EFFECTIVENESS OF DEEP BRAIN STIMULATION (DBS) SURGERY AND ITS CLINICAL OUTCOMES AMONG PARKINSON DISEASE PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

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LIST OF ABBREVIATIONS

PD	Parkinson Disease
IPD	Idiopathic Parkinson Disease
DBS	Deep Brain Stimulation
UPDPRS	Unified Parkinson Disease Rating Scale
ADL	Activities of Daily Living
HUSM	Hospital Universiti Sains Malaysia
QoL	Quality of Life
VIM	Ventral Intermedius Nucleus
GPi	Globus Pallidus
STN	Subthalamic Nucleus

ABSTRAK

Tajuk: Keberkesanan pembedahan rangsangan otak dalam (DBS) dan hasil klinikal di kalangan pesakit parkinson (PD) di Hospital Universiti Sains Malaysia(HUSM)

Latar belakang: Rangsangan otak dalam (DBS) telah membuktikan dirinya sebagai pilihan rawatan yang berdaya maju untuk individu dengan Penyakit Parkinson (PD) yang mempamerkan turun naik motor yang mengganggu dan dyskinesias yang tahan terhadap rawatan farmakologi standard. Pada masa ini, hanya maklumat yang terhad mengenai keberkesanan dan keselamatan DBS untuk rawatan individu dengan PD yang terdapat di Malaysia. Oleh itu, kami berusaha untuk menilai keberkesanan dan komplikasi pasca-DBS di hospital kami, Hospital Universiti Sains Malaysia (HUSM).

Metodologi: Kami menggunakan reka bentuk kohort retrospektif dan kami mengumpulkan data sekunder mengenai pesakit penyakit Parkinson yang menjalani pembedahan (DBS) di hospital kami dari tahun 2008 hingga 2021. Kami menilai keberkesanan DBS pada enam dan dua belas bulan selepas pembedahan menggunakan skor UPDRS III dan Aktiviti Kehidupan Harian (ADL). Objektif kami ditentukan menggunakan ujian Wilcoxon dan Ujian McNemar.
Keputusan: Kajian ini melibatkan seramai 15 peserta. Pada enam bulan, sama ada dengan atau tanpa ubat, rawatan DBS mengakibatkan penurunan statistik yang ketara dalam skor UPDRS III. Walau bagaimanapun, tiada perubahan ketara dilihat dalam tempoh susulan 6 hingga 12 bulan. Selain itu, kami mendapati perbezaan yang signifikan secara statistik dalam peratusan ADL yang dilakukan tanpa DBS pos ubat. Sementara itu, tiada pesakit kami yang mengalami pendarahan serebrum selepas DBS, walaupun tiga memperoleh jangkitan selepas pembedahan.

Kesimpulan: Di Malaysia, DBS telah terbukti sebagai terapi jangka pendek yang selamat dan berkesan untuk orang dengan penyakit Parkinson. Penyelidikan tambahan diperlukan untuk menunjukkan bahawa DBS awal mengurangkan keperluan dan kerumitan ubat PD sambil memberikan peningkatan motor jangka panjang berbanding dengan rawatan perubatan biasa.

Kata Kunci: Penyakit Parkinson, Rangsangan Otak Dalam

ABSTRACT

Title : Effectiveness of deep brain stimulation (DBS) surgery and its clinical outcomes among Parkinson Disease patients in Hospital Universiti Sains Malaysia (HUSM)

Background: Deep brain stimulation (DBS) has proven itself as a viable treatment option for individuals with Parkinson Disease (PD) who exhibit bothersome motor fluctuations and dyskinesias that are resistant to standard pharmacological treatments. At present, only a limited amount of information on the efficacy and safety of DBS for the treatment of individuals with PD is available in Malaysia. As such, we sought to evaluate its efficacy and post-DBS complications at our hospital, Hospital Universiti Sains Malaysia (HUSM).

Methodology: We used a retrospective cohort design and we gathered secondary data on Parkinson disease patients who had (DBS) surgery at our hospital from 2008 to 2021. We assessed the efficacy of DBS at six- and twelve-months post-surgery using the UPDSR III score and Activities of Daily Living (ADL). Our objectives were determined using the Wilcoxon rank sum and the McNemar Test.

Results: This study included a total of 15 participants. At six months, either with or without the medication, DBS treatment resulted in a statistically significant decrease in the UPDRS III score. However, no substantial changes were seen over a 6- to 12-month follow-up period. Additionally, we discovered a statistically significant difference in the percentage of ADL performed without drug post DBS. Meanwhile, none of our patients had cerebral haemorrhage after DBS, although three acquired infection post-operatively.

