The Costs and Benefits of Deep Brain Stimulation Surgery for Patients with Parkinson’s Disease at Different Stages of Severity – An Initial Exploration

by

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Abstract

**Objectives:** To estimate the incremental cost per QALY in patients with Parkinson’s Disease (PD) with varying disease severity and to ascertain which patient subgroup would accrue the greatest net monetary benefits to Ontario’s public health perspective as a result of Deep Brain Stimulation (DBS).

**Design:** A cost-utility study and a net monetary benefit framework approach were applied to 37 PD patients with varying disease stages who underwent DBS treatment.

**Results:** DBS resulted in cost savings of $2,686.3, $2,752.4, and $7348.4 and QALY gains of 0.33, 0.09 and 0.04 in patients with mild, moderate and severe PD. The ICER was $16,076.2/QALY. At $50,000/QALY, the greatest net monetary benefits accrued to Ontario’s MOHLTC were from treating patients with mild PD with DBS.

**Conclusions:** DBS surgery was found to be a cost-effective PD treatment compared to pharmacotherapy. The greatest net monetary benefits were from treating patients with mild PD severity.
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List of Abbreviations

ADL : Activities of Daily Living
DBS : Deep Brain Stimulation
CAPSIT-PD : Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease
CEA : Cost-Effectiveness Analysis
CUA : Cost-Utility Analysis
EQ-5D : EuroQoL-5 Dimension
Gpi : Globulas Palladium
HRQoL : Health Related Quality of Life
HUI : Health Utility Index
HY : Hoehn and Yahr
ICER : Incremental Cost Effectiveness Ratio
L-Dopa : L-Dopamine
MOHLTC : Ministry of Health and Long Term Care
NMB : Net Monetary Benefit
OLS : Ordinary Least Squares
PD : Parkinson’s Disease
PDQ-39 : Parkinson’s Disease Questionnaire-39
PDQ-8 : Parkinson’s Disease Questionnaire-8
QALY : Quality of Adjusted Life Years
QoL : Quality of Life
RCT : Randomized Controlled Trial
SF-36 : Short From-36
STN : Subthalamic Nucleus
UPDRS : Unified Parkinson’s Disease Rating Scale
Vim : Ventral intermediate nucleus
1 Introduction: Parkinson’s Disease

1.1 Deep Brain Stimulation for Symptoms of Parkinson’s Disease

Parkinson’s disease (PD) is a progressive neurodegenerative disorder mainly characterized by the gradual death of selected but heterogeneous populations of neurons [Lang & Lozano 1998]. The pattern of loss of dopaminergic cells in the substantia nigra of the midbrain is the hallmark for PD. As these dopaminergic cells degenerate, there is inadequate dopamine to sustain normal functioning. The symptoms and progression of PD differ between individuals. Common symptoms consist of rigidity, tremor, bradykinesia and postural instability. At present, PD is incurable but can be managed and individuals with PD can live independent, productive lives. However, as the disease advances, patients will require a higher demand of health care services and will inevitably incur both direct and indirect costs due to worse health-related quality-of-life (HRQoL) and greater losses of productivity [Dowding et al., 2006]. It has been shown that direct costs for pharmacologic treatment rise considerably with clinical progression of symptom. Development of pharmacologic and non-pharmacologic therapies that target to slow disease progression may decrease health care resource utilization and associated costs.

Pharmacologic therapies, such as dopaminergic medication, are typically employed as a first-line management for alleviating the primary symptoms of PD. Unfortunately, medication may become less effective as the disease progress and can potentially cause adverse effects such as dyskinesias and motor fluctuations. When response fluctuations in PD are ineffectually controlled medically, patients can spend their waking days fluctuating between ON time (good motor function), ON time with dyskinesias (good motor function disabled by involuntary movements) and OFF time (poor motor function). Individuals whose symptoms cannot be effectively managed by medication may benefit from surgical treatments, such as ablative surgery and deep brain stimulation (DBS).

Ablative surgery consists of pallidotomy, thalamotomy and sub-thalamotomy, which damage the globus pallidus (GPi), thalamic nucleus (Ti) and subthalamic nucleus (STN), respectively. When the suitable target tissue is identified, it is destroyed by a radio frequency or thermocoagulation
method. Unlike ablative surgery, DBS is reversible [Rodriguez-Oroz et al., 2004; MSAC application 1092, 2006], and the procedure is safer also when performed bilaterally. Bilateral DBS is effective in the short-term control of advanced Parkinsonian symptoms and the effects are sustained in patients for at least 10 years [Castrioto, 2010]. DBS is thus the more preferred choice of surgical treatment for individuals with PD [MSAC application 1092, 2006].

DBS consists of the electrical stimulation with implanted electrode of a brain target. The electrode is connected to an external implantable pulse generator. In PD the leads are positioned into one (unilateral) or both (bilateral) sides of the basal ganglia of the brain. The three main target sites for DBS in PD are the thalamus, the STN and the Gpi. The target site chosen for DBS is dependent on the type of PD symptoms.

1.2 Parkinson’s Disease Screening Instruments and Scales

There is a wealth of clinical severity scales and health-related quality-of-life (HRQoL) measures used to assess patient outcomes in PD. The two most common clinical disease severity scales are the Hoehn and Yahr (HY) and the Unified Parkinson’s Disease Rating Scale (UPDRS). The most typically applied HRQoL scale includes the Parkinson’s Disease Questionnaire-39 (PDQ-39). Samples of these scales have been included in Appendices A to C.

The HY scale is a clinician-rated scale that is widely used to grade the severity of PD in both ‘on’ and ‘off’ states [Langston et al., 1992]. It includes stages 1 through 5 [Hoehn and Yahr, 1967]. A modified version of the HY (modified HY) scale was subsequently developed and includes stages 0, 1.5 and 2. [Goetz et al., 2004]. According to this scheme, the disease may be staged as follows: stage 0, no signs of disease; stage 1: PD symptoms on one side of the body only; stage 1.5: unilateral and axial involvement; stage 2: PD symptoms on both sides of the body, no impairment of balance; stage 2.5: mild bilateral disease with recovery on pull test; stage 3: balance impairment, middle to moderate disease, physically independent; stage 4: severe disability, still able to walk or stand unassisted; stage 5: wheelchair bound or bedridden unless assisted. Both the original and modified HY scales have shown their validity in examining motor
severity in patients with the disease [Hoehn & Yahr, 1967; Goetz et al., 2004; Martinez-Martin et al., 2006; Chaudhuri et al., 2007; Krikmann et al., 2008; Virués-Ortega et al., 2009]

The UPDRS is the most commonly used clinical assessment of PD. It is a 42-item four-part ordinal scale that evaluates the patient in the best on periods and the worst off periods. The four parts include: Part I, mentation, behavior and mood; Part II, activities of daily living (ADL); Part III, motor examination; Part IV, complications of therapy [Fahn & Elton, 1987].

The disease specific PDQ-39 instrument is a well-known measure of HRQoL in PD, comprising 39 questions with five answer options. PDQ-39 has eight subscales, namely: mobility, ADL, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort. The results can be expressed either as a summary score of the items of each subscale or as a total score transformed linearly to a 0–100 scale, with higher scores reflecting lower HRQoL [Peto et al., 1998]. The PDQ-39 consists of well-established construct validity and a moderate content validity [Peto et al., 1995; Jenkinson et al., 1999; Marinus et al., 2002]. Further, the internal consistency of the subscales is adequate and the reproducibility of the subtests is good, except for the social support subscale [Peto et al., 1995]. The PDQ-39 seems to be capable of detecting disease deterioration but responsiveness to improvement still needs assessment [Fitzpatrick et al., 1997].

1.3 Review of Individual Deep Brain Stimulation studies in Parkinson’s Disease

1.3.1 Inclusion and Exclusion Criteria of Deep Brain Stimulation in Parkinson’s Disease

The selection of the appropriate candidate is a fundamental step in DBS surgery. The objectives of this are to maximize clinical outcomes and reduce side effects. According to Moro and Lang [2007], the selection process should entail a multidisciplinary team, including a movement disorders neurologist in the field of DBS, as well as a neuropsychologist, a psychiatrist and a stereotactic neurosurgeon [Houeto et al., 2000]. Typically, the neurologist coordinates the selection procedure for the candidate, and only when the candidate passes the necessary steps
required before surgery (brain magnetic resonance imaging [MRI], acute levodopa challenge, neuropsychological and psychiatric consultation), he/she is then referred to the neurosurgeon. After the neurosurgeon has seen the patient, the surgical team meets to give the final verdict for surgery.

While there is variability in the applied inclusion criteria for DBS surgery across centers, the standard procedure is to use the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) for patient selection and assessment [Defer et al., 1999]. The protocol was developed in 1999 to specifically set the minimal requirements for a universal assessment protocol of patient candidates for lesions and DBS. The protocol includes selection criteria, definitions of concepts and terms, suggestions on frequencies and length of assessments, and in-depth discussion of which tests to use for quantification of symptoms and how to perform them [Defer et al., 1999]. CAPSIT-PD inclusion criteria and methodology have considered the previous experience with cerebral transplantation surgeries, ablative surgeries and the early experiences with DBS surgery. While the CAPSIT-PD recommendations are comprehensive and have demonstrated to be overall helpful in potential DBS patients (e.g., definition of levodopa responsiveness, quality of life [QoL] scales, dyskinesia scales or cognitive and behavioral assessments), several items from the selection criteria no longer hold [Lang & Widner 2002; Lang et al., 2006]. For example, medication-induced psychosis and depression are now not part of the exclusionary criteria. Psychiatric symptoms in patients with PD when treated properly enable the patients to have surgery safely [Voon et al., 2005]. Also, there is no clear indication that preoperative depression is a risk factor for postoperative depression [Berney et al., 2002]. Patients are often now referred to the surgical centers by movement disorders specialists, general neurologists and family doctors. A screening protocol for general neurologists and other healthcare practitioners has been proposed to circumvent wrong referrals for DBS surgery to the surgical centers (e.g., those who do not have idiopathic PD or patients with psychosis and dementia) [Okun et al., 2004].

Other factors which are considered important when a PD patient is being considered for DBS surgery include:
Age: while there is no cut-off age requirement, a younger candidate is preferred, so to avoid age-related comorbidities [Lang & Moro, 2007]

Duration of PD: at least 5 years of disease duration is preferred, to avoid misdiagnosis of atypical parkinsonism [Defer et al., 1999]

Severity of PD: when parkinsonian signs or specific side effects of medications begin to impact on the patient's QoL in spite of optimized medical treatment is ideal [Krack et al., 1998; Rodriguez-Oroz et al., 2005; Anderson et al., 2005; Deuschl et al., 2006]

Levodopa response: a patient who experiences very short 'on' periods, but of good quality, is considered a good surgical candidate [Krack et al., 1998; Defer et al., 1999; Vingerhoets et al., 2002; Pahwa et al., 2003; Russman et al., 2004; Kleiner-Fisman et al., 2006]

Comorbidities: several comorbidities often represent major exclusion criteria for DBS surgery. These include coagulopathies, severe and uncontrolled hypertension, cerebral vascular disease, severe coronary artery disease and diabetes, active cancer, and active infection [Ondo et al., 1998; Krack et al., 2003; Gironell et al., 2003; Kleiner-Fisman et al., 2003; Rodriguez-Oroz et al., 2005; Pawha et al., 2005]

Neuropsychology: cognitive impairment is the most frequent reason for exclusion for STN DBS surgery [Moro et al., 1999; Welter et al., 2002; Krack et al., 2003; Schupbach et al., 2005; Setiawa et al., 2006]

Psychiatry: the presence of preoperative depression as a risk factor for postoperative depression is still under investigation [Houeto et al., 2002; Funkiewiez et al., 2004], although its predictive role seems to be poor [Burkhard et al., 2004]

Previous surgeries: previous brain lesions (thalamotomy or pallidotomy) or DBS (Vim/GPi) in the basal ganglia do not seem to interfere with the outcome of a first or second DBS surgery, especially bilateral STN DBS [Moro et al., 2000; Kleiner-Fisman et al., 2004; Fraix et al., 2005].

Brain imaging: there is no consensus regarding what brain imaging abnormalities are sufficient to contraindicate for DBS [Kumar et al., 1998; Broggi et al., 2001; Ostergaard et al., 2002]
Choice of the target: the benefits between STN and GPi are still an ongoing debate

Surgery: most surgical teams use MRI with a stereotactic frame to localize the target and plan the trajectory but MRI images can induce distortion [Simon et al., 2005]. A computerized fusion between MRI and computed tomography (CT) images [Cohen et al., 1995] and microelectrode recording (MER) to localize the target is also viable options.

Management after surgery: the movement disorder specialist deals with these complex issues [Pollak et al., 1998; Deep Brain Stimulation for Parkinson's Disease, 2006] and who may require help from the other team members in certain situations.

Stimulation programming: there is no consensus on when the programming should start and it can be individualized according to the patient's condition, neurologist resources and practical considerations [Lang & Moro, 2006].

Anti-PD medications: STN DBS is the only surgery that allows a significant decrease in anti-PD medications [Kumar et al., 1998; Krack et al., 1998; Moro et al., 1999; Molinuevo et al., 2000; Volkman et al., 2001; Ostergaard et al., 2002; Valdeoriola et al., 2002; Vingerhoets et al., 2002; Krack et al., 2003; Pahwa et al., 2003; Rodriguez-Oroz et al., 2005; Schupbach et al., 2005].

Complications: complications may be related to the device (e.g., lead migration, lead fracture or infection), to the stimulation (e.g., hypophonia, diplopia, balance impairment, hypomania and depression) or have a multifactorial etiology (e.g., weight gain, eyelid-opening apraxia, apathy and speech abnormalities) [Lyons et al., 2004; Hamani et al., 2005].

1.3.2 Effect of Deep Brain Stimulation on Health Outcomes in Patients with Parkinson’s Disease

1.3.2.1 Review of the Individual Studies

In 2005, an Ontario Health Ministry report [OHTAC, 2005] examined two RCTs and 12 observational studies assessing STN DBS in PD. The two RCTs demonstrated a remarkable
beneficial effect of DBS on motor function within a 24-hour time frame in the medication ‘off’ state. The medication ‘off’ state is the worst-case condition for the patient, because he/she is not using any L-dopa, and thus receives no benefit from L-dopa. The RCT and observational studies reported on the change in motor function and L-dopa use at follow-up compared to baseline, which ranged from 6 month to 5-years. Overall, DBS resulted in a statistically significant improvement in motor function, ranging from 22% to 71% when the patient was in the medication ‘off’ state. The improvement in the medication ‘on’ state was less, ranging from 0% to 54%. DBS also resulted in an estimated 50% drop in post-operative L-dopa use. There were reports of permanent adverse events related to the DBS device or procedure, which included intra-cerebral hemorrhage (3%-5%), dementia (4%), pulmonary embolism (1%) and paralysis (1%).

In summary, the report provided evidence that showed DBS could manage advanced symptoms of PD during the first year after surgery. However, results concerning their benefits for a longer term were less forthcoming. The report also concluded that complication rates were less when the surgery was performed in specialized centers, and thus the number of sites should be restricted. Lastly, the report suggested that the cost per DBS case to centers with the appropriate expertise to perform the surgery, and human resource issues were the main constraining reasons in the further adoption of DBS.

1.3.2.2 Results of Post-2005 Studies of Deep Brain Stimulation

Results of the post-2005 literature indicated three RCT studies which compared DBS to medical therapy [Deuschl et al., 2006; Schüpbach et al., 2007; Witt et al., 2008; Weaver et al., 2009] as well as data from the intervention arm of five RCTs which compared DBS to other interventions besides medical therapy [Anderson et al., 2005; Smeding et al., 2005; Esselink et al., 2006; Rothlind et al., 2007; Merello et al., 2008]. There was one RCT [Wojtecki et al., 2006] that studied the efficacy and safety of high vs. low frequency DBS to investigate its effect on verbal fluency. All RCTs had a short follow-up period, ranging from 6-18 months. There were 2 observational studies of the long-term effects of DBS that had a follow-up from six months to five years [Siderowf et al., 2006; Piboolnurak et al., 2007; Wider et al., 2008], and another study
that had the longest follow-up period of ten years [Castrioto et al., 2011]. Finally, there were another six observational studies [Drapier et al., 2005; Erola et al., 2005; Gronchi-Perrin et al., 2006; Montel et al., 2008; Schupbach et al., 2007; Voon et al., 2008] which reported on the QoL and mortality rate as well as two cost-effectiveness studies [Meissner et al., 2005; Valldeoriola et al., 2007].

1.3.2.2.1 Improvement in Motor Function and L-Dopa Use

In general, results from the three RCT studies which compared the efficacy and safety of DBS to medical therapy demonstrated that patients who underwent by DBS improved and sustained their improvement in motor functions and activities of daily living in the “medication-off, stimulation-on” condition for up to 6 months after DBS. In addition, the amount of L-dopa requirement dropped to an estimated 50%. Results from the observational studies strongly suggested significant motor function improvement by DBS could be sustained for up to five years. Results from the 10-year study demonstrated that stimulation-induced motor improvement could be sustained for up to 10 years post DBS surgery. In the same study, patients were reported to display significantly improved UPDRS total motor score (P=0.007), resting and action tremor (P=0.01 and P=0.02, respectively) and bradykinesia (P=0.01) subscores. The UPDRS II scores in the ‘medication-on’ and ‘medication-off’ states, UPDRS IV dyskinesia and motor fluctuations scores, and the levodopa equivalent daily dose were also significantly reduced compared with baseline.

1.3.2.2.2 Quality-Of-Life

Patient quality of life (QoL) was assessed with the 39-item Parkinson’s Disease Questionnaire (PDQ-39). Overall, there was an improvement of about 20% in patients who underwent DBS compared to those who were on medication only. Some patients who were on medication only showed a decline in QoL at 6 months.
1.3.2.2.3 Adverse Events

There was a 2.6-4% risk of permanent adverse events, such as cerebral hematoma, and a 40-50% risk of temporary adverse events associated with the use of DBS. Several studies found a small negative effect of DBS on some aspects of cognitive function and verbal fluency.

1.3.3 Cost-Effectiveness of Deep Brain Stimulation

In the same OHTAC report [2005], the total cost per DBS case, consisting of one-year follow-up, was roughly between $24,420 and $28,420 (hospitalization: $11,597 + device cost: $10,000-14,000 + professional fees: $2,823 – reduction in drug intake: $2,800). On the basis of these costs and an approximated average decrease (improvement) in the UPDRS motor function score of 22 points (or 20%) in the first year post-surgery, the cost-effectiveness of DBS for a 10-point decrease UPDRS motor subscale was about $11,650. The authors approximated that while roughly 1850 people are suitable candidates for DBS surgery, only 60 surgeries are performed annually in Ontario.

A prospective cohort study in Spain [Valdeoriola et al., 2007] compared 14 DBS patients to 15 patients on medical therapy. They found that DBS cost €7,601 more than medical therapy at 12 months. This study found that despite the need for adjustment of stimulation and medication, DBS patients made fewer outpatients visit during the follow-up period than medical therapy patients. Though the pharmacological costs were similar in both groups at baseline, the cumulative costs in the medical therapy group were roughly double that in the DBS group (median cost in the DBS group: €3,132; median cost in the medical therapy group: €5,950). The mean gain in quality-adjusted-life-years (QALYs) were 0.76 ± 0.03 for DBS treatment and 0.54 ± 0.06 for medical therapy. The incremental cost-effectiveness ratio per QALY (ICER/QALY) of DBS compared to medical therapy was €34,839.

Meissner et al. [2005] studied the health care utilization and pharmacological costs of 46 DBS patients over a 3-year period. The found a significant decrease in total health care expenses (€7,223± 717 in the second year post-DBS compared to €15,991± 2636 in the year prior to DBS). The authors estimated that the incremental cost per unit increase in the UPDRS III was 9
€979, 12 months after surgery, a figure which was comparable to the Ontario estimate of $1,165 [OHTAC, 2005].

1.3.4 Summary
The above studies showed reliable evidence that DBS controlled advanced symptoms of PD and could reduce post-surgery doses of L-dopa, improve activities of daily living, mobility and other symptoms measured by the UPDRS in PD patients. However, none of the studies have explored the impact of disease severity and its relation to the benefits and health care cost savings in PD patients from DBS surgical intervention.

