Health Technology Assessment Report
on

COST-EFFECTIVENESS OF DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE IN INDIA

Health Technology Assessment (HTA) Resource Centre

ICMR-National Institute of Epidemiology

STUDY TEAM

Principal investigator: Dr. Bhavani Shankara Bagepally, Scientist-E
ICMR- National Institute of Epidemiology, Chennai

Co-investigators:

- Dr. Akhil Sasidharan, Project Scientist-C
- Dr. S. Sajith Kumar, Project Scientist-C

Health Technology Assessment Resource Centre (HTARC), ICMR- National Institute of Epidemiology, Chennai

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Abbreviations

AAN: American Academy of Neurology

BMT: Best medical treatment

COMT: Catechol-O-methyltransferase inhibitors

CSAI - Continuous subcutaneous apomorphine infusion

DBS: Deep brain stimulation

GPi: Globus pallidus interna

H&Y: Hoehn and Yahr stage

ICER: Incremental Cost-effectiveness Ratio

IPG: Implantable pulse generator

MAO-B: Monoamine oxidase-B inhibitors

NICE: National Institute for Health and Care Excellence

NMDA: N-methyl-D-aspartate

OSA: One-way sensitivity analysis

PD: Parkinson’s disease

PRISMA: Preferred referred Reporting Items for Systematic Reviews and Meta-Analysis

PSA: Probabilistic sensitivity analysis

QOL - Quality of life

SNpc: substantia nigra pars compacta

STN: subthalamic nucleus

UPDRS: Unified Parkinson’s disease rating scale

Table of Contents

1. Executive Summary

To facilitate the process of transparent and evidence informed decision making in the field of health, the Health Technology Assessment in India (HTAIn) has been set up under the Department of Health Research (DHR) of the Ministry of Health and Family Welfare (MoHFW). As part of the generation and compilation of evidence related to the cost-effectiveness, clinical effectiveness, and safety of medicines, devices, and health programmes through Health Technology Assessment (HTA) studies, the ICMR-NIE HTA resource centre was tasked with preparing a proposal for the cost-effectiveness of deep brain stimulation for Parkinson's disease patients in India to inform policy decision-making, ensure people have access to quality healthcare, and ensure the best value is gained from the health budget.

Deep brain stimulation (DBS) is a neurosurgical procedure that involves surgically implanting electrodes into specific brain targets, either the subthalamic nucleus (STN) or the globus pallidus interna (GPi) (unilaterally or bilaterally), for Parkinson's disease (PD) patients when motor fluctuations and dyskinesias become disabling or when symptoms cannot be sufficiently managed by pharmacological therapies. DBS was approved for the treatment of PD in 2002 by the US FDA, and annually, around 500 surgeries are ongoing in India. There is a wealth of evidence available from high-income economies suggesting that DBS is a cost-effective option for patients with advanced PD or with disabling motor fluctuations and dyskinesia. However, while there is evidence that DBS is cost-effective, it may be difficult to interpret in general or specifically in relation to India. Hence, we proposed a health technology assessment to determine the cost-effectiveness of DBS for patients with PD in India. We proposed to conduct an SRMA of CUA evidence for DBS for PD and a Markov model-based cost-utility analysis to determine whether DBS can be a cost-effective option. All available CUA studies were critically examined to understand the cost-effectiveness of DBS in various settings. The unavailability of dispersion measures for ICUR and incremental cost and effectiveness in the included studies limited our capacity to compute the variance of

INB. Consequently, we were unable to perform a meta-analysis to synthesize the available evidence. The cost-effectiveness of DBS for PD varies by study perspective, costs considered, threshold utilized, and stage of PD progression. Standardizing approaches and comparing DBS with other treatments are needed for future research on effective PD management. The implications of the proposed study are meaningful if we wish to proceed with further evaluations to see whether DBS is cost-effective for patients with PD.

The HTAIn Technical Appraisal Committee (TAC) reviewed the proposal and noted that DBS therapy for PD in India is costly primarily due to the hardware device, which needs to be made available at lower rates as a large population in a developing country like India is not able to afford it. The committee agrees with the overall benefit of DBS for PD and how this will improve the quality of life for PD patients. However, the committee questioned whether DBS could be included as a package in the Ayushman Bharat PM-JAY program, implying that since PD prevalence is lower in India, available medical resources could be used for other medical conditions that would add more value to the PM-JAY program. The committee recommended that the present study cannot be undertaken since it may not add immediate value to the Ayushman Bharat PM-JAY. Further, the committee highlighted that, according to the UK National Institute for Health and Clinical Excellence (NICE), subthalamic deep brain stimulation (STN-DBS) is an effective therapy that can immediately improve the quality of life in Parkinson's disease patients. The ICER/QALY in STN-DBS patients has been estimated to be within appropriate limits to consider STN-DBS as an efficient therapy in the UK. The committee's final recommendation was that, since the role of deep brain stimulation is well known for increasing quality of life for PD patients, primary care could include management of Parkinson’s disease as well, and suggestions were made as to whether NHA could fund the proposed study.

2. Background

2.1. Introduction

Parkinson's disease (PD) is a chronic, multifaceted and progressive neurodegenerative disorder of adult-onset affecting the ageing population and is associated with increased morbidity and mortality. PD is the second most common neurodegenerative disorder after Alzheimer's disease (1). PD is characterized by the early and prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the widespread presence of the intracellular protein alpha-synuclein (aSyn). The classic Parkinsonian motor symptoms, such as bradykinesia, tremor, rigidity, and later postural instability, result from dopamine deficiency in the basal ganglia (2). The non-motor symptoms of PD often precede the motor symptoms by more than a decade (3, 4).

Increasing trends in the burden of PD have been observed globally. The overall annual standardised rate of the incidence, prevalence, and years of life lost due to PD has increased from 1990 to 2019 in most countries, including India (5, 6). The estimated prevalence of PD in India (in 2019) is 7,71,000 (95% UI 6,35,000 to 9,19,000), and about 45,300 (95% UI 38,600 to 52,800) deaths were due to PD (6). PD lowers the patients' quality of life with an additional burden on the caregivers, society, and the health system (7).

Deep brain stimulation (DBS) is a neurosurgical procedure which was first introduced in 1987 (8). It involves surgical implantation of electrodes into specific targets within the brain that are connected to a pacemaker positioned below the collarbone (9). DBS is suggested for PD patients when motor fluctuations and dyskinesias become disabling or when symptoms cannot be sufficiently managed by pharmacological therapies (10). DBS was approved for the treatment of essential tremors in 1997, PD in 2002, dystonia in 2003, obsessive-compulsive disorder (OCD) in 2009, and epilepsy in 2018 by the US Food and Drug Administration (8).

2.2. Review of Literature:

2.2.1. Medical therapies for PD

The American Academy of Neurology (AAN) recommends initiating pharmacological therapies as soon as a patient develops a functional disability (11). The medical therapies to treat motor symptoms of PD include the use of Levodopa, Carbidopa, dopamine agonists (both ergot and non-ergot types), monoamine oxidase-B (MAO-B) inhibitors, injectable dopamine agonists (apomorphine), catechol-O-methyltransferase (COMT) inhibitors, N-methyl-D-aspartate (NMDA) receptor inhibitors, and anticholinergic drugs (11). Dopamine agonists, levodopa, or monoamine oxidase B (MAO-B) inhibitors are suggested for early-stage PD patients whose motor symptoms do not affect their quality of life according to NICE, UK recommendations (10). The ergot-derived dopamine agonists to be supplemented with levodopa for PD patients whose symptoms are not sufficiently controlled by non-ergot-derived dopamine agonists or with dyskinesia or motor fluctuations, despite receiving optimal levodopa therapy (10). In the later stages of PD, drug delivery can be supplemented via alternative routes such as intrajejunal infusions, subcutaneous injections, or transdermal patches (11). A continuous subcutaneous apomorphine infusion or intermittent apomorphine injection may also be used as part of Best medical therapy (BMT) for advanced PD (10).

Marsden and other contemporaries recognised the "OFF" phenomenon in PD 40 years ago (12). The ON-OFF phenomenon refers to the fact that patients with advanced PD may experience rapid fluctuations in their motor function. During the "on" state, motor symptoms are controlled relatively well (2). However, rapid wearing-off of the effect of levodopa leaves the patient in the "off" state, in which they have severe Parkinsonian motor features (13, 14). Prolonged use of levodopa can also result in significant motor complications, including dyskinesias and severe ON-OFF motor fluctuations (13, 15). OFF is a change in the clinical state of a PD patient where motor and/or non-motor symptoms appear or worsen and result in

functional disability (12). OFF states include wearing off, ON-OFF phenomenon, early morning akinesia, delayed ON, dose failures, and OFF period dystonia (12). The combination and severity of these symptoms are unique for each patient and improve with PD therapy (12).

Several different rating scales are used to assess an individual's stage of Parkinson's disease (PD). The two most commonly used are the Hoehn and Yahr scale (H &Y) and the Unified Parkinson's Disease Rating Scale (UPDRS). Hoehn and Yahr published the scale in 1967 to describe the progression of PD in five stages (16). A modified H & Y scale was proposed by the Movement Disorder Society (MDS) in 2004 with the addition of stages 1.5 and 2.5 to help describe the intermediate course of the disease (17). Table 1 summarizes the H&Y and modified H &Y scale stages and the time taken to transit from one H &Y stage to another (18). The UPDRS is a similar scale commonly used in clinical studies of PD. In 2008, UPDRS was updated to UPDRS-MDS but retained the four-scale structure with subscales: non-motor experiences of daily living (13 items), motor experiences of daily living (13 items), motor examination (18 items), and motor complications (6 items) (19).