Conclusion: In Malaysia, DBS has been shown to be a safe and effective short-term therapy for persons with Parkinson's disease. Additional research is needed to demonstrate that early DBS decreases the need for and complexity of PD medicines while delivering long-term motor improvement compared to normal medical treatment.

Keywords: Parkinson Disease, Deep Brain Stimulation

CHAPTER 1: INTRODUCTION

1.1 Parkinson Disease (PD)

Parkinson Disease (PD) is a severe chronic neurodegenerative condition characterised by akinesia, tremor, stiffness, and postural instability (Hughes *et al.*, 1992; MOH, 2007). It is primarily caused by dopaminergic neuron loss in the substantia nigra. Numerous studies have revealed that patients with PD die at a rate of 44 percent higher than the age-matched group after 9.4 years with the illness (Diem-Zangerl *et al.*, 2009; Hely *et al.*, 2008). Dementia, nursing facility living, hallucinations, and autonomic dysregulation are all prevalent (50–80%) in 20-year survivors (Hely *et al.*, 2008).

Regardless of the finest medical treatment, which may include levodopa, patients' motor and non-motor impairments will continue to worsen with time. After a five- to seven-year "honeymoon" phase of therapy, dyskinesias (involuntary body movements that may occur as a side effect of Parkinson's drugs) become more common and exacerbate the symptoms of the majority of Parkinson's patients. As a result, the quality of life (QoL) is considerably deteriorated in the latter stages of PD (eight to fifteen years following beginning of illness) (MOH, 2007). Levodopa and a variety of dopamine agonists are available for dopamine replacement treatment in the early stages of the illness, resulting in effective alleviation of motor symptoms. However, this treatment is harmed in the long run by the growing prevalence of motor problems such as wearing-off and sudden-off occurrences, as well as bothersome hyperkinesias (Goetz *et al.*, 2005).

Surgery has long been acknowledged as a beneficial adjunct to medicinal treatment in the management of severe advanced Parkinson's disease. The subthalamic nucleus or the globus pallidus pars internus are targeted during surgery. In the majority of instances, the subthalamic nucleus is the primary target. Surgery entails implanting stimulating electrodes (Deep Brain Stimulation (DBS)) into the appropriate nucleus in order to depolarize it (Deuschl *et al.*, 2006). Similar to a cardiac pacemaker, the electrodes (which are often inserted bilaterally) are then linked to a battery implanted subcutaneously in the pectoral area (MOH, 2007). An alternative to DBS is lesioning surgery, where the target nucleus is destroyed by coagulating it. DBS is preferable to lesioning because it is non-destructive, reversible, adjustable and associated with less side effects (Charles *et al.*, 2004; Deuschl *et al.*, 2006; Hamani *et al.*, 2005; Kleiner-Fisman *et al.*, 2006; Krack *et al.*, 2003). It is, however, more costly (McIntosh *et al.*, 2003).

1.2 Deep Brain Stimulation (DBS)

DBS of the ventral intermedius nucleus (VIM) of the motor thalamus was initially utilised in 1986 to treat medically resistant tremor in PD (Benabid *et al.*, 1987). DBS of different basal ganglia nuclei has evolved into a very successful therapy for a variety of movement disorders in the intervening years. DBS of the internal globus pallidus (GPi) and subthalamic nucleus (STN) (Bove *et al.*) were proven to be effective and safe targets in PD. In contrast to surgical lesioning methods, chronic DBS with conventional stimulation settings for PD causes no, or very little, tissue damage (Burbaud *et al.*, 2002; Kuncel and Grill, 2004; Pilitsis *et al.*, 2008), and is therefore generally reversible. Additionally, unlike lesioning, bilateral DBS may be performed without considerably raising the risk of adverse events. Adjustment of stimulation settings is available surgically and during the course of the illness.

There is a growing amount of published research demonstrating the effectiveness of DBS in Parkinson's disease, including dramatically decreased "off" time, dyskinesias, and medication dosage, as well as significantly improved motor function, disability reduction, and quality of life (Esselink *et al.*, 2004; Schuurman *et al.*, 2000). Parkinson's surgery (DBS or lesioning) may now be reliably conducted with a low rate of morbidity and therefore almost totally replaced lesional surgery in many countries. It is, however, a difficult task. It is ideally conducted at a tertiary facility by an experienced, well-trained, and well-equipped surgical team for maximum outcomes. This multidisciplinary team will assess patients' surgical appropriateness, undertake pre- and post-operative assessment, perform intra-operative neural recording and stimulation, and manage stimulation settings and medication changes post-operatively.