1.4 Objectives
The objectives of this thesis were to estimate the incremental cost per QALY in patients with PD with varying disease severity and to ascertain which patient subgroup would accrue the greatest net monetary benefits to Ontario’s public health perspective, the Ministry of Health and Long Term Care (MOHLTC), as a result of DBS. To answer these two questions, a cost-utility study and a net monetary benefit framework approach were employed.
2 Literature Review

2.1 Background and Context

PD is a chronic, progressive, neurodegenerative disorder characterized by bradykinesia, rigidity, tremor, and postural instability [McNaught & Olanow, 2006; Miyasaki et al., 2006; Rao et al., 2006; Parkinson’s Disease Foundation, 2007; Simuni 2007]. With approximately six million PD patients in the world, PD is the second most common neurodegenerative disease after Alzheimer’s disease (AD) [National Parkinson Foundation, 2011]. In 2003, the Parkinson Society Canada estimated that 100,000 Canadians live with PD [National Parkinson Foundation, 2011]. The lifetime risks of PD are estimated at 2.0% for men and 1.3% for women [McDonald et al., 2000]. With an aging population, the prevalence of PD is anticipated to rise [Huse et al., 2005], and individuals with the disease have a 2.0- to 2.9-fold increased chance of anticipated death than those without [Bennet et al., 1996; Hoehn & Yahr, 1967].

2.2 Epidemiology

The average age of PD onset is approximately 50 to 60 years old, although it may occur at a younger age [Rajput et al., 1984; Baba et al., 2006]. It is estimated that 4-10% of patients with PD exhibit symptoms prior to the age of 40 [MacDonald et al., 2000]. Increasing evidence has suggested a genetic predisposition in numerous early-onset cases. In these cases, patients are typically categorized as those with onset at age 40 or below [Khan et al., 2003; Inzelberg et al., 2004; Bonifati et al., 2005]. PD itself is not fatal but the disease does lead to physical disabilities that predispose to numerous health problems. Examples include deep venous thrombosis, pulmonary embolism [Mosewich et al., 1994], pneumonia, falls, and resulting complications [Fall et al., 2003; Elbaz et al., 2005]. Individuals with PD exhibit a mortality rate of 35% to 65%, higher than those of matched controls [Herlofson et al., 2004; Hughes et al., 2004]. The incidence of PD is higher in males [Alves et al., 2008].
2.3 Etiology and Risk Factors

The etiology of PD is largely unknown and the only proven risk factors for PD are advancing age [Simuni, 2007; Driver et al., 2009] and familiarity for PD. Ten percent of PD cases have a genetic origin, and at least 11 different linkages with 6 gene mutations exist [Olanow & McNaught, 2006; Jenner & Olanow 2006; Pallone, 2007]. Both autosomal dominant and autosomal recessive forms of PD have been identified and most of them cause juvenile or early-onset PD, while others appear to cause parkinsonism that resembles sporadic PD with respect to both clinical and demographical features [Alves et al., 2008]. A variety of non-genetic risk factors that may cause an increased risk for developing PD have been proposed. Examples include smoking and exposure to pesticides [Lai et al., 2002; Elbaz et al., 2007].

2.4 Pathophysiology of PD

PD is mainly caused by the degeneration of dopamine producing cells in the substantia nigra [Kish et al., 1988; Morrish et al., 1995; McNaught & Olanow 2006]. Motor impairment only develops when already 60% to 80% of the cells are destroyed [Morrish et al., 1995; Kish et al., 1998]. However, PD is a multi-system brain disease and involves also the serotonergic, adrenergic and cholinergic systems [Perry et al., 2001]. The disease commences from the brainstem and spreads via the midbrain and mesocortex to the cortex [Braak et al., 2003; 2005]. Neurodegeneration is characterized by Lewy body formation, or typical inclusions of aggregated α-synuclein. There are six stages of progression, of which the first two represent pre-symptomatic stages and the last two represent severe disability and dementia. These changes may be attributed to oxidative stress, mitochondrial dysfunction and impairment of the ubiquitin proteasome system. It remains unclear as to how these pathways lead to premature cell apoptosis and clustering of intracellular α-synuclein are triggered [Andersen et al., 2000; Lucking et al., 2000; Cole et al., 2002].
2.5 Clinical Expression and Course

2.5.1 Motor Symptoms

PD is characterized by four cardinal motor features as well as many other motor symptoms and signs [Hoehn & Yahr, 1967; Lang & Lozano 1998; Marsden, 1989; Giladi et al., 1992; Samii et al., 2004; Simuni, 2007; Rezak, 2007; Pallone, 2007; Fung & Thompson, 2007; Jankovic, 2008]. The four cardinal motor symptoms are tremor, bradykinesia (slowness of movement), rigidity and postural instability (impairment of postural reflexes). However, not every PD patient presents with every symptom. The onset of motor symptoms often initiates asymmetrically but slowly disseminate to the contralateral, although the side of initial onset remains the most affected all through the duration of the disease. In addition to the cardinal signs of PD, other typical motor symptoms of PD include, speech and gait disturbances, freezing of gait, micrographia, mask-like expression and unwanted accelerations. Additional secondary motor symptoms include those below, but not all patients with PD will experience all of these: stooped posture, a tendency to lean forward; dystonia; impaired fine motor dexterity and motor coordination; impaired gross motor coordination; poverty of movement (decreased arm swing); akathisia; speech problems, such as softness of voice or slurred speech caused by lack of muscle control; difficulty swallowing; sexual dysfunction; cramping; and drooling.

2.5.2 Non-Motor Symptoms

Non-motor symptoms in PD are also common. These include mood disturbances such as cognitive disturbances, sensation disturbances, sleep disturbances and autonomic disturbances [Rajput et al., 1976; Evans et al., 1981; Scherman et al., 1989; Fearnley & Lees, 1991; Edwards et al., 1992; Uchiyama et al., 1995; Djaldetti et al., 1996; Soykan et al., 1997; Tandberg et al., 1998; Jiang et al., 1999; Bassotti et al., 2000; Hughes et al., 2000; Levy et al., 2000; Olanow et al., 2000; Rye et al., 2000; Aarsland et al., 2001; Holroyd et al., 2001; Levy et al., 2002; Gjerstad et al., 2002; Homann et al., 2002; Boeve et al., 2003; Leentjens et al., 2004; Krishnan et al., 2003; Aarsland et al., 2003; Janvin et al., 2003; Sakakibara et al., 2003; Braak et al., 2003; Alves et al., 2004; Goetze et al., 2005; Magerkurth et al., 2005; Korchounov et al., 2005; Miller
et al., 2006; Gjerstad et al., 2006; Verbaan et al., 2007; Pedersen et al., 2008; Loo et al., 2008; Poewe, 2009; Chaudhuri et al., 2009; Chaudhuri & Schapira, 2009].

Cognitive disturbances include lowered reaction time (both voluntary and involuntary motor responses are significantly slowed); executive dysfunction, often characterized by difficulties in differential allocation of attention, impulse control, set shifting, prioritizing, evaluating the salience of ambient data, interpreting social cues, and subjective time awareness. This complex is present to some degree in most PD patients and may progress to dementia, a later development in approximately 20–40% of all patients; and memory loss.

Sensation disturbances may include impaired visual contrast sensitivity, spatial reasoning, color discrimination, convergence insufficiency (characterized by double vision) and oculomotor control; dizziness and fainting; usually attributable to orthostatic hypotension, a failure of the autonomous nervous system to adjust blood pressure in response to changes in body position; impaired proprioception (the awareness of bodily position in three-dimensional space); reduction or loss of sense of smell (microsmia or anosmia); pain, for example in muscle, joints, and tendons, which are all attributable to tension, dystonia, rigidity joint stiffness, and injuries.

Sleep disturbances often include excessive daytime somnolence; initial, intermediate, and terminal insomnia; disturbances in REM sleep: disturbingly vivid dreams; and REM Sleep Disorder, characterized by acting out of dream content.

Autonomic disturbance may include urinary incontinence, typically in later disease progression, constipation and gastric dysmotility; altered sexual function, characterized by profound impairment of sexual arousal, behavior, orgasm, and drive is found in mid and late Parkinson disease. Current data addresses male sexual function almost exclusively.

Non-motor symptoms represent close to 90% of all patients with PD and severely affect the QoL in both patients and their caregivers [Weintraub & Stern, 2005; Chaudhuri et al., 2006; Miyasaki et al., 2006; Frank et al., 2006; Barbas, 2006; Pallone, 2007; Simuni, 2007]. Non-motor symptoms may develop during the course of the disease or even precede motor symptoms. In a majority of case, non-motor symptoms dominate the clinical profile of advanced PD and add to
severe disability, reduced health related quality of life (HR-QoL) and increased mortality [Chaudhuri et al., 2006].

2.6 Management of Parkinson’s Disease

Although PD is incurable, disease management aims at the alleviation of the symptoms, improvement of the quality of life, support of patients and caregivers and reduction of disease progression. Management strategies include pharmacotherapy, surgery, and physiotherapy.

2.6.1 Pharmacotherapy

2.6.1.1 Levodopa

Levodopa was introduced in the 1960s and was the first effective symptomatic treatment for PD [Ahlskog, 1992; Waters, 2008]. Levodopa is the precursor of dopamine and is released by the neurons to activate dopamine receptors and thus enable normal function of the movement control centers of the brain [Bennett et al., 1996; National Parkinson Foundation, 2009]. After being absorbed in the gastrointestinal tract, levodopa is transported to the brain, where it is converted into dopamine by dopa-decarboxylase [Nutt et al., 1984; 1985; Wade & Katzman 1975; Wade, 1973]. Levodopa is mainly produced in the substantia nigra compacta, which is severely damaged in PD [Barbeauand & McDowell, 1970]. To decrease peripheral metabolism of levodopa, its application is combined with a peripheral dopa-decarboxylase inhibitor (e.g. carbidopa or benzerazide) [Wade & Katzman, 1975 ; Nutt et al., 1985] so to enable higher levels of levodopa to cross the blood-brain barrier. Unfortunately, one significant side-effect of extended use of levodopa is the development of motor fluctuations and dyskinesia [Quinn et al., 1982; Brooks, 2000; Fahn et al., 2004]. Dyskinesia is the presentation of various types of involuntary movements [Wade et al., 1973]. It is a motor complication and present in 50% of PD patients after 5 years of therapy [Barbeau, 1980; Poewe et al., 1986; Hely et al., 1994; Ahlskog & Muentener, 2001]. After several years of levodopa treatment, PD patients also gradually develop shortening periods of benefit after a single dose, commonly referred to as a “wearing-
off” effect, whereby previously controlled symptoms re-emerge toward the end of the dosing interval [Nutt et al., 1984; Bennett et al., 1996]. PD patients treated with levodopa can encounter an “on-off” effect, characterized by unpredictable and abrupt fluctuations in their motor state from controlled to uncontrolled [Nutt et al., 1984]. Levodopa treatment in PD patients can also cause confusion, sleep disorders, hallucinations, and psychosis [Nutt et al., 1984]. In advanced stages of the disease, the continuous application of levodopa via a trans-abdominal tube is possible [Lundqvist, 2007]. To note, this treatment is not available in Canada yet.

Despite the problems associated to chronic use, levodopa is arguably still the gold standard drug for the treatment of PD, especially in elderly patients. The efficacy of levodopa can be enhanced by the concomitant application with other anti-Parkinson drugs such as dopamine agonists, particularly in the treatment in younger PD patients [Rinne et al., 1998; Montastruc et al., 1994]. By doing so, the associated motor complications with long-term use of levodopa may possibly be delayed or diminished [Cedearbaum et al., 1991].

2.6.1.2 Amantadine and Anticholinergics

The antiparkinsonian effect of amantadine remains poorly understood, but amantadine is a weak NMDA receptor agonist and an anticholinergic. The general belief is that its ability to release dopamine from extravesicular stores is the most significant effect, compared to its dopamine receptors agonist activity, and the likely effect is the inhibition of dopamine reuptake [Bailey & Stone, 1975]. In addition to its use in improving motor symptoms in PD, amantadine can also improve long-term complications of PD treatment, especially dyskinesias [Factor & Molho, 1999].

Anticholinergics were the first drugs used for PD treatment, as they adjust the imbalance between acetylcholine and dopamine in the striatum. Anticholinergic may also be effective as monotherapy in early, tremor-dominant PD and as adjunctive therapy to patients on levodopa [Doshay & Constable, 1949; Strang, 1965; Agate et al., 1956; Sadeh et al., 1982; Goetz et al., 1982; de Smet, 1982; Koller, 1984; Hauser & Olanow, 1988]. Anticholinergics seem mainly to offset rigidity and tremor [Doshay & Constable; 1949; Agate et al., 1956]. However, their effect
on PD symptoms is mild and there are many severe side effects including blurred vision and constipation, dizziness, confusion, memory loss, hallucinations and dyskinesia [Strang et al., 1965; Sadeh et al., 1982; Goetz et al., 1982; de Smet, 1982; Koller, 1984; Hauser & Olanow, 1988]. Consequently, anticholinergics are rarely used anymore.

2.6.1.3 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors increase the levels of dopamine in the striatum by blocking the metabolism of intracerebral dopamine and inhibitors of the enzyme provide benefit in PD [Nicoll, 1998; Westlund, 1994]. Selegeline and rasagiline are the currently used MAO inhibitors. Oral selegeline monotherapy offers modest symptomatic benefit in early PD and might delay the need for dopamine replacement therapy by several months [Lees, 1987; Sivertsen et al., 1989; Heinonen & Rinne, 1989]. The ‘delayed-started’ TEMPO study [Parkinson Study Group, 2004] demonstrated that the earlier introduction of rasagiline induced a superior benefit compared to delayed introduction. Whether this might indicate a neuroprotective or disease-modifying effect is dubious [Parkinson Study Group, 2004].

2.6.1.4 Dopamine Agonists

The dopamine agonists directly stimulate the postsynaptic dopamine receptors and do not need to be converted and stored in the degenerating nigrostriatal neurons [Watts, 1997; Clarke & Guttman, 2002; Schwarz, 2003]. Unlike levodopa, they are independent amino acid transporter for absorption across the gastrointestinal tract [Watts, 1997; Factor, 1999; Clarke & Guttman, 2002; Schwarz, 2003]. However, compared to levodopa, dopamine agonists are less efficient [Jenner, 2003] and most display longer half-lives than levodopa, ensuing in less frequency of daily administration [Jenner, 2003]. The predominant benefit of dopamine agonists compared to levodopa in early PD is that they prolong the onset of dyskinesias and motor fluctuations by 1 to 3 years, most likely because of their extended length of action [Jenner, 2003]. While still unproven, the neuroprotective effect of dopamine agonists is possibly significant. Examples of
the most common dopamine agonists include bromocriptine, pramipexole, ropinirole, rotigotine and apomorfine (this latter not available in Canada).

2.6.1.5 Catechol-O-Methyltransferase Inhibitors

Catechol-O-Methyltransferase (COMT) inhibitors lengthen and increase the duration and effect of levodopa. COMT inhibitors increase ‘on’ time, reduce ‘off’ time, maximize the patient’s ability to perform ADL, improve motor function scores on UPDRS subscales, and may decrease the requirement of levodopa needed [Rajput et al., 1997; Kurth et al., 1997; Baas et al., 1997; Adler et al., 1998; Welsh et al., 2000]. Unlike dopamine agonists, COMT inhibitors exert an effect on levodopa pharmacokinetics after the first dose [Kurth & Adler, 1998]. If dopaminergic side effects occur with COMT inhibitors, the dose of levodopa can be decreased. COMT inhibitors do not need titration for maximal effect, and are an alternative in the treatment of PD patients with fluctuating motor responses [Rajput et al., 1997; Kurth et al., 1997; Baas et al., 1997; Adler et al., 1998; Welsh et al., 2000]. The two COMT inhibitors available are entacapone and tolcapone.

2.6.2 Surgery

With the progression of the disease, PD patients can become less responsive to medications and more prone to their side effects. Surgical treatment is now considered the best indication in such case, and as indicated from above, the most effective neurosurgical method to date is bilateral STN DBS. Patients who potentially benefit from the treatment are those suffering from untreatable tremor or patients with severe motor fluctuations and dyskinesias that cannot be controlled by pharmacotherapy. The inclusion criteria of DBS patients include good responsiveness to levodopa, usually < 70 years of age, absence of dementia and severe psychiatric issues illness.
2.6.3 Deep Brain Stimulation and Parkinson’s Disease

Given that DBS surgery requires the careful selection of patients eligible for this surgery, the selection is made by a multidisciplinary specialized team. Typically, this includes a movement disorders neurologist, functional neurosurgeon, neuropsychologist, psychiatrist, and other specialty areas in cases of underlying conditions.

2.6.3.1 The Mechanisms of Deep Brain Stimulation

DBS surgery implants a platinum-iridium electrode in the brain, connected subcutaneously with a wire to a pulse generator (similar to a cardiac pace-maker) in the subclavicular area of the chest. PD patients who only have symptoms on one side of the body (unilateral) have one electrode implanted. PD patients who have symptoms on both sides of the body (bilateral) have electrodes on both sides of the brain. When the electrode is implanted, the patient is often under local anesthetic and awake. During the surgery, the probe is moved through the targeted area until the surgeon observes that the patient’s symptoms decrease or disappear. It is then that the electrode is permanently placed.

The mechanism of action of DBS is still not quite clear, but the goal of DBS is to interrupt the pathways responsible for the abnormal movements associated with PD. Current hypotheses on the mechanism of action include depolarization blockade [Beurrier et al., 2000], synaptic inhibition [Dostrovsky et al., 2000], synaptic depression [Urbano et al., 2002], stimulation-induced disruption of pathological network activity [Montgomery & Baker, 2000], and stimulation of axons projecting to the STN [Gradinaru et al., 2009]. Depolarization blockade and synaptic inhibition are the two more favored hypotheses, as evidenced by the recordings of reduced somatic activation in the stimulated nucleus [Benazzouz et al., 1995; Dostrovsky et al., 2000]. Conversely, the enhanced projection of neurons does not appear to be mediated by these occurrences [Hashimoto et al., 2003; McIntyre et al., 2004a; 2004b].

Another popular belief is that DBS supersedes unusual irregular train patterns through a high-frequency pattern, and results in inactivity of the remaining parts of the basal ganglia-thalamo-cortical and brainstem motor loop [Garcia et al., 2005]. The relationship between the
stimulation-induced neuronal responses and intrinsic brain movement remains unclear. However, the atypical firing rate and pattern of basal-ganglia neurons, variations in the oscillatory activity and excessive synchronization at multiple levels of the motor loop have been postulated as pathophysiological correlates of motor symptoms in PD [Hammond et al., 2007; Brown & Eusebio, 2008; Montgomery & Gale, 2008; Bergman & Deuschl, 2002; Hutchison et al., 2004; Schnitzler & Gross 2005].

DBS is a highly specialized procedure and require the efforts of a multi-disciplinary team. It is thus crucial that DBS be limited to facilities that can offer the level of medical and technologic expertise necessary for these procedures. Complications of DBS occur and are often classified as procedure-related, device-or hardware-related, and stimulation-related.

2.6.3.2 Complications and Deep Brain Stimulation

2.6.3.2.1 Procedure-Related Adverse Events

Given the invasive nature of the surgery, there is a risk of intraparenchymal hemorrhage in 1% to 5% of cases [Beric et al., 2001; Hariz, 2002; Oh et al., 2002]. The severity of hemorrhage ranges from minor, subclinical bleeds along the implantation tract to severe life-threatening bleeds. An estimate of severe neurologic episodes directly after surgery is 1% to 2% [Poulad et al., 2003]. Another common procedure-related adverse event is lead misplacement, which contributes to suboptimal clinical outcome and adverse effects at low-voltage stimulation.

Other adverse events related to general neurological and surgical complications (and rates of occurrence) have included: depression (4.7%), mania/hypomania (2.0%), peri-operative confusion (13.7%), cerebrospinal fluid leak (0.1%), meningitis (0.1%), venous phlebitis (0.7%), pneumonia (0.4%), urinary tract infections (0.3%), pulmonary embolism (0.5) and seizures (0.9%) [Hariz et al., 2002]. Weight gain was also considered to fall into this category, but was reported to be under-quantified in the studies [Hamani et al 2005].
2.6.3.2.2 Hardware-Related Adverse Events

It is estimated that approximately 2.7% to 50% of patients experience hardware complications from DBS surgery [Hariz et al., 2001; Beric et al., 2001; Hariz, 2002; Oh et al., 2002; Joint et al., 2002]. Infections from DBS implants range from 1% to 15% in patients [Rezai et al., 2006]. Common sites of infections include burr-hole locations, generator pocket and connecting wire. Infections may also occur any time after implantation but are transient. Thus far, there are no reported cases of sepsis or death from an infected DBS electrode [Rezai et al., 2006]. Recurring episodes of active infection are treated by removal of the hardware. If the infection is limited to the IPG, the battery and extension cables are removed with the DBS electrode left in place [Umemura et al., 2003]. A new IPG and extension cable are replaced after 6 to 8 weeks of treatment with antibiotics [Yamada et al., 2002]. Other hardware-related complications consist of electrode fracture, extension-wire failure, lead migration, skin erosion, foreign-body reaction granuloma, seroma, IPG malfunction and pain over the pulse generator [Joint et al., 2002; Deuschl et al., 2006].