Table1: Hoehn and Yahr Scale

Stage	Hoehn and Yahr Scale	Modified Hoehn and Yahr Scale	Median Time to Transit (Months)
1	Unilateral involvement only usually with minimal or no functional disability	Unilateral involvement only	-
1.5	-	Unilateral and axial involvement	
2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance	20
2.5	-	Mild bilateral disease with recovery on pull test	62

3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent	25
4	Severely disabling disease; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted	24
5	Confinement to bed or wheelchair unless aided	Wheelchair bound or bedridden unless aided	26

2.2.2. Clinical Evidence on DBS

Surgical treatment is preferred when motor fluctuations and dyskinesias become disabling despite the responsiveness of the motor symptoms to levodopa. It is suggested that DBS be employed for PD patients whose symptoms cannot be sufficiently managed by BMT (10). Deep brain stimulation (DBS) involves surgical implantation of electrodes into the brain that is connected to a pacemaker positioned below the collarbone (9). The pacemaker stimulates either the subthalamic nucleus (STN) or globus pallidus interna (GPi) (unilaterally or bilaterally) through the electrical leads. DBS provides electrical impulses to specific brain parts to control abnormal, rigid movements associated with PD, thus significantly improving the symptoms. DBS is usually used for patients with motor complications (20). DBS is a reversible intervention and can be adjusted for disease progression (21).

Meta-analysis of randomised control trials (RCTs) has reported that DBS significantly improves the patient's quality of life, symptoms and functionality compared to pharmacological therapies (22, 23). Following DBS, the daily dosage of levodopa, dopaminergic medications, and dyskinetics is reduced. Meta-analysis evidence has shown that STN DBS improves the Unified Parkinson's Disease Rating Scale (UPDRS) II (activities of daily living) and UPDRS III (motor) scores in advanced PD (24). Recent meta-analyses of RCTs show that STN and GPi-DBS were equally effective in improving motor dysfunction (25-27) and activities of daily living for PD (26). A therapeutic synergism of STN DBS and levodopa may prove to be more helpful in lessening the motor severity in PD (28). Independent of the stimulation target,

DBS can reduce tremors in PD patients. However, there was no distinction between GPi DBS and STN DBS regarding the degree of tremor suppression (29). However, recent evidence suggests STN DBS is the viable option instead of GPi DBS for treating tremors (30) and for a greater reduction of medication, but not as significant an advantage as GPi DBS with respect to mood (25).

There is evidence that DBS is useful in refractory patients with serious adverse effects to pharmacological treatment or in PD patients where the benefits surpass the risks of the intervention (31). Various agencies' evidence supports that STN DBS and GPi are effective against motor fluctuations and dyskinesia (32, 33). A recent Systematic Review and Evidence-Based Guideline on STN and GPi DBS for treating patients with PD reported by the Congress of Neurological Surgeons suggests that bilateral STN DBS is at least as effective as bilateral GPi DBS (34). Bilateral STN DBS is suggested when the goal is to reduce dopaminergic medications for patients with PD (34). When the goal is to reduce the severity of "on" medication dyskinesias or if there is significant concern about cognitive decline, bilateral GPi DBS to be considered (34).

2.2.3. Cost-effectiveness Evidence of DBS

A systematic review of the economic analysis reported DBS as a cost-effective intervention for patients with advanced PD, but it has a higher initial cost than pharmacological treatments (35). However, DBS reduces pharmacological treatment costs and can also potentially reduce direct, indirect, and social costs of PD in the long term (35). Table 1 summarises the cost-effective evidence (CUAs) for using DBS for PD from the previously published literature, primarily reported from only high-income countries (HICs). Except for Dams et al. (2016), Fundament et al. (2016), which reported for PD patients with early onset of motor complications (36, 37), and Meng et al. 2020 (38), who reported for a population with tremor-dominant Parkinson's disease, all studies reported for a population with advanced PD, age 60 and above. Most studies reported payer perspectives on either health care or insurance providers, except for

Tomaszewsk et al. (2001) (39) , Fann et al. (2020) (40), and Meng et al. (2020) (38). Across studies, the time horizon ranged from one year to a lifetime.

Four studies reported bilateral DBS (STN) (36, 40-42), and two studies (39, 43) reported bilateral DBS (STN or GPi) compared to the best medical therapy. In seven studies, it was not clearly mentioned whether the type of DBS intervention was STN or GPi (37, 44-49). Meng et al. (2020) (38), compared unilateral DBS with MR-guided focused ultrasound thalamotomy for tremor-dominant Parkinson's disease, and Stroupe et al. (2014) compared Surgical Stimulation Sites for DBS—STN with GPi. (50) Six studies reported DBS as a cost-effective intervention when compared to the best medical therapy for PD patients. (36, 37, 44, 45, 47, 49) Three studies reported DBS as not being cost-effective when compared to the best medical therapy (39, 41, 46); however, two of these had a shorter time horizon of only one year.(41, 46) Additionally, individual studies reported that, DBS, whether compared to CSAI (48) or ASBI, and IDL (43) was not cost-effective for treating PD. A HTA report from the United Kingdom in 2017 reported bilateral DBS (STN or GPi) as not cost-effective compared to BMT or LCIG, but recommended DBS for their clinical settings.(10)

Table 1: Published cost-utility analyses of DBS

First author and year	Population	Country, Perspective, Time horizon	Intervention	Comparator	CE, ICUR
Tomaszewsk, 2001(39)	patients with PD aged 50 years and older	USA, societal, lifetime	Bilateral DBS (STN/GPI)	BMT	$ 49,194
NICE, 2006(3)	patients with PD	UK, NHS, 5 years	DBS	BMT	CE, £ 19,500
Valideoriola, 2007(41)	advanced PD with severe disability related to motor fluctuations, tremor dyskinesias	Spain, 1 year	Bilateral DBS (STN)	BMT	€ 34,389
Dams, 2013(44)	patients aged 60 and above experiencing motor fluctuations and dyskinesias	Germany, health care provider, lifetime	DBS	BMT	CE, € 6,700 (2 year -€ 78,474)
Eggington, 2014(45)	advanced PD	UK, NHS perspective, 5-year time horizon	DBS +BMT	BMT	CE, £ 20,678
Stroupe, 2014(51)	PD patients	USA, health care providers, societal perspective, 3 years	Bilateral DBS (STN)	Bilateral DBS (GPI)	QALYs and costs were similar
Zhu, 2014(42)	advanced PD	China (Hong Kong), 2 years	Bilateral DBS (STN)	BMT	CE, I year: US$123,110 2-year: US$62,846 [Cost per QALY via regression only]

First author and year	Population	Country, Perspective, Time horizon	Intervention	Comparator	CE, ICUR
Walter, 2015(48)	advanced PD	UK, Germany, national healthcare providers, 5 years	CSAI (BMT)	SOC	CE,UK: £6440.45 Germany:€74,695
			LCIG	CSAI (BMT)	UK:£244,684,69 Germany:€272,914
			DBS	CSAI (BMT)	CSAI dominates DBS£ 84,129
Kawamoto,2016(52)	60-year-old Japanese males with PD	Japan,health-care insurance system, 10 years	DBS	MT	CE for intermediate stages of PD
McIntosh,2016(46)	advanced PD	UK, health and social care perspective, 1 year	DBS	BMT	Not CE,£ 468,528
Dams,2016(36)	early stage of PD who had suffered from motor complications for up to maximally 3 years	Germany, health care payer perspective, lifetime horizon	Bilateral DBS (STN) + BMT	BMT	CE, € 22,700
Pietzch,2016(47)	advanced PD	USA, Medicare payer perspective, 10 year horizon	DBS + MT	BMT	CE, $23,404
Fundament,2016(37)	PD patients with early onset of motor complications	UK, payer perspective, 15-year horizon	DBS + BMT	BMT	CE, £ 19,887
Matellano,2016	advanced PD	Spain, National health system, 5-year horizon	Bilateral DBS (STN/GPi)	ASBI	Not CE, € 245,541
			Bilateral DBS	IDL	Not CE, € 453,643

First author and year	Population	Country, Perspective, Time horizon	Intervention	Comparator	CE, ICUR
			(STN/GPi)		
			IDL	ASBI	Not CE, € 528,914
UK NICE 2017(10)	advanced PD	UK, NHS, lifetime time-horizon	Bilateral DBS (STN/GPI) + BMT	BMT	£ 34,500
			DBS (STN/GPI) + BMT	LCIG + BMT	LCIG is dominated by DBS
Fann,2020(40)	late PD	Taiwan, societal perspective, 3,10 year	Bilateral DBS (STN)	medication	CE, 3 yr: $123,436 10yr: $69,033
Meng, 2020 (38)	tremor-dominant Parkinson's disease (TDPD)	Canada, societal perspective, 3 years	MRgFUST	medication	CE, $30,078
			unilateral DBS	MRgFUST	Not CE, $56,503

apomorphine subcutaneous infusion (ASBI), levodopa continuous duodenal infusion pump /carbidopa (IDL), deep brain stimulation (DBS), Continuous subcutaneous apomorphine (CSAI) Levodopa/carbidopa intestinal gel (LCIG) Standard-of-care (SOC), MR-guided focused ultrasound thalamotomy (MRgFUST)

3. Current clinical guidelines available for DBS

The US Food and Drug Administration approved DBS for the treatment of PD in 2002. (8).

UK NICE issued a National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care for PD in 2006 with a prespecified inclusion criteria for selecting suitable patients for DBS.(3) The Inclusion criteria is as follows:

i. An established diagnosis of PD using UK brain Bank criteria.
ii. No contraindications to surgery under general anesthesia.
iii. A life expectancy of 5+ years, considered by a multidisciplinary team assessment.
iv. Motor complications severe enough to compromise function and quality of life significantly.
v. Physician assessment shows patient spends >30% of the day in a disabling “off” state or with disabling dyskinesia.
vi. The patient remains levodopa responsive, with >40% improvement in UPDRS Part 43 scores following the usual levodopa morning dose.
vii. The patient has no clinically significant cognitive impairment on the Dementia Rating Scale (score<6).

Subsequently, UK NICE clinical guideline NG71 (2017) recommended the following for Parkinson's disease in adults (10):

i. Deep brain stimulation can be offered to people with advanced Parkinson's disease best medical therapy, which may include intermittent apomorphine injection and/or continuous subcutaneous apomorphine infusion.

ii. Do not offer deep brain stimulation to people with Parkinson's disease whose symptoms are adequately controlled by best medical therapy.

iii. Consider deep brain stimulation for people with advanced Parkinson's disease whose symptoms are not adequately controlled by best medical therapy.

