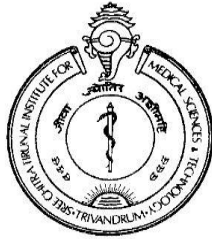


**SREE CHITRA TIRUNAL INSTITUTE FOR
MEDICAL SCIENCES AND TECHNOLOGY**
THIRUVANANTHAPURAM, KERALA



**Challenges and Obstacles to Deep brain stimulation
surgery in Parkinson's disease: Perspective from a
developing country**

Dissertation submitted in partial fulfilment of the rules and regulations for
Post-Doctoral Fellowship in Movement Disorders

By

Dr. Patel Khushboo Subhash

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(01/01/2021 to 31/12/2021)

Month and Year of Submission: December 2021

Department of Neurology

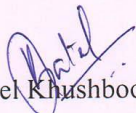
Sree Chitra Tirunal Institute for Medical Sciences and Technology

Thiruvananthapuram

DECLARATION

I, Dr. Patel Khushboo Subhash, hereby declare that this project was undertaken by me under the supervision of Dr Syam K, Professor and In-charge, Comprehensive Care Center for Movement Disorders, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

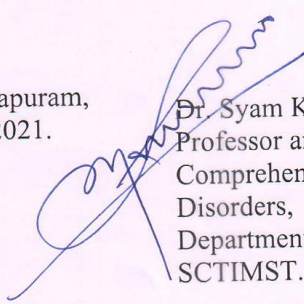
Thiruvananthapuram,
Date: 15-12-2021.


Dr. Patel Khushboo Subhash

Forwarded:

The candidate, Dr. Patel Khushboo Subhash, has completed the project under my guidance.

Thiruvananthapuram,
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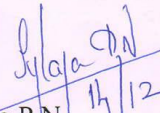


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The candidate, Dr. Patel Khushboo Subhash, has carried out the minimum required project for completion of Post-Doctoral Fellowship in Movement disorder.

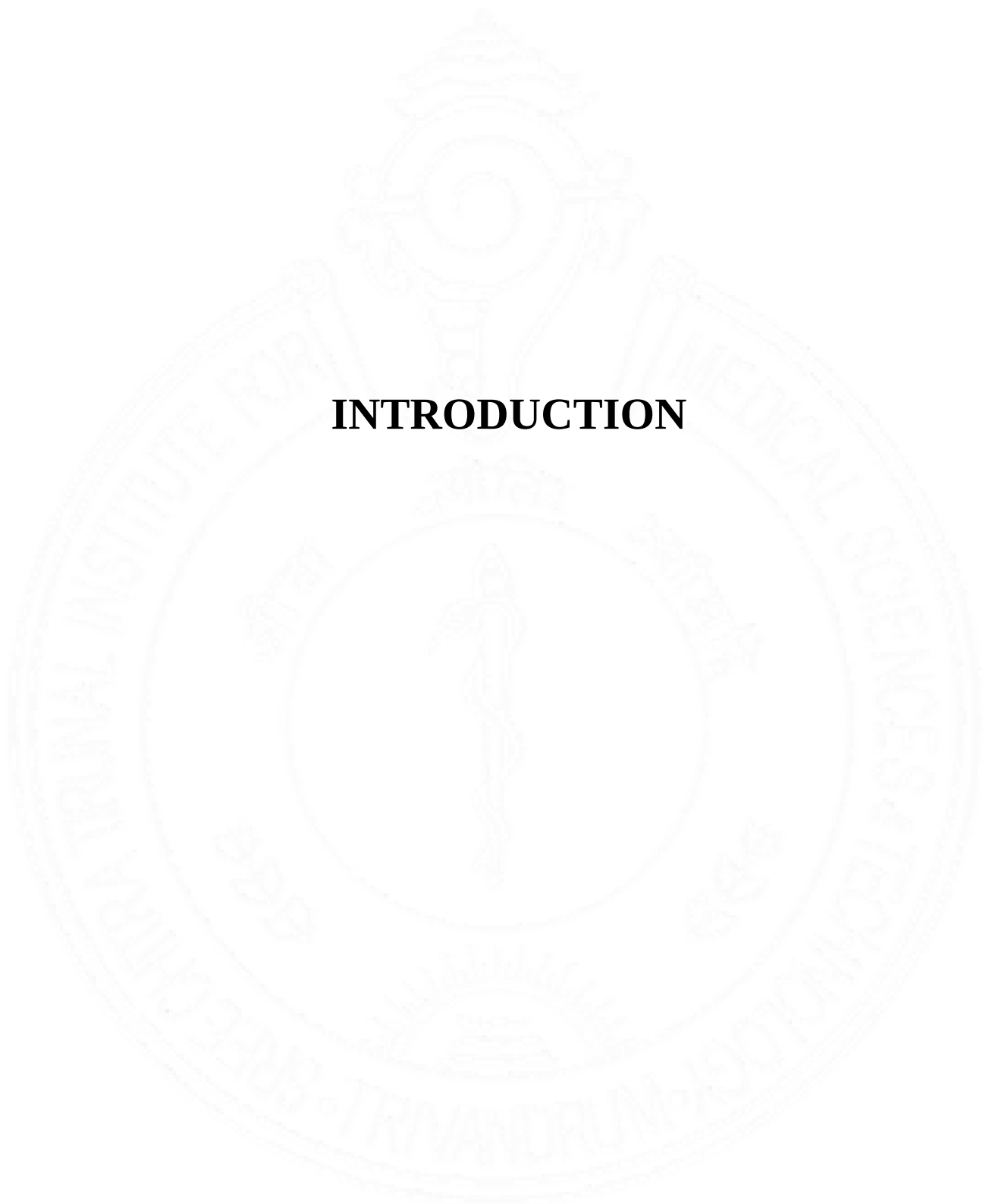
Thiruvananthapuram,
Date: 15-12-2021.