DBS among PD patients in Malaysia

Numerous neurosurgical centres in Malaysia do DBS for idiopathic Parkinson's disease. Among them is Hospital Universiti Sains Malaysia (HUSM), a tertiary medical facility established in 1979 and funded by the government. It is located in the state of Kelantan and serves Malaysia's East Coast community. HUSM now has its own Department of Neurosciences, which combines the disciplines of Neurology, Neurosurgery, Neuroanaesthesiology and Critical Care, Neurorehabilitation, and Neurophysiology (P3Neuro). In 2008, HUSM performed the first DBS surgery for idiopathic Parkinson disease. Patients receiving DBS need treatment by a multidisciplinary team. Preoperatively, patients were evaluated according to local practices to determine the severity of their specific

disorders. Appropriate scoring methods such as the United Parkinson Disease Rating Scale, the Unified Dystonia Rating Scale, the Fahn Marsden Dystonia Scale, the Yale Global Tic Scoring Scale, and the Connors ADHD Score were used to examine patients. The DBS surgeries were performed by experienced neurosurgeons and neuro anaesthesiologists, with assistance of neurologists pre and post operatively. Following surgery, these patients were continuously monitored in clinics to ensure they were progressing according to the same pre-operative rating system.

1.1 Problem statement & Study rationale

DBS replicates the impact of lesions (thalamotomy, pallidotomy, etc.) with a lower risk of persistent neurological impairments (Benabid *et al.*, 1987; Schuurman *et al.*, 2000). DBS is now being used internationally, and the therapy's benefit to risk ratio is being evaluated. A critical concern in this respect is whether the generally favourable response shown in previous research is maintained over time. However, numerous studies have shown a significant positive impact of DBS of the STN or GPi in patients with PD12–24 months after surgery (Herzog *et al.*, 2003; Kleiner-Fisman *et al.*, 2003; Pahwa *et al.*, 2003; Volkmann *et al.*, 2004). Deep brain stimulation (DBS) is also well established for the treatment of Parkinson disease (PD) for up to one or two years, and data shows that subthalamic nucleus DBS improves motor function for up to ten years, but the extent of benefit tends to diminish with time (Limousin and Foltynie, 2019). Meanwhile, a research discovered that STN-DBS remains beneficial 15 years after the intervention, most notably with considerable improvement in motor problems and steady dopaminergic medication decrease. Additionally, despite the typical course of PD over time, with deterioration of levodopa-resistant motor and non-motor symptoms, STN-DBS patients may sustain an improvement in quality of life (Bove *et al.*, 2021).

Despite multiple prospective, randomised trials proving DBS's safety and effectiveness in all stages of PD worldwide, there are limited reports of efficacy of DBS and its clinical outcomes in Malaysia (MaHTAS, 2010). A research including 12 patients in HUSM discovered remarkable improvement in motor function with the administration of the UPDRS (Hooi *et al.*, 2017). Seven patients were diagnosed with Idiopathic PD (IPD) and treated with STN, three were diagnosed with dystonia and treated with GPi, and two were diagnosed with Tourette's Syndrome and treated with targeted medial thalamus-DBS. Patients diagnosed with IPD ranged in age from 46 to 67 years at surgery, with a mean age of 56 years and a

diagnostic age of 45 years. The age at which patients developed dystonia varied from 3 to 57 years, while the age at which they had surgery ranged from 24 to 60 years. Meanwhile, the average age of beginning of Tourette's syndrome was between 9 and 10 years, and the average age of surgery was between 25 and 26 years.

The surgical outcomes of the study also revealed that four out of seven patients diagnosed with IPD improved by at least 50% in their motor symptoms three months after surgery, and all seven patients improved by more than 50% in their motor symptoms secondary to medical therapy three months after surgery. Following their initial improvement at three months, four out of seven patients did not see additional improvement in their motor symptoms at six, twelve, or twenty-four months. Furthermore, these individuals did not see additional improvement in their motor symptoms because of medical treatment. Meanwhile, two out of every three dystonia patients reported improvement in their symptoms. Both patients improved for the first six months after surgery, but then plateaued. One patient with dystonia did not report any improvement or worsening of symptoms over the first six months but did report some improvement at the 12-month follow-up, which then remained stable at the 24-month follow-up. Finally, two individuals with Tourette's Syndrome were shown to improve considerably on the Yale Global Tic Scale and the Connors ADHD Score.