Current German guidelines recommends considering DBS in PD if, (53)

i. presence of motor fluctuations, including levodopa-sensitive off symptoms or treatment-induced dyskinesia;

ii. tremor, which cannot be satisfactorily treated with medication;

iii. levodopa-induced reduction of motor symptoms by >33% of the Unified Parkinson Disease Rating Scale (UPDRS), where tremor may be disregarded from the calculation as it may be refractory to levodopa treatment while still responding well to DBS; and exclusion of dementia, relevant psychiatric or somatic comorbidity, or general contraindication to undergo neurosurgical interventions

American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) recommends the following for PD, (34)

i. Given that bilateral STN DBS is at least as effective as bilateral GPi DBS in treating motor symptoms of Parkinson’s disease (as measured by improvements in UPDRS-III scores) consideration can be given to the selection of either target in patients undergoing surgery to treat motor symptoms (Level I).

ii. When the main goal of surgery is reduction of dopaminergic medications in a patient with Parkinson's disease, then bilateral STN DBS should be performed instead of GPi DBS (Level I).

iii. There is insufficient evidence to make a generalizable recommendation regarding the target selection for reduction of dyskinesias. However, when the reduction of medication is not anticipated and there is a goal to reduce the severity of 'on' medication dyskinesias, the GPi should be targeted (Level I).

iv. When considering improvements in quality of life in a patient undergoing DBS for Parkinson's disease, there is no basis to recommend bilateral DBS in 1 target over the other (Level I).

v. If there is significant concern about cognitive decline, particularly in regards to processing speed and working memory in a patient undergoing DBS, then the clinician should consider using GPi DBS rather than STN DBS while taking into consideration other goals of surgery (Level I).

vi. If there is significant concern about the risk of depression in a patient undergoing DBS, then the clinician should consider using pallidal rather than STN stimulation while taking into consideration other goals of surgery (Level I).

vii. There is insufficient evidence to recommend bilateral DBS in 1 target over the other in order to minimize the risk of surgical adverse events.

4. Epidemiology, disease progression and treatment of PD in India

The prevalence rate of PD shows high heterogeneity based on the geographical region of the Indian subcontinent. There is no comprehensive and extensive epidemiological data on PD available from India (54, 55). A study from the rural parts of northern India reported a crude prevalence rate of 14.1 per 100,000, but the prevalence rate over 60 years was 247 per 100,000 (56). A study from South India reported a similar prevalence rate of 14 per 100,000 in rural areas and 41 per 100,000 in urban areas (57). Studies from the eastern parts of India reported a prevalence rate of 16.1 per 100,000 (58) and 53 per 100,000 (59) in rural areas and a prevalence rate of 40.7 per 100,000 (60) and 45.8 per 100,000 from the urban parts of the eastern region of India (61). A higher crude prevalence rate of 328.3 per 100,000 was reported from an urban Parsi community in western India (56) and a low prevalence rate of 42.3 per 100,000 was reported from a rural part of western India (62).

In 2016, India accounted for more than 10% of the global burden of PD and was home to nearly 0.58 million people living with PD, which translates to a crude prevalence of 252 per lakh (24). According to the GBD 2016, the percentage change in age-standardised rates for PD prevalence increased by 30%, and deaths due to PD changed by 56% from 1990 to 2016 (24). Notably, between 1990 and 2019, India had a rise in the crude and age-standardized prevalence of PD, with a greater increase in crude prevalence. The crude DALY rate of PD increased substantially during the same period and had variations between the Indian states. However, the age-standardised rate did not change significantly. In 2019, among the Indian states, Goa had the highest crude DALY rate. Prevalence increased notably in the older age groups from 1990 to 2019, particularly in those

older than 50 years, both in males and females (6). Genetic heterogeneity in PD has been unambiguously reported across different populations. A recent study of a cohort with early-onset PD provided evidence for a high genetic burden among Indians (63).

Improving the economy and health in India has increased the life span; however, it likely will increase the prevalence of age-related diseases like PD. Over the last three decades, the average lifespan in India has increased by 22 per cent, an increase of 12 years (64). By 2050, the population is predicted to grow by 20 per cent (65). This will lead to an increase in the number of PD patients in India. The increased disease burden will lead to an enormous strain on the economy as well as the healthcare system of the country, which already struggles to cater to the people across the geography and socio-economic strata of the country.

Many antiparkinsonian drugs, such as pramipexole, cabergoline, pergolide, and apomorphine, are limited by their availability in India. Trihexyphenidyl is more commonly prescribed in India for tremors in PD than levodopa because of its low costs, and since levodopa requires a much higher dose, that will consequently increase the treatment costs. DBS is available only in a few centres across the country and is very expensive (66). A recent study from India reported that patients diagnosed with PD spent 6.8% of per capita gross national income (GNI) on medications for PD treatment (67). Since its inception, DBS surgery has been used on more than two lakh patients(68). Due to the operation's expensive costs, which range from 6 Lakh INR to 26 Lakh INR, and the fact that this surgical procedure is only available in Tier 1 cities in India (69), the number of DBS surgeries performed annually in the country is relatively low. The DBS device used for the surgery is the main determinant of the cost variation across centres in India. Non-rechargable batteries costs as much as 5 Lakh INR and rechargable batteries are available from 11 Lakh INR in India (expert opinion). Despite the clinical effectiveness of DBS, economic evaluations are needed to

correlate these clinical improvements with the economic impact of the procedure. The objective of this study was to evaluate the cost-effectiveness of DBS for patients with PD in India.

5. Proposed Health Technology Assessment for DBS in India

With respect to the health economic evidence available from other countries and to generate evidence for recommendation for India, we proposed to do a Health Technology Assessment for DBS for PD patients in India.

Research Question:

Is DBS cost-effective compared to BMT for PD patients who are clinically suitable for the DBS therapy?

5.1. Objectives:

Primary objectives:

1. To conduct a systematic review and meta-analysis of cost-utility evidence of deep brain stimulation for Parkinson's disease
2. To conduct a Markov model-based cost-utility analysis to compare deep brain stimulation (DBS) with best medical therapy (BMT) for persons with PD, disabled with early complications, or refractory to medical care.

5.2. Methods:

5.2.1. Methods for Obj. I: To conduct an SRMA of CUA evidence of DBS for PD

Review question:

Is deep brain stimulation in patients with Parkinson's disease cost-effective in terms of incremental net benefit compared with best medical therapy**?**

Materials and methods:

The methods followed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (70) and the study protocol was pre-registered with PROSPERO, CRD42022345508.

Data Sources: A systematic electronic search was performed in medical databases i.e. MEDLINE through PubMed, Scopus, Embase and CEVR Tufts Medical Centre database from inception through to 25th July 2022. The reference lists of included studies were searched for additional studies.

The search strategy: The search terms are constructed based on domains of population, intervention, comparator, and outcome (PICO) as below. All possible subject headings specific to each database and synonyms will be listed. Then these search terms are combined using Boolean operator OR within the same domains and "AND" Boolean operator between domains of PIO as described. Detailed search terms & search strategy will be developed and reported.

(Appendix I).

PICO:

Population	Patients with Parkinson's disease (PD)
Intervention	Deep Brain Stimulation (DBS)
Comparator	Best medical therapy (BMT)
Outcome	Incremental Cost-effectiveness Ration (ICER) or Incremental Net Benefit (INB)

Inclusion Criteria:

All the full economic evaluation studies reporting results of CUA were eligible for review if they meet all the following criteria.

- Studies in patients with established PD requiring treatment and treated with DBS or DBS STN/GPi alone or in combination with BMT compared with BMT.
- Studies that reported outcomes in Incremental Cost Utility Ratio (ICUR) per QALY, Incremental Net Benefit (INB).

Exclusion Criteria:

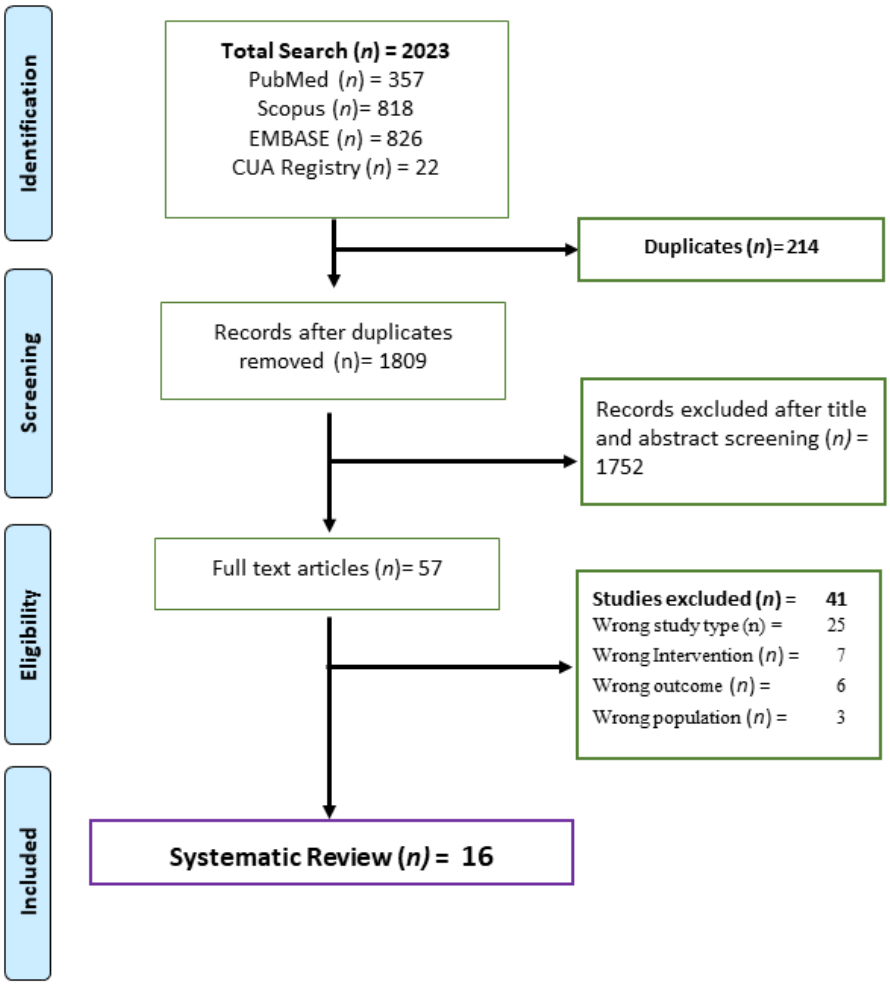
- Studies were excluded if they do not have sufficient data for meta-analysis even after contacting the author (two times).
- Studies that are published in a language that neither reviewers nor translation applications can translate.
- Studies with effectiveness measured other than in QALY, reviews, letters, editorials, abstracts, books, reports, grey literature, and methodological articles.