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INTRODUCTION

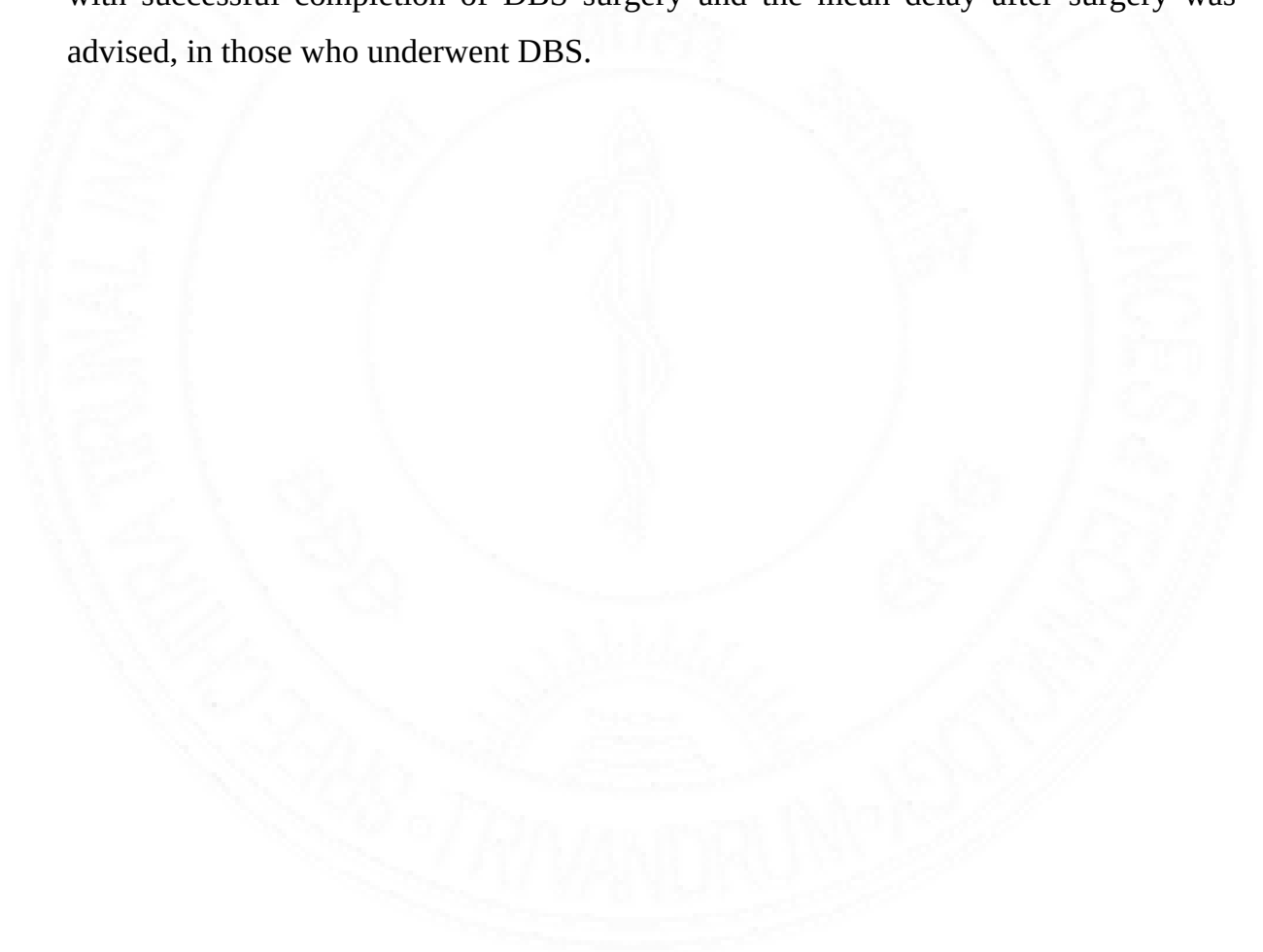


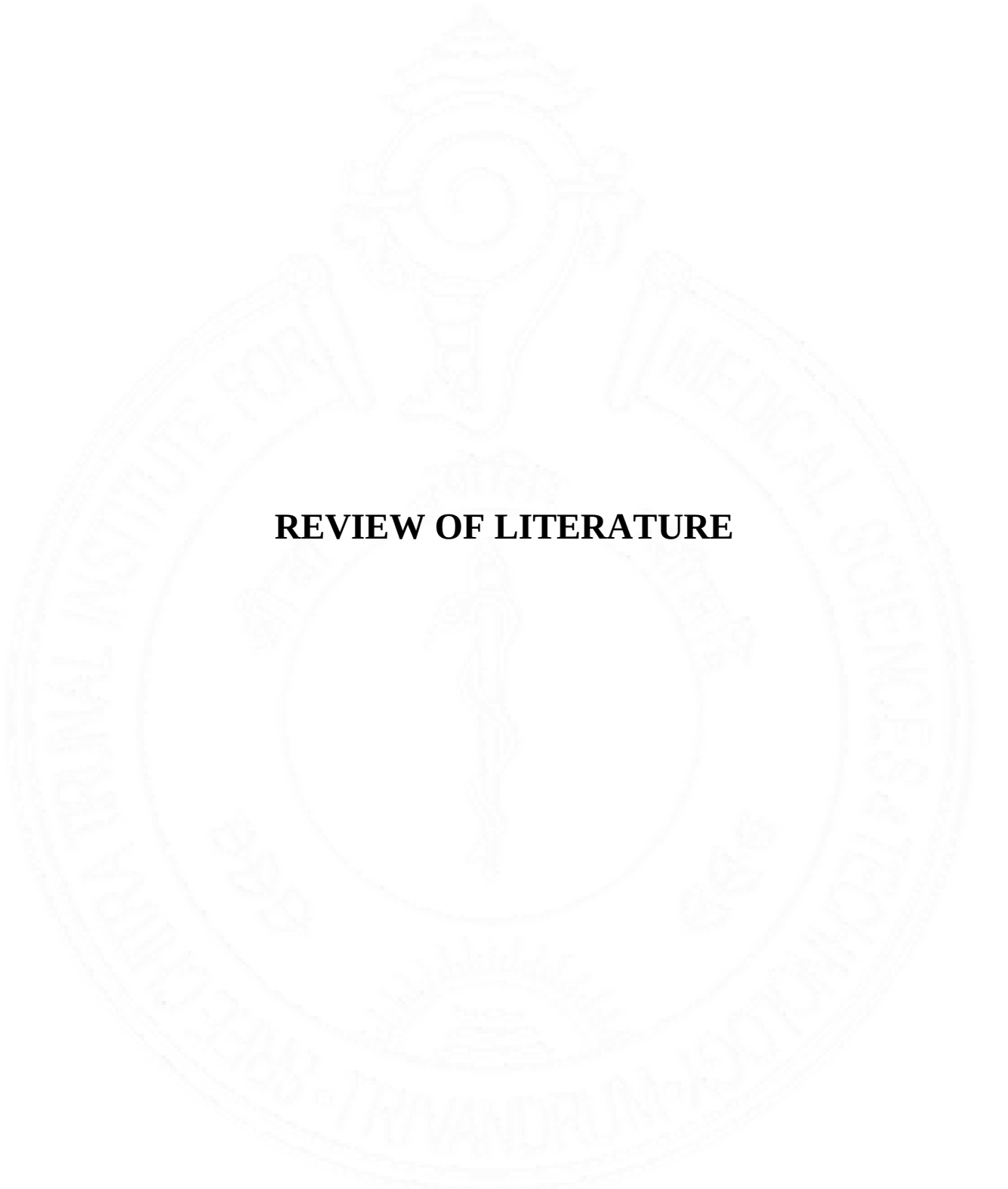
INTRODUCTION:

Deep brain stimulation (DBS) is a functional stereotactic neurosurgical procedure, which is minimally invasive, and used for the treatment of PD patients with motor complications like motor fluctuations and dyskinesias and/ or levodopa unresponsive and disabling tremors. Compared to the lesioning surgery, it is reversible to major extend and adaptable. There are two major sites for stimulation, i.e., the subthalamic nucleus (STN) and the globus pallidus interna (Gpi); STN is the most widely used target. STN DBS surgery improves motor fluctuations, enables a reduction in dopaminergic medications, and thereby, improves levodopa induced dyskinesias.

DBS is generally well tolerated by the patients and is ultimately aimed at improving the functioning and quality of life. However, it is associated with some surgical procedure-related complications and stimulation-associated side effects. These can be minimized by careful patient selection, perioperative management, and postoperative assessments and proper programming of DBS. Patient selection is the most crucial aspect determining the success in DBS surgery. Elderly patients and those with longer duration, and in advanced stage of the disease with significant axial symptoms, and non-motor dysfunction may not have a satisfactory quality of life improvement with DBS surgery. Elderly patients with diffuse cerebral atrophy may pose a significant challenge to the surgical technique as brain atrophy may interfere with a planning a safe surgical trajectory. Younger patients with early motor fluctuations and dyskinesias with less severe non-motor symptoms responds well, and it has been shown that patients who are selected early get better quality of life benefits compared to their counterparts on medical management alone. Medical comorbidities also influence patient selection; those with multiple poorly controlled co-morbidities may not be good surgical candidates. Other than neurological status and medical comorbidities, unrealistic patient expectations, fear of surgery, financial constraints, etc., also play an essential role in patient selection.

Finally, some of the eligible patients who are taken up for the procedure do not complete the surgery due to various problems like poor or no microelectrode recording (MER) indicating malposition of the electrode array or intraoperative surgical complications leading to abandoning the surgical procedure before completion. The intra-operative adverse events that may lead to abandoning the procedure included vasovagal response, hypotension, and seizure. Thus, only a proportion of the patients who are surgical candidates ultimately undergo the procedure successfully and this is likely to be lower in developing countries where insurance coverage is not universal and patients often have to spend from their own pocket for treatment. In this study, we examine the proportion of patients with motor complications of PD or other indications for DBS, who actually undergo the procedure successfully and the reasons for not undergoing, in those who continued on medical management. We also explore the factors associated with successful completion of DBS surgery and the mean delay after surgery was advised, in those who underwent DBS.





REVIEW OF LITERATURE

Review of literature:

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by motor symptoms like rigidity, bradykinesia, rest tremor, and postural instability. PD also has protean non-motor manifestations such as neuropsychiatric symptoms, cognitive abnormalities, autonomic disorders, sleep and gastrointestinal problems (1). The major source of disability in most patients in the early and mid-stages of PD is motor dysfunction, which is responsive to levodopa and other dopaminergic medications. However, there is no disease-modifying or neuroprotective therapy available for PD, and the neurodegeneration progresses despite symptomatic improvement with the dopaminergic medications. As a result, the patients develop motor complications while on treatment with dopaminergic medications. These include motor fluctuations (wearing OFF of the medication effects resulting in predictable, and later unpredictable "OFF" periods, whose duration and severity progressively increases as the disease progresses) and dyskinesias (involuntary movements occurring during the ON periods, when the patient has control of Parkinsonism with levodopa)(1). Advanced Parkinson's disease with a longer duration and higher cumulative levodopa equivalent daily dose are risk factors associated with the development of motor fluctuations (1,2). Around 50% of patients develop motor complications after about five years of medical management, which increases to 90-100% by ten years, and 8 to 64 % develop dyskinesias after 4- 6 years (1).

Deep brain stimulation has emerged as a standard of care for Parkinson's disease patients with motor complications like motor fluctuations and dyskinesias, which are difficult to manage by best medical management. DBS surgery is minimally invasive surgery; wherein deep brain structures are stimulated electrically. It is a symptomatic treatment and doesn't reverse the underlying pathophysiology of the disease. There are two sites for the surgery for PD patients, subthalamic stimulation (STN) and globus Pallidus interna (Gpi); however, STN is predominantly used by most DBS centers. There is no significant difference in outcome for both stimulation sites; however, STN

DBS has sustained benefits in motor symptoms even 5 years after the surgery, whereas long-term outcome with GPi stimulation is less clear (3). STN DBS improves motor symptoms and fluctuations, enabling reduction of dopaminergic medication doses and, thereby, dyskinesias (3). Patients with significant levodopa induced dyskinesias may benefit from GPi stimulation over STN stimulation. Moreover, STN DBS requires a lesser current for stimulation leading to low pulse generator battery consumption, and hence, less frequent pulse generator replacement is needed compared to GPi DBS (3,4).

Patient selection is a key to the success rate for DBS surgery and improvement in the motor symptoms and the quality of life of the PD patients. One of the most important factors for patient selection is age of the patient. Studies have shown that patients undergoing STN or GPi DBS mean age is between 40-60 years (3). Improvement in motor symptoms, and motor fluctuations are similar in younger and older (>60years) patients with STN DBS; however, there is significant improvement in quality of life (QOL) index in younger patients as compared to older patients (3,5). An elderly patient with advanced PD may respond similarly to the younger patient; however, they have 16-fold higher chances of losing ambulatory capacity within one year of surgery (6). Younger patients with early motor fluctuations probably have less non-dopaminergic pathways affected and thus more benefits with STN DBS surgery. With the advance in age there is an increase in non-motor symptoms like dementia, neuropsychiatric manifestations, and DBS refractory symptoms like freezing of gait, postural instability, and falls, which further decreases the beneficial effect of DBS surgery (3,4). Other medical comorbidities also increase with age. Thus, most centers exclude patients with >70 years of age for DBS surgery; however, there is no cut-off for the lower age limit. Younger patient with no comorbidities and non-motor symptoms has a maximum benefit with the DBS surgery. There is no gender difference in selecting patients for DBS surgery; however, the female patients may have more dyskinesias and less emotional wellbeing and thus benefit from earlier surgery (7).

