Interventional procedure overview of MRI-guided focused ultrasound subthalamotomy for treating Parkinson's

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Table 1 Abbreviations

Abbreviation	Definition
C-GIC	Clinician's Global Impression of Change
CI	Confidence interval
DBS	deep brain stimulation
FUS	Focused ultrasound
GPI	Globus Pallidus Internus
LDD	Levodopa daily dosage
LEDD	levodopa equivalent daily dose
MRgFUS	Magnetic Resonance Image guided Focused Ultrasound
MDS-UPDRS	Movement Disorder Society–Unified Parkinson's Disease Rating Scale
PD	Parkinson's
PDQ-39SI	Parkinson's Disease Questionnaire 39 summary index
P-GIC	Patients' Global Impression of Change (P-GIC)
PTT	Pallidothalamic tract
QoL	Quality of Life
RT	Radiofrequency Thalamotomy
RCT	Randomised controlled trial
SD	Standard deviation
STN	Subthalamic nucleus
UDRS	Unified Dyskinesia Rating Scale
VIM	Ventral intermediate nucleus

Indications and current treatment

Parkinson’s is a progressive neurodegenerative condition that damages the brain over many years. It is caused by a loss of the cells in the brain that produce dopamine, which helps to control and coordinate body movements. People with Parkinson's classically present with the symptoms and signs described as 'parkinsonism'. These include bradykinesia (slow movements), rigidity, rest tremor (shaking) and postural instability (loss of balance). In later stages of Parkinson’s, other symptoms (sometimes described as the 'non-motor' manifestations of Parkinson's such as depression, cognitive impairment, dementia and autonomic disturbances) may be prominent. The condition may progress to cause significant impairments, adversely affecting quality of life and, indirectly, the quality of life of family and carers.

For people with early Parkinson's, drug treatments such as levodopa, other dopamine agonists and monoamine oxidase B inhibitors may be considered. In the later stages, other drugs may be used with levodopa (as adjuvants) to reduce the motor complications associated with prolonged levodopa use. Non-pharmacological management such as physiotherapy, occupational therapy and speech and language therapy may be considered. Invasive surgical procedures may be considered for Parkinson’s that does not respond to medical and supportive therapies. These include deep brain stimulation and, less commonly, radiofrequency thalamotomy. Treatments for non-motor symptoms such as sleep disturbance and depression may also be considered.

Unmet need

Treatment for Parkinson’s includes supportive therapies and medications. Surgery may be considered in people whose condition has not responded adequately to best medical therapy. Surgical treatments include deep brain stimulation (DBS) and radiofrequency thalamotomy (RT).

MRI-guided focused ultrasound subthalamotomy is an incisionless procedure that may be beneficial to a subgroup of patients who have asymmetric motor symptoms that cannot be managed properly with medication, who do not wish to take the risks of invasive brain surgery (DBS or RT) or it is not suitable, especially in elderly and frail patients.

What the procedure involves

MRI-guided focused ultrasound subthalamotomy is an incisionless procedure that aims to treat tremor, slowness and stiffness associated with Parkinson’s.

This outpatient procedure is done with the patient lying supine inside an MRI scanner for several hours. The patient's head is shaved and a stereotactic head frame is attached. The person is usually kept awake during the procedure so they can be regularly assessed by the treating physician to evaluate the clinical response (improvement in symptoms or adverse events). Some people may be offered light sedation.

Real-time MRI guidance and thermal mapping are used to identify and adjust the target area of the brain (the subthalamic nucleus) precisely and continuously monitor treatment. Low-power ultrasound is delivered to confirm the location.

Then, several high-power focused ultrasound pulses are delivered to ablate tissue in the subthalamic nucleus (in the dorsolateral motor region and above, and mediodorsally to affect the pallidothalamic tract). The energy released and the location of the ultrasound focus are monitored in real time during the procedure by MRI thermometry and adjusted to reach above the definitive ablation temperature (of 55°C) according to clinical response.

Chilled water is circulated around the head during the treatment to prevent thermal damage to the scalp caused by the increase in bone temperature. The procedure is considered finished when there is sufficient clinical improvement, considering the total amount of energy delivered and the number of sonication. The procedure takes about 2 hours and symptom relief should be immediate.

Outcome measures

MDS-UPDRS is a comprehensive 50 question assessment of both motor and non-motor symptoms and complications associated with Parkinson's. It is used to evaluate various aspects of Parkinson's, monitor progression and response to medications and provide a clinical endpoint in studies. The MDS-UPDRS has 4 sections. These are completed by the person with Parkinson's and their carers, and also by the clinician:

- Part 1: non-motor experiences of daily living
- Part 2: motor experiences of daily living
- Part 3: motor examination
- Part 4: motor complications.

MDS–UPDRS part 1 and 2

Non-motor symptoms and autonomy in functional daily living activities were assessed with parts 1 and 2 of the MDS–UPDRS (scores range from 0 to 52, with higher scores indicating a worse state/greater disability).

MDS-UPDRS motor score 3

Motor symptoms were assessed with MDS–UPDRS part 3 (scores range from 0 to 44, with higher scores indicating a worse condition). A change of 30% in the motor score of MDS–UPDRS is considered clinically meaningful. The scale includes subitems for rigidity, akinesia and tremor (scores range from 0 to 8, from 0 to 20, and from 0 to 16, respectively, with higher scores indicating greater severity in all cases). Tremor score can also be derived from the Clinical Rating Scale, which ranges from 0 to 32 for tremor in the hand.

General motor condition is assessed with total MDS–UPDRS 3 (score ranges from 0 to 132 and includes scores for both the treated and untreated body sides and axial features, with higher scores indicating worse parkinsonism).

MDS–UPDRS 4

Motor complications were assessed with MDS–UPDRS 4 with scores ranging from 0 to 24 (score 0 to 4 for each item) and with the UDRS (scores ranging from 0 to 104, with a high score indicating frequent and disabling motor complications/dyskinesia). The dyskinesia rating scale has 3 parts: an on-dyskinesia patient questionnaire (scored 0 to 44), an off-dystonia patient questionnaire (scored 0 to 16) and an objective, videotaped evaluation to determine the presence and impact of dyskinesia or dystonia during the performance of different tasks such as communication, dressing, drinking from a glass and walking (scored 0 to 44).

Quality of life

Evaluated using the PDQ-39SI with scores ranging from 0 to 100, with a higher score indicating a worse quality of life.

Patients' Global Impression of Change (P-GIC) and Clinician's Global Impression of Change (C-GIC)

Scores ranging from 1 (very much improved) to 7 (very much worsened).

Evidence summary

Population and studies description

This interventional procedure overview is based on 147 patients from 1 RCT, a sub-study of the RCT and 5 prospective studies. Of these 95 patients, there is an overlap of data on 59 patients. So, only 88 patients had the procedure. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 7 studies as the key evidence in table 2 and table 3, and lists 10 other relevant studies in table 5.