Other adverse events from hardware-related complications (and rates of occurrence) have included: lead problems including lead migration, breakage and repositioning (4.5%), swelling in the region of the IPG/extension cables (0.8%) and battery failure (0.4%) [Hariz et al., 2002].

2.6.3.2.3 Stimulation-Related Adverse Events

Electrical brain stimulation can induce behavioral effects that depend on the location of the electrodes, the stimulation parameters, and the type of neural tissue stimulated (i.e. cells vs axons). Stimulation-related adverse events are highly dependent on the anatomic site of the therapeutic target. They can be categorized as side effects solely to stimulation of the surgical site and side effects related to dispersal into adjoining areas of the central nervous system [Krack et al., 2002]. Adverse events related to stimulation (and rates of occurrence) have included: hypophonia, (5.8%), eyelid apraxia (4.6%), increased libido (0.8%), sialorrhea (0.9%) and decreased memory (1.1%) [Hariz et al., 2002].
2.6.4 Deep Brain Stimulation and Other Disorders

Aside from PD, DBS has also been examined in other disorders. These include: Alzheimer’s disease [Laxton, 2010], chronic pain [Katayama, 2001a; Katayama, 2001; Nandi, 2002; Bittar, 2005; Coffey & Lozano, 2006; Rasche, 2006], cluster headache [Fontaine, 2010], epilepsy [Fisher, 2010; Boex, 2011], impulsive or violent behavior [Franzini, 2005], major depression [Lozano, 2008; Malone, 2009; Bewernick, 2010], multiple sclerosis [Hyam, 2007; Mandat, 2010; Thevathasan, 2011], obsessive compulsive disorder [Appleby, 2007; Mallet, 2008], Tourette syndrome [Maciunas, 2007; Welter, 2008; Porta, 2009; Ackermans, 2011]. Studies that examined DBS for treatment of other conditions were chiefly case series with small sample sizes and short-term follow-up. Further well-designed studies are necessary to reveal the benefits of DBS for these conditions.

2.7 Disease Burden

PD places a considerable burden on patients, families of patients, and caregivers [Dowding et al., 2006], and is concomitant with a substantial increase in morbidity and disability [Chaudhuri et al., 2006; Simuni, 2007; Poewe, 2007; Leibson et al., 2006]. The economic burden of the disease is related to direct costs, indirect costs and medical resource utilization [Huse et al., 2005; Dowding et al., 2006; Leibson et al., 2006].

2.7.1 Patients

The HRQoL in PD patients are severely affected by the limitations in functional ability and non-motor symptoms and worsens as the disease progresses [Gage et al., 2003; Dowding et al., 2006; Chaudhuri et al., 2006; Parkinson’s Disease Foundation, 2007; Reese, 2007]. A large study of US veterans demonstrated that HRQoL was worse in PD compared to other 8 chronic conditions, including stroke, heart disease, and diabetes [Gage et al., 2003]. As there is no cure for PD, the most important goals of management are to preserve functionality and HRQoL [Gage et al., 2003; Rao et al., 2006; Pallone, 2007] in individuals with the disease.
2.7.1.1 Factors That Impact HRQOL in PD

Individuals who develop PD at an earlier age have worse HRQoL compared to older-onset patients [Dowding et al., 2006]. Motor fluctuations and dyskinesias resulting from levodopa treatment also contribute to HRQoL decline [Pechevis et al., 2005; Dowding et al., 2006]. Neuropsychiatric non-motor symptoms, in particular depression and cognitive dysfunction [Weintraub et al., 2004; Weintraub & Stern 2005; Ravina et al., 2007], exert the greatest damaging effect on the HRQoL in PD patients. The consequence of the incapability of PD patients to overcome depression and cognitive decline is greater than the limitations imposed by motor hindrance on activities of daily living (ADL) [Weintraub et al., 2004].

2.7.2 Caregivers

The role of a caregiver is physically and mentally difficult. Consequently, caregivers of PD patients suffer from poor HRQoL [Gage et al., 2003; Weintraub & Stern, 2005; Dowding et al., 2006; Hudson et al., 2006; Kim et al., 2007] and are often stressed, fatigued, depressed and experience enormous anxiety. Further, social activities of the caregivers are compromised and they often also experience a financial burden [Hudson et al., 2006; Reese 2007; Kim et al., 2007]. Unlike Alzheimer’s disease, where physical disability does not play a role until the advanced stages of the disease, care is necessary for the physical impairment of the patient and the unavoidable cognitive and psychiatric problems, which can commence early in the disease. Caregiver burden has further been indicated to rise in direct proportion to disease progression and severity [Hudson et al., 2006; Kim et al., 2007].

2.7.3 Society

PD is correlated with a remarkable economic burden in Canada [Eisenberg, 1989; Reeder, 1995; Health Canada, 2002] and other countries [Findley et al., 2003; Guttman et al., 2003; Lindgren et al., 2005; Spottke et al., 2005; Huse et al., 2005; Noyes et al., 2006; Ragothaman et al., 2006;
Leibson et al., 2006; Parkinson’s Disease Foundation, 2007]. In 2002, the estimate of the annual economic burden of PD in Canada was at $5.5 billion (males 56.3%, females 43.4%, 0.3% unspecified) [Health Canada, 2002]. The economic impact of PD consists of direct and indirect costs. Direct costs encapsulate formal medical services, home care, institutional care, and medications attributed to a particular condition [Eisenberg, 1989; Reeder, 1995]. Indirect costs consist of the value of output including labor productivity lost because individuals with a certain disorder cannot work [Health Canada, 2002]. Arguably, certain costs such as informal care provided by family members are considered by some as direct costs and by others, as indirect costs. This problem can be resolved as long as all costs, direct or indirect, are captured from a societal perspective [Gold et al., 1996]. It is important that the constituents in each study, variability in estimates of the costs of these constituents, and the estimates of the population prevalence of PD are captured when undertaking cost analyses. These cost categories are necessary to generate costs per subject. The costs per subject are then multiplied by an estimate of the prevalence of the disease to conclude a final, overall cost approximation.

Cost burden is especially apparent in the more advanced stages of PD as there are greater symptoms, worse HRQoL, diminished productivity, and a higher demand for healthcare services which inevitably will increase both direct and indirect costs [Dowding et al., 2006]. It has been shown that direct costs for pharmacologic treatment rise considerably with clinical progression of symptoms. Development of pharmacologic agents that target to slow disease progression may decrease health care resource utilization and associated costs [Dowding et al., 2006]. With the rising age in the population, the economic burden of PD will escalate dramatically and eventually become a global issue. Within economic constraints, to establish therapies and politics to satisfy the requirements of individuals with PD will be difficult.

2.7.4 Cost Effectiveness, Cost Utility and Net Monetary Benefit Analyses

In health economics, “utility” expresses preference-based measures of health. QALYs offer a standard unit that allows comparisons across diseases and programs. A QALY is acquired by multiplying life years by a weight representing the quality of that year. This weight is termed as the ‘quality weight’, ‘QALY weight’, or ‘Utility Weight’. Several methods exist to capture
preferences for health outcomes and thus determining utility scores. Examples include the time-trade off [Pliskin et al., 1980; Drummond et al., 1987; Johannesson et al., 1994], the visual analogue scale (VAS) [Drummond et al., 1987], and the standard gamble (SG) [Drummond et al., 1987; Johannesson et al., 1994]. While the TTO and VAS represent measurements under certainty, the SG measurement is under uncertainty.

The most commonly used approaches for resource allocation and/or reimbursement decisions are cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). CEA typically assigns a monetary value to a number of outcomes such as life-years gained, points of blood pressure reduced, or disability days saved. CUA assigns monetary value to a single output: quality-adjusted life years (QALY’s). CUA is based on an assumption that utility can be discretely measured. In health care, it is described as a point on a continuum death at 0 to the best possible health at 1 [Drummond et al., 1987]. However, cost-effectiveness analysis and cost-utility analysis also consist of several limitations. Structuring an outcome measure that is consistent with individual preferences is very complex. Further, there is a major confinement with cost-effectiveness analysis, in that it does not ascertain whether a program is efficient (i.e. whether benefits exceed costs). It is possible only to compare the cost-effectiveness ratios, or the incremental cost-effectiveness ratio (ICER), to various options. To ultimately determine if an intervention is worthwhile, it is essential to determine the price that society is willing to pay for a life year or a QALY gained.

According to economic theory, the value of a health gain is the amount of money individuals is willing to forego to attain a specific health improvement [Schelling, 1968; Mishan, 1971]. Preferably, one would therefore measure the willingness-to-pay (λ) for health care so that it could directly be compared with the costs in a net-benefit analysis.

NMB encompasses the calculation of all costs and consequences that arise from an intervention and express the value in monetary units. This effectively enables direct comparisons of competing interventions to help decision-making concerning resource allocations. There are several methods for valuing benefit in a NMB which rely on the direct eliciting of individual patient preferences. Typically, it involves a willingness-to-pay (λ) evaluation, and is based on
the perspective of samples of patients who are inquired how much they would be willing to pay to accrue a benefit or to avoid certain events.

2.8 Quality-of-Life Instruments in Parkinson’s Disease

A QoL evaluation is a survey that captures aspects of functional status (i.e. ability to function in daily activities – physical, mental and social) as well as a sense of well-being. In PD, the Parkinson’s Disease Questionnaire-39 (PDQ-39) is commonly used as a quality of life (QoL) instrument [Jenkinson et al., 1995; Peto et al., 1995; Jenkinson et al., 1999]. Compared to clinical scales in PD, such as the modified Hoehn and Yahr scale [Hoehn & Yahr, 1967] or the Unified Parkinson’s Disease Rating Scale (UPDRS) [Fahn et al., 1987], QoL instruments assess more areas of a patient’s subjective well-being than clinical scales. The PDQ-39 has been shown to have good reliability, validity, responsiveness and reproducibility [Schrag et al., 2000; Just & Ostergaard, 2002]. A shorter form of PDQ-39, named PDQ-8, is also available [Jenkinson et al., 1997; Appendix D]. Other commonly used instruments in PD patients are the Schwab and England disability scale, and two other QoL instruments (EQ-5D and SF-36).

In PD, there is a high correlation with advanced stages of disease, motor complications, and extended ‘off’ states as well as poorer perceptions of health and a decline in QoL [Chrischilles et al., 1998]. Dyskinesias interfere with numerous activities of daily living (ADLs), and consequently, result in poorer HRQoL, and increased healthcare costs [Damiano et al., 2000; Pechevis et al., 2005]. Diphasic dyskinesia are linked with worse HRQoL compared to peak-dose dyskinesias [Chapuis et al., 2005]. Additionally, PD patients at a younger onset of the disease have poorer QoL, stigma of disease, loss of marital satisfaction, and worse depression [Schrag et al., 2003]. Further to the cardinal motor features of PD and motor complications associated with levodopa, non-motor emergence of PD such as fatigue, drooling, sleep dysfunction, sexual dysfunction, confusion, autonomic disturbances, and sensory disturbances negatively impact HRQoL [Martinez-Martin, 1998; Kuehler et al., 2003; Wilkinson et al., 2006]. Moreover, fatigue has also been linked with deteriorating depression and disability [Martinez-Martin et al., 2006]. As the disease proceeds, family members become the primary caregivers, leading to an increased caregiver burden [Lokk, 2006]. From a caregiver viewpoint, the most
problematic symptoms encountered by the patients are motor dysfunction and cognitive decline [Lokk, 2006].

2.8.1 Deep Brain Stimulation and Quality-of-Life in Parkinson’s Disease Patients

A review of the literature between 1987 and 2005 by Diamond & Jankovic [2005] identified eight studies that had HRQoL as an outcome in STN DBS. All eight studies from PD QoL instruments, which varied in length from three months to two years, reported HRQoL improvements of between 14% to 62%. There was a trend to significance for STN DBS over unilateral pallidotomy at six months, however the study failed to show statistical significance (reported as being due to a lack of statistical power). The longest study was two years [Lezcano et al., 2004]. Fourteen consecutive patients were examined using the PDQ-39, with ON medication at baseline (before surgery) and ON medication and ON stimulation during the follow-up. The improvement in QoL of patients two years after surgery was reported as 62%.

A Finnish study by Erola et al. [2005] of 29 successive patients reported the individual PDQ-39 scores both before and 12 months after surgery. In the study, a correlation between patient’s age and PDQ-39 was observed where younger patients demonstrated a greater improvement after surgery. Of the subscales from the questionnaire, only communication in PD patients became worse during follow-up. There was also a correlation between UPDRS-III scores and the PDQ-39 identified.

After 2005, there were 3 notable studies which indicated that DBS and best medical treatment was more effective than best medical treatment alone in the improvement of the QoL in patients with advanced PD [Deuschl et al., 2006; Weaver et al., 2009; Williams et al., 2010]. In the six-month study by Deuschl et al., 2006, neurostimulation of the STN DBS was demonstrated to be more superior compared to medical management alone in PD patients less than 75 years of age with severe motor complications of PD. Similarly, in the study by Williams et al. [2010], the results showed that at 1 year, DBS surgery and best medical therapy improved patient self-reported QoL more than best medical therapy alone in patients with advanced PD. The differences were clinically meaningful, but surgery was not without risk. In the study by Weaver
et al. [2009], the findings indicated that DBS surgery was more effective than best medical therapy in improving on time without troubling dyskinesias, motor function, and QoL at 6 months but was associated with an increased risk of serious adverse events in a randomized controlled trial of patients with advanced PD.

2.9 Summary of Deep Brain Stimulation and Parkinson’s Disease

Disease burden is especially evident in the more advanced stages of PD due to greater symptoms, worse HRQoL, and an increased necessity for healthcare services. New interventions of drugs and non-pharmacologic agents that target to slow disease progression may decrease health care resource utilization and associated costs. Studies on STN DBS have indicated a reduction in the burden of PD and an improvement in the HRQoL in PD patients. Further, DBS therapy has been associated to reduce motor complications and daily intake of levodopa equivalents. In spite of these findings, there has not yet been a DBS study that focused on PD severity and its impact on the overall benefits and health care cost savings.

2.10 Aims of Study

The aims of this study were to determine the incremental cost per QALY in patients with PD with varying disease severity and to ascertain which patient subgroup would accrue the greatest net monetary benefits to Ontario’s public health perspective, the Ministry of Health and Long Term Care (MOHLTC), as a result of DBS. To answer these two questions, the methods of cost utility analysis (CUA) and net monetary benefit analysis (NMB) were employed. Under the perspective of the MOHLTC, the costs and health outcomes of PD patients at varying stages of severity were evaluated for one year. Patients were assigned according to disease severity based on their motor function under medication ‘off” state using the modified Hoehn and Yahr scale.

Because data was available only for patients who underwent DBS, the comparator was assumed to be PD patients with varying severity who did not undergo DBS but were treated with pharmacotherapy. It was also assumed that the pre-surgical health of PD patients who
underwent DBS surgery was identical as their post-surgical health would be had they not undergone DBS in the same time frame.

In the CUA, the incremental costs and health gains of 37 patients with mild, moderate or severe PD who underwent DBS surgery were calculated. Scores from the Parkinson’s disease Questionnaire-39 (PDQ-39) were converted into EuroQuol (EQ-5D) with a pre-determined algorithm [Cheug et al., 2008]. In the NBA, the costs and health effects of the 37 PD patients were calculated using a net monetary benefit approach. In the absence of willingness-to-pay (λ) data, the commonly used threshold of $50,000 Canadian dollars (CDN) was the amount chosen attached to a QALY.
3 Methods

The predominant reasons for patients with PD to consider DBS surgery are due to debilitating motor symptoms that limit the patients’ QoL despite optimum medical therapy. In this study, to assess the extent of disease severity, the modified Hoehn and Yahr (HY) scale [Goetz et al., 2004] was used to judge the motor functions in patients with PD. The scale has demonstrated its validity in measuring motor severity in patients [Hoehn & Yahr, 1967; Goetz et al., 2004; Martinez-Martin et al., 2006; Chaudhuri et al., 2007; Krikmann et al., 2008; Virués-Ortega et al., 2009].

3.1 Patient Selection

Patients enrolled at the Movement Disorder Clinic at the Toronto Western Hospital were eligible for DBS surgery if they met the inclusion and exclusion criteria as specified in Piboolnurak et al. [2007] and Moro et al. [2010]. The ages of the patients ranged from 30 to 75 years. The criteria for inclusion were the presence of at least two cardinal features of parkinsonism (tremor, rigidity, and bradykinesia), a good response to levodopa, a minimal score of 30 points in the motor section of the UPDRS scale (UPDRS III) when the patient has been without medication for approximately 12 hours (scores from this component range from 0 to 108; higher values indicate greater severity of symptoms [Fahn et al., 1987]); and motor complications that could not be controlled with pharmacologic therapy. The criteria for exclusion were major psychiatric illness, cognitive impairment, other substantial medical problems or laboratory abnormalities, presence of a cardiac pacemaker, and previous intracranial surgery. The research protocol was approved by an internal review ethics board (REB) at the Toronto Western Hospital.

The study design utilized a cost-utility analysis (CUA) and a net-benefit analysis (NBA) framework. While data were analyzed from one hundred patients who underwent DBS surgery, there were only 37 PD patients who had completed pre- and post-surgery data. Consequently, only 37 PD patients who underwent DBS could be assessed.
In the cost utility study, the PDQ-39 scores of patients were converted into EuroQoL-5-Dimension (EQ5D) health utility indices so that QALYs could be used. The incremental costs and effects of DBS in patients across three PD subgroups (mild, moderate and severe) were assessed. In the net benefit study, to ascertain which patient subgroup would accrue the greatest net monetary benefits to Ontario’s public health perspective as a result of DBS, the net monetary benefits of patients across each subgroup were analyzed. The progress and outcomes of DBS patients were monitored for one year.

3.2 Surgical Procedures

For each patient, surgical procedures were performed with the same surgical team using the same method during the study period. Thirty seven patients with advanced PD and medical intractable motor complications were treated with bilateral subthalamic (STN) DBS implantation of leads in a single operation. Brain MRIs immediately before the operation were performed in all patients. This was performed with a stereotactic frame to help find the target coordinates using special software (Surgiplan v 2.0; Elektra). Intra-operative micro-recording from the brain helped to locate the position, together with direct target with stimulation when the patient was awake. After the final electrode (Model 3387, Medtronic Inc.) positioning, a post-operative brain MRI was done to verify the placement. The leads were connected through a wire to an implantable pulse generator (Soletra or Kinetra, Medtronic Inc) placed subcutaneously in the subclavicular area.

3.3 Clinical Evaluation

Patients were examined at baseline during clinical assessment anywhere from 6 to 34 days before surgery by the same movement disorder surgical team using outcome measurement scales from clinical severity scales and health-related quality of life (HRQoL) scales. The clinical disease severity scales included the modified-HY scale [Goetz et al., 2004] and the UPDRS scale [Fahn & Elton, 1987]. The HRQoL scale included the PDQ39 [Peto et al., 1998]. Only data from the post-surgical tests performed in PD patients under conditions of medications ‘off’ were included.
The medication ‘off’ condition represents the worst state the patient is experiencing, as the patient is not under L-dopa or any other form of anti-PD drugs. Thus, any improvement in PD symptoms would be purely from DBS.

3.4 Cost Utility Analysis (CUA)

In this study, the incremental costs or savings of each subgroup and the incremental gains or loss in QALYs were determined for each PD subgroup.

3.4.1 Costing

Costing was evaluated from the perspective of Ontario’s public health system, the Ministry of Ontario Health and Long Term Care (MOHLTC). Due to deficient data in obtaining indirect costs resulting from lost productivity for patients and caregivers, a societal perspective could not be adopted. As such, only direct medical costs were included in this study. Costing was performed in Canadian dollars for the year 2012 using 1-year data of PD patients who underwent DBS as a result of motor complications. The total costs of surgery as well as the incremental costs incurred by patients who underwent the intervention were included in this analysis.