Another important factor is the duration of the disease. Patients with at least four years of PD with motor complications are taken up for surgery in most centers performing DBS. There may be an advantage in taking up patients for DBS early, soon after onset of motor complications. One such study comparing the efficacy of advanced PD with early motor fluctuations vs best medical management is the EARLYSTIM study, which enrolled younger patients (average age 52years) with short duration (average duration is 7.3years), recommends the use of STN DBS for PD patients with early motor fluctuations (8). Early surgery reduces the motor symptoms and complications and prevents the functional capacity of PD patients. Patients with early motor fluctuations or dyskinesias have less burden of disease and hence, less DBS refractory symptoms like freezing of gait, postural instability, and falls, and less non-motor symptoms like dementia and neuropsychiatric comorbidities. Accordingly, DBS surgery in PD patients with early motor complications improves the quality of life. However, surgery in too early stages may increase the chances of missing levodopa responsive atypical Parkinsonism, and surgery in such patients may have devastating results; therefore, to minimize such risks, a minimum duration of four years is generally advised (3,4).

The best predictors of benefits with STN DBS are levodopa responsive motor symptoms. In the order- tremors, rigidity, and bradykinesias, improve with STN DBS. A positive Levodopa response test (>33% improvement in OFF UPDRS 3 score) is the best predictor of outcome in STN DBS (3,9). Certain axial symptoms like postural instability, falls, freezing of gait, and dysarthria may respond poorly to STN DBS. Freezing of gait, if responsive to levodopa, generally responds to STN DBS, only to progress in later stages and minimalizes the benefits of STN DBS. Hence, patients with low axial scores and higher appendicular motor scores benefit maximum from the STN DBS. The levodopa dose used for the levodopa challenge test is variable; some believe to use suprathreshold dose of levodopa (1.5 times the morning dose), while others

recommend using the usual dose or 200mg of levodopa. Hence, the best ON state of levodopa responsive PD is the expected benefit from STN DBS surgery (3).

Non-motor symptoms (NMS) like gastrointestinal symptoms, sleep disorder, urinary symptoms, behavioral and cognitive disturbances, pain, and anosmia, impacts the quality of life of PD patient. NMS symptoms might poorly respond to DBS surgery or some may even worsen with DBS surgery; however, improvement in some NMSs like sleep, cardiovascular symptoms, behavioral symptoms, gastrointestinal and urinary symptoms and pain have been shown by some (10). Some other like hyperdopaminergic-state-associated ICD, apathy and depression, and duration of sleep, may also show improvement. In contrast, REM sleep behavioral disturbances, dysphagia, and excessive daytime sleepiness remain unchanged (11). Decline of selected cognitive functions with STN DBS has been described- including reduction in verbal fluency, attention, working memory, and executive functions. This may become clinically significant if the baseline cognitive status is impaired. The risk factors associated with cognitive decline are preoperative cognitive dysfunction, higher age, higher LEDD, and axial symptoms; hence detailed neuropsychology evaluation including frontal lobe assessment is mandatory before STN DBS surgery (3,12). Gpi is less associated with cognitive decline, and therefore mild cognitive decline can be taken up for Gpi DBS rather than STN DBS (13). DBS may have a deleterious effect in those with active neuropsychiatric symptoms, like depression, mood changes, impulsivity and suicidal ideations. Overall worsening of Psychiatric symptoms after STN DBS are associated with baseline psychiatric disturbances, depression, personality trait, previous history of ICD, and unrealistic expectations from DBS surgery (12). Suicidal risk increases to 0.5- 2.6% after STN DBS, predominantly involving young patients with a history of multiple surgeries (3).

Medical comorbidities play a significant role in determining the functional outcome post-DBS surgery. Unstable cardiac disorder, active infection, subcortical atherosclerotic encephalopathy, disabling cerebrovascular disorder, and malignancy are

certain absolute contraindications for DBS surgery and may increase the surgical comorbidities (3). Uncontrolled systemic hypertension and abnormal coagulation parameters are two important determinants for intraoperative complications like hemorrhage. Other than medical comorbidities, significant cortical atrophy on MR imaging precluded correct passage of electrode array and hence is associated with the suboptimal outcome of DBS surgery (3).

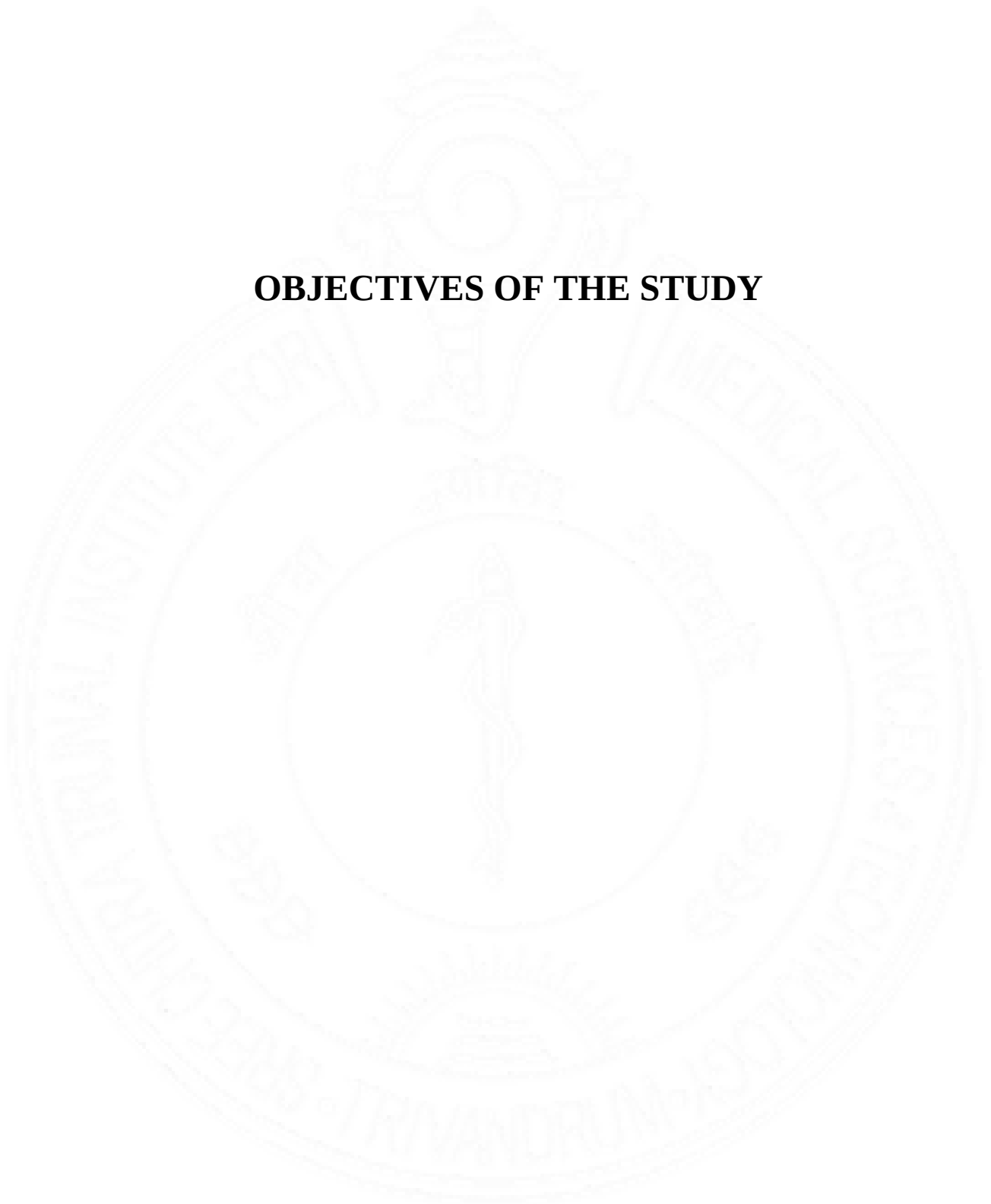
Other than medical comorbidities and neurological status, other factors can affect the final selection for DBS surgery. In developing countries, where medical insurance facilities are not readily available, financial constraints are an essential factor, as it is an expensive surgery. Other than financial constraints, poor family and social support, fear of surgery, transportation difficulties are other important factors that may affect the final decision of DBS surgery (3,14). Fear of surgery and financial constraints may increase the preoperative waiting period in patients willing for surgery (15). In addition, the patient might have unrealistic expectations about symptom improvement after the surgery, which may lead to reduced patient satisfaction and poor surgical outcome (14).

DBS surgery is a functional stereotactic procedure; hence the success of the surgery depends on adequate positioning of the electrode in the target, which is determined by a perioperative CT / MRI brain image using the stereotactic frame. Malpositioning of lead is an essential perioperative complication. Failure to reach the target accurately necessitates replanning of the target and additional passages of MER electrodes, increasing the duration of surgery, and chances of infection and haemorrhage (16). Inadequate control of systemic hypertension, number of passes required to determine adequate MER, mean blood pressure at MER array insertion, and abnormal coagulation parameters, increases the chances of intraoperative haemorrhage, which may lead to hemiplegia or death. Inadequate control of loss of CSF while opening dura mater may

lead to brain shift, increasing the chances of missing the target and less frequently subdural effusion requiring drainage (16,17). Other intra-operative adverse events which may lead to abandoning the procedure included vasovagal response, hypotension, and seizure (18). Dyskinetic storm and perioperative confusion are important complications requiring ICU monitoring. Mispositioning of electrode array, fracture of DBS leads, skin erosions at connection site, and serous collections in IPG (Battery) site are some of the other rare complications associated with DBS, which may lead to removal and / or replacement of the hardware, increasing the cost of procedure and stress of the patients (16,19).

The present study plans to explore all such challenges /obstacles, which finally lead to a continuation of medical management, in patients on follow-up in our Parkinson's and Movement Disorders clinic with motor complications of PD, qualifying for surgery. The study is expected to throw light on some of the correctable factors and enable Physicians to extend the benefits of this surgical procedure to a greater number of deserving patients in future.

