated	dominated	302,683	-0.16	-0.03	-7940
Lasting effect of treatments on UPDRS IV for 3 years - regular progression from year 4	dominated	dominated	dominated	309,574	-0.44	-0.09	-8050
Delay DBS fo ▮▮ ▮▮▮ compared to immediate access to DUODOPA	dominated	dominated	dominated	▮▮▮▮	▮▮▮	▮▮▮	▮▮▮

Note: ICER = incremental cost-effectiveness ratio; MSP = BC Medical Services Plan; QALY = quality –adjusted life years; LY = life years; For the sensitivity analysis using the algorithm published by Dams 2013, we used equation M2 for the European Index due the highest R^2 among the equations requiring UPDRS scores II, III and IV (130)

6.3.4 Subgroup analysis

Subgroup analyses by age were conducted (Table 33, Table 34, and Table 35), with results being similar to those from the base-case analysis (i.e., DBS was dominant for all age groups).

Table 33 Clinical outcomes by age group – deterministic analysis under a 10-year time horizon (results are expressed per patient).

Undiscounted Outcomes							Discounted Outcomes	
	Withdraw	ON time without troublesome dyskinesia (in hours)	Falls with injury	N. DBS systems	N. batteries non-rechargeable	N. batteries rechargeable	Total QALYs	LY
45-64 years								
DBS	0.2067	34,251	0.43	■	■	■	3.44	9.02
Duodopa	0.5338	25,894	0.55				3.01	8.99
65-79 years								
DBS	0.1905	31,860	0.37	■	■	■	3.49	8.37
Duodopa	0.4856	23,896	0.46				3.05	8.26
80+ years								
DBS	0.1307	23,166	0.20	■	■	■	2.88	6.01
Duodopa	0.3275	17,019	0.25				2.48	5.75

Note: QALY = quality –adjusted life years; LY = life years

Table 34 Cost outcomes by age group – deterministic analysis under a 10-year time horizon (results are expressed per patient).

Discounted Outcomes					
	Cost of Treatment	Cost of Oral PD Drugs	Hospital Costs	MSP Costs	Total Costs
45-64 years					
DBS	■	■	■	■	238,575
Duodopa	■	■	■	■	569,452
65-79 years					
DBS	■	■	■	■	225,086
Duodopa	■	■	■	■	521,939
80+ years					
DBS	■	■	■	■	141,526
Duodopa	■	■	■	■	373,501

Note: MSP=Medical Service Plan

Table 35 Cost-effectiveness of DUODOPA for advanced PD patients in BC compared to DBS over a 10-year time horizon by age groups (results are expressed per patient).

DUODOPA vs. DBS			
	45-64 years	65-79 years	80+ years
ICER / QALY	dominated	dominated	dominated
ICER / LY	dominated	dominated	dominated
ICER / Day without troublesome dyskinesia	dominated	dominated	dominated
Incremental costs	330,877	296,853	231,976
Incremental QALY	-0.431	-0.435	-0.397
Incremental LY	-0.03	-0.12	-0.26
Incremental n. hours of time ON without troublesome dyskinesia	-8,356	-7,965	-6,146

Note: ICER = incremental cost-effectiveness ratio; QALY = quality –adjusted life years; LY = life years

Dominated = the intervention costs more and is no more effective than the comparator

6.4   Discussion

Incorporating the best available evidence into a decision-analytic simulation model, we showed that treatment of advanced PD patients in BC with DBS, as compared to DUODOPA, is much more cost-effective in almost every simulated scenario at a wide range of WTP values per QALY. In order for DUODOPA to have a similar cost profile as DBS, a ███████ reduction would be required. However, and critically, this would still not yield the same clinical outcomes as DBS.

When we simulate the effect of both DBS and DUODOPA for patients with rapid disease progression (by doubling the UPDRS progression rate compared with the average), DUODOPA therapy appears to be a cost-effective alternative. This finding should be interpreted as hypothesis generating, and more studies are needed to confirm cost progression with increases in UPDRS, given that all other parameters used in the model were calculated for the average patient (mortality, effect of treatments, utility values, costs), and, therefore, would require adjustments for specific patient populations with rapid progression.

This economic analysis has some key limitations due to the scarce evidence available on direct comparisons between the two treatment options. The effectiveness estimates came from an indirect comparison of DBS or Duodopa to BMT. The entire economic model framework was developed using the indirect comparison, by simulating each patient's trajectory under BMT only, and then applying the effects of DBS or DUODOPA to their own individual disease progression.

The only clinical trial in DUODOPA has a very short follow-up (3 months, compared to BMT) as compared to the DBS studies (up to 12 months), and as such might not have allowed enough time to demonstrate the true effect of the treatment. In fact, on average UPDRS scores in parts I and III in the DUODOPA arm were worse in comparison to the BMT arm (Table 15), which may have affected the model results. Some longer term observational studies suggest that DUODOPA therapy may in fact have a bigger impact than originally found in improving UPDRS scores. (62, 63) Given this possibility, a sensitivity analysis was conducted simulating DUODOPA and DBS to have a similar effect on UPDRS scores. However, this scenario also showed DUODOPA therapy to be dominated by DBS.

Comparison of both technologies in terms of quality of life measured by generic instruments was not possible due to the unavailability of such studies. The QALY estimates were based on a mapping algorithm that generates EQ-5D scores from the UPDRS scores. Even though in theory UPDRS may not be as sensitive as direct quality of life measures, it should still reflect the impact on cognitive impairment or diagnosis of mental illnesses (UPDRS - Part I), daily life activity level (UPDRS - Part II), motor disability (UPDRS - Part III), and motor complications (UPDRS Part IV). The algorithm used in the base case relies on UPDRS parts I, II, and IV (75), and seems to generate EQ-5D scores 30% lower than when applied to the data from the DAPHNE study (105), where both UPDRS and EQ-5D were collected simultaneously. However, this was not considered to be of great concern considering that not only that the sensitivity analysis in which the base case EQ-5D scores were inflated by 30% produced similar results, but also that the use of another validated algorithm that relies on UPDRS part III and IV (130) did not change the direction of the results and continued to showed DBS to be dominant.

Furthermore, because the model effect was produced from an indirect comparison (both DBS and Duodopa were being modeled against BMT only), the choice of algorithm does not favor one technology or the other, keeping the results more in line with the clinical trials. For future calibration of these algorithms and confirmation of the results from this analysis, we would recommend that EQ-5D and complete UPDRS data be routinely collected for patients undergoing either DBS or DUODOPA therapy.

A further limitation that should be acknowledged is the lack of long term local data on MSP costs and hospital expenses for patients undergoing DUODOPA treatment. The DUODOPA costs inputted in this model were extracted from a European study and adjusted to BC costs. Despite our best efforts to make adjustments, local costs directly measured in BC may show differences in costs reported in this study. For this reason, to confirm the results of this cost-effectiveness analysis in the future, we suggest monitoring the costs for any patient who is granted access to DUODOPA in BC (similar to those eligible for DBS).