Three studies (1 RCT, 1 pilot study and 1 long-term prospective cohort study that included patients from both the pilot study [n=10] and the RCT [n=40]) assessed evidence for patients with advanced Parkison's. One small pilot study with 1-year follow up assessed evidence for early-stage Parkinson's in younger patients (Martinez-Fernandez 2024). Table 2 presents study details.

The long-term follow-up prospective cohort study included patients from the pilot study and an RCT, both funded by the device company. All patients were examined and assessed by the same team. 29% (13/45) of patients dropped out from initial studies, and this was mainly related to the covid pandemic (Martinez-Fernandez 2023).

The small pilot study was in a group of patients with Parkinson's with highly asymmetric parkinsonism and short follow-up period. The target was slightly dorsolateral to the conventional localisation of the subthalamic nucleus (STN) (Martinez-Fernandez 2018).

In the small double blinded randomised sham-controlled trial, patients with advanced Parkinson's were randomised in a 2:1 ratio. Although assignment was concealed it was correctly guessed by patients and assessors. The procedure was offered to people in the sham group at the end of the study despite high complication rates. No interim analysis was done for adverse events. 12 patients from the control group crossed over and 11 completed 12 months of follow up. Two patients in each group were lost to follow up at 12 months. No definitive inferences could be made for secondary outcomes because there was no plan for adjustment of the 95% confidence interval (CI). The small sub-study (with 26 people) evaluated social cognitive outcomes before and 4 months after the procedure (Guida 2024).

Another small pilot study with short follow-up was done in patients with less advanced Parkinson's. One small prospective study in patients with asymmetric PD and mild dyskinesia evaluated unilateral treatment at 6- and 12-months

follow-up. The subgroup followed up for 12 months was limited (n=12) (Armengou-Garcia 2024).

One small feasibility study with limited follow-up assessed staged bilateral procedure in 6 young people with PD (mean age 56 years) who had been treated unilaterally, with no permanent adverse events and whose parkinsonism on the untreated side had progressed and was not controlled with medication (Martinez-Fernandez 2024).

Figure 1 Flow chart of study selection

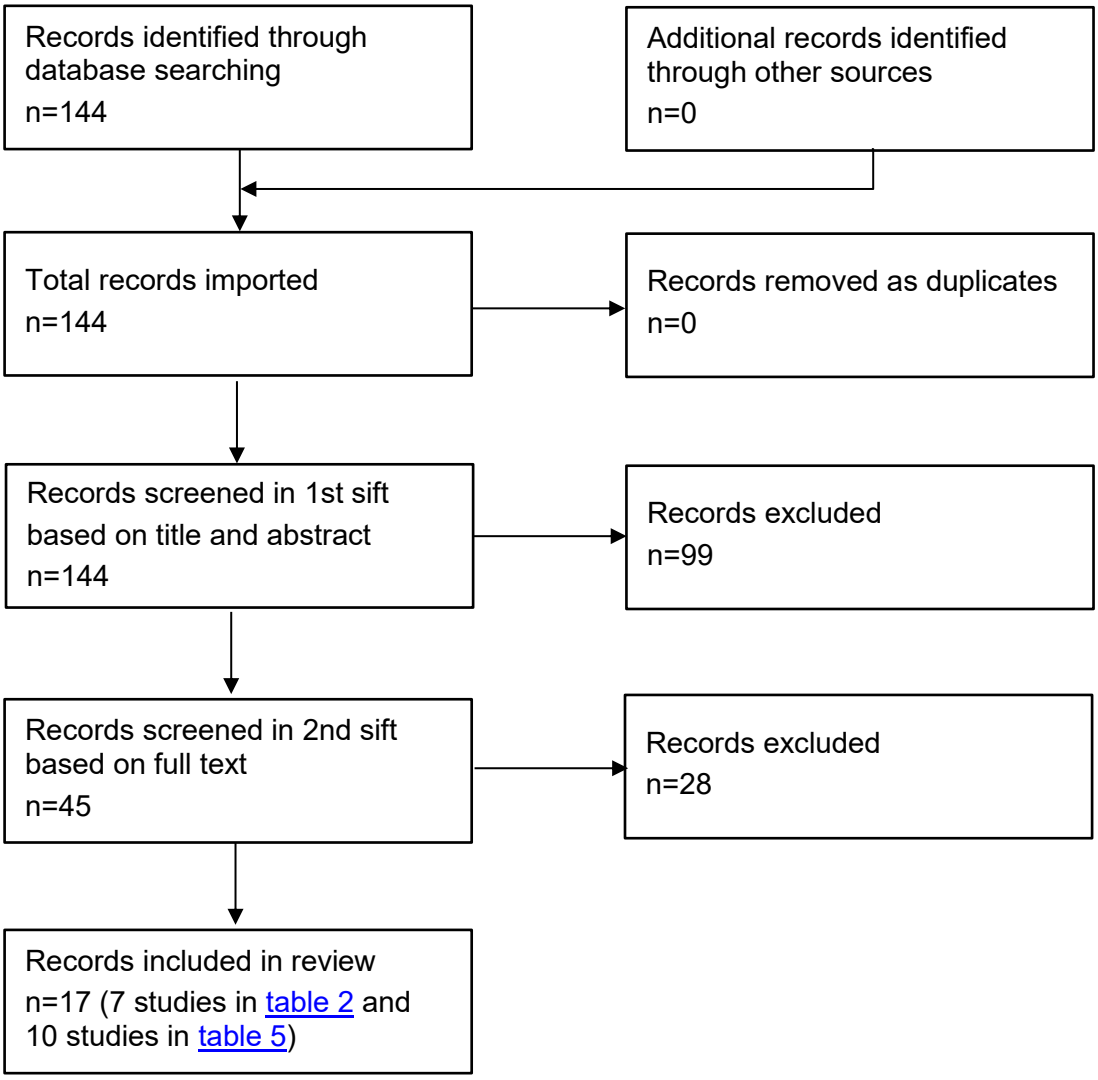

Table 2 Study details

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Martinez-Fernandez 2023 Spain (NCT02912871, NCT03454425)	N=32 (22 male, 10 female) Parkinson's duration mean 6.8 (SD 2.8) years.	Mean 56 (SD 10.1) years	Prospective cohort study (this cohort includes long term follow-up of patients included in the pilot study [n=10] and an RCT [n=36]). 13 of these patients were excluded from the 3-year follow-up.	Patients with asymmetrical PD with suboptimal control of motor signs on the more affected side despite the use of dopaminergic medication, those that were not eligible or were reluctant to have intracranial surgery for DBS.	Unilateral MRgFUS ablation of the STN in conjunction with medication	36 months. 7 patients were followed up for 5 years.
2	Martinez-Fernandez 2018 Spain (NCT02912871)	n=10 (6 male, 4 female) Parkinson's duration mean 6.3 (SD 2.4) years.	59.5 (SD 10.1) years	Prospective cohort study (pilot study)	patients with markedly asymmetric parkinsonism that was medically uncontrolled, refused to undergo	Unilateral MRgFUS ablation of the STN in conjunction with medication	6 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Age	Study design	Inclusion criteria	Intervention	Follow up
					DBS, or not indicated because of mild parkinsonism on the less affected side or the absence of relevant motor complications, or both and those above 70 years.		
3	Martinez-Fernandez 2020 Spain (NCT03454425)	n=40 (26 male,14 female) Parkinson's duration mean 6.2 years.	mean 57 years	Randomised controlled, double blinded trial	patients with highly asymmetric parkinsonism (asymmetry index more than 1.5), refractory to medication, declined to undergo DBS (11 patients); had minor motor signs on the less affected side, no drug-related motor complications that would make the patient a	Unilateral MRgFUS ablation of the STN, n=27 (16 in the left hemisphere and 11 in the right) sham procedure (of ultrasound), n=13 (7 in the left hemisphere, and 6 in the right) medical therapy was used in both groups.	12 months