Total costs included all of the costs that patients incurred as a result of undergoing DBS surgery. These consisted of hospitalization costs, professional fees, diagnostic and laboratory fees and the cost of the DBS device itself associated with the peri-operative stage of the intervention. The peri-operative period accounts for the time before (pre-operative), during (intra-operative) and after (post-operative) DBS surgery. The fees for professional visits, procedures and consultations were obtained from the Ontario Health Insurance Plan (OHIP) Schedule of Benefits and Fees [Schedule of Benefits and Fees, 2012]. Costs of drugs were obtained from the Ontario Drug Benefit Formulary [ODBF, 2012]. A 10% pharmacy mark-up to the ODB plan costs and a pharmacy dispensing fee of $8.40 were included in the calculation of medication costs [ODBF, 2012]. Daily hospital bed/ward costs and operating room costs were obtained from the finance and operating room departments at Toronto Western Hospital. Regarding the
costs of the deep brain implant device (Kineta, Medtronic), these were calculated using the cost of the equipment from Medtronic at the time the patient underwent surgery [http://www.medtronicdbs.com]. Costs were then inflated using the most recent consumer price index to the year 2012 [Statistics Canada, 2012].

Incremental costs encompassed medication costs incurred by patients between the post- and pre-operative periods, as well as complication costs that arose as a result of DBS surgery.

Given that the time horizon for this study did not extend beyond one year, cost and clinical outcomes were not discounted.

3.4.2 Utilities

There are several methods to measure preferences for health outcomes and to determine utility scores. The three common methods are the time trade-off (TTO) method, the visual analogue scale (VAS) and the standard gamble (SG) [Torrance 1986; Torrance & Feeny 1989; Torrance 1997; Morgante et al., 1992] The TTO and VAS methods represent measurements under certainty. The SG represents measurement under uncertainty.

In the TTO, individuals have to choose between a certain period of time in a state of poor health and a shorter period of time in perfect health. In the VAS, individuals have to place various health states on a scale from 0 = death to 100 = perfect health. In the SG, individuals have to risk or ‘gamble’ between staying in a state of reduced health for a certain time period and a medical intervention with the chance of either being restored to perfect health or dying.

Preferences for health outcomes are specific for the cultural context of the individual. Therefore, scoring systems may not be transferred from one country to another without adjustments in validation. Further, individuals who do not experience from the state in question tend to on average assign a lower HR-QoL to the state.

Measuring preferences for health outcomes are complex and time consuming. Consequently, there have been questionnaires developed to bypass these measurements. There are several pre-
scored multi-attribute health status classification systems. The two most widely used systems are the EuroQoL5-Dimension (EQ5D) and the Short Form-6 Dimension (SF-6D).

The EQ-5D system was developed by the Western Europe EuroQoL group. It consists of five domains: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each domain consists of three levels: No problems, some problems, and major problems. The EQ5D enables for scores below zero ranking from -0.4 to 1 [EuroQoL, 1990]. The EQ5D was validated by the preferences for health outcomes of about 3000 individuals in the UK.

The SF-6D system was derived from the health status questionnaire, the Short Form 36 (SF-36) [Brazier et al., 2002]. The SF-36 is commonly used, and the SF-6D provides an instrument for converting these data into utility scores. The instrument contains six dimensions: physical functioning, role limitation, social functioning, pain, mental health, and vitality, each consisting of four to six levels. The instrument was as well validated in the UK. Next to death, the lowest weight is 0.3.

The eight-item Parkinson’s Disease Questionnaire (PDQ-8) [Jenkinson et al., 1997] is a shortened version of the PDQ-39, a commonly used HRQoL instrument for PD [Marinus et al., 2002]. Like many other HRQoL measures, the PDQ-8 was not designed to provide a quantitative utility value. An algorithm to generate EQ-5D health utility indices from the PDQ-8 has been recently developed by Cheung and colleagues [Cheung et al., 2008 ; Appendices E & F] so that a cost-utility analysis was possible when health outcomes were evaluated only by the PDQ-8 or PDQ-39 in studies of PD. The EQ-5D health index has demonstrated its validity in measuring the HRQoL of patients with PD [Schrag et al., 2000; Siderowf et al., 2002]. Further, the EQ-5D and the PDQ-8 share similar health concepts.

In this study, the health outcomes of 37 PD patients were assessed with PDQ-39 before and after DBS surgery. Each of the responses from the 8 key attributes of the PDQ-39 were converted into EQ-5D scores [Cheung et al., 2008]. Questions 1, 2, 3 and 7 in PDQ-8 were equivalent to questions 7, 12, 17, and 37 in PDQ-39. In Cheung’s model, the PDQ-8 mobility, activities of daily living, bodily discomfort, and emotional well-being items were used to predict EQ-5D mobility, self-care, pain/discomfort, and anxiety/depression items, while the PDQ-8 social support, cognition, communications, and stigma items were used collectively to predict the EQ-
5D usual activity item. The ordinary least squares regression model from Cheung’s study [2008] is shown below:

\[
\text{Utility} = 1 - 0.135 \times \text{PDQ}(1) - 0.052 \times \text{PDQ}(2) - 0.034 \times \text{PDQ}(2) - 0.031 \times \text{PDQ}(3) - 0.030 \times \text{PDQ}(7)
\]

### 3.5 Net Monetary Benefit Analysis (NMB)

In this section, the net monetary benefit analysis was used to determine the health and costs of thirty-seven DBS patients with varying PD severity to those who did not undergo DBS treatment. By using a willingness to pay amount (\(\lambda\)), one can then evaluate interventions and therapies using NMB.

Although there is no strict consensus on a \(\lambda\) threshold ratio for cost/QALYs, in the US, the threshold of US$50,000 to $100,000 per QALY often is mentioned in medical literature [Kaplan & Bush 1982; Ubel et al., 2003]. In the UK, £20,000 to £30,000 per QALY (or CDN$28,000 to CDN$45,000) has been accepted as the threshold to decide whether or not the National Institute for Health and Clinical Excellence (NICE) should recommend use of a new healthcare technology [NICE, 2004]. In a Swedish study that investigated an intrastriatal graft of dopamine-rich human embryonic ventral mesencephalic tissue versus standard therapy as an example of early evaluation of a novel/hypothetical intervention for PD, Hjelmgren and co-workers [2006] used \(\lambda\) threshold of €38,000 to €70,000 (or CDN$53,000 to CDN$98,000) per QALY.

In this study, and in the absence of \(\lambda\) data, the commonly-cited \(\lambda\) amount of CDN$50,000 was chosen as the value to attach to a QALY.

The NMB was calculated by:

\[
\text{NMB} = \lambda \Delta E - \Delta C > 0
\]

The intervention is worth funding if NMB > 0.
3.6 Missing Data

Clinical trials are designed to follow patients over time to determine the effect of the study intervention. Missing data or health reported outcomes may often occur. In this study, the issue of missing data was overcome with the application of the last observation carried forward (LOCF) method. The application of LOCF in dementia research has been criticized by several researchers [Aisen et al., 2000; Hills et al., 2002; Lanctôt et al., 2003; Aisen et al., 2003; Bullock et al., 2005; Kaduszkiewicz et al., 2005; Hogan et al., 2006], primarily due to its exclusion of patients’ improving or declining condition at the last measurement point. The LOCF method functions by freezing outcomes at the value observed before the last observation, thereby stopping decline in outcome measures and synthetically stabilizing disease in dropouts. Nevertheless, LOCF is still commonly used and is the main form of intention-to-treat analyses in trials of dementia and PD drugs [Emre et al., 2010; Powe et al., 2011].

Because follow-up data in patients varied anywhere from 6 to 9 months, to perform LOCF in this study, it was assumed that the dosage and costs of medication were unchanged from follow-up to within the end of the year after surgery, as well as from the time surgery began to the start of the year. The LOCF method was applied to four patients from the moderate disease subgroup.

3.7 Main Assumptions

There were two main assumptions that warrant emphasis: 1) The comparator was assumed to be PD patients with varying disease severity who did not undergo DBS surgery, and 2) the pre-surgical health of PD patients who underwent DBS surgery would be identical as their post-surgical health would be had they not undergone surgery in the same time frame.
3.8 Sensitivity Analyses

To examine the effects of altering input parameters that potentially have the most significant impact in the base case results, a series of one-way sensitivity analyses and probabilistic sensitivity analyses (PSA) were undertaken. One way sensitivity analyses are useful when varying one probability or utility estimate from baseline values to see if the optimal strategy changes [Doubilet et al., 1985; Critchfield et al., 1986]. Probabilistic sensitivity analyses are suitable when uncertainties in all values need to be considered simultaneously [Doubilet et al., 1985]. The parameters that underwent the one way sensitivity analyses included the cost of a temporary complication; the cost of a permanent complication; the percentage of drug consumption change based on a temporary complication; and the percentage of drug consumption change based on a permanent complication. The parameters that underwent the PSA included the change in the efficacy of the intervention (QALY) and the change in PD drug costs with or without surgical complications. These parameters were chosen as they were previously shown to dramatically influence the cost-effectiveness of DBS in PD [Tomaszewski & Holloway, 2000 and references herein].

In the one-way sensitivity analyses, the values of percentage change in the drug consumption for no complication, temporary and permanent complications, as well as the one-time costs for permanent and temporary complications were obtained from previously published studies of DBS in PD [Tomaszewski & Holloway, 2000 and references herein].

In the PSA, instead of taking on a single value, the probability of each varying parameter was assumed with a range of possible values and with an associated distribution function. The varying parameters were utility and drug costs. The uncertainty in the utility parameter was characterized by a beta distribution as beta distribution is bounded between 0 and 1. The uncertainty in the drug costs parameter was characterized by a gamma distribution as gamma distribution is constrained to be zero or positive. A Monte Carlo approach was used, where each probability was randomly assigned a value from a beta or gamma distribution, and the expected value of each option was computed. The process was repeated 1000 times.

To determine the specification of the distribution function on the probabilities of each of the varying parameter, this was achieved by setting the mean of each distribution function equal to
the baseline value. This condition assured that the mean value of the expected value of each scenario, over the 1000 runs of the Monte Carlo simulation, would converge to the base expected value [Raiffa, 1968]. The assumption was made that each distribution could be approximated by a normal distribution. This assumption has been suggested before for modeling probabilities [Atichison & Begg, 1976]. The benefits of this assumption were so that each probability of the expected value for each scenario could be determined by its mean ($\bar{x}$) and standard deviation (s) over the number of iterations.

The standard error of the mean (SE$\bar{x}$), the alpha ($\alpha$) value and the beta ($\beta$) value from the expected value for each scenario were deduced as followed:

For a beta distribution:

- $\bar{x}$ = base case value

- SE$\bar{x}$ was calculated from the following equation:

$$s^2 = \frac{1}{n} \sum_{i=1}^{n} (x_i - \bar{x})^2$$

where n = number of observations in the sample; s = standard deviation, which was calculated from:

- S was calculated from:

$$S = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}$$

where $x$ = individual observation

- $\alpha$ was calculated from:
$\hat{\alpha} = \bar{x} \left[ \frac{\bar{x}(1 - \bar{x})}{s^2} \right] - 1$

- $\beta$ was calculated from:

$\hat{\beta} = (1 - \bar{x}) \left[ \frac{\bar{x}(1 - \bar{x})}{s^2} \right] - 1$

For a gamma distribution:

- $\bar{x} = \text{base case value}$

- $\text{SE}\bar{x} = \text{base case value}$

- $\alpha = 1$

- $\beta = \text{base case value}$
4 Results

4.1 Cost Utility Analysis

The purpose of this section was to compare patients with varying degrees of PD severity in terms of incremental costs or incremental savings per unit of QALY gain or loss as a result of DBS. PD patients under ‘off-time’ were categorized into mild, moderate and severe subgroups based on their motor severity as assessed by the modified HY scale. To acquire utility scores, PDQ-39 responses were converted into EQ-5D utilities using a pre-determined algorithm. The algorithm was built based on responses from PD patients derived from each of the 8 key attributes of the PDQ-8 questionnaire. The responses were then converted into EQ-5D scores [Cheung et al., 2008].

4.1.1 Baseline Characteristics

The baseline characteristics of the thirty-seven DBS surgical patients employed in this study are outlined in Table 1. The PD patients in this study were predominantly male, with a ratio of 72.0% male to 23.0% female patients. The median age at disease onset was 44.0 (inter-quartile range, IR, 7.5), the median age at surgery was 58.0 (IR, 8.5), and the median PD duration was 12.0 (IR, 5.6). The median modified HY score was 2.5 (IR, 0.5). Baseline characteristics were similar between males and females.

Table 1. Patient baseline characteristics. Higher scores from the modified Hoehn and Yahr scale indicate worse functioning. “Off-state” is defined as the percentage of waking hours when patients experienced the most PD symptoms because their medication effects have worn off.

<table>
<thead>
<tr>
<th>n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27 (72.3)</td>
</tr>
<tr>
<td>Family history of Parkinson’s Disease</td>
<td>7 (22.6)</td>
</tr>
<tr>
<td>Median, Inter-quartile Range (IR)</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Age at surgery (y)</td>
<td>58, 8.5</td>
</tr>
<tr>
<td>Age of disease onset (y)</td>
<td>44, 7.5</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>12, 5.6</td>
</tr>
<tr>
<td>Male age at surgery (y)</td>
<td>59, 8.5</td>
</tr>
<tr>
<td>Male age at disease onset (y)</td>
<td>44, 55.8</td>
</tr>
<tr>
<td>Male duration of disease (y)</td>
<td>12, 6.5</td>
</tr>
<tr>
<td>Female age at surgery (y)</td>
<td>57, 7.5</td>
</tr>
<tr>
<td>Female age at disease onset (y)</td>
<td>45.5, 12</td>
</tr>
<tr>
<td>Female duration of disease (y)</td>
<td>11.5, 4.5</td>
</tr>
<tr>
<td>Modified Hoehn and Yahr (HY) Score (range, 0-5); “OFF-state”</td>
<td>2.5, 0.5</td>
</tr>
</tbody>
</table>

### 4.1.2 Motor Function in PD Patients to assess Disease Severity

PD patients under ‘off-time’ were categorized into mild (scores between 0 and 2.4), moderate (scores between 2.5 and 3.) and severe (scores ≥3.5) subgroups based on motor severity according to the modified HY scale. Table 2 shows the modified HY scores of PD patients before and after DBS surgery.

Table 2. Outcomes of patients before and after deep brain stimulation. Disease severity was assessed using the modified Hoehn and Yahr Scale under “off-time”. Scores between 0-2.4 were rated as mild motor impairment; scores between 2.5-3.4 were considered as moderate motor
impairment and scores ≥ 3.5 were assigned as severe motor impairment. Higher scores indicate worse functioning. “Off-state” is defined as the percentage of waking hours when patients experienced the most PD symptoms because their medication effects have worn off. Results were presented as median and inter-quartile range (IR). Paired T-tests were used to test the change between the pre- and post-surgery scores; a p-value of <0.05 was considered as significant. NA = none available; P-values could not be calculated due to small sample size (N=2).

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, %</td>
<td>2 (5)</td>
<td>30 (81)</td>
<td>5 (14)</td>
<td>37 (100)</td>
</tr>
</tbody>
</table>

**Modified Hoehn and Yahr Score (range, 0-5)**

<table>
<thead>
<tr>
<th>“OFF-state”</th>
<th>Pre-surgery (median, IR)</th>
<th>Post-surgery (median, IR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2, 0</td>
<td>2, 0.88</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>2.5, 0.5</td>
<td>3, 1</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>4, 1</td>
<td>2, 1</td>
<td>0.0086</td>
</tr>
</tbody>
</table>

There were 2 patients (5%) in the mild subgroup, 30 patients (81%) in the moderate subgroup and 5 patients (14%) in the severe subgroup. Paired t-test was chosen to assess data. Results were presented as median and IR. If a p-value of <0.05 was generated, the results were considered as significant. At baseline, the median modified HY scores for the mild, moderate and severe subgroups were 2 (IR, 0), 2.5 (IR, 0.5) and 4 (IR, 1). After DBS, the median
modified HY scores for the mild, moderate and severe subgroups were 2 (IR, 0), 2 (IR, 0.88) and 3 (IR, 1). The total median modified HY scores before and after DBS were 2.5 (IR, 0.5) and 2 (IR,1). Significance could not be determined in the mild subgroup due to a small sample size (N=2). Significance was reached in the moderate (p=0.000) and severe subgroups (p=0.0088), which suggested that the decrease in the HY scores in these two subgroups at post-surgery was due to DBS.

4.1.3 Health-Related Quality of Life and PDQ-8 Score Conversion to EQ-5D Health Utility Indices

An algorithm was developed by Cheung and co-workers [2008] to generate the EQ-5D health utility index from the PDQ-8 questionnaire [Cheung et al., 2008]. In this study, Cheung’s algorithm was employed to convert the scores from questions 7, 12, 17, and 37 in PDQ-39 (equivalent to questions 1, 2, 3 and 7 of PDQ-8) to EQ-5D utilities so that QALYs could be generated to use in the CUA. The deterministic and regression models used to predict the EQ-5D levels from PDQ-8 responses by the algorithm are shown in Appendices E and F.

Table 3 shows the EQ-5D scores after conversion from the PDQ-39 responses of the 37 PD patients with varying disease severity. PD patients from the mild, moderate and severe subgroups had a mean score of 0.41 (0.63 and 0.60 before surgery) and a median score of 0.40 (IR, 0.32)—0.62 (0.14) and 0.61 (IR 0.04). After surgery, the mean scores were 0.75, 0.74 and 0.63, and the median scores were 0.75 (IR, 0.01), 0.75 (IR, 0.11) and 0.66 (IR, 0.04). There was an improvement in EQ-5D scores after surgery, in increments of 0.33, 0.009 and 0.03 in the mild, moderate and severe subgroups. The relationship in the EQ-5D scores before and after surgery was significant in the moderate (p=<0.001) subgroup but not in the mild (p=0.47) and severe subgroups (p=0.35).

Table 3. Converted EQ-5D scores from PDQ-39 responses of patients with varying degrees of PD severity before and after surgery. PDQ-39 scores were collected before and after DBS surgery and converted into EQ-5D health utility indices using a pre-determined algorithm [Cheung et al. 2008]. The modified Hoehn and Yahr scale was used to assign patients into mild,
moderate and severe disease impairment. Results were presented as mean, median, interquartile range (IR). A p-value of <0.05 was considered as significant.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease Subgroup</th>
<th>EQ5D Pre-Op Health Utility Index</th>
<th>EQ5D Post-Op Health Utility Index</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Mild</td>
<td>0.41</td>
<td>0.75</td>
<td>0.33</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>0.40</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td>0.32</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Moderate</td>
<td>0.63</td>
<td>0.74</td>
<td>0.09</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>0.62</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td>0.14</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Severe</td>
<td>0</td>
<td>0.63</td>
<td>0.03</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>0.61</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td>0.04</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
As it takes one year of perfect health (utility score of 1) to generate one QALY, PD patients from the mild, moderate and severe subgroups gave respective QALYs of 0.33, 0.09 and 0.03.

4.1.4 Peri-operative Costs of DBS Treatment

The various resources and costs associated with the peri-operative period for PD patients who underwent DBS as a surgical intervention are shown below. The peri-operative period accounts for the time before (pre-operative), during (intra-operative) and after (post-operative) DBS surgery.

The costs of resources for each PD patient who underwent DBS surgery from the pre-operative stage are shown in Table 4. Physician costs were adjusted upwards by 2% to reflect the recent Ontario Medical Association agreement. The total costs of resources per patient were $795.

Table 4. Pre-operative costs of professional services for each PD patient who underwent DBS. The item number was according to the OHIP Schedule of Benefits and Fees (2012). Physician costs were adjusted upward 2% to reflect the recent Ontario Medical Association agreement.

<table>
<thead>
<tr>
<th>Resource Item</th>
<th>Item Number</th>
<th>Quantity</th>
<th>Price/Unit ($</th>
<th>Mark Up (2%)</th>
<th>Total Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychological assessment phase - special surgical consultation</td>
<td>A935</td>
<td>1</td>
<td>160</td>
<td>3.2</td>
<td>163.2</td>
</tr>
<tr>
<td>New Neurology Consult</td>
<td>A185</td>
<td>1</td>
<td>176.4</td>
<td>3.2</td>
<td>179.9</td>
</tr>
<tr>
<td>New Neurosurgery consult</td>
<td>A045</td>
<td>1</td>
<td>121.1</td>
<td>3.2</td>
<td>123.5</td>
</tr>
</tbody>
</table>
Table 5 provides a list of the diagnostic and laboratory examinations as well as associated costs for each PD patient who underwent DBS surgery from the pre-operative phase. The cost per item was obtained from the administrative database at the University of Health Network [2012]. The total pre-operative costs of diagnostic and laboratory services for each PD patient who underwent DBS were $413.00.