Appendix Q reports out-of-pocket costs borne by PD patients in BC. This data was obtained through qualitative interviews with patients and is not necessarily generalizable. Importantly, these findings do indicate the relevance of conducting cost-effectiveness analyses from a societal perspective for this patient population. Given the cost effectiveness results in favor of DBS when assessed from a government payer perspective and the extent of the incremental cost of DUODOPA, it is very unlikely that differences in out-of-pocket costs between treatments would change the direction of the results.

Chapter 7 Budget Impact

Summary

    The current capacity for DBS surgery for advanced PD patients in BC would require approximately an additional 152 primary surgeries per year, for the next 4 years, in order to manage the existing pool of patients waiting for treatment and future demand for treatment, and thereafter, maintain an annual capacity for approximately 92 primary surgeries in order to keep wait times below one year.

    In the next 10 years this patient population is estimated to require 155 million in health care costs if treated with DBS (including hospital, MSP, oral PD drugs, and devices costs).

    DBS treatment, despite requiring higher allocation of resources to hospital care and device purchase (including future battery replacements), still results in an overall lower impact to the health care system in comparison to adopting DUODOPA as an alternative treatment to patients who are eligible for DBS surgery. Offering DUODOPA to 20% of this patient population would cost, cumulatively, approximately $\blacksquare$ in DUODOPA gel alone.

    Given the geographic distribution of the patients currently on the waitlist, all health authorities except NHA individually already have a demand for DBS treatment that surpasses the current capacity offered at VGH.

7.1   Objectives

To evaluate the budget impact of a policy change in BC to expand access to DBS treatment for advanced PD patients, as compared to maintaining the status quo or supporting treatment with DUODOPA gel therapy.

7.2   Methods

Four scenarios were created to evaluate the budget impact in BC. The status quo scenario assumes no expansion in capacity is implemented for advanced PD patients. For this scenario, a continuity of the average number of DBS surgeries for advanced PD patients per year (2012-2016 average) was assumed. It should be noted that estimates of budget impact for this scenario do not include the cost of patients that remain untreated (BMT only). The health care management cost of patients left untreated (BMT only) are not captured under the scope

of this project since the cost-effectiveness analysis was not meant to compare DBS with no treatment. However, this is not likely to cause bias towards DBS or DUODOPA.

Scenario A assumes DBS will be offered to every advanced PD patient eligible for surgery within 1-year (from referral to surgery), and accommodates the existing demand (all patients currently on the waitlist) with the assumption that the backlog will be resolved in 4 years (phase-in). Given this scenario, it is possible to estimate the number of surgeries and overall cost related to DBS devices, as well as the anticipated capacity required to address the growing demand of DBS treatment in patients with advanced PD, and the financial impact of this demand on other areas such as MSP, hospitals, and PharmaCare (rather than only reflecting the budget impact for patients under BMT in this analysis).

Scenario B assumes DUODOPA will be offered to every advanced PD patient referred to DBS within 1-year (from referral to treatment), and accommodates the existing demand (all patients currently on the waitlist), with the assumption that the backlog will be resolved in 4 years (phase-in). This scenario estimates the budget impact of addressing the current demand of treatment for patients with advanced PD with DUODOPA rather than DBS.

Scenario C assumes that despite DBS being the most cost-effectiveness option for patients with advanced PD who are eligible for the implant, the health care system will have accepted a market share approach between DBS and DUODOPA (this can be the result of a variety of factors such as capacity limitations, patients' preference, logistical issues, etc.). This scenario assumes an arbitrary 80% market share for DBS and 20% for DUODOPA treatment for all advanced PD patients referred to DBS within 1-year (from referral to treatment). This scenario is assumed to absorb the existing demand for treatment (all patients currently on the

waitlist) in 4 years (phase-in), and estimates the budget impact of addressing the current

demand for treatment for patients with advanced PD with a mix approach of both DBS and

DUODOPA therapy.

In all scenarios, it was assumed that all health care costs, including cost of the devices

and DUODOPA, were paid by the public health care system. It was assumed that existing

capacity would accommodate all the projected referrals for advanced treatment of the aging

population from 2018 onwards (131).

The same deterministic Markov model demonstrated in the economic evaluation (Figure

7) was used for the budget impact analysis. However, the model was configured to simulate the

dynamic population impact over 10 years (2018 to 2027), based initially on the demand for

advanced treatment DBS in year 2016. To estimate the annual demand, the number of patients

in the waitlist by year of referral (t) were added to the number of surgeries three years later

(t+3), under the assumption that patients have on average been waiting a period of 3 years

from the initial referral until surgery (e.g., number of patients on waitlist from 2013 + number

of DBS surgeries in 2016). Years with incomplete data for number of DBS surgeries for PD

patients (e.g. 2017) were imputed with the average number of surgeries per year derived from

historical data. The budget impact analysis was conducted for different age groups. To collate

age-specific results to generate the overall budget impact during this period, age-specific

subgroup weights were assigned based on Statistics Canada's projected population growth and

aging data. (132) Prevalence of advanced PD, as well as the criteria for referral to DBS

(advanced PD Patients), were assumed to remain the same in the BC population.

Every year, a new cohort of patients enter the model from the time of their primary surgery, and thus, the number of battery replacements and costs were calculated cumulatively (starting from 2018). Battery changes for patients who had their primary DBS before 2018 were not included in the budget impact. As such, the reported cost estimates only pertain to the treatments initiating in 2018. The overall budget impact on the province is presented, broken down into the health authorities (HAs) and MSP portions.

In line with CADTH guidelines, no discounting or inflation was applied in the BIA. Costs were expressed in 2016 Canadian dollars. We assumed no changes in price units during the period (meaning that any nominal change in price in the future would be the same as the rate of inflation).

7.3 Results

7.3.1 Status quo

For the status quo scenario in BC █████████████████████████████████████

███████████████████████████████████████ the total cost to treat advanced PD patients requiring DBS implant (and their long-term consequences) was estimated at $19.3 million over 10 years (Table 36). Annual cost was predicted to accumulate from $782,800 in 2018 (for the 2018 cohort of patients) to $3.4 million in 2027 (cumulative costs for the cohorts treated from 2018-2027) (Table 38). These costs are distributed within different funding sources. Of total costs, ██

███

███

surgery within 2018 and 2027. It is estimated that BCCSS services will also have purchased ████

██ within the

same time period.

7.3.2   Estimated demand for advanced treatment among PD patients

Given the growth and aging of the population in BC, and assuming a 4-year phase-in

period to absorb the backlog demand in the current waitlist for DBS, the number of advanced

PD patients requiring primary DBS implant from 2018-2021, is estimated to equal an average of

152 surgeries per year. Once this existing demand is resolved, from 2022, the annual demand

will reduce to 92 DBS implants per year, hereafter increasing in number due to growth of the

population of patients with advanced PD (Table 37).

According to the geographic distribution of the patients currently on the waitlist (Table

37), and assuming the estimated future demand will follow the same pattern, FHA, VCHA and

VIHA each already require one surgeon (with the same current surgical time and availability)

exclusively allocated to the PD population (Table 37), and consequently, other health care

personnel and services needed for the DBS clinic to support pre and post-operative care. The

estimated demand from IHA alone already surpasses the current surgical capacity allocated to

PD patients in BC.