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Age	Study design	Inclusion criteria	Intervention	Follow up
					candidate for DBS, or both (26 patients); or were poor candidates for intracranial surgery owing to advanced age or coexisting conditions (n=3).		
3.1	Guida, 2024, Spain (sub-study - NCT03454425)	n = 26 patients, with 8 females in the FUS group (44%) and 1 female in the sham group (12.5%) Duration from diagnosis was 7.1 years in the active group and 7.5 years in the sham group.	Mean age: 55.2 (SD 9.4 years)	Randomised, controlled, double-blind trial (sub-study) NCT03454425)	Diagnosed with Parkinson's disease according to UK Brain Bank Clinical Criteria, asymmetric parkinsonism, with several exclusion criteria such as severe axial or bilateral parkinsonism.	Unilateral Focused Ultrasound Subthalamotomy (FUS-STN) (n=18) versus sham (n=8)	4 months
4	Martinez-Fernandez 2024	n=12 (10:2) PD median time from diagnosis	median 52 years	prospective cohort study	patients with PD of less than 5 years from diagnosis (early PD).	Unilateral MRgFUS ablation of the STN,	12 months (8 for right side, 4 left side)

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Age	Study design	Inclusion criteria	Intervention	Follow up
	Spain (NCT04692116)	3.0 (2.1 to 3.9) years)			Patients had asymmetrical parkinsonian motor features in the off-medication state with an asymmetry index higher than 1.5.		
5	Martínez-Fernández, 2024, Spain	6 patients, 3 males and 3 females PD median duration of disease 5.7 years (IQR 4.7 to 7.3 years) Median time between the procedures was 3.2 years (IQR 1.9 to 3.5 years).	Median age at the first procedure: 52.6 years	Prospective, open-label, case series study	Patients with Parkinson's disease previously treated with unilateral Focused Ultrasound Subthalamotomy (FUS-STN) and experiencing motor progression on the untreated side.	Staged bilateral Focused Ultrasound Subthalamotomy (FUS-STN)	The follow-up time of the study is 6 months after the second treatment as the primary outcome. However, additional follow-up assessments were also conducted at 1, 3, 12, and 24 months
6	Armengou-Garcia, 2024, Spain	n=20, 18 males, 2 females	Median: 62.5 years	Prospective, single-centre,	Patients older than 30 years (no upper age limit), asymmetric	Unilateral magnetic resonance-guided focused	at 1, 3, 6, and 12

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Age	Study design	Inclusion criteria	Intervention	Follow up
			(IQR: 56.8 to 66.0)	open-label study	parkinsonism, Hoehn and Yahr scale 2.5 or less, clinically significant improvement in MDS-UPDRS III score after levodopa challenge, skull density ratio 0.40 or above.	ultrasound (MRgFUS) lesion of the subthalamic nucleus (STN)	months post-intervention

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Martinez-Fernandez 2023	**MDS-UPDRS motor part III, total score (on medication state), n=30** Baseline mean 24.7 (SD 7.4) 6 months 15.4 (SD 6.3) 1 year 15.3 (SD 5.7) **MDS-UPDRS motor part III, total score (off medication state), n=30** Baseline mean 36.8 (SD 7.4) 6 months 21.8 (SD 7.9)	**Adverse events (graded as mild, moderate or severe)** **During the procedure** 0 **Post procedure (at 4 to 6 months)** Contralateral dyskinesias n=3 [9%] Contralateral levodopa-induced dyskinesias n=5 [16%] Clumsiness/weakness on treated side (moderate) n=1

First author, date	Efficacy outcomes	Safety outcomes
	1 year 23.0 (SD 8.8) **MDS-UPDRS III scores (for treated side of the body and as per locomotor condition)** **off medication state (primary outcome), n=32** Baseline mean 19.0 (SD 3.2) 4 to 6 months 7.7 (4.0) 12 months 8.3 (4.2) 24 months 8.5 (3.5) 36 months 8.9 (3.3) Change in score baseline versus 36 months=10.1, (95% CI 8.7 to 11.6, p<0.001). Change in score 4 to 6 months versus 36 months=-1.2, (95% CI -2.5 to 0.2, p=0.089). **on medication state, n=32** Baseline mean 13.7 (SD 3.7) 4 to 6 months 5.5 (3.4) 12 months 5.5 (3.3) 24 months 5.3 (2.6) 36 months 5.8 (2.9) Change in score baseline versus 36 months=7.8, (95% CI 6.3 to 9.4, p<0.001). Change in score 4 to 6 months versus 36 months=-0.4, (95% CI -1.6 to 0.8, p=0.500).	Facial asymmetry n=1 Speech disturbance: dysarthria n=2 [6%], reduced verbal fluency n=1 Gait disturbances: unsteady gait n=1 Weight gain n=3 [9%] **At 1 year (n=32)** Contralateral levodopa-induced dyskinesias n=4 [12%] Clumsiness/weakness on treated side n=1 Facial asymmetry n=1 Speech disturbance: dysarthria n=1, reduced verbal fluency n=1 Gait disturbances: unsteady gait n=1 Weight gain n=3 [9%] **at 24 months (n=20)** Speech disturbance: mild dysarthria n=1, reduced verbal fluency n=1 Contralateral levodopa-induced dyskinesias n=4 (20%) Clumsiness/weakness on treated side (moderate) n=1 **at 3 years (n=30)** Speech disturbance: mild dysarthria n=1, reduced verbal fluency n=1

First author, date	Efficacy outcomes	Safety outcomes
	Tremor (off medication state) Baseline mean 5.2 (SD 2.3) 4 to 6 months 1.2 (1.4) 1 year 1.1 (1.6) 24 months 1.6 (1.6) 36 months 1.7 (1.8) Change in score baseline versus 36 months=3.5 (95% CI 2.9 to 4.2, p<0.001) Change in score 4-6 months versus 36 months=-0.5 (95% CI −1.0 to 0.1, p=0.079). **Tremor (on medication state)** Baseline mean 3.7 (SD 1.9) 4-6 months 0.9 (1.3) 1 year 0.5 (1.0) 24 months 1.0 (1.3) 36 months 0.9 (1.2) Change in score baseline versus 36 months=2.8 (95% CI 2.1 to 3.5, p<0.001) Change in score 4 to 6 months versus 36 months=0.1 (95% CI −0.5 to 0.6, p=0.807). **Bradykinesia (off medication state)** Baseline mean 10.3 (SD 2.5) 4 to 6 months 5.0 (2.8) 1 year 5.4 (3.0) 24 months 5.2 (2.5)	Contralateral levodopa-induced dyskinesias n=8 (27%) Clumsiness on treated side n=1 Weight gain n=2 Parkinsonism on the nontreated side (needed either DBS or MRgFUS STN), n=3