Table 5. Pre-operative costs of diagnostic and laboratory services for each PD patient who underwent DBS. Costs of services were obtained from the administrative database at the University Health Network.
<table>
<thead>
<tr>
<th>Service</th>
<th>Code</th>
<th>Count</th>
<th>Cost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total diagnostic services</td>
<td></td>
<td></td>
<td></td>
<td>172.7</td>
</tr>
<tr>
<td>Laboratory services</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venipuncture</td>
<td>G489</td>
<td>1</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>aPTT</td>
<td>L445</td>
<td>1</td>
<td>7.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Chloride, plasma</td>
<td>L053</td>
<td>1</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Creatinine, plasma</td>
<td>L067</td>
<td>1</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Bicarbonate, plasma</td>
<td>L061</td>
<td>1</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Sodium, plasma</td>
<td>L226</td>
<td>1</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>PTINR</td>
<td>L445</td>
<td>1</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>CBC</td>
<td>L393</td>
<td>1</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Total laboratory services</td>
<td></td>
<td></td>
<td></td>
<td>33.9</td>
</tr>
<tr>
<td>Total pre-operative costs</td>
<td></td>
<td></td>
<td></td>
<td>413</td>
</tr>
</tbody>
</table>

The costs and resources borne by each PD patient who underwent DBS surgery from the intra-operative stage are shown in Tables 6 and 7. Table 6 outlines the costs of professional services. For each PD patient who underwent DBS, the total intra-operative costs of professional services were approximately $1,673.8.
Table 6. Intra-operative costs of professional services for each PD patient who underwent DBS surgery. The item number was according to the OHIP Schedule of Benefits and Fees (2012). Physician costs were adjusted upward 2% to reflect the recent Ontario Medical Association agreement. The item number was obtained from the website of Medtronic Inc. Where necessary, costs were inflated to the year 2012.

<table>
<thead>
<tr>
<th>Resource Item</th>
<th>Item Number</th>
<th>Quantity</th>
<th>Price/Unit ($)</th>
<th>Mark Up (2%)</th>
<th>Cost ($)</th>
<th>Total Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician reimbursement for functional stereotaxy</td>
<td>N124</td>
<td>2</td>
<td>1,555.2</td>
<td>31</td>
<td>1,586.2</td>
<td>3,712.5</td>
</tr>
<tr>
<td>Electrophysiological assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-channel recording of EEG and EMG, rectification, averaging, back averaging, frequency analysis and cross correlation. Minimum of 3 hours. Physician must be physically present throughout</td>
<td>G266</td>
<td>1</td>
<td>278.9</td>
<td>5.6</td>
<td>284.5</td>
<td>284.5</td>
</tr>
<tr>
<td>Assessment</td>
<td>G267</td>
<td>1</td>
<td>270.1</td>
<td>5.4</td>
<td>275.5</td>
<td>275.5</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------</td>
<td>----</td>
<td>-------</td>
<td>-----</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Implantation or revision of stimulation pack or leads (peripheral nerve, brain)</td>
<td>Z823</td>
<td></td>
<td>307.4</td>
<td>6.1</td>
<td>313.5</td>
<td>313.5</td>
</tr>
<tr>
<td>Anesthetist costs</td>
<td>N124</td>
<td>39</td>
<td>12.51</td>
<td>-</td>
<td>487.9</td>
<td>487.9</td>
</tr>
<tr>
<td><strong>Total operative costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,673.8</td>
</tr>
</tbody>
</table>
Table 7 shows the costs of the DBS device. The costs included the implantable pulse generator (IPG), the electrodes and the extension leads. For each case of bilateral subthalamic nucleus, the implant was approximately $17,976.9.

Table 7. Costs components of deep brain stimulation device.

<table>
<thead>
<tr>
<th>Resource Item</th>
<th>Item Number</th>
<th>Quantity</th>
<th>Price/Unit ($</th>
<th>Cost ($) in Year 2007</th>
<th>Cost ($) in Year 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetra</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELECTORDE LEADS:</td>
<td>3387828</td>
<td>2</td>
<td>1,995</td>
<td>3,990</td>
<td>4,346</td>
</tr>
<tr>
<td>Quadripolar Lead Kit - DBS Lead</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTENSIONS: Low</td>
<td>748225</td>
<td>2</td>
<td>850</td>
<td>1,700</td>
<td>1,852</td>
</tr>
<tr>
<td>Profile DBS Extensions and accessories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy access</td>
<td>7436</td>
<td>1</td>
<td>819</td>
<td>819</td>
<td>891.9</td>
</tr>
<tr>
<td>controller: Patient controller unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PULSE GENERATOR,</td>
<td>7428</td>
<td>1</td>
<td>9,995</td>
<td>9995</td>
<td>10,887</td>
</tr>
<tr>
<td>RECEIVER AND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRANSMITTER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Costs of Kinetra System</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>16,574</strong></td>
<td><strong>17,976.9</strong></td>
</tr>
</tbody>
</table>
Collectively, for each PD patient who underwent DBS surgery, the total intra-operative costs were estimated to be approximately $19,650.

The post-operative costs of professional for each PD patient who underwent DBS surgery are presented in Table 8 and were approximated to be $1,168.7.

Table 8. Post-operative costs of professional services for each PD patient who underwent DBS surgery. The item number was according to the OHIP Schedule of Benefits and Fees (2012). Physician costs were adjusted upward 2% to reflect the recent Ontario Medical Association agreement.

<table>
<thead>
<tr>
<th>Resource Item</th>
<th>Number</th>
<th>Quantity</th>
<th>Price/Unit ($)</th>
<th>Mark Up (2%)</th>
<th>Cost ($)</th>
<th>Total Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Programming of Deep Brain Stimulator: one session</td>
<td>G547</td>
<td>1</td>
<td>185.7</td>
<td>3.7</td>
<td>189.4</td>
<td>189.4</td>
</tr>
<tr>
<td>Additional implantation site(s)</td>
<td>G549</td>
<td>1</td>
<td>157.9</td>
<td>3.2</td>
<td>161</td>
<td>161</td>
</tr>
<tr>
<td>Repeat Neurology consult</td>
<td>A186</td>
<td>1</td>
<td>85</td>
<td>1.7</td>
<td>86.7</td>
<td>86.7</td>
</tr>
<tr>
<td>Neurology partial assessment</td>
<td>A188</td>
<td>1</td>
<td>37.7</td>
<td>0.8</td>
<td>38.4</td>
<td>460.2</td>
</tr>
<tr>
<td>Complex Medical Reassessment</td>
<td>A181</td>
<td>1</td>
<td>71.9</td>
<td>1.4</td>
<td>73.3</td>
<td>73.3</td>
</tr>
<tr>
<td>Neurosurgery partial</td>
<td>A044</td>
<td>1</td>
<td>30</td>
<td>0.6</td>
<td>30.6</td>
<td>30.6</td>
</tr>
</tbody>
</table>
The various post-operative costs of diagnostic and laboratory services for each PD patients who underwent DBS surgery are shown in Table 9 and estimated to be $39.

Table 9. Post-operative costs of diagnostic and laboratory services for each PD patient who underwent DBS surgery. Costs were obtained from the administrative database from the University Health Network [2012].

<table>
<thead>
<tr>
<th>Item</th>
<th>Number</th>
<th>Price/Unit ($)</th>
<th>Total Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venipuncture</td>
<td>G489</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Electrolytes, plasma</td>
<td>L204</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Glucose, random green</td>
<td>L111</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>aPTT</td>
<td>L445</td>
<td>7.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Chloride, plasma</td>
<td>L053</td>
<td>2.6</td>
<td>2.6</td>
</tr>
</tbody>
</table>
In summary, and as shown in Table 10, the total costs of professional, diagnostic and laboratory services associated to the peri-operative period (pre-, intra-, post-surgery) for each PD patient who underwent DBS surgery were estimated to be $22,066.5.

Table 10. Total costs of professional, diagnostic and laboratory services stemmed from the peri-operative stage (pre-, intra-, post-surgery) during DBS intervention from each PD patient.
<table>
<thead>
<tr>
<th>Cost of DBS system</th>
<th>17,976.9</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Post-operative</em></td>
<td></td>
</tr>
<tr>
<td>Professional Fees</td>
<td>1,168.7</td>
</tr>
<tr>
<td>Diagnostic and Laboratory Costs</td>
<td>39</td>
</tr>
<tr>
<td><strong>Total Costs</strong></td>
<td><strong>22,066.5</strong></td>
</tr>
</tbody>
</table>

4.1.5 Medication Costs

Table 11 shows the medication costs incurred by patients in each PD subgroup before and after DBS surgery. PD patients from the mild, moderate and severe subgroups yielded savings of $2,685.3, $6,258.8, and $7,348.4 in medication costs as a result of DBS. Paired t-test analyses revealed significant relationships in medication costs before and after surgery in the moderate (p=0.000) and severe (p=0.006) subgroups but not in the mild (p=0.22) subgroup. PD patients from the severe subgroup had the greatest PD drug cost savings, followed by those from the moderate and mild disease subgroups.

Table 11. Medication costs incurred by PD patients in the mild, moderate and severe PD subgroups before and after deep brain stimulation. Daily medication costs in PD patients from each disease severity subgroup were recorded at baseline and after surgery. Costs were carried backward and forward with the method of last-observation-carried-forward (LOCF) to within one year. The change in medication cost was deduced by taking the cost difference at baseline and at post surgery. PD patients were grouped into mild, moderate and severe disease impairment using the modified Hoehn and Yahr scale. Results were presented as mean, median and inter-quartile range (IR). A p-value of < 0.05 was considered as significant.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease Subgroup</th>
<th>Pre-Op Medication Cost ($)</th>
<th>Post-Op Medication Cost ($)</th>
<th>Cost Savings in Medication ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Mild</td>
<td>6,147.3</td>
<td>3,461</td>
<td>-2686.3</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>6,147.3</td>
<td>3,461</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td>1,857.7</td>
<td>886.1</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>0.221</td>
</tr>
<tr>
<td>Mean</td>
<td>Moderate</td>
<td>7,559.9</td>
<td>4,301.2</td>
<td>-3,258.8</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>6,697.2</td>
<td>3,354.9</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td>6,792.3</td>
<td>2,433.3</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Mean</td>
<td>Severe</td>
<td>8,324.9</td>
<td>976.5</td>
<td>-7,348.4</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>7,590.7</td>
<td>1,068.4</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td>2,528.3</td>
<td>661.3</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
</tbody>
</table>

### 4.1.6 Complication Costs

There were three PD patients who experienced post-surgery hematomas as a result of DBS. Table 12 shows the complication costs borne by each of the three patients who belonged in the moderate disease subgroup. Each case of hematoma resulted in a cost of $4,509.9. One patient hemorrhaged twice and thus resulted in a cost of $10978.4. In addition to the higher associated
costs in these patients, the hematomas also led to a temporary decrease in the efficacy of DBS and diminished health utilities.

Table 12. Complication costs of PD patients. Three patients from the moderate disease subgroup experienced post-operative hematomas as result of DBS surgery. Item number was according to the OHIP Schedule of Benefits and Fees, 2012. ^For inpatient services, OHIP will pay $200 CDN per day. If the services are inpatient services rendered in an operating room, coronary care unit, intensive care unit, neonatal or pediatric special care unit, then OHIP will pay at the higher rate of $400 CDN per day for hospital services.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease Severity</th>
<th>Complication</th>
<th>Item Description</th>
<th>Item Number</th>
<th>Quantity</th>
<th>Price/Unit ($)</th>
<th>Total Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Moderate</td>
<td>Subdural hematoma (2x)</td>
<td>CT scan of neck</td>
<td>X403</td>
<td>2</td>
<td>86.6</td>
<td>173.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hospital bed</td>
<td>^</td>
<td>10 days</td>
<td>400/day</td>
<td>8,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Blood test</td>
<td>As Table 9</td>
<td>2</td>
<td>39</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Blood culture</td>
<td>L264</td>
<td>2</td>
<td>15.6</td>
<td>31.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wound culture</td>
<td>L253</td>
<td>2</td>
<td>12.9</td>
<td>25.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urine culture</td>
<td>L268</td>
<td>2</td>
<td>2.6</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DBS evacuation</td>
<td>N143</td>
<td>2</td>
<td>599.6/ unilateral</td>
<td>2,398.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------</td>
<td>------------------------</td>
<td>-----</td>
<td>---</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBS device removal</td>
<td>Z824</td>
<td>1</td>
<td>266.6</td>
<td>266.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10,978.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Hematoma</td>
<td>X403</td>
<td>2</td>
<td>86.6</td>
<td>173.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT scan of neck</td>
<td></td>
<td></td>
<td>4,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital bed</td>
<td>^</td>
<td>10 days</td>
<td>400 /day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood test</td>
<td>As Table 9</td>
<td>2</td>
<td>39</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood culture</td>
<td>L264</td>
<td>2</td>
<td>15.6</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wound culture</td>
<td>L253</td>
<td>2</td>
<td>12.9</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine culture</td>
<td>L268</td>
<td>2</td>
<td>2.6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBS device removal</td>
<td>Z824</td>
<td>1</td>
<td>266.6</td>
<td>266.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Hematoma</td>
<td>As patient 2</td>
<td></td>
<td></td>
<td>4,509.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4,509.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 4.1.7 Incremental Costs and Incremental QALYs in Patients with Varying PD Severity

The estimated incremental cost savings and incremental QALY gains of patients with mild, moderate and severe PD who underwent DBS are tabulated in Table 13. The incremental costs and outcomes were ranked from the least costly (greatest savings) to the most expensive (least savings). As indicated, the incremental cost savings for patients in the mild, moderate and
severe PD subgroups were $2,686.3, $2,752.4 and $7,348.4. The respective incremental gains in QALYs were 0.33, 0.09 and 0.03.

Compared to PD patients who did not undergo DBS surgery, patients who did undergo the intervention had additional upfront costs. These costs included the costs of the DBS equipment, as well as costs which stemmed from professional, laboratory and diagnostic services during the peri-operative period. To determine the incremental cost effectiveness ratio (ICER) of each strategy, the costs from the peri-operative period were included. The ICER of each PD subgroup was first determined by comparing it with the next most effective ICER. The ICER from the moderate to mild PD subgroups was calculated to be $91,920/QALY. The ICER from the severe to moderate PD subgroups was calculated to be 275.4/QALY. Due to extended dominance, the ICER of $91,920/QALY was excluded because a greater number of QALYs were obtained from the mild subgroup (0.33 versus 0.09) but at a lower cost per QALY ($275.42/QALY). The ICER was re-calculated and determined to be $16,076.2/QALY.
Table 13. The incremental costs and outcomes of DBS treatment for PD patients with varying disease severity compared to pharmacotherapy treatment after considering extended dominance.

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Effect (QALY)</th>
<th>Cost ($)</th>
<th>Costs from peri-operative period (pre-, intra-, post-surgery) including professional, laboratory and diagnostic services + DBS equipment</th>
<th>Total Costs ($)</th>
<th>Incremental Effect (ΔQALY)</th>
<th>Incremental Cost (ΔCost, $)</th>
<th>ICER (ΔCost/ΔQALY)</th>
<th>Dominated?</th>
<th>ICER with dominant strategies excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>0.04</td>
<td>-7,348.4</td>
<td>22,066.5</td>
<td>14,718.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0.09</td>
<td>-2,752.4</td>
<td>22,066.5</td>
<td>19,314.1</td>
<td>0.05</td>
<td>4,596</td>
<td>91,920</td>
<td>Yes, extended</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0.33</td>
<td>-2,686.3</td>
<td>22,066.5</td>
<td>19,380.2</td>
<td>0.24</td>
<td>66.1</td>
<td>275.4</td>
<td></td>
<td>16,067.2</td>
</tr>
</tbody>
</table>
Figure 1 shows the graphical output of the results of each disease subgroup via a cross-effectiveness plane. The points on the graph represented the incremental cost savings and incremental QALY gains from the intervention in each PD subgroup. The location of the points in the south-east quadrant of the cost-effectiveness plane suggested that DBS surgery was more effective and less costly compared to no surgery as a treatment strategy for patients with varying PD severity (i.e. DBS was dominant).

Figure 1. The incremental difference in cost savings and the incremental QALY gains in PD patients from the mild, moderate and severe subgroups. The willingness-to-pay threshold ($\lambda$) was at $50,000/QALY. QALY, quality-adjusted-life years.
4.2 Net Monetary Benefit Analysis (NBA)

To determine which DBS PD subgroup would accrue the greatest net benefits to Ontario’s public health care perspective, the approach of net monetary benefit (NMB) was employed. In NMB, the health and costs of patients are expressed in monetary terms. In the absence of willingness-to-pay ($\lambda$) data, the commonly-cited value of $50,000 was chosen as the amount attached to a QALY.

Table 14 shows the NMB results of PD patients with varying disease severity from DBS compared to no DBS. At $\lambda$ of $50,000/QALY, PD patients in the mild, moderate and severe DBS subgroups gave respective NMBs of $41,252.8, $29,318.9 and $31,414.9. These results suggested that the greatest net monetary benefits accrued to the MOHLTC were from treating mild PD patients with DBS, followed by patients with severe and moderate PD.

Table 14. Results of the net monetary benefit analyses in patients with mild, moderate and severe PD. A willingness-to-pay ($\lambda$) value of $50,000 was chosen to attach to a QALY. NMB = $\lambda \text{\Delta QALY} - \Delta C + C$

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Costs from peri-operative stage (physician, laboratory, diagnostic services + DBS equipment) (C, $)</th>
<th>Effect (\text{\Delta QALY})</th>
<th>Cost (\text{\Delta C,}$)</th>
<th>$\lambda$ ($\lambda$/QALY)</th>
<th>NMB ($)</th>
<th>Highest NMB?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>22,066.50</td>
<td>0.33</td>
<td>-2,686.30</td>
<td>50,000</td>
<td>41,252.8</td>
<td>TRUE</td>
</tr>
<tr>
<td>Moderate</td>
<td>22,066.50</td>
<td>0.09</td>
<td>-2,752.40</td>
<td>50,000</td>
<td>29,318.9</td>
<td>FALSE</td>
</tr>
<tr>
<td>Severe</td>
<td>22,066.50</td>
<td>0.04</td>
<td>-7,348.4</td>
<td>50,000</td>
<td>31,414.9</td>
<td>FALSE</td>
</tr>
</tbody>
</table>
4.3 Sensitivity Analyses

To examine the effects of altering input parameters that potentially have the most dramatic influence in the base case scenario, a series of one-way sensitivity analyses and probabilistic sensitivity analyses (PSA) were undertaken. The parameters that underwent the one way sensitivity analyses included the cost of a temporary complication; the cost of a permanent complication; the percentage of drug consumption change based on a temporary complication; and the percentage of drug consumption change based on a permanent complication. The parameters that underwent the PSA included the change in the efficacy of the intervention (QALY) and the change in PD drug costs with or without surgical complications. These parameters were chosen as they were previously shown to dramatically influence the cost-effectiveness of DBS in PD [Tomaszewski & Holloway, 2000 and references herein]. The input parameters that were varied are tabulated in Table 15.

Table 15: One-Way Sensitivity Analyses of Input Parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$CAD 2012 base-case input/PD severity group</th>
<th>Range evaluated</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBS Specific:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporary DBS complication</td>
<td>10,978.4/mild</td>
<td>1,000-50,000</td>
<td>Tomaszewski &amp; Holloway, 2000</td>
</tr>
<tr>
<td></td>
<td>4,509.9/moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4,5909.9/severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent DBS complication</td>
<td>NA</td>
<td>10,000-1,000,000</td>
<td>Tomaszewski &amp; Holloway, 2000</td>
</tr>
<tr>
<td>Drug consumption (% change)</td>
<td>Cost savings</td>
<td>Complication/Severity</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
<td>------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>None or temporary complication/disease severity subgroup</td>
<td>2,685.3 cost savings when no complication/mild</td>
<td>-50 to -20</td>
<td>Limousin et al., 1998</td>
</tr>
<tr>
<td></td>
<td>2,752.4 cost savings when no complication/moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7,348.4 cost savings when complication/severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent complication</td>
<td>NA</td>
<td>10-100</td>
<td>Tomaszewski &amp; Holloway, 2000</td>
</tr>
</tbody>
</table>

The sensitivity results are depicted in Figure 2. The incremental cost savings and QALY gains in the mild subgroup were sensitive to the costs of temporary and permanent complications resulting from DBS (Figure 2A). Using a lower ($1,000) and upper ($50,000) range estimate for the cost of a temporary complication [Tomasewski and Holloway, 2001; and references herein], the incremental cost and QALY gained with DBS ranged from savings of $33,764.50 to a cost of $615,856.70 per QALY gained. Using a lower ($10,000) and upper ($1,000,000) range estimate for the cost of a permanent complication [Tomasewski and Holloway, 2001; and references herein], the incremental costs per QALY gained associated with DBS ranged from $32,180.2 to $13,210,553.7. In regards to PD patients from the moderate and severe subgroups, the costs of permanent complications had the largest impact resulting from DBS. For PD patients in the moderate subgroup, the lower and upper range estimates yielded incremental costs per QALY gained from $23,317.2 to $2,477,965.7 (Figure 2B). For PD patients in the severe subgroup, the
lower and upper range estimates gave incremental cost savings per QALY gained of $10,892.6 to $6,181,923.7 (Figure 2C).