Study Selection

Two independent reviewers screened all studies that met the eligibility criteria listed from the electronic database search for titles and abstracts for their potential inclusion using the Rayyan-

web application (71). Reviewers independently reviewed the full text of the finalized studies after the title, abstract screening, and detailed deduplication. The reference list of recovered studies was examined for additional suitable papers. The independent assessors' mutual agreement with the arbitrator produced the final list of studies meeting the inclusion and exclusion criteria. Using an apriori data extraction form, data were collected from the final selected studies. The collected data were entered into excel, which was later imported into Stata for meta-analysis. The PRISMA flow chart of the screening process provided shows the study selection process.

Figure 1: Prisma flowchart showing study selection



Data collection process

Data extraction form (DEF) was constructed with five domains, with each domain for general information about the study, general study characteristics, characteristics of the studied population/intervention, details of methods & outcomes of economic evaluations and the data for pooling domain. In general, information domain, author, title, journal, year of publication, and authors' contact were collected. In general, study characteristics domain, study's country, perspective, type of EE, funding and conflict of interest were collected. In characteristics of the studied population/intervention domain, the details of the studied population such as age, type of interventions & comparators used were collected. In the methods and outcomes of the Economic evaluation domain, the details of time horizon, discount rates, details about the model, cost-related details, e.g., category of costs, currency & its year, the data source for costs & outcome measurements, details about uncertainty analysis, and the threshold were collected.

In the data for the pooling domain, the details of both measures of central tendency (mean) and dispersion (SD or SE or 95%CI) related data for costs and outcomes such as QALY, ICER reported along with willingness to pay (WTP)/ threshold (K) were also extracted. To deal with mean and dispersion, five scenarios were constructed as reported in Bagepally et al. (72) From the cost-effective (CE) plane graph, we extracted incremental costs (ΔC) and incremental effectiveness (ΔE) values using Web-Plot-Digitaliser (73).

Main outcome(s)

The main outcome is INB which is calculated from reported economic outcomes such as incremental costs, incremental QALYs, ICER. ICER is defined as the ratio of the difference in costs between two possible interventions, divided by the difference in their effectiveness. We

calculated INB, defined as INB = K*ΔE-ΔC, where K was the WTP threshold, ΔC-incremental cost (i.e., the difference in costs between intervention and comparator), ΔE-incremental effectiveness (i.e., the difference in effectiveness between intervention and comparator). A positive INB favours intervention, i.e., intervention is cost-effective, whereas a negative INB favours the comparator, i.e., intervention is not cost-effective. We used INB instead of ICER as the effect measure because of ambiguity in interpreting ICER and due to its inherent limitations (74). Further incorporating various adjustments while estimating INBs would help compare different cost-effectiveness studies conducted in different countries and at varied time points on a standard scale.

Measures of effect: The Incremental net benefit (INB) will be pooled across the studies for DBS vs best medical treatment.

Data synthesis

INB was converted to a common currency (USD 2022) since included studies reported in different currencies and were from different time points (years). All monetary units, were adjusted for inflation using the consumer price index (CPI) ,except for the non–GDP-based threshold (75) and were converted to purchasing power parities (PPP)-adjusted US dollar (US $) for the year 2022. All data were prepared using Microsoft Excel version 2019 (76) and analyzed using Stata software version 17 (77).

Risk of bias in individual studies:

We assessed quality independently using the modified economic evaluation bias (ECOBIAS) checklist (78). Two independent reviewers used the ECOBIAS checklist for model-based economic studies. Any discrepancies were solved by mutual consensus or with the consensus of the third arbitrator. The checklist includes 11 overall aspects of the study procedure and 11 model-specific aspects. It considers both overall biases (11 items) and model-specific biases, including

structure (4 items), data (6 items), and internal consistency (1 item). Each item was rated as applicable, partially applicable, unclear, no, or not applicable.

5.2.2. Methods for Obj II: Economic evaluation, Markov model-based cost-utility analysis.

Population	Persons with Parkinson's disease disabled with early complications, or refractory to medical care who are clinically suitable for all the below interventions (Usually with HY stage 3 and above).
Intervention	Deep brain stimulation (DBS) + Medical Therapy
Comparator	Best medical treatment (BMT)
Outcome	Incremental Cost-utility Ratio (ICUR) or Incremental Net Benefit (INB)
Study type	Economic model-based Cost-Utility Analysis (CUA)

Perspective- Public Payers (Govt)

Time horizon - The model will be developed over a lifetime time horizon with a cycle length of 6 months

Discounting All future costs and consequences will be discounted at 3% per annum as per WHO guidelines, along with sensitivity analysis with 0 to 6% per annum.

Data collection methods (For clinical parameters)

The data on probability for input parameters will be collected from published literature based on a hierarchy of evidence in the following order (i) systematic review and meta-analysis (SRMA) of randomized controlled trials (RCTs), (ii) Individual RCTs, (iii) SRMA of observational studies

(iv) Clinical trials (v) Observational studies. The primary data source for baseline transitional probabilities between the different health states will also be obtained from published literature.

Estimation of Costs and health outcomes

Cost data

The cost analysis will be undertaken from Public Payers (Govt) perspective in line with current HTAIN guidelines for health-economic analyses. We will consider all the relevant costs relating to each treatment arm. Direct medical costs (DMC) such as costs of DBS, preoperative assessment for surgery; device acquisition (costs of the device, which will include implantable pulse generator, controller electrodes, extensions for initial implantation) and implantation (cost of surgery); adverse event management (surgery-related and hardware related such as infection, lead dislodgement, battery exhaustion, hospitalization for falls); hospitalization (Inpatient care) and hospital-related costs; drug costs (BMT-levodopa and other anti-Parkinson medication); routine follow-up (neurology outpatient visits per cycle); and long term costs for device adjustment costs (monthly follow up); battery replacement or rechargeable battery cost. Direct non-medical costs (DNMC) related to hospitalization, home care, and terminal care costs will also be considered. The costing information will be taken from literature and databases such as primary costing studies (specific to India), Ayushman Bharat Package, and National Health System Cost Database for India developed by Post Graduate Institute of Medical Education and Research (PGIMER) or market prices of drugs.

Further separate (e.g., state-specific) analyses will be performed depending on the availability of cost data. All the costs will be adjusted and reported for 2022 in Indian Rupees (INR). Experts' input will be used in case of the non-availability of published information.

Utility data

Health outcomes should be stated in terms of QALYs, according to the HTAIN recommendations from India for economic assessments, with the EuroQol-5D (EQ-5D) being the chosen indicator of health-related quality of life. The utility values associated with the model health states will be elicited from the published literature using the EQ-5D index with India-specific tariffs.

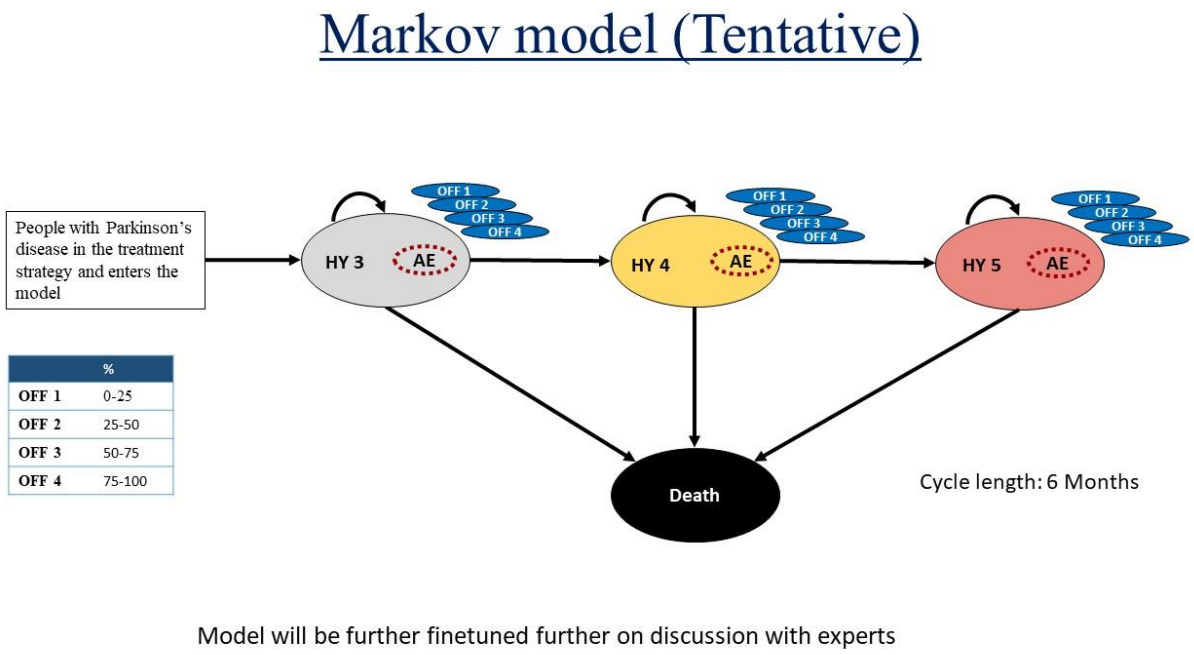
Willingness to Pay Threshold

The willingness to pay threshold (WTP) will be considered for determining cost-effectiveness. Based on World Health Organization (WHO) guidelines, per capita gross domestic product (GDP) based WTP for the year 2022 will be considered as WTP. ICER <1 times GDP of India – will be considered highly cost-effective; 1-3 times GDP of India – Cost-effective; >3 times GDP of India – not cost-effective (79, 80).