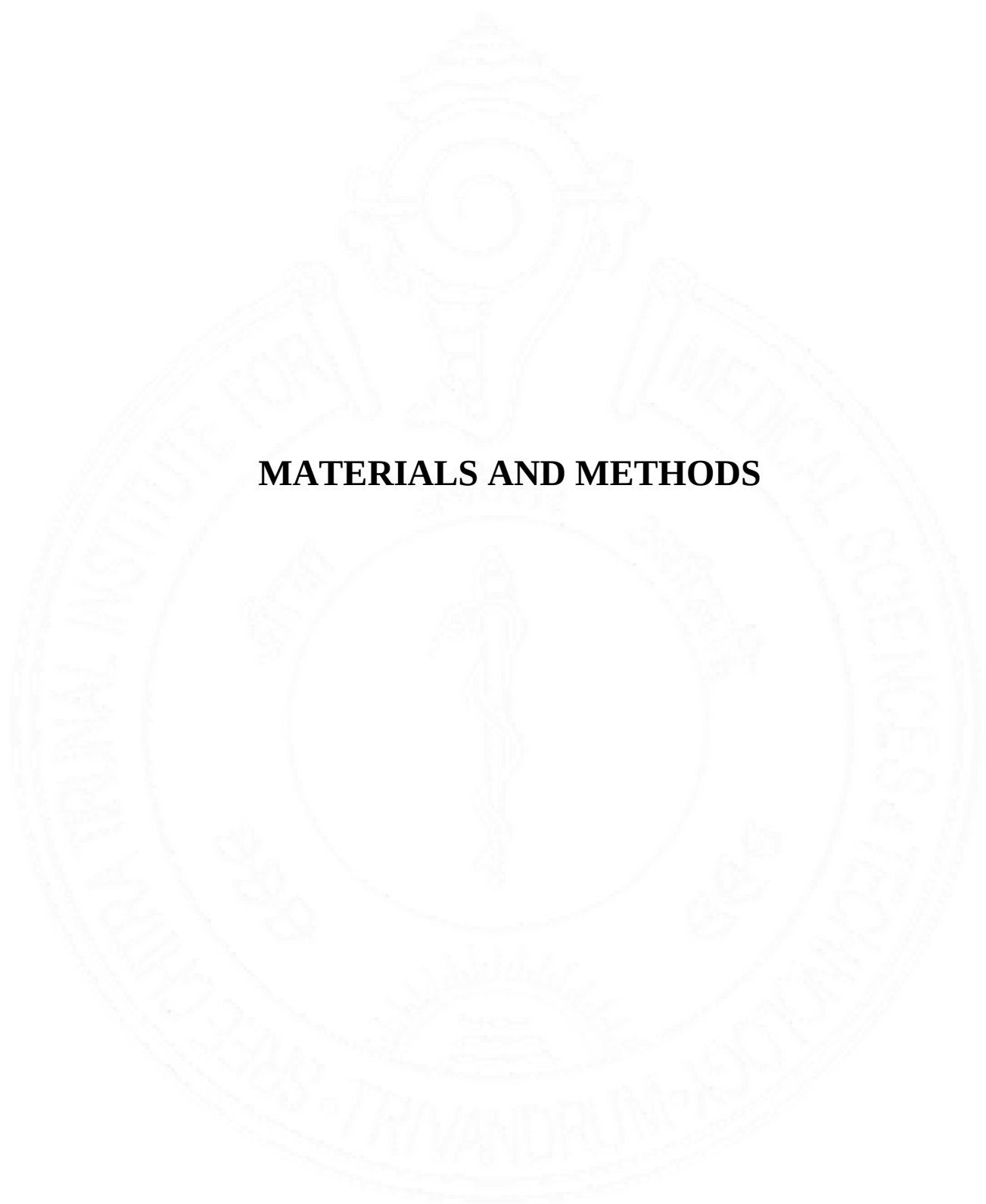
OBJECTIVES OF THE STUDY



AIMS AND OBJECTIVES:

1. To examine the number and percentage of patients with PD who are judged to be candidates for Deep Brain Stimulation surgery by the treating Movement Disorder Specialist in the Movement Disorders Clinic setting of a tertiary care referral hospital.
2. To examine how many of them actually undergo the procedure successfully.
3. To explore the factors leading to non-performance of the surgical procedure in the remaining patients.

MATERIALS AND METHODS



MATERIALS AND METHODS:

A retrospective study was conducted for all patients with PD in the mid-stages (with motor fluctuation and /or dyskinesias) and with motor features qualifying for DBS over a five-year period (From January 1, 2016 to December 31, 2020). All such patients attending our Movement disorder clinic were included in the study.

SELECTION CRITERIA:

Inclusion criteria:

1. Patients with a clinical diagnosis of PD as confirmed by Movement disorder specialists
2. Experience motor fluctuations and/or dyskinesias compromising the quality of life while judged to be on optimal medical management
3. Age > 18 years
4. Disease duration of at least 4 years

Exclusion criteria:

1. Patients in whom a diagnosis of atypical or secondary Parkinsonism was a diagnostic consideration and follow up to rule out the same had been planned
2. Patients lost follow-up after being found to be surgical candidates (and hence not sure whether they got operated on in some other center)

Methodology:

In our movement disorders clinic, patients with PD on follow-up and found to be eligible to consider DBS undergo a preliminary counselling by the movement disorder specialists and an information brochure on DBS either in English or the native language, is given to them based on their choice. All such patients with PD in mid-stages, with motor complications, who were offered the option of DBS surgery were included in the study, if they were on follow-up. If they were not on follow up and the information on whether DBS was done was not available, they were excluded. Their baseline demographic data, Type of PD, duration of illness, duration and severity of non-Motor symptoms, motor fluctuations and dyskinesias severity, LEDD (Levodopa daily equivalent dose), and follow-up duration after the DBS surgery was advised were obtained using a structured questionnaire. Monthly income of the patient and family were divided into lower (<10,000 per month), middle (10,000-50,000 per month), and upper (>50,000 per month). SE classification was not possible as educational qualification of each patient was not available on records.

Freezing of gait defined as the sudden stopping or freezing as if the foot is stuck to the ground by UPDRS 2 score. We defined FOG as mild if the patient had freezing; and, is able to reinitiate walking without support, moderate when patients need walking aids to restart walking, and severe when freezing is present most of the time requiring assistance. Falls were defined as unexpected events leading to patients coming to the ground. Falls were classified as rare (< 5 falls a year), occasional (< 1 fall per month), frequent (> 1 fall per month), and the falls in the ON stage. Motor fluctuations were defined as wearing of effect of medicine, inability to turn ON or sudden OFF disability; by using UPDRS 4 score. OFF disability was scaled using UPDRS 4 score, wherein patients has worsening of motor symptoms with weaning the effect of medications. OFF disability is defined as mild – minimal disability due to slowness and stiffness, moderate – moderately disabling disability requiring support, severe- patient is bed bound or wheel chair bound due to severe motor symptoms. Dyskinesias were defined using rush dyskinesias rating scale wherein zero scale is absence of dyskinesias, 1- minimal

dyskinesias, 2- dyskinesias may interfere in voluntary movements, but non disabling, 3- severe dyskinesias interfering in ADL, and 4- violent dyskinesias.

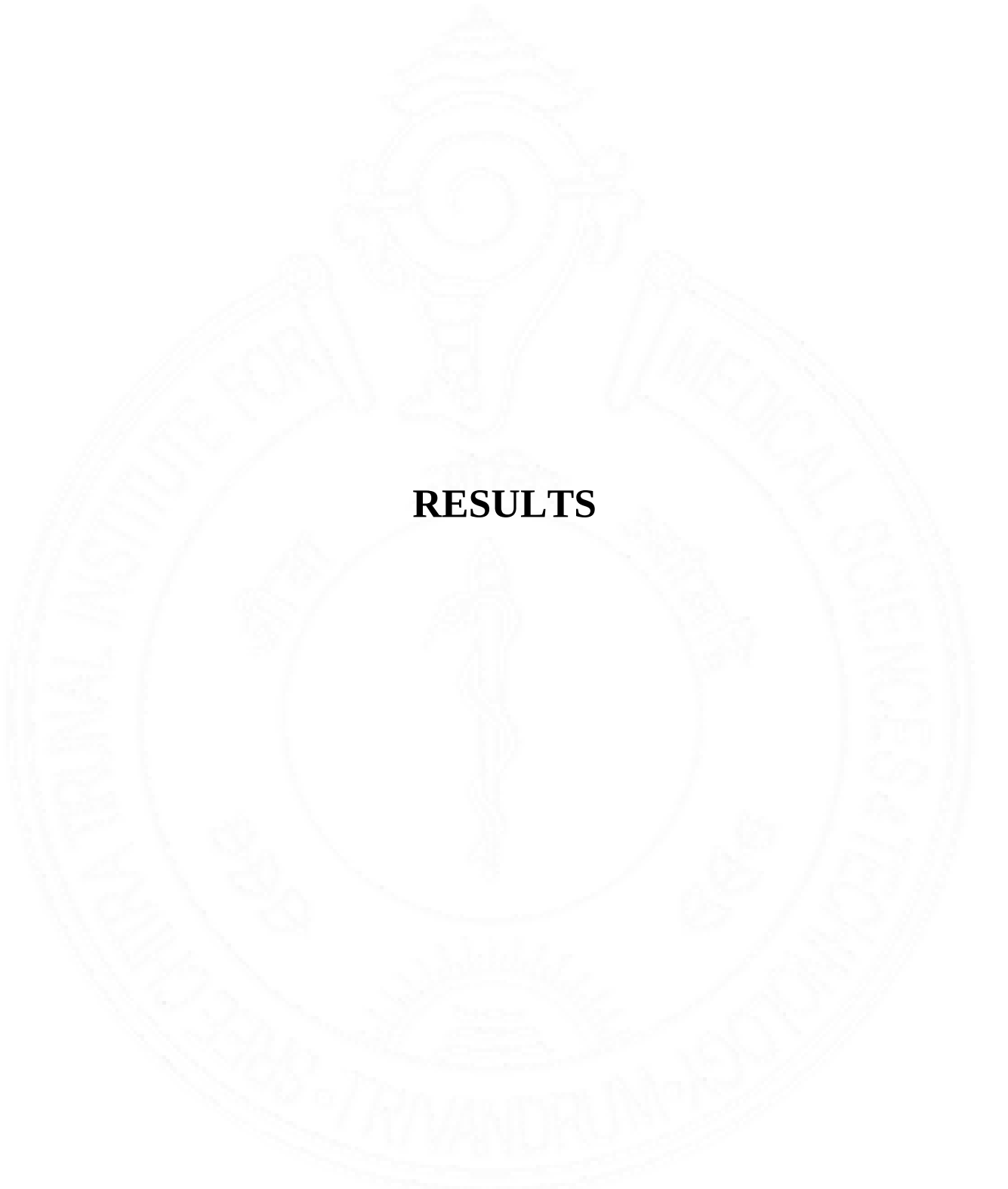
The proportion of patients who were advised DBS but did not undergo surgery, the reasons for not undergoing surgery, or causes of abandoning surgery after admission were collected and analysed.