Figure 2. A series of one-way sensitivity analyses for incremental cost savings and incremental QALY gains (in Canadian Dollars, 2012). A. Mild PD subgroup; B. Moderate PD subgroup; C: Severe PD subgroup

A. Mild PD Subgroup
B. Moderate PD Subgroup

Base case ($30,582.2 savings per QALY gained)

- Drug consumption % change, permanent complication (increase by 10% to 100%)
- Drug consumption % change, none or temporary complication (decrease by 20% to 50%)
- Permanent DBS complication, one-time cost ($10,000-$1,000,000)
- Temporary DBS complication, one-time cost ($1,000-$50,000)
C. Severe PD Subgroup

The net monetary benefit framework was used to rank the most cost effective strategy in the base case and in the following probabilistic sensitivity analyses (PSA). The data used for the PSA for each PD subgroup are shown in Tables 16-18. Each table consists of the bases-case value, the assigned distribution, the mean (=base-case), the standard error, the alpha and the beta values of the needed probabilities, based in part on the estimates in the analysis. The determination of these values was described in Section 3.8.
Table 16: Data from patients in the mild PD subgroup used for PSA.

<table>
<thead>
<tr>
<th>Names of Variable</th>
<th>Base-case value</th>
<th>Distribution</th>
<th>Mean ($\bar{x}$)</th>
<th>Standard Error (SE)</th>
<th>Alpha ($\alpha$)</th>
<th>Beta ($\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy of Intervention (QALY)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complications, before surgery</td>
<td>0.041</td>
<td>Beta</td>
<td>0.041</td>
<td>0.01</td>
<td>15.7</td>
<td>371.9</td>
</tr>
<tr>
<td>No complications, after surgery</td>
<td>0.37</td>
<td>Beta</td>
<td>0.37</td>
<td>0.0095</td>
<td>955.3</td>
<td>1626.6</td>
</tr>
<tr>
<td><strong>Cost Parameter ($)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug costs, no complications, before surgery</td>
<td>6,147.3</td>
<td>Gamma</td>
<td>6,147.3</td>
<td>6,147.3</td>
<td>1</td>
<td>6,147.3</td>
</tr>
<tr>
<td>Drug costs, no complications, after surgery</td>
<td>3,461.1</td>
<td>Gamma</td>
<td>3,461.1</td>
<td>3,461.1</td>
<td>1</td>
<td>3,461.1</td>
</tr>
</tbody>
</table>
Table 17: Data from patients in the moderate PD subgroup used for PSA.

<table>
<thead>
<tr>
<th>Names of Variable</th>
<th>Base-case value</th>
<th>Distribution</th>
<th>Mean ((\bar{x}))</th>
<th>Standard Error (SE(\bar{x}))</th>
<th>Alpha ((\alpha))</th>
<th>Beta ((\beta))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of Intervention (QALY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complications, before Surgery</td>
<td>0.63</td>
<td>Beta</td>
<td>0.63</td>
<td>0.02</td>
<td>366.5</td>
<td>215.2</td>
</tr>
<tr>
<td>No complications, after surgery</td>
<td>0.74</td>
<td>Beta</td>
<td>0.74</td>
<td>0.02</td>
<td>355.2</td>
<td>124.8</td>
</tr>
<tr>
<td>Cost Parameter ($)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug costs, no complications, before surgery</td>
<td>7,599.9</td>
<td>Gamma</td>
<td>7,599.9</td>
<td>7,599.9</td>
<td>1</td>
<td>7,599.9</td>
</tr>
<tr>
<td>Drug costs, no complications, after surgery</td>
<td>4,301.2</td>
<td>Gamma</td>
<td>4,301.2</td>
<td>4,301.2</td>
<td>1</td>
<td>4,301.2</td>
</tr>
<tr>
<td>Drug costs, with complications,</td>
<td>7,599.9</td>
<td>Gamma</td>
<td>7,599.9</td>
<td>7,599.9</td>
<td>1</td>
<td>7,599.9</td>
</tr>
<tr>
<td>Drug costs, with complications, after surgery</td>
<td>4,847.5</td>
<td>Gamma</td>
<td>4,847.5</td>
<td>4,847.5</td>
<td>1</td>
<td>4,847.5</td>
</tr>
</tbody>
</table>
Table 18: Data from patients in the severe PD subgroup used for PSA.

<table>
<thead>
<tr>
<th>Names of Variable</th>
<th>Base-case value</th>
<th>Distribution</th>
<th>Mean ((\bar{x}))</th>
<th>Standard Error ((SE))</th>
<th>Alpha ((\alpha))</th>
<th>Beta ((\beta))</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Efficacy of Intervention</em> (QALY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complications, before Surgery</td>
<td>0.6</td>
<td>Beta</td>
<td>0.6</td>
<td>0.6</td>
<td>153.3</td>
<td>102.2</td>
</tr>
<tr>
<td>No complications, after surgery</td>
<td>0.63</td>
<td>Beta</td>
<td>0.63</td>
<td>0.63</td>
<td>99.3</td>
<td>58.3</td>
</tr>
<tr>
<td><em>Cost Parameter</em> ($)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug costs, no complications, before surgery</td>
<td>8,324.9</td>
<td>Gamma</td>
<td>8,324.9</td>
<td>8,324.9</td>
<td>1</td>
<td>8,324.9</td>
</tr>
<tr>
<td>Drug costs, no complications, after surgery</td>
<td>976.5</td>
<td>Gamma</td>
<td>976.5</td>
<td>976.5</td>
<td>1</td>
<td>976.5</td>
</tr>
</tbody>
</table>
Figures 3 to 5 depict the PSA results from each PD subgroup. In regards to PD patients from the mild subgroup (Figure 3), in 63% of the 1000 MC simulations, DBS led to cost savings and improvements in QALYs (Figure 3A). This suggested that in 63% of the 1000 runs, using the best set of estimates of probabilities and utilities, DBS was the optimal strategy, when compared to pharmacotherapy, to treat patients with mild PD severity. Most of the points from the scatter plot fell into the NE and SE quadrants of the cost effectiveness plane and suggested that the intervention was more or less costly and more effective compared to no surgery. The results of the PSA were also presented by cost-effectiveness acceptability curve (CEAC) (Figure 3B). The CEAC indicated the probability that DBS was cost effective compared with usual care (i.e. best medical treatment with no surgery), over a range of the decision-maker's willingness to pay or maximum acceptable ceiling ratio ($\lambda$). If $\lambda$ was $50,000/QALY$, which is the commonly cited willingness-to-pay threshold, the probability that DBS was cost effective was 0.997. If $\lambda$ was $100,000/QALY$, which is the next commonly cited value, the probability that the intervention was cost effective was 1.000.

Figure 3. Probabilistic sensitivity analysis and cost-effectiveness acceptability curve for patients with mild PD severity. Complication costs were included. A. Probabilistic sensitivity analysis in a cost-effectiveness plane for patients with mild PD. B. Cost-effectiveness acceptability curve showing the probability that DBS was cost-effective compared with usual care (best medical treatment, no surgery) for patients with mild PD. QALY, quality-adjusted-life years.
A. Probabilistic sensitivity analysis in a cost-effectiveness plane for patients with mild PD severity.
B. Cost-effectiveness acceptability curve showing the probability that DBS was cost-effective compared with usual care (best medical treatment, no surgery) for patients with mild PD severity.

In regards to the PD patients from the moderate subgroup, in 61.9% of the 1000 MC simulations, surgery led to cost savings and improvements in QALYs (Figure 4A). This suggested that in 61.9% of the 1000 runs, using the best set of estimates of probabilities and utilities, DBS was the optimal strategy, when compared to pharmacotherapy, to treat patients with moderate PD severity. Most of the points from the scatter plot were located into the NE and SE quadrants of the cost effectiveness plane, and suggested that the DBS was more or less costly and more effective compared to no surgery. Results of the CEAC indicated that if \( \lambda \) was $50,000/QALY, the probability that DBS was cost effective was 0.666. If \( \lambda \) was $100,000/QALY, the probability that the intervention was cost effective was 0.828.

Figure 4. Probabilistic sensitivity analysis and cost-effectiveness acceptability curve for patients with moderate PD severity (including complication costs). A. Probabilistic sensitivity analysis in a cost-effectiveness plane for patients with moderate PD. B. Cost-effectiveness acceptability curve showing the probability that DBS was cost-effective compared with usual care (best
medical treatment, no surgery) for patients with moderate PD. QALY, quality-adjusted-life years.

A. Probabilistic sensitivity analysis in a cost-effectiveness plane for patients with moderate PD severity (complication costs were included).
B. Cost-effectiveness acceptability curve showing the probability that DBS was cost-effective compared with usual care (best medical treatment, no surgery) for patients with moderate PD severity (complication costs were included).

If complication costs were excluded from the PD moderate subgroup, DBS led to cost savings and improvements in QALYs in 62.5% of the 1000 MC simulations (Figure 5A). If $\lambda$ was $50,000/QALY, the probability that DBS was cost effective was 0.895. If $\lambda$ was $100,000/QALY, the probability that the intervention was cost effective was 0.961 (Figure 5B).

Figure 5. Probabilistic sensitivity analysis and cost-effectiveness acceptability curve for patients with moderate PD severity (excluding complication costs). A. Probabilistic sensitivity analysis in a cost-effectiveness plane for patients with moderate PD. B. Cost-effectiveness acceptability curve showing the probability that DBS was cost-effective compared with usual care (best medical treatment, no surgery) for patients with moderate PD. QALY, quality-adjusted-life years.
A. Probabilistic sensitivity analysis in a cost-effectiveness plane curve for patients with moderate PD severity (complication costs were excluded).
B. Cost-effectiveness acceptability curve showing the probability that DBS was cost-effective compared with usual care (best medical treatment, no surgery) for patients with moderate PD severity (complication costs excluded).

In regards to PD patients from the severe subgroup, there was evidence that the intervention was less costly and more or less effective as there were some points in the scatterplot that fell into the SE quadrant (less costly, more effective) and there were other points that were located in the SW quadrant (less costly, less effective). Consequently, CEAC did not asymptote to 1 but asymptoted to a value less than 1. Since not all the points involved health gains (30%), the CEAC fell continuously once $\lambda$ exceeded $40,000/QALY$. At $\lambda$ of $40,000/QALY$, the probability that DBS was cost-effective was 0.917. At $\lambda$ $50,000/QALY$, the probability that DBS was cost effective was 0.914. If $\lambda$ was $100,000/QALY$, the probability that the intervention was cost effective was 0.881 (Figure 6).

Figure 6. Probabilistic sensitivity analysis and cost-effectiveness acceptability curve for patients with severe PD. A. Probabilistic sensitivity analysis in a cost-effectiveness plane for patients with severe PD. B. Cost-effectiveness acceptability curve showing the probability that DBS was
cost-effective compared with usual care (best medical treatment, no surgery) for patients with severe PD. QALY, quality-adjusted-life years.

A. Probabilistic sensitivity analysis in a cost-effectiveness plane for patients with severe PD.

B. Cost-effectiveness acceptability curve showing the probability that DBS was cost-effective compared with usual care (best medical treatment, no surgery) plane for patients with severe PD.
Levodopa combined with adjunct medical therapy is the standard medical treatment for individuals with PD. However, prolonged use of levodopa can cause disabling motor fluctuations and dyskinesias. When medication is no longer effective or produces unacceptable side effects, surgical treatments may be a possible alternative. The main surgical treatments for PD are ablative surgery and DBS. Ablative surgery is not performed in Ontario and has largely been replaced by DBS. This is in part because DBS is potentially reversible and is perceived to be associated with improved safety and effectiveness, and in part because ablative surgery is irreversible and regarded as having limited effectiveness and significant safety concerns. While the mechanism of action for DBS is unclear, its effect on the patient may result in the stabilization of motor function throughout the day. The on-off fluctuations refer to the extremes of maximal benefit of the drug (‘on’ state) and minimal benefit of the drug (‘off’ state). DBS is thought to be most effective in the ‘off’ state, when the relief of symptoms from drugs is minimal and thus helps to stabilize symptoms throughout the day.

In this study, the objectives were to determine the incremental costs per QALY in patients with PD with varying disease severity and to ascertain which patient subgroup would accrue the greatest net monetary benefits to Ontario’s public health perspective (MOHLTC) as a result of DBS intervention. To fulfill these aims, the approaches of cost utility and net monetary benefit analyses were applied. The analyses examined the progress and outcomes of 37 PD patients with varying PD stages who underwent DBS. While the most rigorous study design for assessing the validity of a therapy is considered to be an RCT that compares outcomes in a group of patients who have undergone the therapy in question with outcomes in a group of patients who have not [Guyatt et al, 1993; Sackett et al., 2000], due to the lack of data concerning the comparator group, the comparator was assumed to be standard treatment or pharmacotherapy (i.e. no DBS surgery).

The results from this study revealed the total costs of bilateral STN DBS insertion in each PD patient to be about $22,066.5. While this figure was higher than the reported values of £6,505.2/year (or £32,526 over 5 years) from a UK study [McIntosh et al., 2003] and $13,010.4 to $14,604.8/year from an Australian report [MSAC, 2006], it was in close agreement to the
reported figure of $24,420-$28,420 calculated per DBS case from the Ontario Health Technology Assessment report [2005]. While the insertion of a DBS system incurred upfront costs compared to the alternative treatment (pharmacotherapy), cost savings can be achieved from its effect of controlling the motor symptoms of PD as disease progresses and allowing patients to live in more functional health states for longer periods of time with improved QoL.

In a modelled cost-effectiveness study by Tomazewski and Holloway [2001], DBS was compared to best medical management in the treatment of PD and an ICER of US$49,000/QALY was produced. In this study, an ICER of $16,076.2/QALY was determined. Acknowledging that a full economic evaluation would routinely involve the comparison of two or more treatment options, a direct comparison of the lower ICER determined from this study should therefore not be made to that of Tomazewski and Holloway’s [2001]. Due to the lack of data concerning patients who did not undergo DBS surgery in the present analysis, assumptions had to be made regarding the comparator. The comparator was assumed to be standard treatment or pharmacotherapy (i.e. no DBS surgery). Another assumption made was that the pre-surgical health of patients with PD who underwent DBS surgery would be identical as their health would be in the same time frame post-surgery had they not undergone surgery. The results from the present analysis did demonstrate that the neurological intervention generated cost savings for patients with mild, moderate and severe PD. DBS resulted in incremental cost savings of $2,686.3, $2,752.4, and $7,348.4 and incremental QALY gains of 0.33, 0.09 and 0.04 in patients with mild, moderate and severe PD. At a willingness-to-pay threshold of $50,000/QALY, the greatest net monetary benefits accrued to Ontario’s MOHLTC were from treating patients with mild PD severity with DBS.

There were statistically significant changes observed between the pre- and post-surgery modified HY and the PDQ-39 converted EQ-5D scores in the moderate PD subgroup. However, significant relationships could not be reached in the pre- and post-surgery modified HY and EQ-5D scores in patients from the mild and severe PD subgroups. This was most likely due to the effects of small sample size in each group (mild, N=2; moderate, N=5). The overall results from this study were similar to those reported from other DBS studies which showed that the surgery was effective in reducing the symptoms of PD [examples in Just and Ostergaard, 2002; Hamani et al., 2005; Weaver et al., Deuschel et al., Williams et al., Moro et al., 2011, and many others].
and in decreasing the need for pharmacotherapy [examples, Hjort et al., 2004; Capecci et al., 2004; Esselink et al., 2004; Weaver et al., Desuchel et al., Williams et al., Moro et al., 2010; Castrioto et al., 2011]. Studies have also reported a small proportion of people stop taking drugs completely as a result of DBS [the Medical Advisory Secretariat, 2005] due to a reduction in drugs used pre- and post-operatively [Dodel et al., 1998; Spottke et al., 2002; McIntosh et al., 2003; Meissener et al., 2005]. In addition to cost-savings, DBS may also result in cost savings from its effect in controlling the motor symptoms of PD as disease progresses, enabling patients to live in more functional states of health for longer periods of time with improved QoL. It may be argued that mortality due to falling, for example, may decrease with improvements in motor skills as a result of DBS. These savings could be realized through a reduced demand for services or a lower expenditure on certain services as follows: 1) DBS patients require less dependency for a given level of pharmacotherapy compared to those who received best medical therapy; 2) Improved functions of ADL lessens the requirement for community services, such as GP visits; 3) Improved functions of ADL leads to a decrease in entry into nursing homes; 4) DBS patients have improved motor skills and thus a decrease in the need for allied health services, such as physiotherapy and speech therapy; 5) Improved motor skills may lead to a decline in adverse events, such as incidence of falls or pneumonia and the associated treatment costs, such as hospitalization and medication.

Due to a lack of data concerning indirect costs borne by this sample of PD patients, returning to full-time employment or household chores were not a clinical endpoint in this study, as a result, a societal perspective could not be adopted in this study. Indirect costs associated with DBS may be considerable. Spottke et al. [2002] reported that only one of their 16 patients was able to return to full-time employment. In the study by Moro et al. [1999], five home makers were reported to regain the ability to look after their families.

Although DBS is non-ablative and is minimally invasive, the procedure may give rise to complications and side effects, some of which are neither reversible nor adaptable. The complications from DBS can arise before surgery, during surgery and in the immediate post-operative period, and after surgery. It has been reported that haematomas typically occur during surgery and range from 2.1% to 12% [Anderson et al., 2005; Herzog et al., 2005; Loher et al., 2002]. While none of the three patients with moderate PD were left with significant cognitive
squeal, such as long-term disability necessitating supervised care or death, they did suffer post-operation hematomas. The event led to an increase in treatment costs, diminished QoL and effectiveness of DBS therapy were observed. Overall, as a treatment for PD patients, DBS was demonstrated to be a safe procedure. Complications arising from surgery were more likely to be hardware-related rather than neurologic.

The results from the net monetary benefit analyses demonstrated that compared to no DBS surgery, the greatest net monetary benefits (health + costs) accrued to Ontario’s Ministry of Health and Long Term Care were from treatment towards PD patients with mild severity, followed by those with moderate than severe PD. These results, and those recently published by Deuschl et al. [2013], strongly suggested that DBS of the STN at an early stage of PD, before the emergence of debilitating motor function, may be more responsive and effective in patients in ameliorating motor complications than at an advanced stage of the disease.

Because of the uncertainty of data used in the model, possible variability in the outcomes using sensitivity analyses were explored in the three PD subgroups. Results from the one-way sensitivity analyses indicated that in each subgroup, cost savings were most sensitive to the cost of a permanent complication. In the mild PD subgroup, the cost savings per QALY gained were sensitive to the cost of a temporary complication and the cost of a permanent complication. In the moderate and severe subgroups, the cost savings per QALY gained were most influenced by the costs of permanent complications and less so by the costs of temporary complications. In the PSA, the findings from the cost-effectiveness acceptability curves revealed that when changes were made in the effects (QALYs) and costs (with or without complications), in the mild and moderate PD subgroups, the probability that DBS was more costly and more effective and less costly and more effective compared to no DBS were approximately 63.0% and 62.2%. The probability that the intervention was less costly and more effective and less costly and less effective in the severe subgroup was 68.2%.
6 Limitations

Acknowledging the limitations of the data as well as the limitations of retrospective studies, this work provided preliminary approximation of the cost-effectiveness/utility and net monetary benefits of DBS surgery for patients with varying degrees of PD severity (mild, moderate and severe). It must be noted that a full economic evaluation would routinely involve the comparison of two or more treatment options. Due to limited data, the results from this study were obtained without a treatment group and based on the assumptions made regarding the standard treatment (i.e. best medical therapy). This study could therefore only be considered a provisional study of health care costs and that direct assessments with the ICERs from other various studies on PD and DBS should not be made. Regarding the standard treatment, it seemed reasonable to assume that the pre-surgical health of patients with PD who underwent DBS would be identical as their health would be in the same time frame post-surgery had they not undergone DBS.