Conceptual framework of the Model

The Economic model will be adapted from previously published models considering the Hoehn and Yahr (HY)-OFF health-states (36, 44, 45, 47, 52). The rationale for considering HY-OFF states III through V as Markov was that these disease states without treatment would represent the chronic progressive nature of the disease. Under any treatment, patients may improve clinically to attain an HY-ON state equal to or better than an HY-OFF state. Costs and utilities will be modelled as a result of the HY-ON state. DBS will be compared to BMT using the same model structure. The conceptual framework of the PD outcome model is shown in Figure 1. However, the proposed model is tentative and will be suitably modified with suggestions from disease expert neurologists or movement disorder specialists.

Figure 2: Conceptual framework – Markov model



Model will be further finetuned further on discussion with experts

Overview of Tentative model

Markov modelling will be considered to be a suitable approach since it fits well with a chronic disease, the different stages of the disease, the repetition of treatment, and probabilities that change over time. The schematic Markov model is represented in Figure 1b. In the Markov model, there are four health states each for different severity of the PD, including Hoehn and Yahr (HY)-OFF states -HY3, HY4, HY5 and death (absorptive state). Each of the disease severity states will have different proportions of time spent in the "OFF" state would be included. Within each HY-OFF state, HY-ON states are assigned to represent the effect under treatment. Costs and utilities will be modelled as a result of HY-ON state and off state. Each HY-ON state is linked to specific costs and utilities and is adjusted for motor complications and for various comorbidities. The information on the proportions will be published literature or from expert opinion. The cycle length is six months. The PD patients enters the model at the HY3 stage. A half-cycle correction will be

applied. We will consider treatment-specific and disease-related adverse events (AEs) in the model. Three AE types among DBS patients will be included, i.e., surgery-related AEs (such as bleeding events and infections); hardware-related AEs (e.g., lead fractures and migrations); and other AEs such as worsening of mobility.

Results reporting:

Deterministic Markov model results will be reported as Quality Adjusted Life Years (QALYs) and per Life Years (LYs) as the measure of effectiveness. The total costs and total QALYs gained for the intervention and comparator will be calculated for a lifetime. Incremental cost/QALY will be determined as the difference between the total cost/QALY of the intervention and the comparator. ICER is obtained by taking the ratio of incremental costs over incremental QALY.

ICER = (Costs of DBS - Costs of BMT) / (QALY of DBS - QALY of BMT)

Incremental Net Benefit is calculated using the formula.

$$INB = K * \Delta E - \Delta C$$

Where K is the willingness to pay threshold, which is one time of GDP of India for the year 2022, ΔE is the incremental QALY, and ΔC is incremental costs.

Budget impact analysis

If intervention is cost-effective then to conduct Budget impact analysis using the standard methods for a period of 5 years.

Sensitivity analysis

The robustness of the model will be assessed using sensitivity analysis including one-way sensitivity analysis and probabilistic sensitivity analysis (PSA). In one-way sensitivity analysis, upper and lower limits with 25% or 95% Confidence Interval values of the model inputs depending

on the availability will be used and reported as tornado diagrams. PSA will be performed with Monte Carlo simulation for 5000 times based on its data distribution. Costs data would be simulated using Gamma distribution, prevalence &/or proportions with normal distribution and transitional probabilities using beta distribution. Results will be reported with a cost-effectiveness plane and CE-acceptability curve. Total and incremental discounted costs, QALYS, and the resulting ICER will be computed for each scenario. The overall analysis and reporting of results were conducted in compliance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)(81).

Expected outcome and impact

HTA evidence would be generated on the cost-effectiveness of DBS in the treatment of PD for evidence-based policy decision making in this regard, as the treatment cost is not affordable by most of the patients. Its impact on the budget would also be determined.

6. Results: Systematic review of CUA evidence for DBS in PD

6.1. Results

A systematic search of multiple peer-reviewed repositories yielded 2,023 studies, from which fifty-seven articles underwent full-text screening. Of these, sixteen articles focused on cost-utility analyses were included in the final analysis. The screening process is provided in PRISMA flow chart, Figure 1. These sixteen studies reported nineteen comparisons (36, 44, 45, 82-94) (Figure 1). Among these, DBS was compared with BMT in 12 studies with 14 comparisons (36, 44, 45, 83, 85-90, 92, 93), while single studies compared DBS with bilateral radiofrequency ablation (bRF) (91), magnetic resonance-guided focused ultrasound thalamotomy (MRgFUS) (94), apomorphine subcutaneous infusion (ASBI) (84), and Continuous Subcutaneous Apomorphine Infusion (CSAI)(82). The majority of studies involved individuals with advanced PD, though one study focused on early-stage PD (36) and another on tremor-dominant PD (TDPD) (94). (Table 1) Eleven studies with thirteen comparisons adopted a payer's perspective (36, 44, 45, 82-86, 90, 92, 93), while the remaining five studies with six comparisons were conducted from a societal perspective (87-89, 91, 94). All studies included in our review were conducted in high-income countries, with four comparisons from the UK (45, 82, 85, 90), three comparisons from the USA (86, 89, 91) and Germany (36, 44, 82), two comparisons from Spain (83, 84), Taiwan (87) and Hong Kong (92), and one study each from Sweden (88), Japan (93), and Canada (94). Ten studies utilized a Markov model (36, 44, 45, 82, 84-88, 93), while two studies employed a decision tree (91, 94) and prospective studies (83, 92), respectively. Furthermore, McIntosh et al. (2015) conducted an alongside trial (90), and Tomaszewski et al. (2000) used a semi-Markov process(89). Some studies used a 6-month cycle length (45, 85, 93), while Dams et al. 2013 used a 1-year cycle length (44), and Fann et al. (2020) used a 3-month cycle length (87).

Table 1: Characteristics of the Included Cost Utility Studies for DBS

Author_Year	Comparator	Target population	Perspective	Country (Currency)	Analytic approach	Time Horizon	Discount Rate for costs,	Incr cost (Mean±SD)	Incr Qaly (Mean±SD)	ICUR reported	Reported Findings	INB (USD 2022)	Current Findings
Norlin_2021	BMT	PD H&Y 1 to 5	Societal	Sweden (SEK)	Markov	5 yrs	3	-165,135	1.22		CE	36,389	CE
Mahajan_2021	bRF	PD suitable for surgical intervention	Societal	USA (USD)	DT	22 mos	NS	-2,940	0.048	-59,620	CE	5,637	CE
Meng_2021	MRgFUS thalotomy	Tremor dominant PD	Societal	Canada (CAD)	DT	3 yrs	1.5*	8,726	0.15	56,503	NCE	-1,488	NCE
Fann_2020	BMT	Late PD	Societal	Taiwan (USD)	Markov	3 yrs	3	44,896	0.519	123,436	NCE	-162,229	NCE
	BMT	Late PD	Societal	Taiwan (USD)	Markov	10 yrs	3	53,322	1.309	69,033	CE	11,983	CE
Vivancos_2016	ASBI	Late PD	Payer	Spain (Euro)	Markov	5 yrs	3.5	-20,871	-0.085	245,541	CE	36,706	CE
Dams_2016	BMT	Early PD	Payer	Germany (Euro)	Markov	Lifetime	3	36,400	1.6	22,700	CE	10,515	CE
Pietzch_2016	BMT	Late PD	Payer	USA (USD)	Markov	10 yrs	3	39,484	1.69	23,404	CE	35,579	CE
Fundament_2016	BMT	Advanced PD	Payer	UK (Pound)	Markov	15 yrs	3.5	26,799	1.34	19,887	CE	-10,340	NCE
Mc Intosh_2016	BMT	Advanced PD	Payer	UK (Pound)	AT	1 yr	3.5	9,256 ±827.04	0.01 ± 0.03	468,528	NCE	-9,166	NCE
Kawamoto_2016	BMT	60-year-old Japanese male PD	Payer	Japan (Yen)	Markov	10 yrs	NS	17,500,000	6.7	3,100,000	CE	62,421	CE
Walter_2015	CSAI	Advanced PD	Payer	UK (Pound)	Markov	Lifetime	3.5	9,479	-0.1		NCE	-20,093	NCE
	CSAI	Advanced PD	Payer	Germany (Euro)	Markov	Lifetime	3	1,237	-0.08		NCE	-4,290	NCE
Zhu_2014	BMT	Advanced PD	Payer	China-Hongkong (USD)	PS	1 yr	3	926	0.203	123,110	NCE	-2,3403	NCE
	BMT	Advanced PD	Payer	China-Hongkong (USD)	PS	2 yrs	3	421	0.158	62,846	CE	-12,203	CE
Eggington_2014	BMT	Advanced PD	Payer	UK (Pound)	Markov	5 yrs	3.5	20,727	1.002	20,678	CE	-10,324	NCE
Dams_2013	BMT	Advanced PD	Payer	Germany (Euro)	Markov	lifetime	3	6,994	1.05	6,677	CE	34,358	CE
Valldeoriola_2007	BMT	Advanced PD	Payer	Spain (Euro)	PS	1 yr	NA	7,601	0.221	34,389	CE	-6,090	NCE
Tomaszewski_2001	BMT	PD patients aged ≥50 H&Y 3 and 5)	Societal	USA (USD)	sM	lifetime	3	35,000	0.72	49,194	NCE	-24,225	NCE

Intervention is DBS for all studies *Only for cost.

bRF bilateral radiofrequency ablation, MRgFUS Magnetic Resonance-guided focused Ultrasound Surgery, BMT Best Medical Therapy, ASBI Apomorphine Subcutaneous Infusion, CSAI Continuous Subcutaneous Apomorphine Infusion, H&Y Hoehn and Yahr, MM Markov model, sM semi-Markov process, PS Prospective study, DT Decision tree, AT Alongside trial CE cost effective, NCE not cost effective, ICUR Incremental cost utility ratio, , INB Incremental net benefit, USD US dollar, NS is not specified and NA is not applicable

While disease progression is often determined according to Hoehn and Yahr (H&Y) stages, Fann et al. (2020) utilized regression analysis to obtain a H&Y stage proxy based on the UPDRS motor score (87). Dams et al. (2016) used the algorithm by Young et al. (2013) for early PD(95). Among the 16 CUAs, nine comparisons utilized a 3% discount rate for both cost and effects (36, 44, 82, 86-89, 92), while four comparisons employed a 3.5% discount rate for both costs and effects (45, 82, 84, 85). One study from Canada only reported a discount rate of 1.5% for effects (94). Kawamoto et al. (2016) did not report the discount rate for costs and effects (93).