Table 36 Status quo: total costs for management of advanced PD patients by DBS treatment over 10 years, under the current capacity in BC (undiscounted).

Status Quo	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2018-2027
Total Costs	782.8 K	949.8 K	1.1 M	1.4 M	1.7 M	2.0 M	2.3 M	2.7 M	2.9 M	3.4 M	19.3 M

Note: costs of patients implanted with DBS prior to 2018 are not include in the cumulative analysis.
MSP= Medical Service Plan

Table 37 Demand for treatment among advanced PD patients in BC, and by health authority, over 10 years

	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2018-2027

Note: HA= Health Authority; FHA= Fraser Health Authority; VCHA= Vancouver Coastal Health Authority; VIHA= Vancouver Island Health Authority, IHA= Interior Health Authority; NHA= Northern Health Authority. The total number of referrals were estimated first, and then distributed by health authority according to their current proportion of patients in the waitlist, assuming the referral patterns will remain the same. There might be differences between the individual number of surgeries per health authority and the total per each year due rounding techniques.
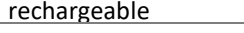
7.3.3 Scenario A – DBS treatment to all eligible patients (compared to the status quo)

Table 38 shows the estimated annual costs and budget impact evaluation. Assuming that all eligible patients will be treated with DBS, total costs were estimated at $155.7 million over 10 years. Annual costs were predicted to accumulate from 7.8 million in 2018 (for the 2018 cohort of patients) to $24.9 million in 2027 (cumulative costs for the cohorts treated from 2018-2027, Table 38 Scenario A: total costs and budget impact for the management of advanced PD patients with DBS in BC over 10 years.). Of total share of costs, MSP is estimated to bear $▬▬▬▬, PharmaCare is estimated to bear ▬▬▬▬ in PD oral drugs, and health authorities are estimated to bear $▬▬▬▬ in hospital costs, in addition to ▬▬▬▬ in DBS systems and battery replacements for the cohorts undergoing surgery within 2018 and 2027.

Compared to the current capacity, over 130 additional primary surgeries would be required per year, for the next 4 years, to absorb this demand. Hereafter, roughly 70 additional surgeries per year, compared to the current capacity, would be required to absorb the demand with wait periods no longer than 1 year.

BC will be required to purchase an additional ▬▬▬ complete DBS systems, ▬▬ conventional batteries ▬▬▬ rechargeable batteries within the same period (compared to the current capacity). Compared to costs under the status quo, an incremental cost of over ▬▬ ▬▬▬▬ is expected with DBS devices alone.

Table 38 Scenario A: total costs and budget impact for the management of advanced PD patients with DBS in BC over 10 years.

	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2018-2027
Total Costs	7.8 M	9.5 M	11.4 M	14.1 M	13.2 M	15.7 M	17.6 M	20.1 M	21.6 M	24.9 M	155.7 M
Impact to attend demand with DBS (vs. Status quo)											
Overall	7.0 M	8.5 M	10.2 M	12.7 M	11.5 M	13.7 M	15.3 M	17.4 M	18.6 M	21.5 M	136.4 M
rechargeable											

Note: n. DBS systems are higher than the number of primary surgeries to account for the rate of serious adverse events leading to re-operation and replacement of the DBS system.

MSP= Medical Service Plan

7.3.4 Scenario B – DUODOPA treatment instead of DBS to all eligible patients (compare to DBS)

██

██

██

The total costs were estimated at $431.6 million over 10 years. This cost was predicted to accumulate from $12.7 million in 2018 (for the 2018 cohort of patients) to $62.7 million in 2027 (cumulative costs for the cohorts treated from 2018-2027, Table 39). Of total costs, MSP is estimated to bear $████████, PharmaCare is estimated to bear ████████ in PD oral drugs added of $████████ for DUODOPA gel alone, and health authorities are estimated to bear $████████ in hospital costs for the cohorts undergoing DUODOPA treatment within 2018 and 2027.

Compared to treating the same patients with DBS, DUODOPA treatment is estimated to avoid costs with oral PD drugs and hospital costs. This is mainly due to the lower cost for the surgery to implant PEG-J catheters, and that complications from DUODOPA treatment are less invasively treated as compared to the device-related complications under DBS. However, there would still be an overall incremental cost of $275.8 million over 10 years, mostly driven by the cost of DUODOPA gel.

Table 39 Scenario B: Total costs and budget impact for the management of advanced PD patients with DUODOPA in BC over 10 years.

	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2018-2027
■	■	■	■	■	■	■	■	■	■	■	■
■	■	■	■	■	■	■	■	■	■	■	■
■	■	■	■	■	■	■	■	■	■	■	■
■	■	■	■	■	■	■	■	■	■	■	■
Total Costs	12.7 M	22.9 M	32.6 M	41.4 M	44.4 M	48.1 M	51.6 M	55.7 M	59.4 M	62.7 M	431.6 M
Budget Impact to attend the demand with Duodopa (vs. DBS)											
■	■	■	■	■	■	■	■	■	■	■	■
■	■	■	■	■	■	■	■	■	■	■	■
■	■	■	■	■	■	■	■	■	■	■	■
■	■	■	■	■	■	■	■	■	■	■	■
Overall	4.9 M	13.4 M	21.2 M	27.3 M	31.2 M	32.4 M	34.0 M	35.6 M	37.8 M	37.8 M	275.8 M

(DUODOPA— Scenario B)

Notes: MSP= Medical Service Plan; PEG= Percutaneous endoscopic gastrostomy

7.3.5   Scenario C – DBS (80%) and DUODOPA (20%) to the treatment of all patients eligible

to either therapy (compared to DBS alone)

Assuming that all eligible patients will be treated, a share market approach between

treatments will emerge despite the better cost-effectiveness profile of DBS, and thus, requiring

the health care system to provide an additional 236 primary surgeries for the implantation of

PEG-J catheter to initiate DUODOPA treatment, and an additional 784 primary DBS surgeries.

The total costs were estimated at $210.9 million over 10 years. This was predicted to

accumulate from $8.8 million in 2018 (for the 2018 cohort of patients) to $32.4 million in 2027

(cumulative costs for the cohorts treated implanted from 2018-2017, Table 40).

Of total costs, MSP is estimated to bear $▮▮▮▮▮▮▮, and PharmaCare is estimated to

bear ▮▮▮▮▮▮ in PD oral drugs added of $▮▮▮▮▮▮ for DUODOPA gel alone.

Health authorities are estimated to bear $▮▮▮▮▮▮ in hospital costs, in addition to

▮▮▮▮▮▮▮ in DBS systems and battery replacement for the cohorts undergoing surgery

within 2018 and 2027. BC is estimated to purchase ▮▮▮ complete systems, ▮▮ conventional

batteries ▮▮▮▮ rechargeable batteries within the same period.