Statistical methods

The data was entered into a spreadsheet and was analysed with SPSS version 20 software (SPSS IBM, Armonk, New York). Numerical variables were summarized as means and standard deviations. Pearson correlation was undertaken to examine the relationship of various factors with gender, type of PD, neuropsychiatric comorbidities, and medical comorbidities. A P value less than 0.05 was considered statistically significant.

Ethical considerations

This study was reviewed and approval of the Institutional Ethics Committee. (Approval number is SCT/IEC/1701/August/2021, and approved on 20th September, 2021)



RESULTS

RESULTS:

A total of 1717 charts of patients who had presented to our movement disorders clinic between January 1, 2016, to December 31, 2020, with a diagnosis of Parkinsonism as documented in the electronic medical records (EMR), were screened for the purpose of the study. Among them, 594 patients either had a diagnosis of Atypical Parkinsonism (Progressive supranuclear palsy, Corticobasal syndrome, Multiple system atrophy, and Dementia with Lewy body), or were thought to have atypical features for a diagnosis of PD, 56 patients had a diagnosis of secondary Parkinsonism (Vascular Parkinsonism, drug-induced Parkinsonism, Normal pressure hydrocephalus, etc.) or rare heredo-degenerative conditions like Neurodegeneration with Brain Iron Accumulation (NBIA), and 50 patients were found to have an alternate diagnosis during follow up (Essential tremor, dystonic tremor, myopathy etc.) were excluded from the study. After this, there were a total of 1017 patients diagnosed with PD. Among them, 224 patients fulfilled the eligibility criteria for inclusion in the study. The remaining 793 patients did not satisfy our patient selection criteria for DBS during the study period- they were either having a duration less than four years, or having well controlled motor symptoms while on medical management or too old to be considered for DBS at the time of initial evaluation itself.

Among the 224 patients who were advised DBS, 142 (63%) were male, and 82 (36%) were female with a male: female ratio of 1.73. The predominant subtype of PD was mixed type -134 (59%) patients, followed by akinetic rigid- 52 (23%) patients, and Tremor dominant -38 (16%) patients. The mean age at the time of advising DBS was 58 ± 9.81 years and the mean duration of PD was 9.18 ± 4.41 years. The mean duration of rigidity and bradykinesias was comparable to the total duration of PD (8.11 ± 4.41 and 8.07 ± 4.48 years, respectively) compared to the tremor duration of 6.70 ± 5.24 years in 177 patients. Gait disturbances during off period was reported almost all patients (209 of 224, 93.3%) with mean duration of 4.21 ± 3.74 years. The non-motor symptoms reported includes, constipation in 96 patients (42.85%) (mean duration 2.87 ± 4.31 years), sleep disorder including REM behavior disorder in 97 patients (43.3%)

(mean duration 2.21 ± 3.80 years), anosmia in 34 patients (15.17%) (mean duration 1.21 ± 3.35 years), neuropsychiatric disturbances in 104 patients (46.42%) (mean duration 1.13 ± 2.47 years), urinary bladder dysfunction in 70 patients (31.25%) (mean duration 0.80 ± 1.74 years) and cognitive changes in 47 patients (20.98%) (mean duration 0.43 ± 1.36 years). The baseline characteristics of the PD patients eligible for the surgery considering the mid-stage disease and motor complications like motor fluctuations and/or dyskinesias are described in Table 1.

Table 1. Baseline characteristic of the PD patients eligible for the surgery considering the mid-stage of disease and motor complications like motor fluctuations and/or dyskinesias

Serial number	Variable	Number of patients (percentage)	Duration (years) with SD
1.	Mean age of the PD patients	224	58 ± 9.81
2.	Mean duration of PD	224	9.18 ± 4.41
3.	Type of PD Tremor dominant Akinetic rigid syndrome Mixed type	 38 (16.96%) 52 (23.21%) 134 (59.82%)	
4.	Socioeconomic status Lower Middle Upper	 94 (41.96%) 106 (47.32%) 24 (10.71%)	
5.	Employment of the patients Government servant Professional (Pvt/ Self Employed)	 65 (29.01%) 21 (9%)	

	Non-professional self-employed	20 (8.9%)	
	Agriculturist	15 (6.69%)	
	Manual Laborer	41 (18.30%)	
	Housewife	62 (27.67%)	
6.	Employment of the caregiver		
	Government servant	53 (23.66%)	
	Professional (Pvt/ Self Employed)	16 (7.14%)	
	Non-professional self-employed	9 (4.01%)	
	Agriculturist	8 (3.57%)	
	Manual Laborer	22 (9.82%)	
	Housewife	111 (49.55%)	
7.	Cognitive status		
	Absent	178 (79.46%)	
	Mild Cognitive abnormality	41 (18.3%)	
	Cognitive decline	5 (2.23%)	
8.	Depression		
	Absent	163 (72.76%)	
	Mild depression, requiring no treatment	29 (12.94%)	
	Moderate depression, well-controlled on drugs	30 (13.39%)	
	Severe depression	2 (0.8%)	
9.	Psychosis		
	Absent	195 (87.05%)	
	Mild psychosis, requiring no treatment	1 (0.4%)	

	Moderate psychosis, controlled on drugs	21 (9%)	
	Severe Psychosis	7 (3.1%)	
10.	ICD		
	Absent	218 (97.32%)	
	Present	6 (2.67%)	
11.	Anxiety		
	Absent	162 (72.32%)	
	Present	62 (27.67%)	
12.	Mean duration of Motor fluctuations		2.80 ±1.93
13.	OFF disability		
	Mild	22 (9.81%)	
	Moderate with independent for ambulation	93 (41.51%)	
	Moderate requiring assisted ambulation	80 (35.71%)	
	Severe	21 (9.37%)	
14.	Hoehn and Yahr scale (H & Y) scale		
	1.5	2 (0.8%)	
	2	14 (6.25%)	
	2.5	58 (25.89%)	
	3	107 (47.76%)	
	4	41 (18.30%)	
	5	2 (0.8%)	
15.	Mean Levodopa equivalent daily dose (LEDD)		769.91 ± 279.04

The predominant neuropsychiatric manifestations were depression, psychosis, anxiety, and impulse control behavior (ICD); anxiety is the most common manifestation affecting 62 (27.67%) patients, followed by depression in 61 (27.23%) patients, psychosis in 29 (12.94%) patients, and ICD in 6 (2.67%) patients.

Freezing of gait (FOG) was present in 165 (73.66%) patients and absent in 59 (26.33%) patients. Mild FOG is present in 62 (27.67%) patients, moderate FOG in 71 (31.69%) patients, and 32 (14.28%) patients had severe FOG. Falls were absent in 178 (79.46%) patients, rare in 28 (12.5%) patients, occasional in 12 (5.35%) patients, frequent falls in 4 (1.78%) patients, and falls in ON in 2 (0.89%) patients.

The motor fluctuation was present in 216 (96%) of patients, with the mean duration 2.80 ± 1.93 years. Hoehn and Yahr (H & Y) stage of 1.5 in 2 (0.8%) patients, 2 in 14 (6.25%) patients, 2.5 in 58 (25.89%) patients, 3 in 107 (47.76%) patients, 4 in 41 (18.30%) patients, and 5 in 2 (0.8%) patients. The mean Levodopa equivalent daily dose (LEDD) is 769.91 ± 279.04 . OFF disability as defined by UPDRS 4 score is mild in 22 (9.81%) patients, moderate stiffness and slowness, however independent for ambulation in 93 (41.51%) patients, moderate disability requiring assistance for ambulation in 80 (35.71%) patients, and 21 (9.37%) patients were bound to a wheelchair. Dyskinesias were scored as the time duration of dyskinesias, and its functional impairment on the quality of life as defined by UPDRS 4. There are 45 (20.08%) patients with no dyskinesias and only motor fluctuations, 85 (37.94%) patients with mild dyskinesias, 58 (25.89%) patients with moderate, but non disabling dyskinesias, 21 (9.37%) patients with moderately severe dyskinesias, and 11 (4.91%) with functionally disabling dyskinesias.

The medical comorbidities in the patients were Type 2 diabetes mellitus in 43 (19.19%) patients, systemic hypertension in 68 (30.3%) patients, cardiac disorder in 14 (6.25%) patients, and dyslipidemia in 9 (4.01%) patients.