Health resource costs were derived from various sources, including national guidelines, national health insurance databases, clinical trials, hospital cost departments, and published studies. These sources included Medicare in the USA (89), the National Health Insurance of Spain (83), clinical databases in Sweden (88), the Hospital financial department in China (92), the PD SURG clinical trial (45, 90), and guidelines from the Japanese Society of Neurology (93), and German Parkinson's guidelines (82), among others. Most of the studies utilized input parameters sourced from the EARLYSTIM Trial (96), the Deuschl RCT (97), or the PDSURG trial (98) for the model effectiveness measures. Time horizons for the studies ranged from one year to a lifetime, with Fann et al. (2020) and Zhu et al. (2014) providing two horizons, a shorter and longer one (87, 92). Walter et al. (2015) provided data from two countries, Germany and the UK (82). Four studies with five comparisons reported a lifetime horizon (36, 44, 82, 89).

All CUAs included direct costs specific to DBS costs, such as surgery, calibration, pulse generator replacement, temporary and permanent DBS complications. For the annual drug costs follow-up visits, annual home or nursing home care, and hospital admissions costs were considered. Only one recent CUA used Diagnosis Related Groups (DRG) for battery exchange, (36) while older studies used DRG for cardiac pacemaker exchange (44). However, equipment costs such as DBS

implants were not included in some studies, and Mahajan et al.(2021) used Medicare reimbursement as a proxy for the societal cost (91), and Zhu et al.(2014) collected baseline costs retrospectively (92). Some studies excluded the costs of adverse events for DBS (93), and some studies assumed the costs to be constant over time, even when cost data were collected over a more extended period of time (85).

All other studies reported country-specific thresholds except two studies. Zhu et al. (2014) did not provide a willingness-to-pay threshold and reported that the treatment cost exceeded the recommended cost-effective range in Europe but was in the upper end of the cost-effective range in the United States. Fann et al. (2020) used a threshold of three times the GDP per capita in Taiwan. The year of reference for the studies ranged from 2001 to 2020. Only four studies reported results of probabilistic sensitivity analysis (82, 85, 87, 90, 93).

6.1.1. Quality Appraisal:

The risk of bias in the selected studies was assessed using the ECOBIAS checklist (31). Nearly, 80% of the studies used the BMT as a comparator and all comparators were adequately described. Data transparency was reported to be adequate across all studies. Sufficient information was provided on costs, effectiveness, discount rates, and funding sources. Selection bias related to model choice was negligible. However, the studies were found to have a high risk of bias related to time horizon, as most studies did not employ a lifetime horizon. Further, the chance of limited scope bias was higher, and the internal consistency related to mathematical logic was not evident in nearly all studies.

Figure 3: Assessment of Risk of Bias Using ECOBIAS Checklist

Author_Year	Norlin_2021	Mahajan_2021	Meng_2020	Fann_2020	Fann_2020	Vivancos_2016	Dams_2016	Pietzch_2016	FUCndament_2016	Mc Intosh_2016	Kawamoto_2016	Walter_2015	ZhUC_2014	Eggington_2014	Dams_2013	Valldeoriola_2007	Tomaszewski_2001
Narrow perspective bias	Y	Y	Y	Y	Y	P	P	P	P	P	P	P	N	N	N	N	N
Inefficient comparator bias*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Cost measurement omission bias	Y	Y	P	P	P	P	P	Y	P	Y	P	P	P	Y	P	P	P
Intermittent data collection bias	Y	P	P	P	P	P	P	Y	P	P	P	P	P	Y	P	P	P
Invalid valuation bias	Y	Y	P	P	P	P	Y	Y	P	Y	P	P	Y	Y	P	P	P
Ordinal ICER bias	Y	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Double-counting bias	UC	UC	UC	UC	P	UC	P	UC	P	P	P	P	P	UC	P	P	UC
Inappropriate discounting bias	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	P	Y	Y	Y
Limited sensitivity analysis bias§	P	P	P	UC	UC	P	P	UC	P	P	UC	UC	P	UC	P	UC	P
Sponsor bias	Y	Y	N	P	P	N	Y	Y	Y	Y	P	P	Y	Y	Y	P	N
Reporting and dissemination bias	UC	Y	UC	Y	Y	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC
Structural assumptions bias	Y	Y	P	Y	Y	P	Y	Y	P	P	Y	Y	Y	Y	P	Y	P
No treatment comparator bias*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wrong model bias	Y	P	P	Y	Y	P	P	P	P	P	Y	Y	P	P	P	Y	P
Limited time horizon bias	P	Y	P	Y	Y	P	Y	P	P	N	Y	Y	Y	P	P	Y	P
Bias related to data identification	P	P	P	P	P	P	P	Y	Y	Y	P	P	P	Y	Y	P	P
Bias related to baseline data	Y	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Bias related to treatment effects	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Bias related to quality-of-life weights (utilities)	Y	Y	P	P	P	P	Y	Y	Y	Y	P	P	Y	Y	Y	P	P
Non-transparent data incorporation bias	Y	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Limited scope bias§	P	UC	UC	P	P	UC	UC	P	P	P	P	P	UC	P	P	P	UC
Bias related to internal consistency	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC	UC

6.1.2. Cost-effectiveness of DBS vs BMT:

A total of 14 comparisons from 12 studies reported on the cost-effectiveness (CE) of deep brain stimulation (DBS) compared to best medical treatment (BMT) (36, 44, 45, 83, 85-90, 92, 93). Ten comparisons reported DBS as cost-effective based on ICUR results (36, 44, 45, 83, 85-88, 92, 93). However, only six comparisons were cost effective based on our incremental net benefit (INB) results (Table 1).

Fann et al. (2020) provided CE estimates for short-term and long-term evaluation (3-year and 10-year time horizon) from a societal perspective (87), while Zhu et al. 2014 reported on a 1-year and 2-year time horizon from a healthcare provider perspective (92). Although Fann et al. (2020) indicated that DBS was not cost-effective over a 3-year horizon, it became cost-effective over a 10-year horizon. Conversely, Zhu et al. (2014) reported that DBS was cost-effective over a two-year horizon but not over a one-year horizon. However, INB calculations showed that it is not cost-effective for both time horizons. Of the ten studies that reported DBS as cost-effective, three studies; Valldeoriola et al., 2007, Eggington et al. (2014); Fundamet et al. (2016) and were not deemed cost-effective based on our incremental net benefit (INB) results (Table 1).

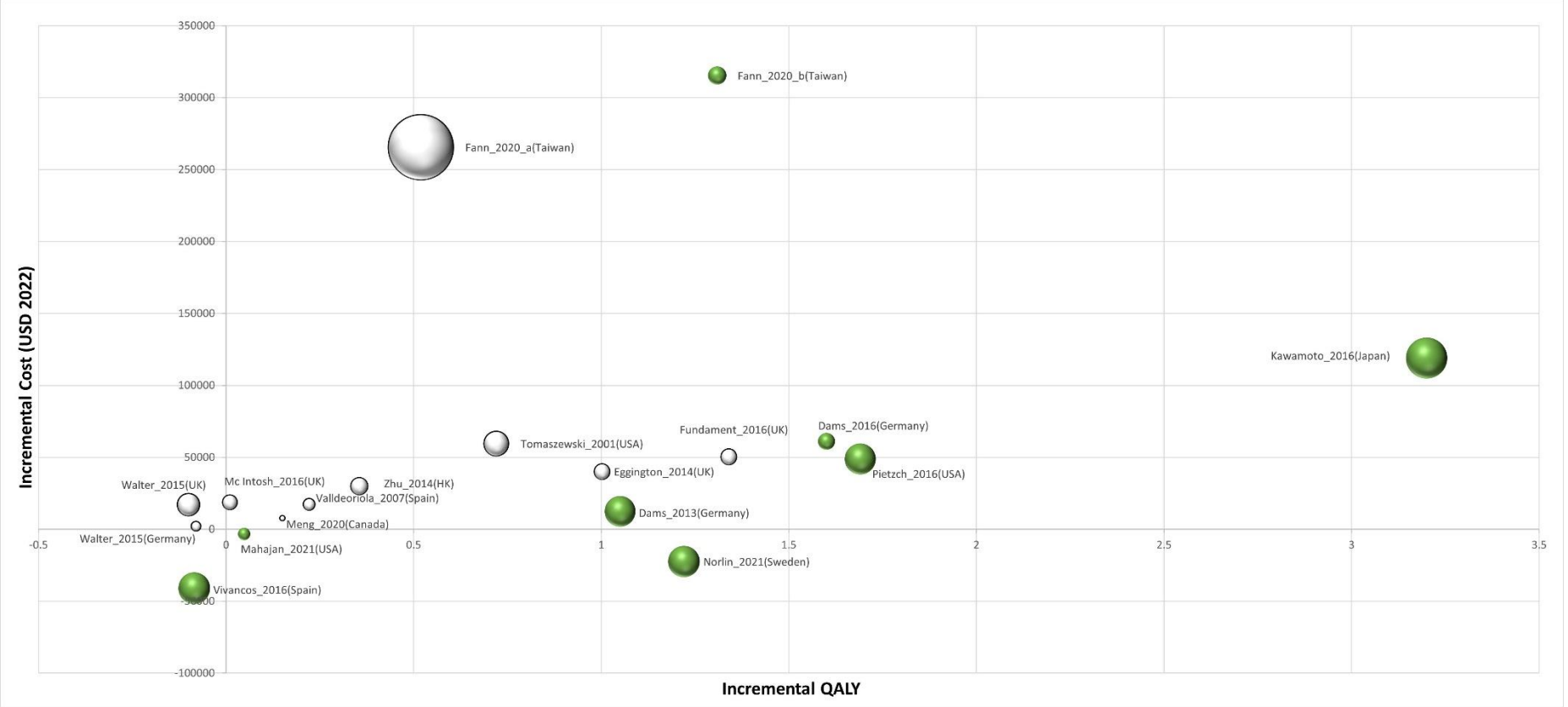
Specifically, INB analysis showed that some four comparisons that reported DBS as not cost-effective when compared to BMT remained not cost-effective after INB calculations (87, 89, 90, 92). Furthermore, four comparisons that reported DBS as cost-effective when compared to BMT became not cost-effective (83, 85, 92, 99). It is worth noting that three of the comparisons with shorter time horizon studies remained not cost-effective (87, 90, 92). Studies with a longer time horizon (>5 years) generally reported DBS as cost-effective compared to BMT, except for Thomaazweski et al (2000), which stated QOL had to increase by 18% for DBS to become cost-