The health care system would avoid $5.8 million in expenses with DBS devices, and

other costs with hospital care and oral PD drugs. However, these costs avoided would not offset

the costs of the DUODOPA gel, resulting in an incremental cost of $55.2 million over 10 years in

comparison to treating all patients with DBS.

Table 40 Scenario C: total costs and budget impact for the management of advanced PD patients with DBS (██%) and DUODOPA (██%) in BC

	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2018-2027
Total Costs	8.8 M	12.1 M	15.6 M	19.6 M	19.4 M	22.2 M	24.4 M	27.2 M	29.1 M	32.4 M	210.9 M

Budget Impact to attend the demand with Duodopa and DBS (vs DBS alone)

DBS (80%) + DUODOPA (20%)

	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2018-2027
Overall	984.2 K	2.7 M	4.2 M	5.5 M	6.2 M	6.5 M	6.8 M	7.1 M	7.6 M	7.6 M	55.2 M

DBS primary surgeries

Note: n. DBS systems are higher than the number of primary surgeries to account for the rate of serious adverse events leading to re-operation and replacement of the DBS system.

7.4   Discussion

The current capacity for DBS surgery being offered to the advanced PD population in BC is substantially below the current demand for treatment of advanced PD patients in the province, and thus has led to an ever-increasing backlog demand over the years.

In order to manage the existing and future demand for treatment, BC will require to provision health care resources for approximately 152 primary surgeries per year (DBS implants or PEG-J implants) for this patient population, for the next 4 years, and maintain a capacity for approximately 92 primary surgeries hereafter in order to keep wait times below one year.

This economic analysis has some key limitations. Concerns about the quality of the data were already discussed in the cost-effectiveness analysis; however, it is important to reinforce that costs for treating patients with DUODOPA (excluding the cost of the drug itself) were extracted from a European study. In the event of a policy change extending DUODOPA access to patients eligible for DBS, it is recommended to monitor implantation to elicit the MSP and hospital costs for those patients to confirm the costs-effectiveness ratio and calibrate the budget impact analysis. More so, it is hard to make a robust prediction about the real impact of the expansion of current DBS services on the health care system. MSP, PharmaCare, and health authorities already bear some costs related to the patients who are left untreated (BMT only); however, these are not reflected under the scope of this analysis. It would require a separate study to establish how much such patients (under BMT only) are already costing the system from the moment they are eligible for DBS but remain to be untreated with DBS or DUODOPA.

In order to increase access to advanced treatments, the most cost-effective option with the lowest impact seems to be the increase in capacity of DBS surgeries across BC. Health

authorities will require an implementation study to assess the current surgical capacity, and health care personnel training (availability of surgeons, specialized nurses, OR time and equipment, etc.) within their regions, and evaluate whether to continue to centralize the advanced treatments within VCHA infrastructure, or whether as to decentralize certain service such as the support from the DBS clinic for pre-operative evaluation and post-operative DBS calibrations, battery changes to minimize travel time for patients to access care, and optimize the VCHA services for highly specialized services (the DBS implant itself). In the next 10 years, this patient population is estimated to require 155 million for health care costs if treated with DBS.

Offering DUODOPA as an alternative treatment for advanced patients who are eligible to DBS for whatever reason (patient preference, lack of available surgical capacity, etc.), even at a small proportion (20%), would result in even higher costs to expand access to treatment, with a different impact to each of the multiple funding sources involved in the health care management of this patient population. Therefore, the costs avoided with oral PD drugs, DBS devices and hospital costs, would not offset the incremental cost of DUODODPA (55 million in 10 years).

References

1. Sato K, Hatano T, Yamashiro K, Kagohashi M, Nishioka K, Izawa N, et al. Prognosis of Parkinson's disease: time to stage III, IV, V, and to motor fluctuations. Mov Disord. 2006 Sep;21(9):1384-95.

2. Canadian Pharmacists Association. RxTx, Parkinson's disease [Internet]. 2017 [Accessed Sep 14, 2017]. Available from: www.myrxtx.ca.

3. Poewe W. The natural history of Parkinson's disease. Journal of neurology. 2006;253 Suppl 7:VII2-6.

4. Coelho M, Ferreira J. The Natural History of Parkinson's Disease. In: Falup-Pecurariu, C, Ferreira, J, Martinez-Martin, P, Chaudhuri, KR, editors. Movement Disorder Curricula. 1st ed. Vienna, Austria: Springer-Verlag Wien; 2017. p. 129-37.

5. Rodriguez-Blazquez C, Forjaz MJ, Lizan L, Paz S, Martinez-Martin P. Estimating the direct and indirect costs associated with Parkinson's disease. Expert Rev Pharmacoecon Outcomes Res. 2015;15(6):889-911.

6. Low V, Ben-Shlomo Y, Coward E, Fletcher S, Walker R, Clarke CE. Measuring the burden and mortality of hospitalisation in Parkinson's disease: A cross-sectional analysis of the English Hospital Episodes Statistics database 2009-2013. Parkinsonism Relat Disord. 2015 May;21(5):449-54.

7. Findley LJ, Wood E, Lowin J, Roeder C, Bergman A, Schifflers M. The economic burden of advanced Parkinson's disease: an analysis of a UK patient dataset. J Med Econ. 2011;14(1):130-9.

8. CIHI. The Burden of Neurological Diseases, Disorders and Injuries in Canada. Ottawa: 2007 p. Avaliable at http://www.cpa.ca/cpasite/UserFiles/Documents/Practice_Page/Burden_neuro_diseases_en.pdf.

9. Wong SL, Gilmour H, Ramage-Morin PL. Parkinson's disease: Prevalence, diagnosis and impact. Ottawa, Canada: 2014. 10-4 p. Report No.: 82-003-X. Avaliable at http://www.statcan.gc.ca/pub/82-003-x/2014011/article/14112-eng.pdf.

10. Duodopa Issue Summary [Internet]. Vancouver: Parkinson Society British Columbia; 2017; [1]

11. Health DC-VC. DBS Clinic database. Message to C2E2 HTA Team. Confidential files communication in 07/09/2017.

12.   DBS Clinic. Deep Brain Stimulation. Message to C2E2 HTA Team. Email communication in July 20, 2017.

13.   BC Ministry of Health. HTA: DBS and Duodopa. Message to C2E2. communication in September 25, 2017.

14.   Christenson JG, Dairman W, Udenfriend S. On the Identity of DOPA Decarboxylase and 5-hydroxytryptophan Decarboxylase. Proceedings of the National Academy of Sciences of the United States of America. 1972;69(2):343-7.

15.   BC Pharmacare. Duodopa eligibility criteria. Message to C2E2 HTA Team. Email communication in June 27, 2017.

16.   BC Ministry of Health. Health Ministry to cover Parkinson's medication [Internet]. 2017 [Accessed June 27, 2017]. Available from: https://news.gov.bc.ca/releases/2017HLTH0032-000307.

17.   Perestelo-Perez L, Rivero-Santana A, Perez-Ramos J, Serrano-Perez P, Panetta J, Hilarion P. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. Journal of neurology. 2014;261(11):2051-60.

18.   Honey DC. Deep Brain Stimulation [Internet]. 2017 [Accessed September 11, 2017]. Available from: http://drhoney.org/dbs/.