First author, date	Efficacy outcomes	Safety outcomes
	36 months 5.5 (2.5) Change in score baseline versus 36 months=4.8 (95% CI 3.8 to 5.9, p<0.001) Change in score 4 to 6 months versus 36 months=-0.5 (95% CI −1.4 to 0.4, p=0.311). **Bradykinesia (on medication state)** Baseline mean 7.3 (SD 2.4) 4 to 6 months 3.6 (2.8) 1 year 3.9 (2.6) 24 months 3.2 (2.1) 36 months 4.0 (2.2) Change in score baseline versus 36 months=3.3 (95% CI 2.3 to 4.3, p<0.001) Change in score 4-6 months versus 36 months=−0.4 (95% CI −1.1 to 0.3, p=0.252). **Rigidity (off medication state)** Baseline mean 3.5 (SD 0.9) 4 to 6 months 1.5 (1.3) 1 year 1.7 (1.2) 24 months 1.6 (1.1) 36 months 1.7 (1.0) Change in score baseline versus 36 months=1.8 (95% CI 1.4 to 2.1, p<0.001) Change in score 4 to 6 months versus 36 months=−0.3 (95% CI−0.6 to 0.1, p=0.174) **Rigidity (on medication state)** Baseline mean 2.8 (SD 1.1)	

First author, date	Efficacy outcomes	Safety outcomes
	4 to 6 months 0.9 (1.0) 1 year 1.1 (1.2) 24 months 1.0 (1.1) 36 months 1.0 (0.8) Change in score baseline versus 36 months=1.8 (95% CI 1.4 to 2.2, p<0.001) Change in score 4 to 6 months versus 36 months=−0.1 (95% CI −0.3 to 0.2, p=0.645) **MDS-UPDRS III for the untreated side** **off-medication state** Baseline mean 6.6 (SD 3.1) 4 to 6 months 7.1 (3.2) 1 year 7.5 (4.0) 24 months 8.5 (3.2) 36 months 10.1 (4.6) Change in score baseline versus 36 months=−3.7 (95% CI −5.4 to −2.0, p<0.001) Change in score 4 to 6 months versus 36 months=−3.4 (95% CI −4.9 to −0.9, p <0.001). **on-medication state** baseline mean 4.3 (SD 2.9) 4 to 6 months 5.3 (2.9) 1 year 5.5 (3.1) 24 months 5.0 (2.5)	

First author, date	Efficacy outcomes	Safety outcomes
	36 months 6.6 (4.2) Change in score baseline versus 36 months=−2.7 (95% CI −4.4 to −0.9, p=0.016) Change in score 4 to 6 months versus 36 months=−1.7 (95% CI −3.3 to −0.1, p=0.041). **MDS-UPDRS part IV, for levodopa-related motor complications** **total score** Baseline mean 2.9 (SD 3.4) 4 to 6 months 2.2 (3.0) 1 year 2.0 (2.4) 24 months 1.7 (1.8) 36 months 2.6 (2.2) Change in score baseline versus 36 months=0.1 (95% CI −1.2 to 1.3, p=0.642) Change in score 4-6 months versus 36 months=−0.7 (95% CI −1.6 to 0.2, p=0.050). **sub-scores** **Dyskinesia** Baseline mean 0.3 (SD 0.8) 4 to 6 months 0.5 (1.1) 1 year 0.7 (1.0) 24 months 0.6 (1.0) 36 months 0.6 (0.9)	

First author, date	Efficacy outcomes	Safety outcomes
	Change in score baseline versus 36 months=−0.3 (95% CI −0.7 to 0.1, p=0.123) Change in score 4 to 6 months versus 36 months=−0.2 (95% CI −0.6 to 0.2, p=0.238). **motor fluctuations** baseline mean 2.0 (SD 2.2) 4 to 6 months 1.4 (1.9) 1 year 1.1 (1.6) 24 months 1.0 (1.4) 36 months 1.9 (1.7) Change in score baseline versus 36 months=0.0 (95% CI −0.9 to 0.9, p=0.725) Change in score 4 to 6 months versus 36 months=−0.6 (95% CI −1.4 to 0.2, p=0.068). **Dystonia (off medication state)** baseline mean 0.6 (SD 1.1) 4 to 6 months 0.3 (0.5) 1 year 0.3 (0.5) 24 months 0.1 (0.3) 36 months 0.2 (0.4) Change in score baseline versus 36 months=0.4 (95% CI −0.01 to 0.8, p=0.062) Change in score 4 to 6 months versus 36 months=0.07 (95% CI −0.1 to 0.2, p=0.484).	

First author, date	Efficacy outcomes	Safety outcomes
	Functional disability/activities of daily living (assessed using the MDS-UPDRS II) baseline mean 10.0 (SD 5.4) 4 to 6 months 6.8 (5.6) 1 year 8.8 (5.3) 24 months 9.6 (7.9) 36 months 10.3 (6.1) Change in score baseline versus 36 months=1.3 (95% CI −1.0 to 3.7, p=0.352) Change in score 4 to 6 months versus 36 months=−2.5 (95% CI −4.1 to −0.7, p=0.011). **Quality of life (assessed using PDQ39)** baseline mean 17.7 (SD 11.2) 4 to 6 months 11.3 (9.1) 1 year 15.5 (9.4) 24 months 16.1 (10.1) 36 months 16.1 (9.7) Change in score baseline versus 36 months=3.1 (95% CI−0.8 to 6.6, p=0.106) Change in score 4 to 6 months versus 36 months=−5.2 (95% CI −8.1 to −2.0, p=0.004). **Drug changes** **LEDD (milligrams)** baseline mean 728.2 (SD 260.5) 4 to 6 months 636.1 (319.9)	

First author, date	Efficacy outcomes	Safety outcomes
	1 year 683.4 (291.9) 24 months 771.0 (332.3) 36 months 835.4 (330.0) Change in score baseline versus 36 months=107.3 (95% CI −5.4 to 220.1, p=0.061) Change in score 4 to 6 months versus 36 months=186.1 (−100.5 to 271.8, p<0.001). **LDD (milligrams)** baseline mean 453.9 (SD 229.9) 4 to 6 months 390.6 (231.4) 1 year 426.1 (231.82) 24 months 431.1 (213.8) 36 months 515.7 (220.8) Change in score baseline versus 36 months=66.5 (95% CI −29.9 to 162.9, p=0.169) Change in score 4 to 6 months versus 36 months=116.5 (95% CI −49.2 to 183.8, p< 0.001). **Patient satisfaction at 3 years (assessed using global impression of change questionnaire)** satisfied with the treatment 89.7% (26/29) better global status 82.8% (24/29).	
Martinez-Fernandez 2018 Spain NCT02912871	**Change in motor status (assessed with MDS-UPDRS III score), mean (SD)** **MDS–UPDRS III, treated side off-medication** baseline mean 16.6 (SD 2.9) 6 months 7.5 (3.9)	**Adverse events** **During the procedure** Transient warm cranial sensations (related to sonication), n=2