However, the research, on the other hand, gave a descriptive finding and lacked statistical analysis to support any theory. Additionally, individuals with movement disorders such as IPD, dystonia, and Tourette's Syndrome were included in the research population. However, there are no published findings in Malaysia on the clinical results of Idiopathic PD patients treated with DBS (MaHTAS, 2010). Additionally, knowing the endurance of STN DBS treatment is crucial when contemplating its applicability in PD due to the increased duration of exposure. Adoption of STN in DBS as a supplementary treatment for PD patients would need not just a multicenter, pivotal study demonstrating safety and efficacy, but also long-term benefit and safety in trials testing the long-term consequences of early DBS.

1.2 Research Question(s)

1. What is the median difference of motor function scale at 6 months and 12 months post Deep Brain Stimulation Surgery among Parkinson Disease patients in Hospital Universiti Sains Malaysia (HUSM) between 2008 until 2021?
2. What is the prevalence of post-operative complications post Deep Brain Stimulation Surgery among Parkinson Disease patients in Hospital Universiti Sains Malaysia (HUSM) between 2008 until 2021?

1.3. Objective

1.3.1 General

To determine effectiveness of deep brain stimulation (DBS) and its clinical outcomes post-surgery among Parkinson disease patients in Hospital Universiti Sains Malaysia (HUSM).

1.3.2 Specific

1. To determine median difference of motor function scale at 6 months and 12 months post Deep Brain Stimulation Surgery among Parkinson Disease patients in Hospital Universiti Sains Malaysia (HUSM) between 2008 until 2021.
2. To determine prevalence of post Deep Brain Stimulation Surgery complications among Parkinson Disease patients in Hospital Universiti Sains Malaysia (HUSM) between 2008 until 2021.

CHAPTER 2: LITERATURE REVIEW

2.1 Effectiveness of DBS

The Grenoble group that pioneered the DBS procedure (Benabid *et al.*, 1987; Limousin *et al.*, 1995) reported on the effectiveness of STN DBS in 42 patients following a 5-year follow-up period (Krack *et al.*, 2003). They discovered that DBS provided a sustained anti-parkinsonian impact and decreased dyskinesias generated by levodopa. Several other organisations have observed similar findings in a smaller number of individuals (Kleiner-Fisman *et al.*, 2003; Rodriguez-Oroz *et al.*, 2004). Meanwhile, according to a study (Gervais-Bernard *et al.*, 2009), 42 consecutive patients with idiopathic PD had bilateral STN stimulation surgery. One week before to surgery, and one and five years postoperatively, patients were evaluated clinically using the UPDRS, the Mattis Dementia Rating Scale, and the Beck Depression Inventory (BDI). These examinations were conducted before to surgery in two circumstances. Firstly, after the administration of a preliminary dosage of levodopa (while on medication), and secondly, following a minimum 12-hour break from antiparkinsonian medicine (off medication). Postoperative assessment was performed in four conditions: on-stimulation and no medication; off-stimulation and no medication; on-medication and no stimulation; and on-medication and on-stimulation. At five years, they discovered that STN stimulation lowered the UPDRS motor score by 55% relative to baseline in non-medication settings. Tremor, stiffness, bradykinesia, postural stability, and gait all improved by 74%, 66%, 59%, 17%, and 37%, respectively. The UPDRS component II (Activities of Daily Living / ADL) scores were dropped by 38%. After surgery, the daily dosage of dopaminergic medication was lowered by 54.4 percent. The authors concluded that bilateral STN stimulation remained the best therapy option for advanced PD (Gervais-Bernard *et al.*, 2009).

Another study examined the effect of STN-DBS on 103 consecutive individuals with severe PD 12 months after surgery (Tir *et al.*, 2007). Between May 1998 and March 2003, they had bilateral STN-DBS at Lille University Medical Centre in Lille, France. Clinical evaluations were conducted before to and 12 months after surgery using the UPDRS Parts II, III, and IV A; the Schwab and England (S&E) scale; and cognitive evaluation. Additionally, patient-reported overall improvement was assessed. At one year, the UPDRS Part III score (motor symptoms) dropped by 43% in the off drug/on stimulation condition. The UPDRS Part II scores (ADL) decreased by 34% in the off-drug/on-stimulus condition. The S&E scale score increased by 45 percent when compared to the pre-surgery drug-free state. Additionally, the

UPDRS Part IV A score (severity of dyskinesia-related impairment) dropped by 61% in the on drug/off stimulation condition. The mean score for overall improvement as reported by patients was 70.7 percent. The authors found that the effectiveness of STN-DBS is typically equivalent to that reported by other groups, but at the lower end of the stated range of values (Tir *et al.*, 2007).