19.   Okun MS, Zeilman PR. Parkinson's Disease: Guide to Deep Brain Stimulation Therapy. Hagerstown, MD: National Parkinson Foundation; p. 1-56. Accessed Sep 25, 2017. Available from: http://www.parkinson.org/sites/default/files/Guide_to_DBS_Stimulation_Therapy.pdf.

20.   Okun MSZ, P.R. Parkinson's Disease: Guide to Deep Brain Stimulation Thearpy [Internet]. National Parkinson Foundation; 2017 [Accessed September 25, 2017]. Available from: http://www.parkinson.org/sites/default/files/Guide_to_DBS_Stimulation_Therapy.pdf.

21.   Sidiropoulos C, LeWitt PA, Odekerken VJ, Schuurman PR, de Bie RM. GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-up. Neurology. 2016 Aug 16;87(7):745-6.

22.   Taba HA, Wu SS, Foote KD, Hass CJ, Fernandez HH, Malaty IA, et al. A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. J Neurosurg. 2010;113(6):1224-9.

23.   Vancouver Coastal Health. Deep Brain stiumulation (DBS). In: Health, VC, editor. Vancouver: Vancouver Coastal Health; 2016.

24. Boston Scientific. Guide DBS-Deep Brain Stimulation System [Internet]. Boston Scientific; 2017 [Accessed September 25]. Available from: http://www.bostonscientific.com/en-EU/products/deep-brain-stimulation-systems/Guide-DBS.html.

25. Medtronic. Deep Brain Stimulation for Parkinson's [Internet]. Medtronic; 2017 [Accessed Septermber 25]. Available from: https://www.medtronicdbs.com/.

26. UC Davis. UC Davis tests deep brain stimulation as a treatment for cognitive changes in Parkinson's [Internet]. 2015 [updated May 12, 2015; Accessed October 03, 2017]. Available from: https://www.ucdmc.ucdavis.edu/publish/news/newsroom/9998.

27. RxTx. Duodopa full monograph. Available for subscribers. [Internet]. 2017 [Available from: https://www-myrxtx-ca.ezproxy.library.ubc.ca/search

28. Abbvie. Duodopa intestinal gel [Internet]. Electronic Medicines Compendium (emc); 2016 [updated May 24, 2016; Accessed September 19]. Available from: https://www.medicines.org.uk/emc/medicine/20786#USEHANDLING.

29. imshakydad. Living with Parkinson's Diseaseand more! [Internet]: wordpress.com. 2015. [cited 2017]. Available from: https://imshakydad.wordpress.com/tag/duodopa/.

30. Brain and Spine Team. Parkinson's Drug Pump Shows Promise [Internet]. Cleveland Clinic; 2013 [updated April 23, 2013; Accessed September 25]. Available from: https://health.clevelandclinic.org/2013/04/parkinsons-drug-pump-shows-promise-video/.

31. McNamara E. Parkinson's patients may have chace to go pill-free. KCTV5 News. 2015 August 09, 2015.

32. Abbvie. Duodopa. Message to C2E2 HTA Team. Email communication in August 09, 2017.

33. BCCSSS. DBS - History of purchases in BC. Message to C2E2. Confidential Files communication in Jul 7, 2017.

34. CADTH. Apomorphine CDR [Internet]. 2017 [Accessed Sep 15, 2017]. Available from: https://www.cadth.ca/apomorphine.

35. Health Canada. Movapo product monograph [Internet]. 2016 [Accessed Sep 15, 2017]. Available from: https://pdf.hres.ca/dpd_pm/00037170.PDF.

36. Valldeoriola F, Grandas F, Santos-Garcia D, Regidor I, Catalan MJ, Arbelo JM, et al. Long-term effectiveness of levodopa-carbidopa intestinal gel in 177 Spanish patients with advanced Parkinson's disease. Neurodegener Dis Manag. 2016 Aug;6(4):289-98.

37.   Walter E, Odin P. Cost-effectiveness of continuous subcutaneous apomorphine in the treatment of Parkinson's disease in the UK and Germany. J Med Econ. 2015 Feb;18(2):155-65.

38.   CADTH. Rotigotine - CDR [Internet]. 2015 [Accessed 28/11/2017]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0432_complete_Neupro_Resb_Nov-24-15_e.pdf.

39.   Senek M, Nielsen EI, Nyholm D. Levodopa-entacapone-carbidopa intestinal gel in Parkinson's disease: A randomized crossover study. Movement disorders : official journal of the Movement Disorder Society. 2017;32(2):283-6.

40.   Ray Chaudhuri K, Qamar MA, Rajah T, Loehrer P, Sauerbier A, Odin P, et al. Non-oral dopaminergic therapies for Parkinson's disease: current treatments and the future. NPJ Parkinsons Dis. 2016;2:16023.

41.   CADTH. Deep brain stimulation for Parkinson's disease and neurological movement disorders: A review of the clinical and cost-effectiveness and guidelines. Canada: 2010 22 June 2010. 6 p. Avaliable at https://cadth.ca/deep-brain-stimulation-parkinsons-disease-and-neurological-movement-disorders-review-clinical-and-0.

42.   CADTH. Deep brain stimulation for Parkinson's disease and neurological movement disorders: Clinical effectiveness, cost-effectiveness, and guidelines. Canada: 2011 31 August 2011. 13 p. Avaliable at https://www.cadth.ca/deep-brain-stimulation-parkinsons-disease-and-neurological-movement-disorders.

43.   Pan I, Dendurkru N, McGregor M. Subthalamic deep brain stimulation (DBS): Clinical efficacy, safety and cost compared to medical therapy for the treatment of Parkinson's disease. Canada: 2009 27 November 2009. 41 p. Report No.: 38. Avaliable at www.mcgill.ca/tau/.

44.   Medical Advisory Secretariat (Ontario). Deep brain stimulation for Parkinson's disease and other movement disorders: An evidence-based analysis. Canada: 2005 March 2005. 56 p. Report No.: 2. Avaliable at www.health.gov.on.ca/ohtas.

45.   Medical Serives Advisory Committee. Deep brain stimulation for the symptoms of Parkinson's disease. Canberra, Australia: 2001 April 2001. 60 p. Avaliable at.

46.   Health Information and Quality Authority (Ireland). Health technology assessment of a national deep brain stimulation service in Ireland. Ireland: 2012 11 October 2012. 101 p. Avaliable at https://www.hiqa.ie/reports-and-publications/health-technology-assessments/hta-deep-brain-stimulation.

47.   CADTH. CEDAC final recommendation on reconsideration and reasons for recommendation: Levodopa/Carbidopa (Duodopa). Canada: 2009 22 July 2009. 3 p. Avaliable at https://www.cadth.ca/levodopa-carbidopa-6.

48.   Pharmaceutical Benefits Advisory Committee (Australia). Public summary document: Levodopa with Carbidopa, intestinal gel, 20mg-5mg per mL, Duodopa. Australia: 2008 March 2008. 7 p. Avaliable at.