This analysis was limited in several ways. First, the QoL/utility evidence in relation to DBS effectiveness was lacking. Consequently, sensitivity analyses of this parameter were not possible. While the PDQ-39 is a PD specific QoL instrument and is intended to assess more areas of a patient’s subjective well-being than are assessed by clinical scales, like most disease-specific scales, the PDQ-39 cannot be used in a CUA. This is because the instrument does not measure QoL on the 0 (death) to 1 (perfect health) scale necessary to construct QALYs [Blumenschein & Johannesson, 1996]. Owing to the scarcity and difficulty in accessing data, utility data was estimated from an algorithm that enabled conversion of PDQ-8 scores into EQ-5D scores [Cheung et al., 2008]. While the algorithm was constructed from a Singaporean population, there did not appear to be race-related differences amongst PD patients [MSAC assessment report, 2008]. Of interest was the correlation between the estimated EQ-5D scores and the HY scores. In each PD subgroup, the change in the pre- and post-surgery EQ-5D scores did not correlate with those from the HY scores. PD patients in the severe subgroup showed the least improvement in the EQ-5D scores but the greatest improvement in the modified HY scores. The opposing trend also followed in the mild and moderate PD subgroups. A likely explanation may be that conversion could not fully capture the most important aspects of PD that affected
these patients, and that the conversion may have missed certain attributes that were more important to some PD patients than others. The QoL is also a difficult construct to apply broadly. While the efficacy of DBS from this population represented very good surgical candidates, and thus suggested better outcomes, the efficacy may not have fully reflected real-world effectiveness in more heterogeneous populations.

A second limitation was that long-term DBS effectiveness data were absent altogether. The one year time horizon over which this analysis was evaluated, was insufficient to allow quantification of longer-term gains if the improvements in patients’ ADL and control of their motor symptoms last beyond five years, when re-tuning and battery replacement of the system that contribute a large proportion of the total costs of DBS typically takes place. Battery replacement was excluded in this study because it is usually not required in the first year of surgery. Other longer-term gains likely to result from DBS include a reduction in falls - a common problem for patients with PD [Guttman et al., 2003; Wielinski et al., 2005; Woodford and Walker, 2005] - and decreased impairments in ADL as a result of improved controlled of motor symptoms.

Third, this analysis held current costs constant over time and were not inflated for future years. This may have possibly underestimated the average costs for each disease subgroup and overestimated the final ICERS.

Fourth, the method examined in the study was only STN stimulation targets. As Lang [2000] pointed out, the efficacy and varied doses of anti-PD medication may be key differences depending on whether STN or GPi are the stimulation targets. The base case values in this study were derived from exploring STN only. To the extent that costs and efficacy differ between the two techniques, so too may the outcomes when examining at GPi. For instance, if GPi were analyzed, the benefits of less medication may be larger for patients in each subgroup. Substantive differences in the ICERs from each patient subgroup could also occur if the DBS procedure was GPi- or Vim-targeted.

Related to this was the exaggerated portrayal of temporary and permanent complications. While not all clinical scenarios were accounted for, it did present adequate information to characterize base case that, until extraordinarily high rates of severe morbidity or mortality were accomplished, DBS remained effective.
The sixth limitation was the small number of PD patients included in the analysis, in particular from the mild and severe subgroups. This limitation resulted in an inability of significant relationships formed between the pre- and post-surgery costs and utilities, as judged by p-values greater than 0.05. Only after more patients undergo DBS and monitoring has taken place over a longer period will long-term meaningful and reasonable prospective data be available.

Rather than excluding all the variables that contained missing data, the approach taken to address the issue was to apply the method of last-observation-carried-forward (LOCF). By omitting variables with missing values, there is a potential that if the variables with missing values differed systematically from the completely observed cases, a bias in the complete-case analysis may occur. In LOCF, the last measurement point or observation is frozen, thereby stopping decline in outcome measures. Several researchers have disapproved of the application of LOCF in dementia research [Aisen et al., 2000; Hills et al., 2002; Aisen et al., 2003; Lanctôt et al., 2003; Kaduszkiewicz et al., 2005; Bullock et al., 2005; Hogan et al., 2006]. Since disease progression is a crucial element of dementia, halting progression after the last point is thought to be clearly violated. LOCF excludes whether the patient’s condition improves or declines at the last measurement point but instead freezes outcomes at the value observed before the last observation, thereby stopping decline in outcome measures and synthetically stabilizing disease in dropouts [Streiner et al. 2002]. Factors such as disease severity, symptoms, group assignment or drug side effects [Mallinckrodt et al., 2001; 2003; Gadbury et al., 2003; Unnebrink & Windeler, 2010] that influence patients’ responses are not entirely captured in LOCF. However, despite its inappropriate use in drug trials in dementia and PD research, the technique is most commonly used and it is still the main form of intention-to-treat analyses in trials of dementia and PD drugs [Emre et al. 2010; Powe et al. 2011].

Another limitation of the results was the assumption made in the frequency of patients’ purchases of medication, which may have given rise to inaccurate estimates of the total costs of medicine, due to the inclusion of dispensing fees. However, given that the dispensing fee is not costly, it was unlikely that the assumption could have severely impacted the total costs of medication in patients across each PD subgroup.
Finally, confounding factors such as age, family income and social support and the impact of these factors on the effect of DBS and QoL in patients were not considered. As noted before, QoL data in PD are sparse and typically rarely captured in a randomized fashion. It may therefore be necessary to perform separate analyses for selected strata of patients with PD based on income or degree of social status. The incremental improvement in QoL could be different across disease subgroups when examined independently by these factors.
7 Policy Implications Regarding Deep Brain Stimulation as a Treatment Strategy in Parkinson’s Disease

The findings from this study revealed that overall; DBS appeared very favorable and could be interpreted by policy-makers as paramount evidence to strongly endorse the decision to further support the technology in PD patients. However, the findings from this study also posed a series of ethical questions inherent in neurological intervention. The following section provides a discussion on several ethical challenges concerning DBS technology as a treatment method in PD. Recommendations to changes in policy guidelines associated with these concerns have been put forward.

7.1 Policy Changes Concerning Deep Brain Stimulation Committee and Candidacy

The DBS committee typically includes neurologists, neurosurgeons, and nurses/physician assistants. Many committees also include a neuropsychologist or psychiatrist in the evaluation procedure and in team discussions. Regarding selection of potential candidates for surgery, a consensus is usually reached among the committee members. Although all committee members can express their opinions equally, there are different roles and levels of responsibility. If the surgeon believes that DBS surgery should not be performed, the committee cannot (and should not) force the surgeon to perform the operation. In a situation where there is a lack of consensus among the committee and the surgeon believes the surgery is ethically admissible, the surgeon and movement disorder neurologists have the strongest opinions. However, in a case where consensus cannot be reached, the final choice as to whether or not to proceed with surgery rests with the surgeon, as the surgeon is the team member who is chiefly responsible for the patient’s care during surgery. It is important to therefore consider guidelines that can improve clinical decision-making process amongst the committee regarding patient selection for DBS surgery. One option is to implement a ‘shared’ decision-making process, whereby effective communication by committee members of the essential elements, the risks and benefits and the use or not of DBS for the patient is encouraged.
Another challenge faced by the committee is whether the implantation of the DBS electrode(s) will add to greater disability than that apparent prior to surgery. This is particularly relevant in the borderline cases in which there are major concerns regarding pre-operative cognitive function or neuropsychiatric status but the concerns are not great enough to be complete contraindications to surgery. While the committee works under a patient-centered model, there are limits as to the types of risks/harms which the committee are prepared to place the patient. Patients cannot demand to receive DBS surgery from a physician if the physician believes the risks outweigh the benefits. Finding this boundary is very tedious in patients with advanced PD who have consumed almost all treatment modalities and are desperate for a final treatment attempt. Adding to this difficulty, there is a scarcity in the literature regarding whether these patients will inevitably have greater neuropsychiatric difficulties after surgery. Consequently, to prevent patients from this subgroup from unnecessary future health risks, it is essential to have policy guidelines in place so to ensure these patients are protected. Examples may include further evaluations and examinations, close and frequent monitoring of the patient.

Unique to functional neurosurgery teams, is the reliance on neuroimaging technologies in guiding clinical decision-making. Policy guidelines are required to address the thorny ethical issues inherent in the interpretation of neuroimaging [Simon et al., 1999; Illes et al., 2005; Ford et al., 2005]. From a scientific angle, the complexity of neuroscience research creates challenges for integration of knowledge and proper interpretation of findings. As such, there is the difficulty of interpreting neuroimaging results versus the interpreter’s own knowledge.

Additionally, from the social and cultural perspectives, interpretations of imaging data can be influenced by both cultural and anthropological elements. The introduction of new concepts of self in neuroimaging results highlights the interaction of interpretation levels. With the existence of so many ideas and self-interpretation of results, it is important to establish policy guidelines that can foster discussions among neuroscientists whose methods may vary and interpretations of results differ. These discussions may extend to encompass researchers in the humanities area regarding theories such as morality, moral judgments and moral emotions - theories that require important assessment before one can critically investigate the results. Open dialogue with the public can also be encouraged, which is equally as essential given that various cultural and religious viewpoints subject findings to various interpretations and ethical boundaries. Reliable
dissemination of information through the media and public education are also fundamental in narrowing the gap between scientists and concerned individuals, in particular if the complexity and abstractness of results escalate. Interpretation requires imagination and knowledge of scientific and cultural deductions. Hence, policy guidelines committed to openly examining the epistemological confines of imagery [Racine & Illes, 2004], interdisciplinary assessments, and public perspectives on these issues are required.

Ethical interpretation of neuroimaging findings may also necessitate traditional bioethical input. As such, it is important to establish policy guidelines that encourage bioethicists and neuroscientists to work together. Bioethicists can bring ethical knowledge to the discussion, identify and clarify moral issues that neuroscientists may be unable to do so. Bioethicists can function as facilitators in situations when various interpretations of results occur, as they can contribute to a greater understanding of the issues. Bioethicists and neuroscientists may be well served by working in conjunction to comprehend the effect of the neuroimaging and the effect it can have on individuals and collectively on society.

7.2 Policy Changes Concerning Patients with Parkinson’s Disease who Undergo Deep Brain Stimulation

At the end stage of PD, patients have already undergone a change in their self-identities due to the tremendous unpredictability in their motor symptoms that changes both their ability to interact with the world around them and their dependence on others for basic care. Despite these inevitable changes, DBS has the potential to alter the brain itself that results in a more fundamental change in the self and being. These changes may consist of risks to memory, executive function, language, or personality variables. For more vulnerable patients, there are concerns that they might be more susceptible to neurocognitive or neuropsychiatric risks. These patients may be asked to weigh the likelihood of an improvement in physical function versus possible risks to cognition. Most patients indicate that they would give almost anything to gain physical improvement. The physical symptoms may be so debilitating that the patient may not be capable of fully appreciate the possible cognitive and neuropsychiatric consequences of the decision. The presence of cognitive deficits, including inadequate insight, can further add to the
complexity of the problem. To clearly identify the values and preferences of patients, there needs to be established guidelines by policy makers that can help to improve patients’ decision-making process. To include and consider the opinions of patients in the decision-making procedure, one option is to encourage active participation of patients. For patients with cognitive deficits, visual decision support tools that promote decision-making may be used to help them clarify their values and preferences about the benefits and risks associated with having surgery or not.

The actual DBS procedure presents challenges regarding peri-operative (pre-; intra-; post-operative) management. For example, many functional neurosurgeons prefer to have the patient awake during the surgical procedure. The patient’s co-operation during surgery enables the surgeon to complete mapping studies such that the surgery is individually designed to deliver maximum benefits with minimal side-effects. However, neurosurgical procedures on patients who are awake can provide intrinsic challenges to the surgical team as patients with psychiatric disorders might have severe difficulties obeying with instructions or the demands of surgery and may even retract consent intra-operatively. This necessitates guidelines from policy makers to establish tighter rules of the neurosurgical procedure. One option may be to strengthen the exclusion criteria for patients who undergo DBS by completely eliminating the option of surgery for those with intermediate to high levels of psychiatric disorders, anxiety and/or cognitive deficits. In clinical studies, the exclusion criteria must be well-founded in evidence. In the absence of good-quality evidence, then best scientific and intellectual reasoning should apply. The criteria need to be applied consistently and uniformly to similar patients independent of confounding factors such as social, financial or cultural status. Another option is to develop a standardized protocol or quality-control of the provision of the intervention so that best practices can be achieved.

Functional neurosurgical patients can also present unique management problems post-surgery. Titrating stimulation settings and medications in patients with ongoing neurodegenerative disorders with possible severe neuropsychiatric symptoms can be tedious and a committed multidisciplinary team is pertinent. Further, as an increasing number of centers begin to offer DBS surgery to patients, other ethical challenges may arise. One example is the issue of human resources. Consequently, policy changes regarding expansion of DBS in non-specialized
settings must be addressed. One option is to increase the supply of physicians, who are sufficiently trained in DBS, to perform the surgery. In addition, policy changes concerning the commitment of centers to care for patients after surgery must also be considered. Given the expertise required to program and manage these patients, it is not appropriate to assume that local community physicians can, or should, manage their care. Furthermore, many local physicians may be uncomfortable taking on managing patients with implantable brain devices and insist that the patients be followed for most of their health care requirements by the surgery team. If a patient does not have the means for appropriate follow-up, a surgical center could place the patient at surgical risks for little or no benefit. Accordingly, there must be policy guidelines in place to ensure that there is the commitment and availability of long-term care for patients who require such care after DBS, and that these should be made explicit prior to posing the intervention. DBS surgery may successfully improve the patient’s motor function such that the patient is much more mobile. Unfortunately, the combination of impulsivity and greater mobility contribute to increased risks for falls and injuries. This highlights the continual issues through the course of a patient’s life with respect to the stimulator. When the stimulation causes social harm or inducing a mood in which patients may not appreciate the harms they are doing to themselves, it is the team’s responsibility and obligation to the patients and family members to reduce the stimulation. However, to reduce the motor benefits by decreasing the stimulation in order to shield the patients or their relatives from imminent injury can be viewed as unethical. The situation becomes more difficult if the patient refuses and does not provide consent to allow the stimulation to be reduced. In the situations as described, it is important to have policy guidelines to safeguard a patient’s judgment of values, so that the autonomy of the patient is protected. A true respect for patient autonomy is a respect for constant expression of values and goals. However, expressions of values become particularly problematic when a patient’s thinking or mood alters as a result of DBS. This confounds the determination after surgery as to what degree surgery is subverting the patient’s capacity to judge his or her best interests. Accordingly, it is important that there are policy guidelines that enable therapeutic privilege to be invoked in order to alter stimulation settings without consent. This should of course be exercised infrequently and with a tremendous amount of forethought by the committee. Finally, the device is not self-sustaining and future surgeries to replace worn out generators are required.
This calls for guidelines for potentially declining the request to replace the generator because of dangerous patient behavior.

7.3 Policy Changes to Family/Caregivers of Patients with Parkinson’s Disease who Undergo Deep Brain Stimulation

In addition to the impact DBS surgery has on patients, it is also important to recognize that families and caregivers are also at stake personally. The surgery may not only provide the patient the ability to function volitionally, but also release caregivers from assisting the patient with basic activities of daily living throughout the day. There are cases where family members may specifically wish that DBS can bring upon a reduced caregiver burden. This wish might skew the caregiver’s guidance toward influencing the patient to accept greater risks for the caregiver’s interest. Contrariwise, if the surgery places a risk of exacerbating executive dysfunction or if the family member enjoys the caregiver role, the individual may have great interest in dissuading the patient from undergoing the surgery because of the burden it may place on the family and/or the caregiver’s identity. In view of these potential situations, investments should be made in caregivers of PD by the government. Currently, there is no policy that provides the support needed by informal caregivers and the recipients of care with PD. With the number of hours they provide in caregiving, and the potential costs they save society and the health care system, policies and program plans must be in place to ensure that caregivers are given the support they need. To promote caregiver support, several changes can be made by policy makers. One option is to encourage tax credits and tax breaks to alleviate the financial burden of caregivers, particularly as many of them have either to leave their employment to become full-time caregivers or return to work to supplement their income. This option can also help to avoid the number of persons living in circumstances of neglect and abandonment as families or friends chose not to assume informal caregiving responsibilities. Further, carrying the economic burden of informal caregiver employees should not be left to private workplace policy because inequalities can be created, especially for those in low-paying high labor force supply positions, or uneven competitive disadvantage for employers in the marketplace [MOHLTC, 2009]. Another option is to increase access to information, education, training, support programs and
services for caregivers. If the quality of information available is improved and carers are aware of how to access the full range of resources in the community, more effective ways in managing patients can be promoted and the quality of life for patients and caregivers alike are improved. In addition, caregivers can set realistic expectations and be more understanding toward the care recipient [Shim, 2011]. Approaches to address these needs for health care providers and the larger public community could include an awareness of the care recipient’s and caregiver’s needs during the visit and maintenance of open communication, the provision of healthcare and possibly newer online provider–patient–caregiver communication models [Washington et al, 2011; Shim, 2011]. The need for general information about the care recipient’s disease and illness may be addressed through the provision of general information in either printed form or online [Washington et al, 2011; Shim, 2011]. Concerning discussions around the rate of deterioration, one must speak truth to caregivers, so that caregivers do not create expectations that cannot be met. Nurses and social workers can help in this regard. Practitioners can provide information and counseling to patients and kin concerning the social, psychological and interactional aspects of chronic illness [Berry and Murphy, 1995]. Education can teach nurses and carers the importance of the caregiver’s attitude toward the care recipient which in turn could increase their awareness of the importance of identifying difficulties in caregiver–care recipient relationships. Not only will this build empathy toward patients, but can also improve the job satisfaction of caring [Shim, 2011]. Positive relationship strategies can also promote strong relationship between carers and their patients. A combined program of empathy building and positive relationship strategy training could thus be applied to informal caregivers. Another strategy can also include the use of a health care team in which some members of the team have specific duties to optimize patient and caregiver education and communication in a proactive manner.

### 7.4 Policy Changes to Healthcare Providers to Patients with Parkinson’s Disease who Undergo Deep Brain Stimulation

One major ethical challenge for health care workers caring for functional neurosurgery patients is the importance of balancing their roles as health care providers versus their roles as
researchers. Functional neurosurgery patients present distinctive opportunities to acquire further understanding of the brain. Ethical conflicts can arise between health care providers’ wish to further discover the bounds of a technology and better comprehend the brain functions all the while safeguarding patient protection. Innovative patient care and technologies intrinsically involve risks as outcome data are not always obtainable. Health care providers are not always mindful of their own intellectual desires, values and how they might persuade clinical decision-making. Consequently, it is important to implement policy strategies to ensure the line between innovative clinical care and research are not crossed. One option is to impose guidelines for researchers to be forthright and candid with their new clinical care and research ideas.

Another ethical element to be added is the potential secondary gains of institutions from DBS. It is therefore most imperative that policy guidelines are in place to ensure the necessary and vital associations between for-profit device and instrumentation companies and healthcare providers are both transparent and structured in a manner to decrease the temptation to subvert the scientific endeavors. Surgeons and researchers depend on the trust of patients and society to perform good-quality work. One way of doing this is to create guidelines that can enforce up-front collaborations to include a multidisciplinary set of professionals’ opinions in patient and surgical candidate selection and to establish a concerted affiliation with the hospital ethics committee or review board.

### 7.5 Is Deep Brain Stimulation Technology in the Treatment of Parkinson’s Disease a Good Thing or a Bad Thing?

Further to the aforementioned ethical challenges associated with DBS as a treatment method for patients with Parkinson’s Disease, there is an overwhelming amount of evidence regarding the contribution of novel technologies; not simply to absolute health care costs in any given fiscal year, but to its hyperinflationary growth trajectories. Annual expenditures on health technologies, such as those of DBS, have demonstrated to surpass inflation by 2–3 percentage points [Newhouse, 1992]. In the United States, it has been argued that technological change attributed to greater than 50%, and potentially as much as three-quarters, of the total escalated health expenditures in the previous half century [Newhouse 1992]. The Congressional Budget
Office in 2008 similarly concluded that approximately half of the increase in health care expenditures was due to novel health technologies, including those of DBS [CBO, 2008]. As also observed by Cutler and McClellan [2001], technological change accounted for the bulk of medical care cost increases over time [p. 11; see also McGuire and Serra-Sestre 2009].