effective.. The INB calculation also showed the same; however, for DBS vs BMT, Fundament et al (2016) and Eggington et al. (2014) was found not to be cost-effective on INB calculation. Figure 4 illustrates the incremental cost in USD, adjusted for PPP and CPI for 2022, plotted against incremental QALYs, with the size of each data point representing the incremental net benefit (INB).

6.1.3. Cost-effectiveness of DBS vs. Other Device-Aided Therapies (DAT):

Four studies with six comparisons reported on the cost-effectiveness of DBS compared to other treatments (82, 84, 91, 94). DBS was reported to be cost-effective when compared to bRF (91) and ASBI (84), with our INB calculations also reporting them as cost-effective. However, DBS was not cost-effective compared to MRgFUS thalotomy for TDPD from a societal perspective (94). A study by Walter et al. (2015) concluded that CSAI could be a viable alternative treatment for advanced PD patients, as it was found to dominate DBS in terms of cost-effectiveness (82). However, the study reported that the utilities and costs were similar for both treatment options in the UK and Germany from a healthcare providers' perspective (82). Our INB results confirmed these findings that DBS is not cost-effective compared to CSAI.

Figure 4: Cost effectiveness plane indicating each study results on the cost effectiveness of Deep brain stimulation.



The Size of the blob indicate the incremental net benefit (INB).

6.2. Discussion

This systematic review synthesized cost-effectiveness evidence for DBS in PD from published cost-utility analyses. The majority of the included studies compared DBS with BMT among advanced PD patients. While a few other comparisons include bRF, MRgFUS, ASBI, and CSAI. The included studies in the review are all from high-income countries, with the UK, USA, and Germany being the most represented. Most studies adopted a payer's perspective, with a few considering a societal perspective. Health resource costs and analytical time horizons varied among studies, ranging from one year to a lifetime. Most studies' indicate that DBS is a cost-effective for PD compared to BMT. However, the cost-effectiveness of DS varies according to the country, time horizon, perspective adopted, and threshold used.

Reported cost-effectiveness of DBS varied based on the source of effectiveness and cost data being considered. Eggington et al. (2014) reported favourable ICERs using clinical data from the Deuschl RCT (97). In contrast, McIntosh et al. (2015), done alongside the PD SURG study, reported less favorable results for DBS (100). The PD SURG study had used a micro-costing methodology to ascertain costs associated with DBS and BMT, as well as their long-term implications (100). Nevertheless, considering the elapsed time since the clinical investigation, the possibility of including outdated practices cannot be disregarded. Regarding other DATs, the effectiveness evidence for LCIG, and apomorphine pumps is limited (88). Walter et al. (2015) concluded CSAI dominated DBS, even though costs and utilities were nearly the same for both treatment options. Although MRgFUS remains a viable option to DBS, the cost-effectiveness advantage is less substantial (94). Furthermore, even though Mahajan et al. (2021) had reported lower treatment costs for Focused Ultrasound (FUS) (91), the FUS equipment is quite costly; hence, even if the procedure is cost-effective, its immediate adoption and scalability may be

limited. More studies are needed to comparing the cost-effectiveness of DBS with levodopa-carbidopa intestinal gel, subcutaneous apomorphine infusion in order to inform decision-making regarding the most effective and efficient treatment approach. Also, future studies should investigate the cost-effectiveness of DBS for different subgroups of PD patients, such as those with early-stage or TDPD, as well as for different DBS targets.

Owing to a myriad of pragmatic factors, prior cost-effectiveness analyses pertaining to DBS have been hindered by several limitations. These include the absence of randomized comparisons (83), an exclusive focus on costs with a narrow perspective and constrained cost considerations (83, 89), insufficient data concerning adverse events and associated costs (93, 101), limited sample sizes for resource utilization and outcomes (83), limited samples for utility estimates (101), inadequate assessment of quality of life parameters (89, 92), a dearth of information pertaining to operative resource details (83), the exclusion of health and social service follow-up costs (83, 101), an absence of suitable missing data analyses(101), and a reliance on fee-based pricing (83), cost estimates for both permanent and temporary DBS complications were predicated on considerably outdated evidence (44). In addition, the models included the differences in drug costs only for PD-specific medications, and non-PD medications were not considered.

In conducting cost-effectiveness analysis for DBS in PD differences in methodology, estimation duration, and input cohorts, such as disease progression across nationalities or races, may impact the results. For example, the difference in QALY gain varies between Asian countries, with Taiwan having a lower QALY gain than Japan for a 10-year estimation. The higher cost of initial implantation in Taiwan could account for the varying outcomes in cost-effectiveness. Also, the 2-year ICUR for CUA based on real data in Hong Kong, was much lower than the 3-year ICUR estimation from Taiwan. Further, implementing DBS treatment for PD presents various

complexities. The lack of well-established eligibility criteria and frequent contraindications hinder the appropriate assignment of this treatment modality (102). Additionally, a scarcity of neurologists with expertise in DBS and other DAT's poses organizational challenges for its broader application (88). Long waiting times for initiating DAT, particularly DBS, are common and further exacerbated by the ongoing pressures on healthcare delivery due to the COVID-19 pandemic (103). The underutilization of DBS may be attributed to suboptimal economic incentives within distinct cost-bearing entities, necessitating further investigation into financial frameworks for treatment allocation (44). Further, there is a conspicuous paucity of data from lower-middle-income countries (LMIC) and low-income countries (LIC) regarding the cost-effectiveness of DBS for PD.

In the context of decision making for PD treatmets, it is important of acknowledge the key sources of uncertainty in economic modeling, namely the Markovian assumption that current health rather than previous health history determines the unit costs for health states. It is often not clear in the context of PD whether patients who receive less supportive care, those who moved to less expensive home care, or those who returned to work without delay when PD symptoms improved are reassigned from worse to better health states. Consideration should be given to potential cost offsets associated with reductions in productivity loss and home care, as these depend on the stage of disease at the time of treatment initiation. Additionally it is important to acknowledge that if DBS is intiated too late in the PD disease progression, the cost offsets would be consideribly less. Therefore, careful evaluation of the potential benefits and costs of DBS therapy, including the potential for cost offsets, should be considered when making decisions regarding PD treatment. The unavailability of dispersion measures, such as standard deviations or confidence intervals, for ICUR and incremental cost and effectiveness in the included studies limited our capacity to

compute the variance of INB. Consequently, we were unable to perform a meta-analysis to synthesize the available evidence. There is no clear trend suggesting that DBS is cost-effective for PD patients who do not respond well to medical therapy. The heterogeneity of study methodologies, perspectives, and outcomes in the CUA's makes it challenging to draw definitive conclusions. As such, it is crucial to consider the individual patient's clinical characteristics, disease stage, and response to medical therapy when making treatment decisions.

6.3. Conclusion

In conclusion, while DBS has demonstrated promising results for the management of PD, there is a need for further research to fully understand whether it is cost-effective. The cost-effectiveness evidence for DBS in PD is context-specific and varies depending on the study perspective, costs considered, threshold utilized and the stage of PD progression. Moreover, there is a dearth of data from LICs and LMICs on the cost-effectiveness of DBS for PD. Future research should focus on evaluating the cost-effectiveness of DBS in distinct subgroups of PD patients, including those with early-stage or tremor-dominant PD, and those undergoing DBS at different targets. Furthermore, it is crucial to standardize approaches in CUAs, comparing DBS with other regular or current practice treatment options for any relevant policy translation for the clinical management of PD. Consensus on the most appropriate methodology, perspective, and reporting guidelines would greatly improve the comparability of study results and facilitate decision-making for healthcare providers, policymakers, and patients.

7. Critique of the proposed study by HTAIn Technical Appraisal Committee (TAC)

7.1. Critique of the decision problem in the submitted proposal

The population defined in the scope is Persons with Parkinson's disease disabled with early complications, or refractory to medical care who are clinically suitable for all the below interventions (Usually with HY stage 3 and above). However, the committee sought and recommended clarity in the clinical decision as to which stage of the PD patients can undergo a DBS therapy. The committee agreed that any PD patients recommended after clinical evaluation for DBS surgery, in H& Y stage III or above or with tremor is usually recommended to undergo DBS therapy.

7.2. Summary of the key issues in the clinical effectiveness evidence

The committee questioned the availability of clinical evidence from India and discussed how the implementation of DBS for PD is in a benign state in India and has not penetrated even outside of Tier 1 cities, and the number of surgeries performed annually is around 500.