First author, date	Efficacy outcomes	Safety outcomes
	change from baseline –9.1 (4.7); –53% **MDS–UPDRS III, treated side on medication** baseline 11.9 (3.1) 6 months 5.8 (3.5) change from baseline –6.1 (4.1); –47% **Tremor** off medication state baseline 4.2 (2.1) 6 months 1.2 (1.8) change from baseline –3.0 (1.8); –77% on medication state baseline 3.7 (1.9) 6 months 0.9 (1.7) change from baseline –2.8 (1.9); –80% **Bradykinesia** off medication state baseline 9.4 (2.7) 6 months 5.6 (2.9) change from baseline –3.9 (4.0); –37% on medication state baseline 6.5 (2.0) 6 months 4.7 (2.1) change from baseline –1.9 (2.9); –23% **Rigidity** off medication state baseline 2.9 (0.7)	Transient pin-site head pain (related to head frame), n=6 Nausea (related to sonication), n=4 Other events: back pain (n=2), anxiety (n=2), transient high blood pressure (n=5). **6 months after the procedure** Related to subthalamotomy Transient mild gait ataxia, n=6 Facial palsy/asymmetry (n=1, resolved by follow-up). Post-discharge behavioural changes like impulsivity/disinhibition and abnormal cheerfulness (n=2, resolved within a month). Off-medication upper limb choreic dyskinesias (5 days after subthalamotomy, disappeared after 6 months), n=1 Involuntary movements in treated arm/ on-medication upper limb dyskinesia (n=1, resolved after reduction in drug dose). Subjective speech disturbance (n=1). Other events: weight gain (n=2), fatigue (n=1), anxiety (n=1).

First author, date	Efficacy outcomes	Safety outcomes
	6 months 0.8 (0.8) change from baseline –2.1 (1.0); –71% on medication state baseline 2.2 (1.2) 6 months 5.8 (3.5) change from baseline –2.0 (1.4); –88% **MDS–UPDRS III, untreated side, off-medication** baseline 5.5 (2.5) 6 months 6.2 (3.4) change from baseline 0.3 (1.7); 8% **MDS–UPDRS III, untreated side, on-medication** baseline 3.2 (3.1) 6 months 4.3 (2.8) change from baseline 1.1 (2.8); 14% **total MDS-UPDRS III score** off medication state baseline 32.7 (5.4) 6 months 21.2 (8.2), change from baseline –11.6 (6.9); –36% on medication state baseline 21.5 (6.3) 6 months 14.5 (5.3), change from baseline –7 (8.1); –26% **MDS–UPDRS IV scores** baseline 4.2 (4.3)	

First author, date	Efficacy outcomes	Safety outcomes
	6 months 1.7 (2.2) change from baseline –2.4 (2.7); –45% **UDRS scores** baseline 10.1 (13.1) 6 months 5.3 (7.5) change from baseline –4.7 (11.6); –32% **MDS–UPDRS I** baseline 5.9 (3.1) 6 months 5.5 (4.9) change from baseline –0.4 (3.4); –18% **MDS–UPDRS II** baseline 7.9 (4.3) 6 months 6.6 (7.1) change from baseline –1.3 (4.9); –32% **LDD (mg)** baseline 732.7 (346.4) 6 months 564.4 (286.8) change from baseline –164.6 (131.9); –24% **Quality of life** **PDQ-39SI score** baseline 12.6 (8.8) 6 months 10.4 (9.1) change from baseline–2.4 (8.2); –19% **Treatment benefit (assessed with P-GIC and C-GIC)**	

First author, date	Efficacy outcomes	Safety outcomes
	All patients except one had experienced a clinical improvement after 6 months according to the P-GIC. Neurologists found all patients very much improved as per GC-GIC scores.	
Martinez Fernandez 2020, NCT03454425	**MDS-UPDRS-III scores (for the more affected side), change at 4 months** off medication state (primary outcome) MRgFUS: baseline= mean 19.9 to 9.9; mean difference=9.8 (95% CI 8.6 to 11.1), 52.6% sham procedure: baseline=mean 18.7 to 17.1; mean difference= 1.7 (95% CI 0.0 to 3.5), 4.2% score difference between the groups=8.1 points (95% CI 6.0 to 10.3, p<0.001) on-medication state MRgFUS subthalamotomy: baseline=mean 14.2 to 7.8, mean difference=6.4 (95% CI 5.2 to 7.6), 46.5% sham: baseline=mean 11.9 to 11.8, mean difference=0.1 (95% CI −0.3 to 0.6) 6.0% Score difference between the groups=5.9 points (95% CI 3.8 to 8.0). **MDS-UPDRS-III sub scores (at 4 months)** **off medication** Rigidity MRgFUS: baseline=mean 3.5 to 1.6, mean difference=1.9 (95% CI 1.6 to 2.2), 60.0%	**Adverse events** MRgFUS Subthalamotomy total n=144 (mild 96, moderate 40, severe 8) sham procedure total n=31 (mild 13, moderate 16, severe 2). Intraprocedural adverse events Nausea, emesis, dizziness, head tilting, head discomfort, pin-site head pain, headache, back or neck pain, high blood pressure, fatigue, occurred in both groups but more frequently in the treatment group than in the control group; these events resolved after the procedure. Anxiety (in 6) and right inner ear pain (in 1) were reported in the treatment group. Other adverse events not related to the procedure Rib fracture (in 2), fall (in 2) and dysuria (in 1) were reported in the treatment group. **MRgFUS subthalamotomy group** Dyskinesia in off medication state 22% (6/27), mostly resolved within 4 months. Chorea, n=5; Ballism, n=1