Of 224, 31 (15%) patients underwent DBS, 174 (77.67%) deferred the procedure, and 19 patients lost follow-up. A baseline comparison of patients who opted vs. deferred is shown in Table 2. The mean age of the patients (58.27 ± 10.14 and 56 ± 7.292 respectively, P value 0.313) and duration of the patients (8.99 ± 4.45 and 10.35 ± 4.02 respectively, P value 0.112) who deferred and underwent DBS were comparable with no statistical significance. Motor complications like motor fluctuations were of lesser duration in patients who deferred surgery 2.75 ± 1.91 compared to 3.16 ± 2.06 years in patients who opted for DBS surgery, however it was not statistically significant (P value 0.274). Patients with more severe OFF disability opted for DBS rather than patients with less severe OFF disability (2.74 ± 0.72 and 2.32 ± 0.92 , P value 0.016). Dyskinesias were more severe in the patients who opted for DBS than deferred DBS (1.9 ± 0.944 and 1.35 ± 1.08 , P value 0.008). H and Y scales were comparable in both the groups with a mean score of 2.96 ± 0.60 in DBS deferred patients and 3.16 ± 0.61 in DBS opted patients (P value 0.101). LEDD was more in patients who opted for DBS than DBS deferred patients (825.81 ± 310.87 and 760.93 ± 273.47 , respectively, P value 0.230).

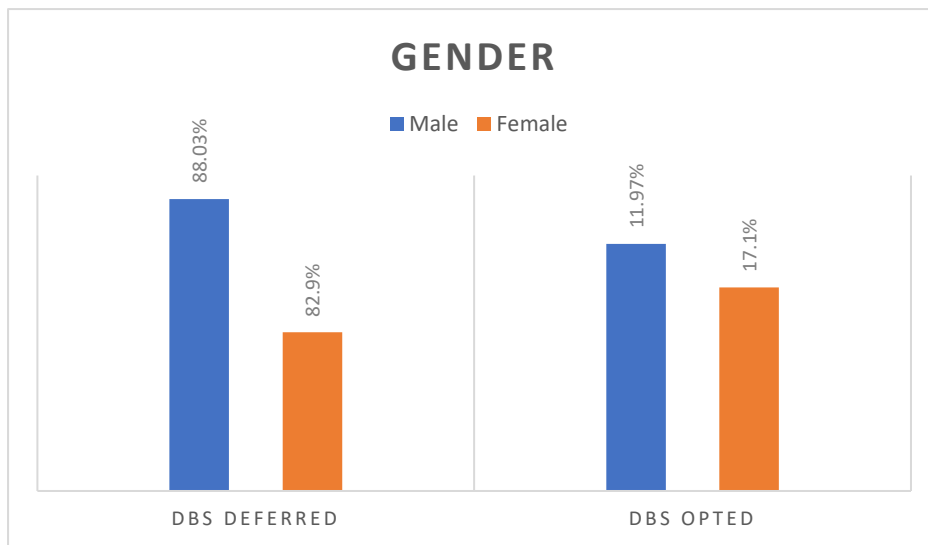
Table 2: Comparison of variables in patient who deferred DBS vs Opted for the procedure.

Variable	Deferred DBS	DBS done	Total	P value
	Mean	Mean		
Age of Patient (years)	58.27 ± 10.14 (23-79)	56 ± 7.292 (41-68)	58.01 ± 9.80 (23-79)	0.313

Duration of PD (years)	8.99 ± 4.45 (2-25)	10.35 ± 4.02 (4-18)	9.18 ± 4.41 (2-25)	0.112
Motor fluctuations (years)	2.75 ± 1.91 (0-10)	3.16 ± 2.06 (1-9)	2.81 ± 1.93 (0-10)	0.274
OFF disability	2.32 ± 0.92 (0-4)	2.74 ± 0.72 (2-4)	2.37 ± 0.91 (0-4)	0.016
Dyskinesias severity (UPDRS 4)	1.35 ± 1.08 (0-4)	1.9 ± 0.944 (0-4)	1.43 ± 1.08 (0-4)	0.008
H and Y scale	2.96 ± 0.60 (1.5-5)	3.16 ± 0.61 (2-4)	2.99 ± 0.60 (1.5-5)	0.101
LEDD	760.93 ± 273.47 (100-1900)	825.81 ± 310.87 (300-1550)	769.91 ± 279.04 (100-1900)	0.230

The study population consists of 142 males: 82 females, a ratio of 1.73; however, 125 (88%) males deferred for DBS and 17 (11.97%) opted, and 68 (82.9%) female deferred DBS, and 14 (17%) opted, with no statically significant difference (P value 0.287).

Figure1: Bar diagram with gender distribution in patients who deferred vs opted DBS.



A neuropsychiatric disorder like anxiety and ICD were comparable in both groups with no statistical significance (P value 0.539 and 0.195, respectively). Finally, medical comorbidities like Type 2 diabetes mellitus, systemic hypertension, dyslipidaemia, and cardiac disorder were comparable in both groups.

Table 3: Medical comorbidities in patients who deferred vs opted surgery

Medical comorbidities		DBS deferred	DBS opted	P value
Diabetes mellitus	Absent	79.3%	90.3%	0.147
	Present	20.7%	9.7%	

Hypertension	Absent	71%	61.3%	0.276
	Present	29%	38.7%	
Dyslipidaemia	Absent	96.4%	93.5%	0.361
	Present	3.6%	6.5%	
Cardiac disorder	Absent	93.8%	93.5%	1.000
	Present	6.2%	6.5%	

224 patients, 205 were included, and 19 (8.48%) patients were lost to follow-up. Of 205, 128 (62.43%) decided against surgery due to financial reasons, poor motivation, fear of surgical procedure and its complications, poor social support, and transport facilities, and wanted to wait for advance disease stage, 37 (18.04%) who underwent evaluation by the neurologist, psychiatrist and psychologist, and were found unfit due to advanced age, advanced disease with refractory symptoms, neuropsychiatric symptoms, PD dementia, and medical comorbidities. 9 (4.39%) patients were taken up for the DBS surgery and developed various complications like poor MER, adverse effects (AEs) during stimulation, complications during frame fixation, and intraoperative complications. This is depicted in the Pie diagram below.

Figure 2:

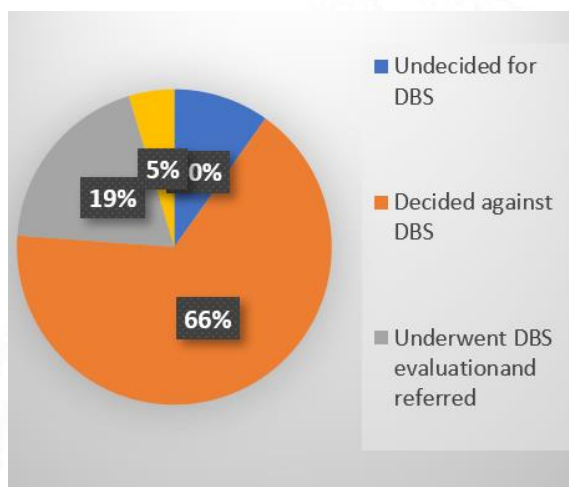
A. Current status of the patients who were offered DBS surgery

B. Reasons for patient and family to defer surgery

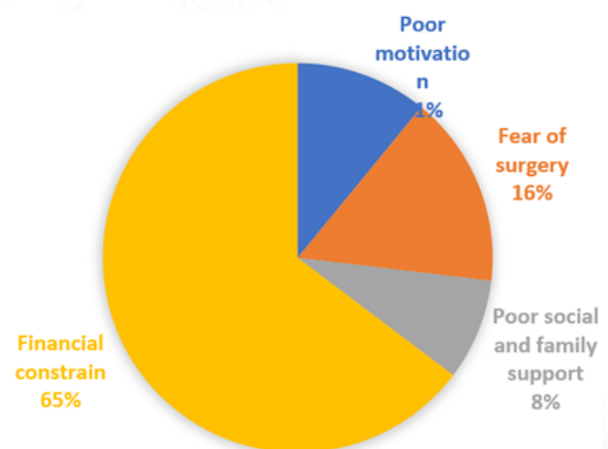
C. Reasons for being unfit after preoperative evaluation for DBS surgery

D. Reasons to abandoning surgery for patients taken up for DBS

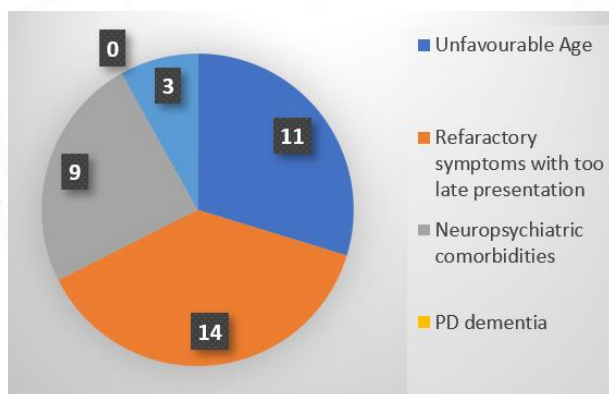
A.



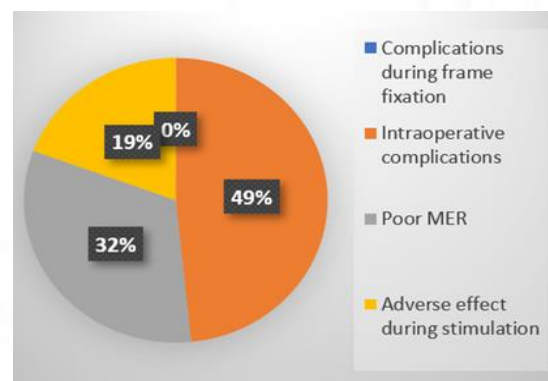
B.



C.



D.



128 of 205 patients decided against DBS surgery due to various reasons. Financial constrain was the most common factor for families and patients to defer the surgery,

which included 77 (60.15%) patients, followed by fear of surgery and its outcome in 19 (14.84%) patients, poor motivation in 13 (10.15%) patients, poor social support in 10 (7.81%) patients, and wanted to wait for an advanced stage as patients were still able to ambulated unassisted on medical management in 9 (7.03%) patients.