49.   Scottish Medicines Consortium. co-careldopa (levodopa 20mg/mL and carbidopa monohydrate 5mg/mL) intestinal gel (Duodopa) SMC no. (316/06). Glasgow: 2016 6 May 2016. 13 p. Avaliable at https://www.scottishmedicines.org.uk/files/advice/DAD_co-careldopa_2nd_Resubmission_FINAL_May_2016_for_website.pdf.

50.   All Wales Medicines Strategy Group. Final appraisal report: co-careldopa intestinal gel (Duodopa). Wales: 2007 August 2007. 23 p. Avaliable at http://www.awmsg.org/awmsgonline/app/appraisalinfo/94.

51.   Smith A, Farrah K. Deep Brain Stimulation and Levodopa-Carbidopa Intestinal Gel as Interventions for Advanced Parkinson Disease: A Review of the Qualitative Patient Perspectives andExperiences Literature. Vancouver: CADTH; 2017 Semptember 8, 2017. 22 p. Avaliable at.

52.   Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology. 1967;17(5):427-41.

53.   OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2 [Internet]. Oxford Centre for Evidence-Based Medicine; [Accessed Sep 23, 2017]. Available from: http://www.cebm.net/index.aspx?o=5653.

54.   CADTH. CADTH database search filters [Internet]. [Accessed March 8, 2017]. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#syst.

55.   Scottish Intercollegiate Guideline Network (SIGN). Search filters [Internet]. [Accessed March 8, 2017]. Available from: http://www.sign.ac.uk/methodology/filters.html.

56.   Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Internet]. The Cochrane Collaboration; 2011 [updated March 2011; Accessed Sep 23, 2017]. Available from: www.handbook.cochrane.org.

57.   Downs S, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of epidemiology and community health. 1998;52(6):377-84.

58.   The Nordic Cochrane Centre. Review Manager (RevMan). Copenhagen: The Cochrane Collaboration; 2014.

59.   CADTH. ITC user guide [Internet]. 2009 [Accessed Sep 23, 2017]. Available from: https://www.cadth.ca/resources.

60.   Clarke CE, Worth P, Grosset D, Stewart D. Systematic review of apomorphine infusion, levodopa infusion and deep brain stimulation in advanced Parkinson's disease. Parkinsonism and Related Disorders. 2009;15(10):728-41.

61.   Wirdefeldt K, Odin P, Nyholm D. Levodopa-Carbidopa Intestinal Gel in Patients with Parkinson's Disease: A Systematic Review. CNS Drugs. 2016;30(5):381-404.

62.   Merola A, Espay AJ, Romagnolo A, Bernardini A, Rizzi L, Rosso M, et al. Advanced therapies in Parkinson's disease: Long-term retrospective study. Parkinsonism & related disorders. 2016;29:104-8.

63.   Merola A, Zibetti M, Angrisano S, Rizzi L, Lanotte M, Lopiano L. Comparison of subthalamic nucleus deep brain stimulation and Duodopa in the treatment of advanced Parkinson's disease. Movement Disorders. 2011;26(4):664-70.

64.   Fahn S, Elton R, Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn, S, Marsden, C, Calne, D, Goldstein, M, editors. Recent Developments in Parkinson's Disease. 2. Florham Park, NJ: Macmillan Health Care Information; 1987. p. 153-63.

65.   Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. New England Journal of Medicine. 2006;355(9):896-908.

66.   Okun MS, Gallo BV, Mandybur G, Jagid J, Foote KD, Revilla FJ, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurology. 2012;11(2):140-9.

67.   Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol. 2014 Feb;13(2):141-9.

68.   Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ, Jr., et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63-73.

69.   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.

70.   Nyholm D, Askmark H, Gomes-Trolin C, Knutson T, Lennernas H, Nystrom C, et al. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. Clin Neuropharmacol. 2003;26(3):156-63.

71.   Nyholm D, Nilsson Remahl AIM, Dizdar N, Constantinescu R, Holmberg B, Jansson R, et al. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. Neurology. 2005;64(2):216-23.

72.   Slevin JT, Fernandez HH, Zadikoff C, Hall C, Eaton S, Dubow J, et al. Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: an open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients. J Parkinsons Dis. 2015;5(1):165-74.

73.   Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013 Mar-Apr;16(2):231-50.

74.   Valldeoriola F, Puig-Junoy J, Puig-Peiro R, Workgroup of the Ss. Cost analysis of the treatments for patients with advanced Parkinson's disease: SCOPE study. J Med Econ. 2013;16(2):191-201.

75.   Fundament T, Eldridge PR, Green AL, Whone AL, Taylor RS, Williams AC, et al. Deep Brain Stimulation for Parkinson's Disease with Early Motor Complications: A UK Cost-Effectiveness Analysis. PLoS One. 2016;11(7):e0159340.

76.   Kristiansen IS, Bingefors K, Nyholm D, Isacson D. Short-term cost and health consequences of duodenal levodopa infusion in advanced Parkinson's disease in Sweden: an exploratory study. Appl Health Econ Health Policy. 2009;7(3):167-80.

77.   Lowin J, Bergman A, Chaudhuri KR, Findley LJ, Roeder C, Schifflers M, et al. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. J Med Econ. 2011;14(5):584-93.

78.   Lowin J, Sail K, Baj R, Jalundhwala YJ, Marshall TS, Konwea H, et al. The cost-effectiveness of levodopa/carbidopa intestinal gel compared to standard care in advanced Parkinson's disease. J Med Econ. 2017 Sep 21:1-9.

79.   Kamusheva M, N G, G P, Email Petrova G, guenka, petrova@gmail, et al. Intestinal gel Levodopa + Carbidopa in Parkinson's patients with frequent and prolonged akinesia - an economic evaluation. Intl J Pharm Sci Rev Res. 2013 October;22(1):244-6.

80.   Lundqvist C, Beiske AG, Reiertsen O, Kristiansen IS. Real life cost and quality of life associated with continuous intraduodenal levodopa infusion compared with oral treatment in Parkinson patients. J Neurol. 2014 Dec;261(12):2438-45.

81.   Dams J, Siebert U, Bornschein B, Volkmann J, Deuschl G, Oertel WH, et al. Cost-effectiveness of deep brain stimulation in patients with Parkinson's disease. Mov Disord. 2013 Jun;28(6):763-71.

82. Eggington S, Valldeoriola F, Chaudhuri KR, Ashkan K, Annoni E, Deuschl G. The cost-effectiveness of deep brain stimulation in combination with best medical therapy, versus best medical therapy alone, in advanced Parkinson's disease. Journal of neurology. 2014;261(1):106-16.

83. Pietzsch JB, Garner AM, Marks WJ, Jr. Cost-Effectiveness of Deep Brain Stimulation for Advanced Parkinson's Disease in the United States. Neuromodulation. 2016;19(7):689-97.

84. Tomaszewski KJ, Holloway RG. Deep brain stimulation in the treatment of Parkinson's disease: a cost-effectiveness analysis. Neurology. 2001 Aug 28;57(4):663-71.

85. McIntosh E, Gray A, Daniels J, Gill S, Ives N, Jenkinson C, et al. 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.