Moreover, the effectiveness of the surgery was evaluated in 72 patients who had follow-up examinations from 3 to 12 months post-operatively in the same cohort research (Tabbal *et al.*, 2007). All assessments included scores on the motor part of the Unified PDRating Scale (UPDRS) before and after stimulation was turned on for at least 10 to 15 minutes. It was observed that STN DBS lowered overall UPDRS motor scores in 72 patients by 47 percent at the time of follow-up examination, from 43.4 16.1 with stimulators off to 22.8 11.6 with stimulators on (P 0.001). The following changes occurred in the UPDRS motor subscores: rest tremor improved by 74% (P 0.001); rigidity improved by 58% (P 0.001); bradykinesia improved by 37% (P 0.001); pull test improved by 35% (P 0.001); gait improved by 44% (P 0.001); axial signs improved by 42% (P 0.001); and speech improved by 13% (P 0.001). The authors found that the STN DBS surgical approach for PD is rapid, effective, and associated with a low risk of complications (Tabbal *et al.*, 2007).

Besides, another research corroborated that DBS was the most effective treatment for tremor associated with Parkinson's disease, and that symptomatic improvement was permanent even after more than ten years of follow-up (Hitti *et al.*, 2019). At long-term follow-up, however, non–tremor motor symptoms such as freezing and dysarthria remained. While many individuals may have seen a brief improvement in their symptoms after surgery, this improvement was not maintained at long-term follow-up. A meta-analysis established that STN and GPi DBS result in long-lasting tremor reduction up to five years after surgery (St George *et al.*, 2010). Another research discovered that although tremor had decreased over the course of an 11-year mean follow-up, speech had deteriorated (Rizzone *et al.*, 2014).

Additionally, a research discovered that DBS-treated PD patients retained their capacity to execute fundamental activities such as dressing oneself after a lengthy period of follow-up. On the other hand, most patients were unable to do more difficult chores independently during long-term follow-up, such as meal preparation or errand running (Hitti *et al.*, 2019). One research revealed that patients' self-reported improvements in ADLs persisted for up to five years after surgery (Lezcano *et al.*, 2016). Another study compared PD patients treated with STNDBS to those treated with medication alone after a six-year follow-up period and

discovered that the ability to perform ADLs (as measured by the mean UPDRS-II [Unified PDRating Scale II] score) remained stable in the DBS group but deteriorated in the medication-alone group (Merola *et al.*, 2014).

2.2 Complications Post DBS

To investigate the long-term effectiveness and safety of bilateral subthalamic nucleus (BSN) stimulation in advanced PD(PD), a cohort research was done (Gervais-Bernard *et al.*, 2009). The research discovered two brain haemorrhages, three device infections, two phlebitis, and one pulmonary embolism among the 42 original patients. Additionally, two patients required electrode relocation. Among the 23 patients observed for five years, the most common long-lasting adverse effects were dysarthria (56%), sadness (39%), eyelid opening apraxia (30.4%), and apathy (4.3%). The authors found that the surgical process, the device, and the stimulation all had minor and infrequent adverse effects (Gervais-Bernard *et al.*, 2009).

Another research evaluated the effect of deep brain stimulation (DBS) of the subthalamic nucleus (SN) 12 months following surgery in 103 consecutive patients with severe PD(PD) (Tir *et al.*, 2007). Following STN-DBS, the most common surgical problems were infections, intracerebral hematomas, electrode fractures, and improper lead placements. Additionally, they noticed cognitive deterioration and depression in 7.7% and 18% of patients, respectively. Contrary to effectiveness, the authors found that the incidence of adverse effects cannot be anticipated (Tir *et al.*, 2007).

However, the true therapeutic value of DBS in advanced PDmust account for the 2% risk of intracranial haemorrhage associated with surgery (Umemura *et al.*, 2003) and the 2.8% risk of permanent neurological deficit (The Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001). Additionally, complications linked with the implant, such as infections, skin erosion, and lead breakage, are also commons (Lyons *et al.*, 2004; Oh *et al.*, 2002) and may necessitate treatment discontinuation. At 3–4 years, the frequency of adverse events was high, particularly among those implanted in the STN (Rodriguez-Oroz *et al.*, 2005). These complications included cognitive impairment and mental symptoms (hallucinations, psychosis, etc.), as well as mood problems and issues with speech, mobility, and balance.