First author, date	Efficacy outcomes	Safety outcomes
	Sham: baseline=mean 3.8 to 3.7, mean difference=0.1 (95% CI −0.3 to 0.6), 0.0% Score difference between the groups=1.8 (95% CI 1.3 to 2.3) Bradykinesia MRgFUS: baseline=mean 10.8 to 6.8, mean difference=4.0 (95% CI 3.2 to 4.7), 33.3% Sham: baseline=mean 9.7 to 8.3, mean difference=1.4 (95% CI 0.3 to 2.4) 9.1% Score difference between the groups=2.7 (95% CI 1.4 to 4.0) Tremor MRgFUS: baseline= mean 5.6 to 1.6, mean difference=4.0 (95% CI 3.3 to 4.6), 83.3% Sham: baseline= mean 5.2 to 4.9, mean difference=0.3 (95% CI −0.6 to 1.3), 0.0% Score difference between the groups=3.6 (95% CI 2.5 to 4.8) **on medication** Rigidity MRgFUS: baseline= mean 2.6 to 1.3, mean difference=1.3 (95% CI 1.0 to 1.6), 50.0% Sham: baseline= mean 2.6 to 2.8, mean difference=−0.2 (95% CI −0.6 to 0.2), 0.0% Score difference between the groups=1.5 (95% CI 1.1 to 2.0) Bradykinesia	New onset dyskinesia in on medication state 22% (6/27), persisted in 2 people at 12 months. Weakness 19% (5/27) persisted in 2 people at 12 months. Isolated facial asymmetry 11% (n=3), mostly resolved within 4 months. Speech difficulties 56% (15/27), mainly transient dysarthria n=7, (persisted in 1 person at 1-year follow- up) slurred speech n=8 Gait disturbances 48% (13/27) unsteady gait n=10 (persisted in 1 person at 1 year follow-up), ataxia n=3 other events: upper limb dysmetria in 2, impulsive binge eating in 1 (resolved after 2 months), weight gain in 2 and somnolence in 1 (resolved after 24 hours) were also reported. Perilesional oedema in all, resolved by 4 months.

First author, date	Efficacy outcomes	Safety outcomes
	MRgFUS: baseline= mean 7.9 to 5.6, mean difference=2.3 (95% CI 1.5 to 3.1), 27.3% Sham: baseline= mean 6.4 to 5.6, mean difference=0.8 (95% CI −0.3 to 2.0), 12.7% Score difference between the groups=1.5 (95% CI 0.1 to 2.9) Tremor MRgFUS: baseline=mean 3.8 to 1.1, mean difference=2.7 (95% CI 2.1 to 3.3), 92.9% Sham: baseline=mean 2.9 to 2.9, mean difference=0.0 (95% CI −0.8 to 0.9), 0.0% Score difference between the groups=2.7 (95% CI 1.6 to 3.7) **MDS-UPDRS II score (change at 4 months)** MRgFUS: baseline=mean 11.3 to 7.2, mean difference=4.1 (95% CI 2.2 to 5.9), 42.9% Sham: baseline=mean 12.5 to 13.4, mean difference=−1.4 (95% CI −4.0 to 1.2), −11.8% Score difference between the groups=5.5 (95% CI 2.2 to 8.7) **MDS-UPDRS III total score (change at 4 months)** Off-medication state MRgFUS: baseline=mean 39.9 to 24.7, mean difference=15.2 (95% CI 13.5 to 17.0), 34.2% Sham: baseline=mean 40.1 to 37.8, mean difference=2.3 (95% CI −0.2 to 4.8), 6.3%	

First author, date	Efficacy outcomes	Safety outcomes
	Score difference between the groups=12.9 (95% CI 9.9 to 16.0) On-medication state MRgFUS: baseline=mean 26.9 to 18.5, mean difference=8.4 (95% CI 6.6 to 10.3), 33.9% Sham: baseline=mean 25.1 to 25.9, mean difference=−0.8 (95% CI −3.4 to 1.8), 0.0% Score difference between the groups=9.2 (95% CI 6.0 to 12.4). **MDS-UPDRS IV total score (change at 4 months)** MRgFUS (n=17): baseline=mean 4.0 to 2.9, mean difference=1.1 (95% CI 0.0 to 2.1), 40.0% sham (n=9): baseline=mean 5.1 to 6.3, mean difference=−1.2 (95% CI −2.7 to 0.3), 0.0% Score difference between the groups=2.3 (95% CI 0.5 to 4.1) Dyskinesia MRgFUS (n=4): baseline=mean 0.3 to 0.3, mean difference=0.0 (95% CI −0.4 to 0.3) sham (n=4): baseline=mean 1.1 to 1.5, mean difference=−0.4 (95% CI −0.9 to 0.2) Score difference between the groups=0.3 (95% CI −0.3 to 1.0) Motor fluctuations MRgFUS (n=16): baseline=mean 3.0 to 2.1, mean difference=0.9 (95% CI 0.2 to 1.6), 26.8% sham (n=9): baseline=mean 3.5 to 4.1, mean difference=−0.6 (95% CI −1.6 to 0.4), 12.5%	

First author, date	Efficacy outcomes	Safety outcomes
	Score difference between the groups=1.5 (95% CI 0.2 to 2.7) Dystonia, in the off-medication state MRgFUS 7(n=8): baseline=mean 0.7 to 0.5, mean difference=0.2 (95% CI −0.1 to 0.5), 75.0% sham (n=3): baseline=mean 0.5 to 0.7, mean difference= −0.2 (95% CI −0.6 to 0.2) Score difference between the groups=0.4 (95% CI −0.1 to 1.0) **PDQ-39 SI (change at 4 months)** MRgFUS: baseline=mean 21.7 to 14.3, mean difference=7.4 (95% CI 4.1 to 10.6), 38.5% Sham: baseline=mean 23.9 to 22.3, mean difference=1.6 (95% CI −3.1 to 6.2), 29.0% Score difference between the groups=5.8 (95% CI 0.1 to 11.4) **LDD (milligrams) (change at 4 months)** MRgFUS: baseline=mean 729.7 to 635.2, mean difference=−94.5 (95% CI −151.9 to −37.2), 7.5% Sham: baseline=mean 881.7 to 859.2, mean difference=22.5 (95% CI −60.2 to 106.4), 0.0% Score difference between the groups=−117.0 (95% CI −218.0 to −16.0 **P-GIC at 4 months**	

First author, date	Efficacy outcomes	Safety outcomes
	clinical improvement reported by 85% (23/27) in MRgFUS group and 15% (2/13) in sham group. **Additional analysis** MDS-UPDRS III score for the more affected side in the crossover subgroup (n=12) baseline 19.5 (SD 3.9) 4 months 11.6 (95% CI 8.4 to 14.8), 68.0%	
Guida, 2024, Spain (sub-study – NCT03454425)	**Motor Outcome (Treated Side Improvement - MDS-UPDRS III)** Baseline (mean, SD): Not explicitly provided. 4 Months (mean, SD): Not directly provided. ○ Change in score baseline versus 4 months: Improvement of 8.4 points favouring active treatment, P-value: Bayesian analysis provided strong evidence favouring active treatment (BF+0= 13.72). [Notes: This study did not report any p value, they reported Bayesian factor (another option of reporting significance). The value of BF+0 = 13.72 suggests strong evidence favouring the active treatment over no treatment, as a Bayes Factor greater than 10 typically indicates substantial evidence for the alternative hypothesis. This means that the data are approximately 13.72 times more likely under the active treatment hypothesis than under the null hypothesis, indicating a significant positive effect of the treatment on the motor outcome (MDS-UPDRS III score) at 4 months.]	**Motor Safety:** • While the study focused on efficacy in improving motor symptoms, no adverse motor outcomes were reported in terms of safety.