86. Meissner W, Schreiter D, Volkmann J, Trottenberg T, Schneider GH, Sturm V, et al. Deep brain stimulation in late stage Parkinson's disease: a retrospective cost analysis in Germany. J Neurol. 2005 Feb;252(2):218-23.

87. Spottke EA, Volkmann J, Lorenz D, Krack P, Smala AM, Sturm V, et al. Evaluation of healthcare utilization and health status of patients with Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus. J Neurol. 2002 Jun;249(6):759-66.

88. Valldeoriola F, Morsi O, Tolosa E, Rumia J, Marti MJ, Martinez-Martin P. Prospective comparative study on cost-effectiveness of subthalamic stimulation and best medical treatment in advanced Parkinson's disease. Mov Disord. 2007 Nov 15;22(15):2183-91.

89. Zhu XL, Chan DT, Lau CK, Poon WS, Mok VC, Chan AY, et al. Cost-effectiveness of subthalmic nucleus deep brain stimulation for the treatment of advanced Parkinson disease in Hong Kong: a prospective study. World Neurosurg. 2014 Dec;82(6):987-93.

90. Dams J, Bornschein B, Reese JP, Conrads-Frank A, Oertel WH, Siebert U, et al. Modelling the cost effectiveness of treatments for Parkinson's disease: a methodological review. Pharmacoeconomics. 2011 Dec;29(12):1025-49.

91. Palhagen SE, Sydow O, Johansson A, Nyholm D, Holmberg B, Widner H, et al. Levodopa-carbidopa intestinal gel (LCIG) treatment in routine care of patients with advanced Parkinson's disease: An open-label prospective observational study of effectiveness, tolerability and healthcare costs. Parkinsonism Relat Disord. 2016 Aug;29:17-23.

92. Fraix V, Houeto JL, Lagrange C, Le Pen C, Krystkowiak P, Guehl D, et al. Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006 Apr;77(4):443-9.

93.	Lad SP, Kalanithi PS, Patil CG, Itthimathin P, Batya S, Bronte-Stewart H, et al. Socioeconomic Trends in Deep Brain Stimulation (DBS) Surgery. Neuromodulation. 2010 Jul;13(3):182-6.

94.	McIntosh E, Gray A, Aziz T. Estimating the costs of surgical innovations: the case for subthalamic nucleus stimulation in the treatment of advanced Parkinson's disease. Mov Disord. 2003 Sep;18(9):993-9.

95.	Hunka K, Suchowersky O, Wood S, Derwent L, Kiss ZH. Nursing time to program and assess deep brain stimulators in movement disorder patients. J Neurosci Nurs. 2005 Aug;37(4):204-10.

96.	McIntosh ES. Perspective on the economic evaluation of deep brain stimulation. Front Integr Neurosci. 2011;5:19.

97.	Ottridge RS, Rick CE, Daniels J, Patel S, Ives N, Gill S, et al. Implantable pulse generator lifespan in the PD SURG trial. Abstracts of the Sixteenth International Congress of Parkinson's Disease and Movement Disorders. June 17-21, 2012. Dublin, Ireland. Mov Disord. 2012 Jun;27 Suppl 1:S1-639.

98.	Weaver FM, Stroupe KT, Cao L, Holloway RG, Vickrey BG, Simuni T, et al. Parkinson's disease medication use and costs following deep brain stimulation. Mov Disord. 2012 Sep 15;27(11):1398-403.

99.	Johnson S, Davis M, Kaltenboeck A, Birnbaum H, Grubb E, Tarrants M, et al. Early retirement and income loss in patients with early and advanced Parkinson's disease. Appl Health Econ Health Policy. 2011 Nov 01;9(6):367-76.

100.	McCrone P. Capturing the costs of end-of-life care: comparisons of multiple sclerosis, Parkinson's disease, and dementia. J Pain Symptom Manage. 2009 Jul;38(1):62-7.

101.	Ishihara LS, Cheesbrough A, Brayne C, Schrag A. Estimated life expectancy of Parkinson's patients compared with the UK population. J Neurol Neurosurg Psychiatry. 2007 Dec;78(12):1304-9.

102.	CADTH. Guidelines for the Economic Evaluation of Health Technologies. Ottawa: CADTH; 2017 p. Avaliable at https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

103.	Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Movement disorders : official journal of the Movement Disorder Society. 2004;19(9):1020-8.

104. Goulionis JE, Vozikis A. Medical decision making for patients with Parkinson disease under Average Cost Criterion. Aust New Zealand Health Policy. 2009 Jun 24;6:15.

105. Abbvie. Long-term Study of Duodopa (Levodopa/Carbidopa) in Advanced Parkinson's: Health Outcomes & Net Economic Impact (DAPHNE) [Internet]. 2016 [Accessed July 28, 2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT00141518.

106. Gan J, Xie-Brustolin J, Mertens P, Polo G, Klinger H, Mollion H, et al. Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: three years follow-up. Journal of neurology. 2007;254(1):99-106.

107. Gervais-Bernard H, Xie-Brustolin J, Mertens P, Polo G, Klinger H, Adamec D, et al. Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: five year follow-up. Journal of neurology. 2009;256(2):225-33.

108. Kim HY, Chang WS, Kang DW, Sohn YH, Lee MS, Chang JW. Factors related to outcomes of subthalamic deep brain stimulation in Parkinson's disease. J Korean Neurosurg Soc. 2013;54(2):118-24.

109. Schupbach WMM, Chastan N, Welter ML, Houeto JL, Mesnage V, Bonnet AM, et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J Neurol Neurosurg Psychiatry. 2005;76(12):1640-4.

110. Weaver FM, Follett KA, Stern M, Luo P, Harris CL, Hur K, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. Neurology. 2012;79(1):55-65.

111. Zibetti M, Merola A, Rizzi L, Ricchi V, Angrisano S, Azzaro C, et al. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2011;26(13):2327-34.

112. LeWitt PA, Boroojerdi B, Surmann E, Poewe W, Group SPS, Group SPS, et al. Rotigotine transdermal system for long-term treatment of patients with advanced Parkinson's disease: results of two open-label extension studies, CLEOPATRA-PD and PREFER. J Neural Transm (Vienna). 2013;120(7):1069-81.

113. Kishore A, Rao R, Krishnan S, Panikar D, Sarma G, Sivasanakaran MP, et al. Long-term stability of effects of subthalamic stimulation in Parkinson's disease: Indian Experience. Movement disorders : official journal of the Movement Disorder Society. 2010;25(14):2438-44.

114. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria: 2016. Website: https://www.R-project.org/.

115.   Fernandez HH, Standaert DG, Hauser RA, Lang AE, Fung VS, Klostermann F, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord. 2015 Apr;30(4):500-9.

116.   Parkinson Canada. About Parkinson's [Internet]. 2017 [Accessed September 11, 2017]. Available from: http://www.parkinson.ca/site/c.kgLNIWODKpF/b.5184077/k.CDD1/What_is_Parkinsons.htm.

117.   Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson disease?: a prospective population-based long-term study. Neurology. 2010 Oct 05;75(14):1270-6.