2.3 Conceptual framework

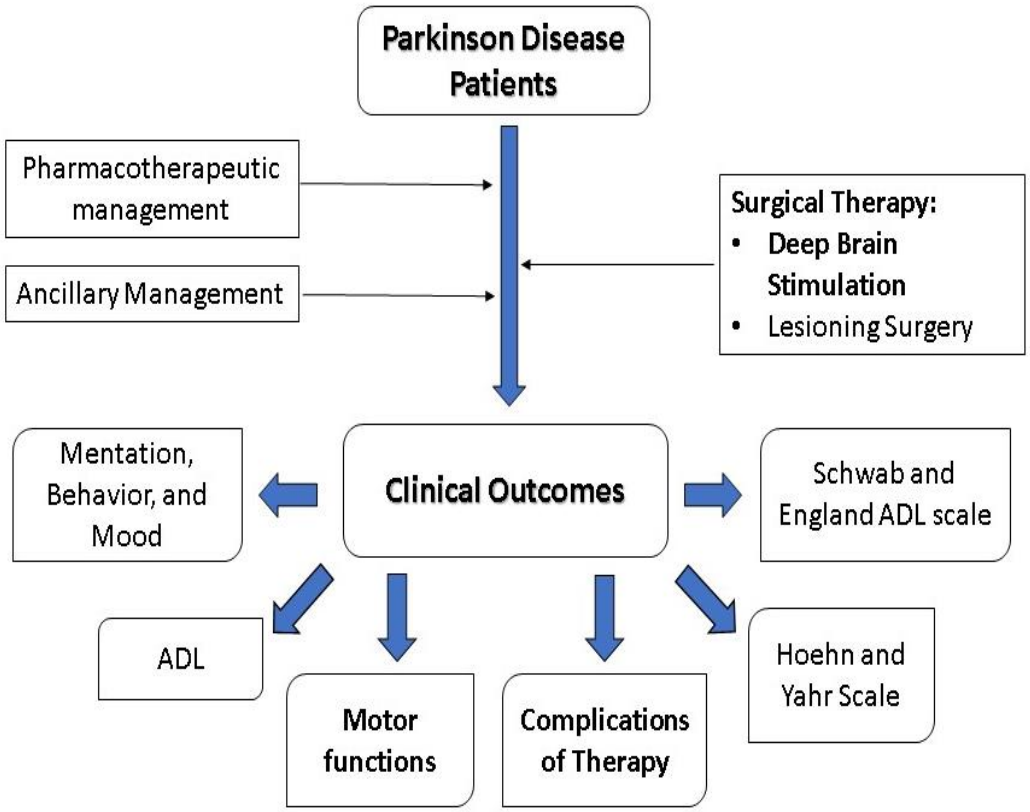

Figure 1: Conceptual Framework of this study

CHAPTER 3: STUDY PROTOCOL

3.1 Study Design

In this study, we will be using a retrospective cohort design.

3.2 Study Area

The study area was Neuroscience Department, Hospital Universiti Sains Malaysia (HUSM).

3.3 Study Population

Reference population – Parkinson disease patients in Kelantan.

Target population- Parkinson disease patients who had followed up with Neuroscience Department, HUSM.

Source population / sampling pool – Parkinson disease patients who had deep brain stimulation (DBS) surgery in HUSM.

Sampling frame – List of Parkinson disease patients who had deep brain stimulation (DBS) surgery in HUSM between 2008 until 2021.

3.4 Subject Criteria

Inclusion: Idiopathic type of Parkinson disease patients that underwent DBS surgery and completed neurologist followed up for at least 12 months will be recruited.

Exclusion: Other type of Parkinson such as Juvenile Parkinson's, Drug-induced parkinsonism, Multiple system atrophy, Progressive supranuclear palsy, Corticobasal syndrome, Dementia with Lewy bodies and Vascular Parkinsonism will be excluded. Also, we will exclude any patient who default the follow up or passed away during the follow up period.