First author, date	Efficacy outcomes	Safety outcomes
	Facial Emotion Recognition (FER) - Total Score Baseline (mean, SD): ○ FUS: 49.7 (SD 7.2) ○ Sham: 50.6 (SD 9.1) 4 Months (mean, SD): ○ FUS: 51.3 (SD 6.3) ○ Sham: 48.5 (SD 9.4) Change in score baseline versus 4 months: ○ Score change: FUS: +1.6 (SD 4.7); Sham: -2.1 (SD 2.4) ○ P-value: Anecdotal evidence for improvement in FUS vs. sham (BF+0 = 1.52). **Reading the Mind in the Eyes (RME) Test - Affective Theory of Mind** Baseline (mean, SD): ○ FUS: 21.4 ((SD 4.7) ○ Sham: 21.0 (SD 5.8) 4 Months (mean, SD): ○ FUS: 21.0 (SD 4.1) ○ Sham: 17.8 (SD 5.6) Change in score baseline versus 4 months: ○ Score change: FUS: -0.4 (SD 2.9); Sham: -3.1 (SD 2.7) ○ P-value: Moderate evidence of improvement in FUS compared to sham (BF+0 = 2.86). **Theory of Mind Picture Stories Task (ToM PST) - Cognitive Theory of Mind (Order Score)** Baseline (mean, SD):	

First author, date	Efficacy outcomes	Safety outcomes
	○ FUS: 30.1 ± 6.9 ○ Sham: 31.3 ± 6.9 4 Months (mean, SD): ○ FUS: 32.5 ± 5.2 ○ Sham: 30.7 ± 6.5 Change in score baseline versus 4 months: ○ Score change: FUS: +2.3 (SD 2.6); Sham: -0.6 (SD 3.2) ○ P-value: Anecdotal evidence of improvement (BF+0 = 2.07). **Theory of Mind Picture Stories Task (ToM PST) - Total Score** Baseline (mean, SD): ○ FUS: 51.7 (SD 8.6) ○ Sham: 51.6 (SD 10.5) 4 Months (mean, SD): ○ FUS: 54.4 (SD 6.9) ○ Sham: 51.1 (SD 9.4) Change in score baseline versus 4 months: ○ Score change: FUS: +2.7 (SD 3.3); Sham: -0.5 (SD 3.5) ○ P-value: Anecdotal evidence of improvement in FUS compared to sham (BF+0 = 2.68). **Facial Emotion Recognition (FER) - Fear Recognition** Baseline (mean, SD): ○ FUS: 2.2 (SD 1.3) ○ Sham: 3.8 (SD 1.8) 4 Months (mean, SD): ○ FUS: 2.6 (SD 1.2)	

First author, date	Efficacy outcomes	Safety outcomes
	○ Sham: 2.7 (SD 1.5) Change in score baseline versus 4 months: ○ Score change: FUS: +0.3 (SD 1.6); Sham: -1.1 (SD 1.9) ○ P-value: Moderate evidence of improvement (BF+0 = 1.98). **Facial Emotion Recognition (FER) - Disgust Recognition** Baseline (mean, SD): ○ FUS: 6.3 (SD 1.6) ○ Sham: 6.5 (SD 2.0) 4 Months (mean, SD): ○ FUS: 6.5 (SD 1.6) ○ Sham: 5.8 (SD 2.0) Change in score baseline versus 4 months: ○ Score change: FUS: +0.2 SD 1.2); Sham: -0.6 (SD 1.5) ○ P-value: Anecdotal evidence of improvement (BF+0 = 1.04).	
Martinez Fernandez 2024	**MDS-UPDRS III score for the treated side, median (range)** off-medication state baseline 14.5 (12.7 to 17.2) 12 months 4.0 (2.0 to 7.2), p=0.002 sub scores tremor baseline 2.0 (1.0 to 4.2) 12 months 0.0 (0.0 to 0.0), p<0.001 rigidity	**Adverse events (mainly mild and transient)** Dyskinesia on treated side (off medication state) n=1, at 3 months New onset drug induced dyskinesia on treated side (3 in upper limb and 1 in lower limb) 33% (4/12) of these 1 persisted at 3 months.

First author, date	Efficacy outcomes	Safety outcomes
	baseline 3.0 (2.0 to 4.0) 12 months 1.0 (0.7 to 1.2) p<0.001 bradykinesia baseline 9.0 (8.0 to 10.0) 12 months 3.0 (1.7 to 5.0) p=0.002 on medication state, median (range) baseline 9.5 (6.7 to 13.2) 12 months 2.5 (1.0 to 4.2), p=0.001 sub scores tremor baseline 1.5 (0.7 to 2.2) 12 months 0.0 (0.0 to 0.0), p<0.001 rigidity baseline 2.0 (1.0 to 3.2) 12 months 0.0 (0.0 to 1.0) p<0.001 bradykinesia baseline 6.0 (4.5 to 7.2) 12 months 2.0 (1.0 to 3.0) p=0.008 **MDS-UPDRS III for the untreated side off-medication, median (range)** baseline 4.5 (3.7 to 6.0) 12 months 5.0 (2.0 to 6.5), p=0.420 **MDS-UPDRS III for the untreated side on-medication, median (range)**	Isolated facial asymmetry 50% (6/12) (reported at different follow-up periods, of these 1 persisted at 12 months) Speech abnormalities (mild slur) 17% (2/12), 1 of which persisted at 12 months. Contralateral weakness n=1, resolved within 24 hours mild transient gait instability 42% (5/12), resolved within 2 weeks Pericranial hypoesthesia n=1, at 3 months Hiccups n=1 within 24 hours Foot dystonia 17% (2/12), resolved by 6 months Weight gain 58% (7/12), persisted at 12 months Cheerfulness n=1, resolved by 3 months. perilesional oedema in all, resolved by 6 months no cognitive worsening or behavioural changes were observed.

First author, date	Efficacy outcomes	Safety outcomes
	baseline 2.0 (1.0 to 2.2) 12 months 3.0 (1.0 to 5.2), p=0.131 **MDS-UPDRS III total off-medication median (range)** baseline 26.5 (23.2 to 32.2) 12 months 13.0 (8.7 to 18.0), p=0.002 **MDS-UPDRS III total on-medication median (range)** baseline 18.0 (12.7 to 19.5) 12 months 8.0 (6.0 to 10.7), p=0.016 **MDS-UPDRS IV, median (range)** baseline 1.0 (0.0 to 3.0) 12 months 1.0 (0.0 to 1.0), p=0.408 Dyskinesia baseline 0.0 (0.0 to 0.0) 12 months 0.0 (0.0 to 0.0), p=0.392 Motor fluctuations baseline 0.5 (0.0 to 3.0) 12 months 0.0 (0.0 to 0.2), p=0.102 Off-dystonia baseline 0.0 (0.0 to 0.0) 12 months 0.5 (0.0 to 1.0), p=0.275 **MDS-UPDRS I, median (range)**	