118.   Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010 Jun 03;362(22):2077-91.

119.   Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003 Nov 13;349(20):1925-34.

120.   Wider C, Pollo C, Bloch J, Burkhard PR, Vingerhoets FJ. Long-term outcome of 50 consecutive Parkinson's disease patients treated with subthalamic deep brain stimulation. Parkinsonism Relat Disord. 2008;14(2):114-9.

121.   Contreras A, Grandas F. Risk of falls in Parkinson's disease: a cross-sectional study of 160 patients. Parkinsons Dis. 2012;2012:362572.

122.   Mizuno Y, Shimoda S, Origasa H. Long-term treatment of Parkinson's disease with levodopa and other adjunctive drugs. J Neural Transm (Vienna). 2017 Jan 16, 2017.

123.   Grifi M, Gorecki M, Schuepbach M. From The Unified Parkinson's Disease Rating Scale (UPDRS) To The EQ-5D Utility Index: Development of A New Mapping Algorithm In Parkinson's Disease (PD. Presented at.

124.   BC Ministry of Health. DAD/Pharmacare/MSP costs - Patients submitted to DBS FY 2011/12 to 2015/16. Message to C2E2. Confidential files communication in Oct 2017.

125.   Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. Arch Neurol. 2010 Jan;67(1):64-70.

126.   Special authority department Diaob, Pharmaceutical services division. Duodopa - Price Infor. Email communication with. Message to Conte, T. Confidential files communication in

127.   Boston Scientific. Deep Brain Stimulation. Message to C2E2 HTA Team. communication in September 27, 2017.

128.   Medtronic. Deep Brain Stiumulation. Message to C2E2 HTA Team. communication in September 27, 2017.

129.   Canada S. Consumer Price Index, health and personal care, by province [Internet]. Canada: Statistics canada; 2015 [Accessed 10/08/2016]. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ161a-eng.htm.

130.   Dams J, Klotsche J, Bornschein B, Reese JP, Balzer-Geldsetzer M, Winter Y, et al. Mapping the EQ-5D index by UPDRS and PDQ-8 in patients with Parkinson's disease. Health Qual Life Outcomes. 2013 Mar 08;11:35.

131.   BC Health Technology Assessment Review Office. Number of Colon Resection & Colectomy Surgeries by Primary Diagnoses (ICD10) and Age Group Message to Conte, T. Confidential files communication in

132.   Canada S. Projected population, by projection scenario, age and sex, as of July 1, Canada, provinces and territories annual (persons x 1,000).Table 052-0005. British Columbia. Both sexes. Projection scenario M5: medium-growth, 2009/2010 to 2010/2011 trends. [Internet]. Canada: Statistics Canada; 2016 [Accessed 10/11/2016]. Available from: http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=520005

133.   Antonini A, Isaias IU, Canesi M, Zibetti M, Mancini F, Manfredi L, et al. Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome. Movement disorders : official journal of the Movement Disorder Society. 2007;22(8):1145-9.

134.   Antonini A, Mancini F, Canesi M, Zangaglia R, Isaias IU, Manfredi L, et al. Duodenal levodopa infusion improves quality of life in advanced Parkinson's disease. Neurodegener Dis. 2008;5(3-4):244-6.

135.   Antonini A, Fung VSC, Boyd JT, Slevin JT, Hall C, Chatamra K, et al. Effect of levodopa-carbidopa intestinal gel on dyskinesia in advanced Parkinson's disease patients. Movement disorders : official journal of the Movement Disorder Society. 2016;31(4):530-7.

136.   De Fabregues O, Dot J, Abu-Suboh M, Hernandez-Vara J, Ferre A, Romero O, et al. Long-term safety and effectiveness of levodopa-carbidopa intestinal gel infusion. Brain Behav. 2017;7(8):e00758.

137.   Fasano A, Ricciardi L, Lena F, Bentivoglio AR, Modugno N. Intrajejunal levodopa infusion in advanced Parkinson's disease: long-term effects on motor and non-motor symptoms and impact on patient's and caregiver's quality of life. Eur Rev Med Pharmacol Sci. 2012;16(1):79-89.

138.   Nilsson D, Nyholm D, Aquilonius SM. Duodenal levodopa infusion in Parkinson's disease--long-term experience. Acta Neurol Scand. 2001;104(6):343-8.

139.   Odin P, Ray Chaudhuri K, Slevin JT, Volkmann J, Dietrichs E, Martinez-Martin P, et al. Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program. Parkinsonism & related disorders. 2015;21(10):1133-44.

140.   Pickut BA, van der Linden C, Dethy S, Van De Maele H, de Beyl DZ. Intestinal levodopa infusion: the Belgian experience. Neurol Sci. 2014;35(6):861-6.

141.   Puente V, De Fabregues O, Oliveras C, Ribera G, Pont-Sunyer C, Vivanco R, et al. Eighteen month study of continuous intraduodenal levodopa infusion in patients with advanced Parkinson's disease: impact on control of fluctuations and quality of life. Parkinsonism & related disorders. 2010;16(3):218-21.

142.   Santos-Garcia D, Anon MJ, Fuster-Sanjurjo L, de la Fuente-Fernandez R. Duodenal levodopa/carbidopa infusion therapy in patients with advanced Parkinson's disease leads to improvement in caregivers' stress and burden. Eur J Neurol. 2012;19(9):1261-5.

143.   Santos-Garcia D, Sanjurjo LF, Macias M, Llaneza M, Carpintero P, de la Fuente-Fernandez R. Long-term exposure to duodenal levodopa/carbidopa infusion therapy improves quality of life in relation especially to mobility, activities of daily living, and emotional well-being. Acta Neurol Scand. 2012;125(3):187-91.

144.   Schuepbach WMM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. The New England journal of medicine. 2013;368(7):610-22.

145.   Zibetti M, Merola A, Ricchi V, Marchisio A, Artusi CA, Rizzi L, et al. Long-term duodenal levodopa infusion in Parkinson's disease: a 3-year motor and cognitive follow-up study. Journal of neurology. 2013;260(1):105-14.

146.   Zibetti M, Merola A, Artusi CA, Rizzi L, Angrisano S, Reggio D, et al. Levodopa/carbidopa intestinal gel infusion in advanced Parkinson's disease: a 7-year experience. Eur J Neurol. 2014;21(2):312-8.

147.   Fasano A, Liu LW, Poon YY, Lang AE. Initiating intrajejunal infusion of levodopa/carbidopa intestinal gel: an outpatient model. Mov Disord. 2015 Apr;30(4):598-9.

148.   StatBureau. Eurozone Inflation Calculators [Internet]. 2017 [updated October 15, 2017; Accessed October 23]. Available from: https://www.statbureau.org/en/eurozone/inflation-calculators?dateBack=2012-7-1&dateTo=2016-12-1&amount=1.

149.   Exchange-Rates.org. World Currency Exchange Rates and Currency Exchange History [Internet]. 2017 [Accessed October 23]. Available from: http://www.exchange-rates.org/Rate/EUR/CAD/12-30-2016.