3.5 Sample Size Estimation

For the first Objective, we applied the 2 means (paired) - Hypothesis Testing Formula using an online Sample Size Calculator (Arifin, 2022) to estimate our sample size. Details of the formula is listed below:

- Standard deviation of difference (σd) :8.33 (Aviles-Olmos *et al.*, 2014)
- Expected difference: 8
- Significance level (α): 0.05 Two-tailed
- Power (1 - β): 80 %
- Expected dropout rate: 10 %
- Sample size, n = 7
- Sample size (with 10% dropout), n *drop* = 8
- Total sample size = **16**

For the second objective, we applied the Single Proportion Formula using an online Sample Size Calculator (Arifin, 2022) to estimate our sample size. Details of the formula is listed below:

- Proportion of post operative complications = *P*
- Z value based on 95% CI = 1.96
- Precision (Δ) = 0.2
- Drop-out rate = 10 %

Complications	**(*P*)**	**Sample Size, n**	**Literature Reviews**
Intracranial haemorrhage	0.08	9	(Hooi *et al.*, 2017)
Infection	0.17	16	(Hooi *et al.*, 2017)
Device-related	0.06	7	(Hooi *et al.*, 2017)
Neuropsychological	0.24	20	(Aviles-Olmos *et al.*, 2014)

Final sample size required in this study is **20 samples.**

3.6 Sampling Method

A purposive sampling method applied as we collected all samples available due to scarcity of data available for this study

3.7 Research Tool

Unified Parkinson Disease Rating Scale (UPDRS)

It is a rating tool used to gauge the severity and progression of PD in patients (Fahn *et al.*, 1987). The UPDRS scale consists of the following six segments:

1) Mentation, Behavior, and Mood,
2) ADL,
3) Motor sections,
4) Complications of Therapy (in the past week)
5) Modified Hoehn and Yahr Scale, and
6) Schwab and England ADL scale.

The first four segments include 42 items that are divided into four subscales. The UPDRS was created in 1987 by neurologists as a gold standard for tracking the response to treatments used to alleviate Parkinson's signs and symptoms. Parts 1–3 are graded on a 0–4 rating system. Part 4 is graded on a yes/no scale. Increased severity is indicated by higher scores. The patient is then evaluated using the H and Y Scale and the Schwab and England Activities of Daily Living Scale. In terms of reliability, the UPDRS has shown strong internal consistency across several trials and throughout Hoehn and Yahr disease severity stages (Louis *et al.*, 1996; Martínez-Martín *et al.*, 1994). The whole UPDRS, as well as the Activities of Daily Living and Motor Examination components, were determined to have good inter-rater reliability (Rabey *et al.*, 1997; Siderowf *et al.*, 2002). Correlation values within classes were quite high: overall score: 0.92; mentation: 0.74; activities of daily living: 0.85; motor: 0.90 (Stebbins *et al.*, 1999; Stebbins and Goetz, 1998). Meanwhile, it has been proven that the UPDRS has adequate face validity (Camicioli *et al.*, 2001) and that it is responsive to changes in clinical state (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). In this research, we use an original UPDRS III scale that focuses only on the motor segment.

3.8 Operational Definition

The 'off' and 'on' pharmacological states were defined as the motor scores after 12 hours without treatment (unless unacceptable for specific individuals) and the maximal improvement following a dosage of levodopa equivalent to 150 percent of the customary first morning dose. After surgery, patients who had discontinued levodopa were given the same dose as preoperatively. Post-operative assessments were performed in the following order: I 'off' medication without stimulation; (ii) 'off' medication with stimulation; (iii) 'on' medication without stimulation; and 'on' medication with stimulation. The off and on stimulation settings were assessed 60–120 and 30 minutes after the stimulator was turned off and on, respectively.

3.9 Data Collection

We will use secondary data sources such as medical records of Parkinson disease patients who had deep brain stimulation (DBS) surgery at HUSM from 2008 to 2021. The data will be gathered through HUSM's medical records department.

After analysing patient case files, data on patient characteristics such as age, gender, race, length of illness and comorbidities, clinical state, intraoperative findings, and postoperative problems will be collected. No personal information will be gathered as part of our research. The data will be gathered using a proforma checklist and will be encrypted and available only to researchers through a password-protected computer.