Of 37 patients who underwent evaluation, 11 (57.89%) patients were denied surgery due to advanced age (> 70 years), 14 (73.6%) patients had an advanced stage with DBS refractory symptoms like FOG, postural instability, and falls, 9 (47.3%) had neuropsychiatric comorbidities and, 4 (21.05%) had medical comorbidities precluding surgery.

9 patients were taken up for DBS surgery and developed complications, leading to abandoning of surgery. 3 (33.33%) patients developed intraoperative complications like seizures, or vasovagal event, 2 (22.22%) patients had poor MER, and 4 (44.44%) developed adverse effects on stimulation, hence surgery was abandoned.

Predictors leading to deferral of surgery:

Pearson correlation was used for one-on-one comparison of factors leading to defer surgery and the variables of the patients. Patients who deferred surgery due to poor motivation has a positive correlation to mild OFF stage (mild slowness and stiffness and gait disturbances, however requires no assistance for ADLs) (P value 0.013). We found no correlation to other parameters like H & Y scale severity, cognition, and neuropsychiatric manifestations.

Table 4: Predictors of poor motivation

Variables	P value
OFF severity	
Mild	0.013
Moderate	0.172
Severe	0.632
H & Y scale	
Mild	0.891
Moderate	0.548
Severe	0.552
Cognitive decline	
Mild	0.469
Moderate to severe	0.575
Depression	
Mild	0.117
Moderate to severe	0.550

Patients who deferred surgery due to fear of surgery and its complications, had no correlation to OFF disability, H & Y scale, and cognitive status; however, had correlation to mild depression (P value 0.006), however patients with moderate and severe depression had no correlation (P value 0.075).

Table 5: Predictors of fear of surgical complications:

Variable	P value
OFF severity	
Mild	0.158
Moderate	0.181
Severe	0.774
H & Y scale	
Mild	0.726
Moderate	0.460
Severe	0.634
Cognitive decline	
Mild	0.983
Moderate to severe	0.480

Depression	
Mild	0.006
Moderate to severe	0.075

Patient who wanted to wait for later or advance stage of the disease, were found to have positive correlation to mild H & Y scale (scale of 1, 1.5, 2 and 2.5), and moderate H & Y scale (scale 3) (P value 0.005 and 0.015, respectively). Other factors like OFF disability were not comparable.

Table 6: Predictors leading to wait for advance stage of disease

Variable	P value
OFF severity	
Mild	0.157
Moderate	0.517
Severe	0.682
H & Y scale	
Mild	0.005
Moderate	0.015
Severe	0.794



DISCUSSION

DISCUSSION:

DBS is considered a relatively safe and minimally invasive surgery for managing PD patients with motor complications like motor fluctuations and dyskinesias. However, DBS is most effective if the patient opts for the surgery during the therapeutic window period (motor complications poorly managed with medications and least comorbidities and refractory symptoms). In our study of 224 patients, 174 patients deferred surgery for various reasons, and only 31 underwent DBS; hence, only 13% of patients opted for surgery. The developing country has limited access to medical insurance facilities, and hence financial constraints are the most common factor precluding the surgery, as it is an expensive procedure. Our study found similar results, with financial constrain being the most common factor precluding surgery. However, other factors like fear of surgery, poor motivation, and poor social and family support lead to deferring the procedure.

There was no gender difference in patients who deferred and opted for the procedure. The mean age and the duration of PD were comparable in both groups. The motor fluctuations and H & Y scale were comparable in both the groups; however, patients with more severe OFF disability and dyskinesias opted for DBS surgery. Hence, patients with more disability as defined by OFF disability and severe dyskinesias affecting the quality of life were more inclined to opt for DBS surgery. DBS is symptomatic management for PD and improves quality of life by reducing motor fluctuations and dyskinesias. However, the patients with advanced-stage may be associated with severe non-motor manifestations and DBS refractory symptoms, medical comorbidities reducing the therapeutic window for benefit for PD patients. EARLYSTM study results have described the benefits of DBS surgery in PD patients with early motor complications compared to best medical management, improving patients quality of life (8). Hence, timely referral to DBS center and better counselling may help patients make better decisions.

The patient who opted for the DBS procedure had a lag of 13 months compared to 5 months (the time taken to decide against surgery) for patients who deferred the procedure, suggesting the patient needs time to prepare for surgery, arrange finances, and leave for the surgery. However, the lag period may be minimized by increasing the financial support to patients through NGOs and social welfare schemes.

Patients once agree to the procedure need a detailed examination to rule out severe and disabling neuropsychiatric manifestations, cognitive decline, active infection, and control of medical comorbidities, as they may affect the outcome of DBS surgery. Our study found advanced stage of PD with DBS refractory symptoms (postural instability, freezing of gait, and falls) as the most common reason for being unfit for surgery, followed by advanced age, uncontrolled severe neuropsychiatric symptoms, and medical comorbidities.

The mild OFF-stage severity positively correlates to poor motivations in our study populations (0.013). Patients with mild H & Y stage (stage of 1, 1.5, 2, and 2.5) and moderate (stag of 3) were associated with family deferring the procedure as they wanted to await advanced stage of the disease (P value 0.005 and 0.015, respectively). H & Y stage defines the severity of the disease and is associated with quality of life; hence, milder stages are less associated with disability. However, patients with early motor fluctuations benefit maximum from the surgery and have a more remarkable improvement in the quality of life (8). Furthermore, patient with early motor fluctuations has less DBS refractory symptoms, with the least non-motor and medical comorbidities. Hence, we recommend that patients with early-stage illness and low OFF-stage severity need recurrent counselling and frequent follow-up to understand the benefits, limitations, and need to operate in the therapeutic window for the maximum benefit of DBS surgery.

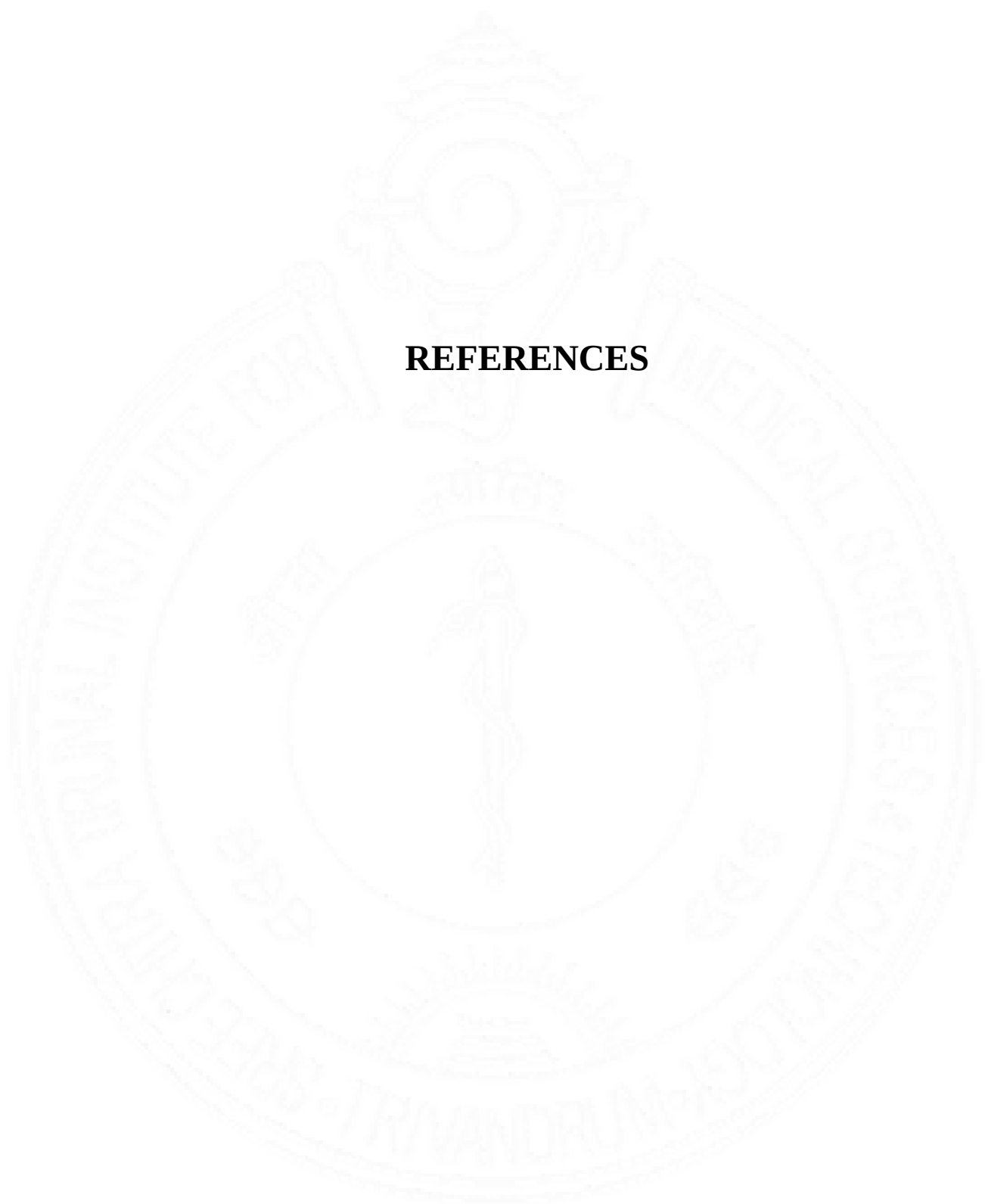
Non-motor comorbidities have an enormous impact on the quality of life of PD patients; depression, anxiety, and other neuropsychiatric disorders are some of them. Patient and treating physicians usually neglect mild depression, which requires no treatment, as it is non disabling, and will add the burden of extra medications and psychiatric follow up, however; in this study, we found a positive correlation between mild depression with patient deferring surgery due to fear of complications of the surgery (P value 0.006). Contrary to the belief, moderate or severe depression is associated with fear of surgery and may postpone the procedure (15). Hence, a meticulous history and good observation are needed to diagnose mild depression and treat it, which is necessary for a better understanding of the procedure. Furthermore, it may help patients trust the doctor and encourage them for the surgery.