7.3. Summary of the key issues in the cost effectiveness evidence

DBS therapy for PD in India is very costly. The committee also contemplated that the cost is primarily due to the hardware device, which needs to be made available at lower rates as a large population in a developing country like India is not able to afford it. The committee agrees with the overall benefit of DBS for PD and how this will improve the quality of life for PD patients. However, the committee questioned whether DBS could be included as a package in the PMJAY program, implying that because PD prevalence is lower in India, available medical resources could be used for other medical conditions that would add more value to the PMJAY program.

7.4. Conclusion

Our systematic review of CUA studies revealed that the cost-effectiveness of DBS for PD varies by study perspective, costs considered, threshold utilized, and stage of PD progression. The unavailability of dispersion measures, such as standard deviations or confidence intervals, for ICUR and incremental cost and effectiveness in the included studies limited our capacity to compute the variance of INB. Consequently, we were unable to perform a meta-analysis to synthesize the available evidence. Standardizing approaches and comparing DBS with other treatments are needed for future research on effective PD management. However, the availability, accessibility, affordability. with equity in distribution to be considered by the policy makers while considering implementation of such an advanced level of services.

The committee considers that the present study may not be undertaken since it may not add immediate value to the Ayushman Bharat PM-JAY since DBS therapy is very costly and will take more money and time to penetrate into places other than Tier 1 cities, where it is currently restricted. The presented cost effectiveness results from different countries may provide a possible insight into the direction of the cost-effectiveness of DBS therapy for PD in India.

With respect to the current proposed study, there is a wealth of evidence available from other high-income economies, and even though there is evidence that DBS is cost-effective, it may be difficult to interpret generally or specifically with respect to India as such. However, the implications of the proposed study are meaningful if we wish to proceed with further evaluations to see whether DBS is cost-effective for patients with PD.

The committee reported that since DBS is an expensive treatment that has been developed for Parkinson's disease (PD), a cost-utility analysis for India is required. Further, the committee highlighted that, according to the UK National Institute for Health and Clinical Excellence (NICE), subthalamic deep brain stimulation (STN-DBS) is an effective therapy that can immediately improve the quality of life in Parkinson's disease patients. The ICER/QALY in STN-DBS patients has been estimated to be within appropriate limits to consider STN-DBS as an efficient therapy in the UK. The committee's final recommendation was to establish a decision-making mechanism for Parkinson's disease, similar to the UK's NICE, so that medical resources can be redistributed openly and justly in accordance with the ICER. Additionally, the committee mentioned that since the role of deep brain stimulation is well known for increasing quality of life for PD patients, primary care should include management of Parkinson's disease as well, and suggestions were made as to whether NHA could fund the proposed study.

APPENDIX I

Search strategy

	PubMed Search	Hits as on 25th July 2022
P	("movement disorders"[Mesh] OR "abnormal movements" OR "movement disorders" OR "parkinson disease"[Mesh] OR "Parkinson disease" OR parkinson's OR parkinsonism OR parkinson OR parkinsonian syndrome) OR (parkinson)	219,760
I	"parkinson surgery" OR "parkinson treatment" OR "deep brain stimulation"[Mesh] OR "deep brain stimulation" OR neuromodulation OR "Neurosurgical Procedures" OR "Neurosurgical Procedures"[Mesh] OR neurostimulation OR "Brain Stimulations" OR "Electrical Stimulation of the Brain" OR DBS OR "Globus Pallidus"[Mesh] OR "Globus pallidus" OR GPi OR "Subthalamic Nucleus" OR "Subthalamic Nucleus"[Mesh] OR STN OR "Ventral Thalamic Nuclei"[Mesh] OR "ventral thalamic nuclei" OR VIM OR "Electric Stimulation Therapy"	1,693,483
O	QALY OR “quality adjusted” OR “life year” OR “life years” OR DALY OR “disability adjusted” OR “cost effective” OR cost-utility OR “cost utility” OR ICER OR ICERS OR INB OR "economics"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms]	749,704
	P I O	357

	Embase Search	Hits as on 25th July 2022
P	'parkinson disease'/exp OR 'lewy bodies of parkinson disease' OR 'lewy bodies of parkinson`s disease' OR 'lewy bodies of parkinsons disease' OR 'lewy body parkinson disease' OR 'lewy body parkinson`s disease' OR 'lewy body parkinsons disease' OR 'parkinson dementia complex' OR 'parkinson disease' OR 'parkinson`s disease' OR 'parkinsons disease' OR 'idiopathic parkinsonism' OR 'paralysis agitans' OR 'primary parkinsonism'	213,264
I	'brain depth stimulation'/exp OR 'brain depth stimulation' OR 'bra stimulation' OR 'brain stimulus' OR 'deep brain stimulation' OR 'e OR 'excitation, brain' OR 'deep brain stimulator'/exp OR 'activa t 'activa dbs' OR 'dbs reclaim' OR 'medtronic dbs' OR 'percept (dee 'percept dbs' OR 'percept pc' OR 'suretek' OR 'vercise' OR 'vercis OR 'vercise gevia' OR 'vercise pc' OR 'deep brain electrical stimu brain stimulation device' OR 'deep brain stimulation system' OR ' 'brain depth stimulation'/exp OR 'brain depth stimulation' OR 'bra stimulation' OR 'brain stimulus' OR 'deep brain stimulation' OR 'e OR 'excitation, brain' OR 'deep brain stimulator'/exp OR 'activa t 'activa dbs' OR 'dbs reclaim' OR 'medtronic dbs' OR 'percept (dee 'percept dbs' OR 'percept pc' OR 'suretek' OR 'vercise' OR 'vercis OR 'vercise gevia' OR 'vercise pc' OR 'deep brain electrical stimu brain stimulation device' OR 'deep brain stimulation system' OR '	61,170
O	'cost benefit analysis'/exp OR 'cost analysis' OR 'cost benefit' OR 'cost benefit analysis' OR 'cost benefit ratio' OR 'cost-benefit analysis' OR 'cost minimization analysis'/exp OR 'cost minimization' OR 'cost minimization analysis' OR ‘quality of life’ OR ‘QALY’ OR ‘quality adjusted’ OR ‘life year’ OR ‘life years’ OR ‘DALY’ OR ‘disability adjusted’ OR ‘ICER’ OR ‘ICERS’ OR INB OR 'cost effectiveness analysis'/exp OR 'cost effectiveness' OR 'cost effectiveness analysis' OR 'cost effectiveness ratio' OR 'cost efficiency analysis' OR ‘willingness to pay’ OR 'cost utility analysis'/exp OR 'cost utility' OR 'cost utility analysis'	987,255
	P I O	2,388
	#5 AND **'human'**/de AND **'article'**/it	826

	Scopus search	Hits as on 25th July 2022
P	("movement disorders" OR "abnormal movements" OR "movement disorders" OR "parkinson disease" OR "Parkinson disease" OR parkinson's OR parkinsonism OR parkinson OR parkinsonian syndrome) OR (parkinson)	917,850 document results
I	"parkinson surgery" OR "parkinson treatment" OR "deep brain stimulation" OR "deep brain stimulation" OR neuromodulation OR "Neurosurgical Procedures" OR "Neurosurgical Procedures" OR neurostimulation OR "Brain Stimulations" OR "Electrical Stimulation of the Brain" OR dbs OR "Globus Pallidus" OR "Globus pallidus" OR gpi OR "Subthalamic Nucleus" OR "Subthalamic Nucleus" OR stn OR "Ventral Thalamic Nuclei" OR "ventral thalamic nuclei" OR vim OR "Electric Stimulation Therapy"	536,525 document results
O	"cost effectiv*" OR "cost utility" OR "cost benefit" OR "cost-benefit" OR "quality adjusted life years" OR qaly OR ly OR "life year$" OR daly OR “disability adjusted” OR "incremental cost effective ratio" OR "ICER" OR "incremental net benefit" OR inb OR “cost-effectiveness” OR “cost effectiveness ratio” OR “cost efficiency analys?s” OR “cost utility”	2,341,410 document results
	P & I & O	5,824 document results
	TITLE-ABS-KEY (P & I & O)	1,762 document results
	TITLE-ABS-KEY ("movement disorders" OR "abnormal movements" OR "movement disorders" OR "parkinson disease" OR "Parkinson disease" OR parkinson's OR parkinsonism OR parkinson OR parkinsonian AND syndrome OR (parkinson)) AND ("parkinson surgery" OR "parkinson treatment" OR "deep brain stimulation" OR "deep brain stimulation" OR neuromodulation OR "Neurosurgical Procedures" OR "Neurosurgical Procedures" OR neurostimulation OR "Brain Stimulations" OR "Electrical Stimulation of the Brain" OR dbs OR "Globus Pallidus" OR "Globus pallidus" OR gpi OR "Subthalamic Nucleus" OR "Subthalamic Nucleus" OR stn OR "Ventral Thalamic Nuclei" OR "ventral thalamic nuclei" OR vim OR "Electric Stimulation Therapy") AND ("cost	818 document results

	effectiv*" OR "cost utility" OR "cost benefit" OR "cost-benefit" OR "quality adjusted life years" OR qaly OR ly OR "life year$" OR daly OR "disability adjusted" OR "incremental cost effective ratio" OR "ICER" OR "incremental net benefit" OR inb OR "cost-effectiveness" OR "cost effectiveness ratio" OR "cost efficiency analys?s" OR "cost utility") AND (LIMIT-TO (DOCTYPE , "ar"))	

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Yes
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Yes
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Yes
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Yes
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Yes
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Yes
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Yes
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Yes
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Yes
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Yes

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Yes
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Yes
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Yes
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Yes
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Yes
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Yes
Study characteristics	17	Cite each included study and present its characteristics.	Yes
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Yes
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Yes
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Yes
	23b	Discuss any limitations of the evidence included in the review.	Yes
	23c	Discuss any limitations of the review processes used.	Yes
	23d	Discuss implications of the results for practice, policy, and future research.	Yes
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Yes
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Yes
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Yes
Competing interests	26	Declare any competing interests of review authors.	Yes
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

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