3.10 Study Flowchart

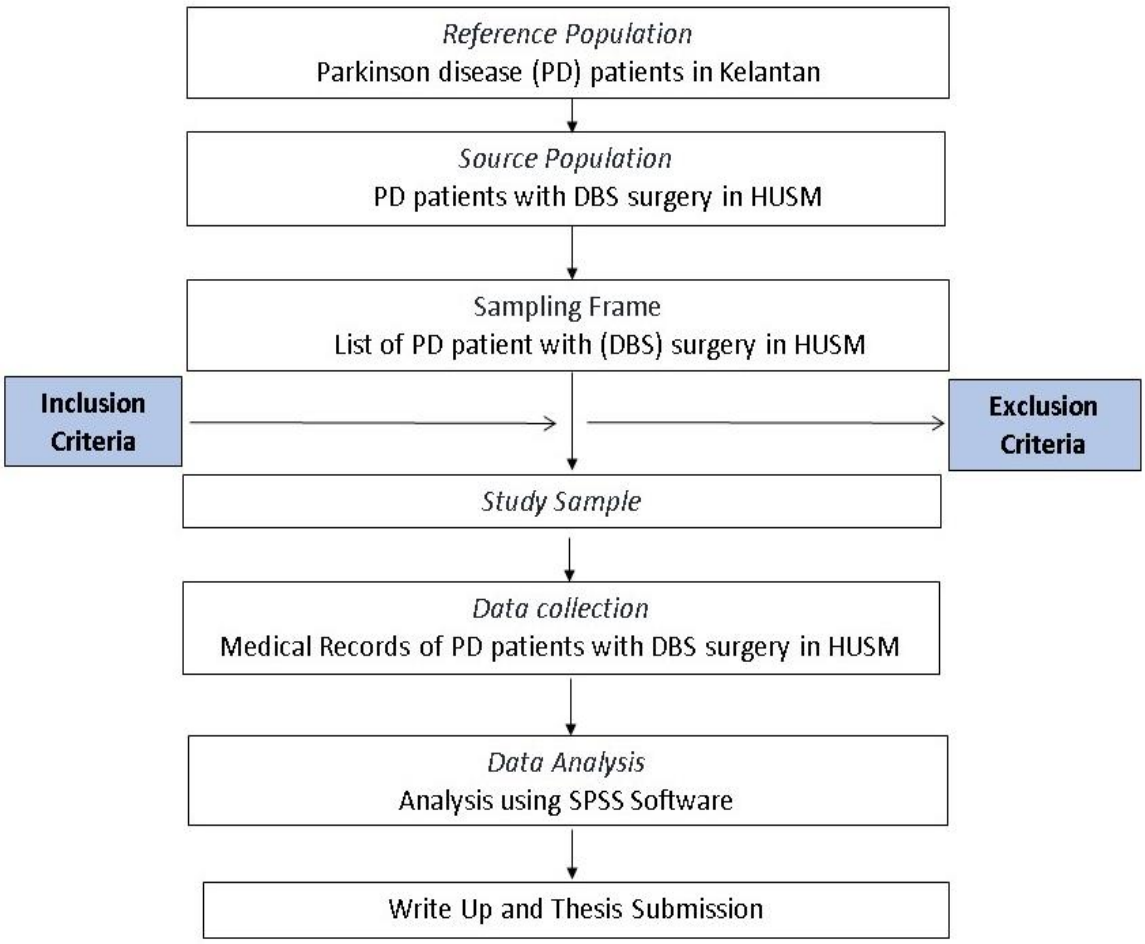

Figure 2: Study Flowchart of this study

3.11 Data Analysis

The sociodemographic features of subjects will be summarised using descriptive statistics. Due to the limited sample size and anticipated non-normal distribution of data, numerical data will be provided as median (Interquartile (IQR)). Frequency and percentages will be used to show categorical data.

The Wilcoxon rank sum test will be used to compare median scores at 6 and 12 months post-operatively for the first objective. The significance level was chosen at 5%. All stated P-values are two-sided. Meanwhile, the second objective will rely entirely on descriptive statistics. SPSS Software version 26 (SPSS Inc, Chicago, IL) will be used to perform the analysis.

3.12 Ethical Approval

3.12.1 Subject vulnerability

There is no subject vulnerability as we only utilized secondary data such as medical records.

3.12.2 Declaration of absence of conflict of interest

There is no conflict of interest in this propose study.

3.12.3 Privacy and confidentiality

All forms are anonymous and will be entered into Excel or SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the responders individually.

3.12.4 Community sensitivities and benefits

There is no community sensitivities or issues that can triggers social stigma as we only utilized secondary data.

Meanwhile, our proposed study will benefit the community by improving the clinical management and care of Parkinson disease patients. Also, we hope that more DBS surgery for treatment of Parkinson disease patients can be performed through the evidence found in this study.

3.12.5.Ethical approval letter

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)

Human Research Ethics Committee USM (HREC)

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Protocol Title: Efficacy of Deep Brain Stimulation (DBS) Surgery and Its Clinical Outcomes in Parkinson Disease Patients at Hospital Universiti Sains Malaysia (Hospital USM).

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