Our study is the first of a kind describing various factors leading to DBS surgery procrastination. Financial constrain is the most important factor; however, other important factors like fear of surgery and surgical complications, poor motivation, and poor social support are also important. Detailed counselling with frequent follow-up may help them understand the procedure better. Among the various reasons for patients being unqualified for the surgery, advanced stage with refractory symptoms, advanced age, neuropsychiatric comorbidities, and medical comorbidities are important causes; hence the timely referral to a DBS center and adequate control of non-motor symptoms and medical comorbidities is necessary. Increasing the awareness about DBS surgery among the referring Physician may serve the purpose. Our study has one limitation of reduced follow-up rate due to the Covid 19 pandemic, and hence, many patients were contacted telephonically, reducing the reliability of answers. However, the sample size of 224 patients from 1017 patients increases the study's strength.

Conclusions:

In this study in consecutive patients attending the movement disorders clinic in our tertiary care referral centre, we found that 22.02 % of patients with PD had motor complications not optimally managed on best medical therapy. Among these patients who were considered for DBS, 13.83 % only had the procedure successfully undertaken. Among those in which it was deferred, 18.04 % were deferred due to disease-related /co-morbidity related contraindications. Remaining patients opted against surgery due to psychosocial or financial reasons; financial was the most important reason. Patients with more severe motor symptoms and complications tended to opt for surgery, and there was no gender difference in the proportion of those who opted and underwent DBS. In 22.5 % of patients who were taken up for surgery, the procedure was abandoned due to various intra-operative complications

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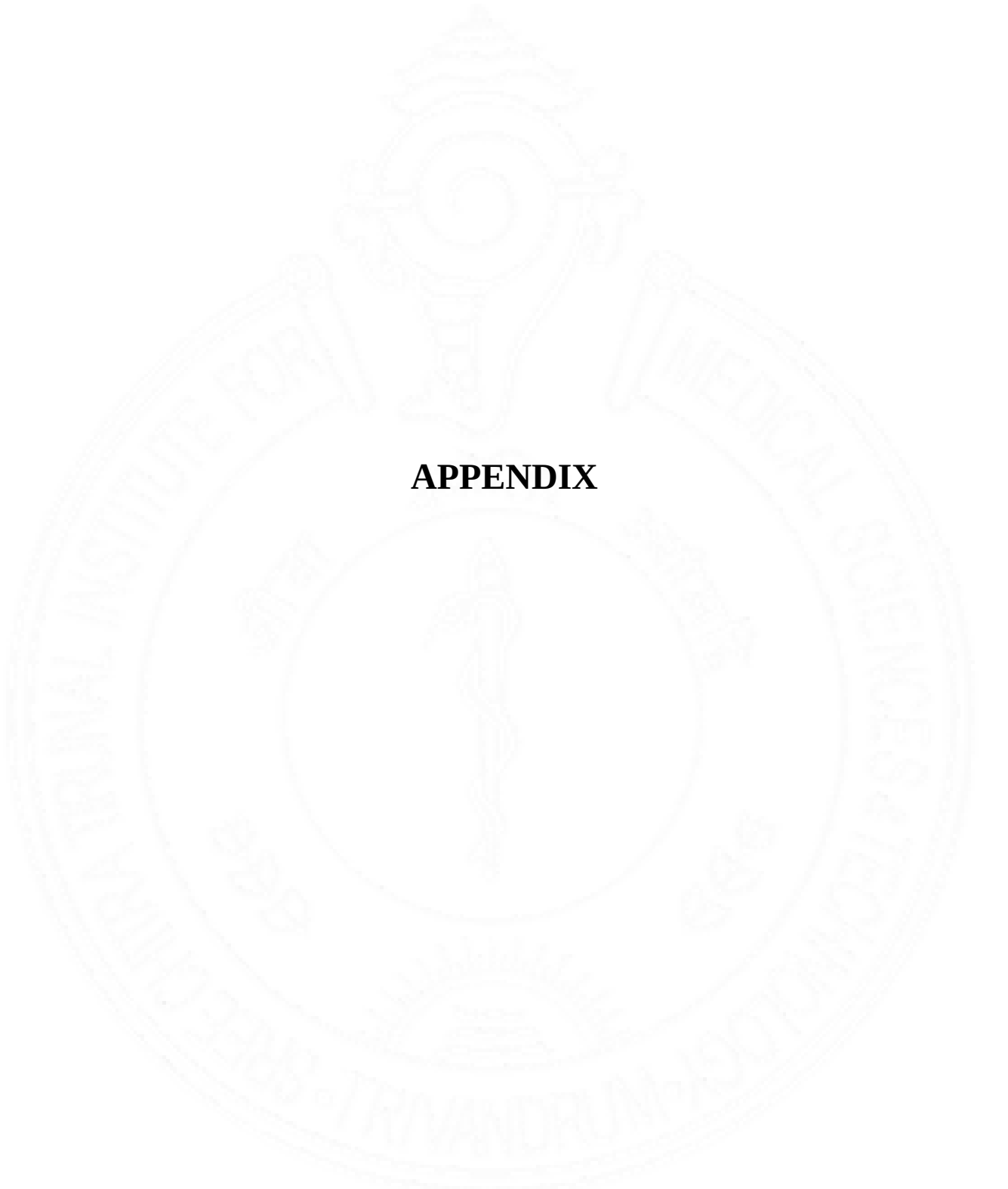
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APPENDIX

ABBREVIATIONS

PD- Parkinson's disease

DBS- Deep brain stimulation

STN- Subthalamic nucleus

Gpi- Globus pallidus interna

MR imaging- Magnetic resonance imaging

MER- Microelectrode recording

QOL- Quality of life

EARLYSTIM- Early neurostimulation for Parkinson's disease

UPDRS 3 – Unified Parkinson's disease rating scale 3

NMS- Non motor symptoms

ICD- Impulse control disorder

REM- Rapid eye movement

LEDD- Levodopa equivalent daily dose

CT- Computed tomography

CSF- Cerebrospinal fluid

ICU- Intensive care unit

IPG- Implantable pulse generator

EMR- Electronic medical record

H & Y scale- Hoehn and Yahr scale

MMSE- Mini mental status examination

MoCA- Montreal cognitive assessment

FOG- Freezing of gait

ADLs- Activity of daily living

NGO- Non-Government organisation



PROFORMA

Serial No:

Master chart No:

Age:

Sex:

Type of Parkinson's disease:

Duration of symptoms:

Rest tremor

Slowness

Stiffness

Gait difficulty

Bowel disturbances

Bladder disturbances

Sleep disturbances including RBD

Cognitive decline

Psychiatric disturbances

Anosmia

Duration of illness when diagnosis of PD was made:

Monthly family income:

Level of education:

Occupation:

Primary care giver

Level of education of primary care giver

Income:

SCTIMST Follow-up patient / referral from elsewhere for DBS:

Non-motor symptoms:

Cognitive symptoms: Yes / No. If Yes, details

Mood changes: Yes / No. If yes, details

History of treatment for neuropsychiatric symptoms:

Depression:

Psychosis:

Others:

Clinical features on Examination:

1. Rigidity
2. Slowness
3. Gait disturbances
4. Tremors
5. Fog and falls
6. Dysarthria
7. Motor fluctuation- ON and OFF phase
8. Dyskinesia

Sign:

UPDRS 3 score

1. ON phase
2. OFF phase

Risk factors:

1. Diabetes mellitus
2. Systemic hypertension
3. Cardiac comorbidities
4. Dyslipidemia
5. Dementia
6. Others

Reason for deferral of surgery

1. Neuropsychological complications
2. Inadequate motivation
3. Poor social support
4. Financial crisis
5. Age of the patient

6. Unrealistic expectations
7. Advanced stage of the disease
8. L dopa unresponsive symptoms- axial symptoms
9. Active illness
10. Uncontrolled blood pressure
11. Others (give details)

Intraoperative complications:

1. Poor MER
2. Brain shifts during surgery
3. Seizure
4. Hemorrhage
5. Pyramidal side effects
6. Vasovagal response
7. Ocular side effects

Medication:

Levodopa equivalent dose LEDD

Levodopa

Amantadine

Dopamine agonist

COMT inhibitors

MAO B inhibitors

Safinamide

Trihexyphenidyl

IEC approval letter



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1701 /August/ 2021

20.09.2021

Dr. Patel Khushboo Subhash
PDF, Movement Disorder
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Patel Khushboo Subhash,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "CHALLENGES AND OBSTACLES TO DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE - PERSPECTIVE FROM A DEVELOPING COUNTRY (IEC/1701)" on 18th August, 2021.

The following members of the Ethics Committee were present at the meeting held on 18th August, 2021 at Residences and Offices of IEC Members via Video Conference

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Dr. Achuth Sankar S. Nair	Ph.D (i.Engineering ii.Music)	Male	Social Scientist	No
6.	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
7.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
8.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
9.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
10.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
11.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 19.07.2021
2. TAC Approval Letter
3. IEC Application form
4. Project Proposal
5. CV of PI and Co-PIs

Revised submission

1. Covering letter addressed to the Member Secretary, IEC, SCTIMST dated 07.09.2021
2. Covering letter addressed to the Chairperson, IEC, SCTIMST
3. IEC Application form
4. Proforma
5. Declaration Form
6. CV of PI and Co-PIs

IEC Decision

The IEC approved the conduct of the study in the present form

This approval is in continuation of IEC Regn No. ECR/189/Inst/KL/2013/RR-16, subject to IEC Renewal pending process with CDSCO

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,



G. Srinivas
Member Secretary, IEC