Where health care costs typically increase at hyperinflationary rates, there is also an entire range of services that have very little association with any particular technology that may unexpectedly become unaffordable for the most disadvantaged individuals of society. The hospital that spends millions of dollars in acquiring several novel imaging devices may need to upsurge prices on several of its non-imaging-related products and services, the impacts of which will be unduly borne by those already unable to afford health care services. Even improving financial access to the imaging devices may not have a substantial effect on the total increase in health care expenditures driven by such novel technologies. To the degree society agrees that obligations to social justice demand that the needs of the most disadvantaged be given relative priority in public health policy [Daniels, 2008; Powers and Faden, 2006], the implementation of novel technologies may exist in tension with such obligations even further than questions of access to the actual technology itself. As applied to DBS in Ontario, even if the province does not require payment from patients who undergo the surgical procedure, there lies the concern of reimbursement capacity, which in the long term, may be insufficient to meet the demands of the escalating number of users of this technology. For these reasons, the concern of DBS as a treatment method for patients with PD goes well beyond the issue of affordability.

While DBS may very well improve the overall health of patients with PD, there is the concern that DBS may expand health inequalities [Capewell and Graham 2010; Glied and Lleras-Muney, 2008]. To the extent possible, it is paramount that individuals who suffer most have access to therapies to alleviate that suffering. The simplest barrier is often a lack of finance. Interventions that require novel technologies have been demonstrated to unfairly help those with the most resources available to them [Capewell and Graham, 2010]. Social disadvantages tend to cluster, which suggests that those most deprived - who are often at the greatest risk of developing sickness - are victims to social stigma and harmful economic circumstances that conglomerate to diminish their prospects of acquiring the benefits of the interventions [Capewell and Graham, 2010; Graham, 2004; Wolff, 2009].
In the case of DBS in Ontario, the argument is that evaluations of costs and benefits from a micro-level may be insufficient without a simultaneous population-level assessment. On a micro-level, it is certainly relevant and possible that hospitals can attain economies of scale by performing larger volumes of DBS procedures [Eskandar et al., 2003], and that DBS technology maybe a cost-effective intervention for persons with PD [Bell, Mathieu, and Racine, 2009]. However, from a population-level perspective, the implementation of DBS could well make other kinds of care needed by the relevant patient population difficult to obtain. Given that there is a limited supply of physicians who are sufficiently trained to perform DBS surgeries in Ontario, only those possessing financial and geographic resources sufficient to locate and secure the services of an appropriately trained provider may be able to access the intervention. While the long-term effects of DBS technologies on the health of the relevant patient populations have been very promising, the evidence related to technology and inequalities DBS could possibly widen general health inequalities [Benach et al., 2011]. From a social justice perspective, inequalities are of deepest ethical concern when they “contribute to systematic patterns of disadvantage” [Powers and Faden, 2006]. Consequently, the extent to which DBS may actually expand inequalities between the affluent and already disadvantaged and vulnerable groups may be an important ethical issue.

Another very real ethical question in terms of public health policy concerns the relative priority of DBS as a treatment strategy to patients with PD based on their disease severity. It is difficult to decide whether priority of DBS should be allocated to individuals whose suffering and failure to function in everyday life is most marked, or be given to patients who can receive the greatest beneficial effects. In this study, given that the greatest net monetary benefits accrued to the Ministry of Health was from treating patients with mild PD severity, this would rank them a higher priority for DBS surgery, followed by patients with moderate and severe PD. These findings may have several implications for the management of patients with PD, the health care environment that provides medical and supportive care to patients with PD, as well as to their families and to society in general. It is very possible that greater efforts and resources may be shifted away from PD patients with moderate/advanced severity and directed towards those with mild severity. Not only will this lead to an increase in caregiver burden to patients in these subpopulations but will further the decline of their health states. There will also be the issue of
health inequalities and the potential of this having a spill-over effect into other dimensions of their quality-of-life and well-being.

In spite of these possible implications, the idea that DBS treatment should be given priority to PD patients with mild severity over those with moderate/severe PD is in agreement with the current adopted view of the international criteria, which limits the proportion of patients with late-stage PD to undergo DBS. While neurostimulation of the STN is recommended for the management of motor fluctuations and dyskinesias in patients with advanced PD and severe motor complications [Pahwa et al., 2006; Fox et al., 2011], for many of these patients, amelioration of motor complications may be too late - the onset of symptoms, such as cognitive impairment, that are unresponsive to treatment offsets the benefit of improved motor function. Further, patients with advanced PD typically require heavier levels of care, are overall more disabled, are expected to deteriorate at a greater rate and are less capable in pursuing or continuing a normal life. Given that motor improvement has been shown to sustain for as long as 10 years in a small number of selected patients [Castrioto et al., 2011], this would also argue in favor of using DBS in carefully chosen, young patients with a recent onset of motor fluctuations. Treatment at the earlier stages of PD can also decrease the rate of disease progression, which can lead to downstream cost-savings by reducing the social and economic impacts of the disease. Further, early treatment may be more effective in reducing distress for the individual as well as their family/carers. Reasoning that earlier intervention with DBS might deliver an improved motor benefit before disability from other symptoms was recently demonstrated by Deuschl and colleagues [Schuepbach et al., 2006; 2013; Tanner 2013]. Schuepbach and colleagues evaluated neurostimulation combined with best available medical treatment in patients with PD and early motor complications. In this 2-year trial, 251 patients with PD and early motor complications (mean age, 52 years; mean duration of disease, 7.5 years) were randomly assigned to undergo DBS plus medical treatment or medical treatment alone. Improvement in patients was assessed with PDQ-39 as well as patient diaries. The patient-determined outcomes revealed improved function during times of poor mobility as well as longer periods of good mobility, and arguably presented the most important assessment of the clinical value of the technology. As assessed by the UPDRS, motor function was also revealed to benefit from DBS in this group of patients. The authors concluded that DBS was superior to medical
treatment alone at a relatively early stage of PD, before the appearance of severe disabling motor complications. DBS surgery may thus be a therapeutic option for patients at an earlier stage than present recommendations suggest [Horstink et al., 2006; Fox et al., 2011]. In view of these findings, with DBS intervention given priority to PD patients with mild disease severity, the clinical benefits and cost savings may be larger in the long-term.
While severity at the ‘off’ state was chosen as the primary objective for the analysis, some might argue that frequency of time spent in the ‘on’ state is more important. There are many costs and effectiveness studies of drug treatment or surgery in PD that have measured progression by the number of ‘on’ times per day [Nuijten et al., 2003; 2004; Hudry et al., 2006; Hjelmgren et al., 2006; Espay et al., 2010;] or the use of HY scale [Smala et al., 2003; Lindgren et al., 2003; Findley et al., 2005]. Adverse events such as motor complications have also been considered [Lindgren et al., 2003; Smala et al., 2003; Haycox et al., 2009]. Thus, an extension of the current analysis can include differentiation of patients’ disease progression into ‘on’ and ‘off’ stages. It may also be worthwhile to explore various methods in examining disease progression to improve assignment of patients into various PD subgroups. Examples may include differentiating patients on the basis of their responses to medication, their predictable wearing-off periods, or their on-off fluctuations. Other options may include basing it on the frequency and degree of dyskinesias or possible yo-yo responses to treatment by the patient.

While costs can be evaluated from different perspectives (healthcare provider/third-party payer/societal), it has been proposed that, depending on the research question, costs should be evaluated and reported from the societal as well as the chosen perspective [Gold et al., 1996]. In this study, due to a lack of data on indirect costs stemmed from lost productivity for patients and caregivers, a societal perspective could not be adopted. Consequently, to improve comparability of results, future work can include tracking and collecting indirect cost and effect data so that a societal viewpoint is possible.

Motor complications such as dyskinesias and motor fluctuations particularly affect HR-QoL and PD-related treatment costs [Winter et al., 2011]. Most of the published PD and DBS studies included motor complications to varying degrees, and many of the studies focused primarily on motor symptoms and motor disability. Only one study [ven den Hout and Matthews, 2009] has considered the impact of non-motor symptoms, such as dementia, on cost-effectiveness. The current analysis included only motor symptoms and excluded non-motor symptoms including behaviour and psychological symptoms, as well as other co-morbidities such as gastrointestinal symptoms or sleep disorders. Given that non-motor symptoms and co-morbidities also
contribute to the economic burden and the HR-QoL of patients with PD, it may be worthwhile to also include these aspects in future analyses too.

To enable quantification of longer-term gains including those concerning patients’ improvements in QoL, ADL and motor symptoms, as well as reductions in the intake of anti-PD medications, a longer time horizon of the analysis may be adopted. The results from Piboolnurak et al. [2007] and Castrioto et al. [2011] demonstrated that improvements of motor outcomes and reductions in medications in PD patients as a result of DBS may be sustainable for 5 to 10 years. On the basis of these findings, it may be worthwhile to extend the time horizon of the current study to 10 years. In doing so, the costs of battery replacement, which typically occurs every 5 years, can also be captured.

The disutilities and utilities of DBS over the long-term were unknown in this study. An extension of the work can include monitoring the clinical effects of DBS in PD patients over a longer period of time and capturing patient preferences directly with EQ5D, rather than obtaining values from conversion of PDQ8 scores to EQ5D. Another option is to employ another algorithm to for conversion of PDQ8/39 scores to EQ5D or other health utility indices (e.g. HUI).

Finally, alternative treatments of DBS of other targets, such as the globus pallidus could also be compared with neurostimulation of the subthalamic nucleus in a population with early motor complications. The costs, effects and benefit of pallidal stimulation may be similar to or less than the benefit of stimulation of the STN.

In summary, while there are several policy changes decision makers should focus on regarding DBS as a treatment strategy for patients with PD, the findings from this study, and those recently published by Deuschl et al. [2013], strongly suggested that DBS of the STN at an early stage of PD, before the emergence of debilitating motor function, may be more responsive and effective in patients in ameliorating motor complications than at an advanced stage of the disease. DBS surgery as a treatment method in PD enabled cost savings and QALY gains to patients with varying PD severity. The greatest net monetary benefits accrued to the Ministry of Health was from treating patients with mild PD severity. The findings provided important information for health policy decision-makers when determining the magnitude of resources to be allocated to
DBS as a treatment strategy in PD, in particular, those toward patients at an early stage rather than at the advanced stage of the disease.
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NICE Guide to the Methods of Health Technology Appraisal London NICE 2004


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http://www.health.gov.on.ca/english/providers/program/drugs/odbf_mn.html

Ontario Health Insurance (OIP) Schedule of Benefits:  
http://www.health.gov.on.ca/english/providers/program/ohip/sob/sob_mn.html


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Appendices
Appendix 1: The Unified Parkinson’s Disease Rating Scale (UPDRS)

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment
   0 = None.
   1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
   2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
   3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
   4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
   0 = None.
   1 = Vivid dreaming.
   2 = "Benign" hallucinations with insight retained.
   3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
   4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression
   0 = None.
   1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
   2 = Sustained depression (1 week or more).
   3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
   4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
   0 = Normal.
   1 = Less assertive than usual; more passive.
   2 = Loss of initiative or disinterest in elective (nonroutine) activities.
   3 = Loss of initiative or disinterest in day to day (routine) activities.
   4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech
   0 = Normal.
   1 = Mildly affected. No difficulty being understood.
   2 = Moderately affected. Sometimes asked to repeat statements.
   3 = Severely affected; not all words are legible.
   4 = Unintelligible most of the time.

6. Salivation
   0 = Normal.
   1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
   2 = Moderately excessive saliva; may have minimal drooling.
   3 = Marked excess of saliva with some drooling.
   4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
   0 = Normal.
   1 = Rare choking.
   2 = Occasional choking.
   3 = Requires soft food.
   4 = Requires NG tube or gastrostomy feeding.

8. Handwriting
   0 = Normal.
   1 = Slightly slow or small. all words are legible.
   2 = Moderately slow or small; all words are legible.
   3 = Severely affected; not all words are legible.
   4 = The majority of words are not legible.
9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have startlesation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity
(Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair
(Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

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28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (fastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?
0 = No
1 = Yes
37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?
(Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

V. MODIFIED HOEHN AND YAHRL STAGING

STAGE 0 = No signs of disease.
STAGE 1 = Unilateral disease.
STAGE 1.5 = Unilateral plus axial involvement.
STAGE 2 = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
STAGE 4 = Severe disability; still able to walk or stand unassisted.
STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50% = More dependent. Help with half, slower, etc. Difficulty with everything.
40% = Very dependent. Can assist with all chores, but few alone.
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10% = Totally dependent, helpless. Complete invalid.
0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.
## Appendix 2: The Modified Hoehn and Yahr Scale

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage 0</td>
<td>No signs of disease</td>
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<tr>
<td>Stage 1</td>
<td>Unilateral plus axial involvement</td>
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<tr>
<td>Stage 1.5</td>
<td>Bilateral disease, without impairment of balance</td>
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<tr>
<td>Stage 2</td>
<td>Mild bilateral disease, with recovery on pull test</td>
</tr>
<tr>
<td>Stage 2.5</td>
<td>Mild to moderate bilateral disease; some postural instability; physically independent</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Severe disability, still able to walk or stand unassisted</td>
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<tr>
<td>Stage 4</td>
<td>Wheelchair bound or bedridden unless aided</td>
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</table>
Appendix 3: Parkinson’s Disease Questionnaire-39

(Taken from PDQ-39 © Isis Innovation Limited, 1993).

**DUE TO HAVING PARKINSON’S DISEASE, how often have you experienced the following, during the last month?**

<table>
<thead>
<tr>
<th>Due to having Parkinson’s disease, how often during the last month have you ....</th>
<th>Never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always or cannot do at all</th>
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<tbody>
<tr>
<td>1. Had difficulty doing the leisure activities which you would like to do?</td>
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<td>2. Had difficulty looking after your home, e.g. DIY, housework, cooking?</td>
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<td>3. Had difficulty carrying bags of shopping?</td>
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<td>4. Had problems walking half a mile?</td>
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<td>5. Had problems walking 100 yards?</td>
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<td>6. Had problems getting around the house as easily as you would like?</td>
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<td>7. Had difficulty getting around in public?</td>
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<td>8. Needed someone else to accompany you when you went out?</td>
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<td>9. Felt frightened or worried about falling over in public?</td>
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</table>

Please check that you have ticked one box for each question before going on to the next page.
Due to having Parkinson’s disease, how often during the last month have you ....

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<tr>
<th></th>
<th>Never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Often</th>
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<td>Been confined to the house more than you would like?</td>
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<td>Had difficulty washing yourself?</td>
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<td>Had difficulty dressing yourself?</td>
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<td>Had problems doing up buttons or shoe laces?</td>
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<td>Had problems writing clearly?</td>
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<td>Had difficulty cutting up your food?</td>
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<td>Had difficulty holding a drink without spilling it?</td>
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<td></td>
<td>Felt depressed?</td>
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<td>18.</td>
<td></td>
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<tr>
<td></td>
<td>Felt isolated and lonely?</td>
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<tr>
<td>19.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Felt weepy or tearful?</td>
<td></td>
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</tr>
</tbody>
</table>

Please check that you have ticked one box for each question before going on to the next page.
Due to having Parkinson’s disease, how often during the last month have you ...

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Felt angry or bitter?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Felt anxious?</td>
<td></td>
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<tr>
<td>22. Felt worried about your future?</td>
<td></td>
<td></td>
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<tr>
<td>23. Felt you had to conceal your Parkinson’s from people?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>24. Avoided situations which involve eating or drinking in public?</td>
<td></td>
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<td></td>
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<tr>
<td>25. Felt embarrassed in public due to having Parkinson’s disease?</td>
<td></td>
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</tr>
<tr>
<td>26. Felt worried by other people’s reaction to you?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>27. Had problems with your close personal relationships?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>28. Lacked support in the ways you need from your spouse or partner?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If you do not have a spouse or partner, please tick here</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29. Lacked support in the ways you need from your family or close friends</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please check that you have ticked one box for each question before going on to the next page.
Due to having Parkinson’s disease, how often during the last month have you .... Please tick one box for each question

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>30. Unexpectedly fallen asleep during the day?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>31. Had problems with your concentration, e.g. when reading or watching TV?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>32. Felt your memory was bad?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>33. Had distressing dreams or hallucinations?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>34. Had difficulty with your speech?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>35. Felt unable to communicate with people properly?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>36. Felt ignored by people?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>37. Had painful muscle cramps or spasms?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>38. Had aches and pains in your joints or body?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>39. Felt unpleasantly hot or cold?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Please check that you have ticked one box for each question.
Appendix 4: Parkinson’s Disease Questionnaire-8

Taken from PDQ-8 © Isis Innovation Limited, 1993).

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Occasionally</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always or cannot do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Had difficulty getting around in public?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Had difficulty dressing yourself?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Felt depressed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Had problems with your close personal relationships?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Had problems with your concentration, e.g., when reading or watching TV?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Felt unable to communicate with people properly?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Had painful muscle cramps or spasms?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Felt embarrassed in public due to having Parkinson’s disease?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please check that you have answered all the questions

Thank you for completing the questionnaire
# Appendix 5: EQ-5D Item Algorithm Determining EQ-5D Functional Levels from PDQ-8

(Taken from Cheung et al., 2008).

<table>
<thead>
<tr>
<th>EQ-5D item</th>
<th>Algorithm determining EQ-5D functional levels from PDQ-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>“No problems” if PDQ-8 mobility = “never” or “occasionally”;</td>
</tr>
<tr>
<td></td>
<td>“Some problems” if PDQ-8 mobility = “sometimes” or “often”;</td>
</tr>
<tr>
<td></td>
<td>“Extreme problems” if PDQ-8 mobility = “always”</td>
</tr>
<tr>
<td>Self-care</td>
<td>“No problems” if PDQ-8 activities of daily living = “never” or “occasionally”;</td>
</tr>
<tr>
<td></td>
<td>“Some problems” if PDQ-8 activities of daily living = “sometimes” or “often”;</td>
</tr>
<tr>
<td></td>
<td>“Extreme problems” if PDQ-8 activities of daily living = “always”</td>
</tr>
<tr>
<td>Usual activities</td>
<td>“No problems” if all of PDQ-8 social support, cognition, communications, and stigma = “never” or “occasionally”;</td>
</tr>
<tr>
<td></td>
<td>“Extreme problems” if any of PDQ-8 social support, cognition, communications, and stigma = “always”;</td>
</tr>
<tr>
<td></td>
<td>“Some problems” if otherwise.</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>“No problems” if PDQ-8 bodily discomfort = “never” or “occasionally”;</td>
</tr>
<tr>
<td></td>
<td>“Some problems” if PDQ-8 bodily discomfort = “sometimes” or “often”;</td>
</tr>
<tr>
<td></td>
<td>“Extreme problems” if PDQ-8 bodily discomfort = “always”.</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>depression “No problems” if PDQ-8 emotional well-being = “never” or “occasionally”;</td>
</tr>
<tr>
<td></td>
<td>“Some problems” if PDQ-8 emotional well-being = “sometimes” or “often”;</td>
</tr>
<tr>
<td>“Extreme problems” if PDQ-8 emotional well-being = “always”.</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 6: Regression of the EQ-5D Utility Index Upon PDQ-8 Scores by the Ordinary Least Squares (OLS).

(Taken from Cheung et al., 2008).

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Getting around&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.052</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. Dressing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.034</td>
<td>0.001</td>
</tr>
<tr>
<td>3. Felt depressed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.031</td>
<td>0.002</td>
</tr>
<tr>
<td>3. Felt depressed (binary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Problems with concentration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.030</td>
<td>0.004</td>
</tr>
<tr>
<td>7. Painful cramps or spasms&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.030</td>
<td>0.004</td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.135</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-square</td>
<td>52.1%</td>
<td></td>
</tr>
<tr>
<td>Mean absolute deviation</td>
<td>0.085</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The complete questions for items 1, 2, 3, 5 and 7 are “Had difficulty getting around in public?”, “Had difficulty dressing yourself?”, “Felt depressed?”, “Had problems with concentration?”, and “Had painful muscle cramps and spasms?”, respectively. The answers “never”, “occasionally”, “sometimes”, “often”, and “always” are coded as 0, 1, 2, 3 and 4, respectively.

<sup>b</sup> The answer “never” is coded as 0; all other answers are coded as 1.