First author, date	Efficacy outcomes	Safety outcomes
	baseline 4.0 (3.0 to 6.0) 12 months 2.0 (1.0 to 3.5), p=0.023 **MDS-UPDRS II, median (range)** baseline 6.0 (2.0 to 7.2) 12 months 3.0 (1.0 to 5.0), p=0.022 **PDQ-39SI, median (range)** baseline 11.6 (8.1 to 21.8) 12 months 6.7 (3.5 to 10.6), p=0.035 **LEDD (mg), median (range)** baseline 560.0 (498.7 to 668.7) 527.5 (340.0 to 606.2), p=0.161 **LDD (mg), median (range)** baseline 300.0 (237.5 to 312.5) 12 months 225.0 (200.0 to 312.5), p=0.255. **P-GIC at 12 months and patient satisfaction** 91.7% (11/12) reported a better global status compared with baseline (according to P-GIC questionnaire), while all patients reported being satisfied with the treatment.	
Martínez-Fernández, 2024, Spain	**MDS-UPDRS motor part III, total score (on medication state)**	**Contralateral Dyskinesia:** • Incidence: Four out of six patients experienced contralateral dyskinesia within the first week after the second

First author, date	Efficacy outcomes	Safety outcomes
	Baseline: 27.0 (mean, IQR 21.2 to 29.0) 3 months: 18.0 (IQR 10.2 to 27.2) 6 months: 12.5 (IQR 7.5 to 15.2) 12 months: 17.5 (IQR 10.5 to 24.7) 24 months: 15.0 (IQR 8.0 to 18.5) Change in score baseline vs 6 months: 11.0 (95% CI, 0.9 to 23.7; p=0.03) **MDS-UPDRS motor part III, total score (off medication state)** Baseline: 37.5 (IQR 34.2 to 40.0) 3 months: 21.5 (IQR 10.2 to 35.0) 6 months: 20.5 (IQR 8.7 to 24.0) 12 months: 27.0 (IQR 13.5 to 37.5) 24 months: 25.0 (IQR 12.0 to 31.5) Change in score baseline vs 6 months: 23.0 (95% CI, 7.0 to 33.7; p=0.03) **MDS-UPDRS III scores (for treated side of the body and as per locomotor condition) off medication state** Baseline: 17.0 (IQR 16.0 to 19.5) 3 months: 5.5 (IQR 0.5 to 13.5) 6 months: 5.5 (IQR 3.0 to 10.2) Change in score baseline vs 6 months: 9.5 (95% CI, 3.2 to 17.7; p=0.02) **MDS-UPDRS III scores (for treated side of the body and as per locomotor condition) on medication state**	Focused Ultrasound Subthalamotomy (FUS-STN). • Severity: For three patients, the dyskinesia was mild, characterized by upper limb choreiform movements during levodopa intake. One patient, however, experienced more severe hemichorea-hemiballismus, which significantly interfered with daily activities. **Management**: • The dyskinesia was managed by reducing the levodopa dose, which led to the complete and almost immediate resolution of dyskinesia in the three patients with mild symptoms. The severe case showed progressive improvement. **Resolution:** • All instances of dyskinesia resolved by 3 months. **Speech Disturbances** • Incidence: Four patients developed speech disturbances following the second FUS-STN procedure. • Types: Three patients experienced dysarthria (difficulty in articulating words), and one patient had reduced

First author, date	Efficacy outcomes	Safety outcomes
	Baseline: 11.0 (IQR 9.2 to 15.0) 3 months: 4.5 (IQR 1.2 to 11.5) 6 months: 4.0 (IQR 2.2 to 5.7) Change in score baseline vs 6 months: 6.5 (95% CI, 0.2 to 13.1; p = .02) **Tremor (off medication state)** Baseline: 5.5 (IQR 3.5 to 6.0) 6 months: 0.5 (IQR 0.0 to 1.7) Change in score baseline vs 6 months: 5.0 (p = .02) **Tremor (on medication state)** Baseline: 3.5 (IQR 3.0 to 4.7) 6 months: 0.0 (IQR 0.0 to 0.7) Change in score baseline vs 6 months: 3.5 (p = .03) **Bradykinesia (off medication state)** Baseline: 9.5 (IQR 8.0 to 11.0) 6 months: 3.0 (IQR 2.2 to 6.7) Change in score baseline vs 6 months: 6.5 (p = .007) **Bradykinesia (on medication state)** Baseline: 7.5 (IQR 5.5 to 8.7) 6 months: 2.5 (IQR 1.2 to 4.5) Change in score baseline vs 6 months: 5.0 (p = .02) **Rigidity (off medication state)** Baseline: 3.5 (IQR 3.0 to 4.0) 6 months: 1.5 (IQR 0.2 to 2.7) Change in score baseline vs 6 months: 2.0 (p = .007)	verbal fluency, particularly during spontaneous speech. • Duration: These speech disturbances gradually improved over time. By the 6-month follow-up, mild dysarthria persisted in one patient, and another patient continued to experience reduced verbal fluency. However, these conditions did not significantly interfere with daily communication. **Dysphagia and Gait Imbalance:** • Incidence: One patient experienced transient impairment of preexisting dysphagia (difficulty swallowing) and mild gait imbalance. • Duration: Both symptoms appeared in the first week after the second FUS-STN and resolved spontaneously by the 3-month follow-up. **Neuropsychological Outcomes**: • Testing: Neuropsychological tests were conducted before and after the second FUS-STN procedure. • Findings: No behavioural or cognitive disturbances were detected. The tests assessed various cognitive domains including attention, memory,

First author, date	Efficacy outcomes	Safety outcomes
	Rigidity (on medication state) Baseline: 3.0 (IQR 2.2 to 3.0) 6 months: 1.0 (IQR 0.2 to 1.7) Change in score baseline vs 6 months: 2.0 (p = .01) **MDS-UPDRS part IV (related to 2nd procedure),** Baseline: 3.5 (IQR 2.2 to 4.0) (before 2nd procedure) 6 months: 1.0 (IQR 1.0 to 2.5) (after second procedure) Change in score baseline vs 6 months: p = .10 **Sub-scores of Dyskinesia** Baseline: Not provided 6 months: 1.0 (IQR 0.2 to 1.0) Change in score baseline vs 6 months: p = .70 **Sub-scores of motor fluctuations** Baseline: 1.5 (IQR 1.0 to 2.7) 6 months: 0.0 (IQR 0.0 to 0.7) Change in score baseline vs 6 months: p = .23 **Dystonia (off medication state)** Baseline: 0.5 (IQR 0.0 to 1.0) 6 months: 0.0 (IQR 0.0 to 0.7) Change in score baseline vs 6 months: p = .47 **Functional disability/activities of daily living (assessed using MDS-UPDRS II)** Baseline: 7.5 (IQR 6.2 to 10.2)	language, executive function, and visuospatial function, as well as behaviour-related issues such as depression, anxiety, and apathy. **Brain MRI Findings**: • Brain MRIs performed after the second FUS-STN treatment showed no radiological complications, confirming the absence of significant brain lesions or other structural issues post-treatment. **Severity of Adverse Events:** • The majority of adverse events were mild, with 9 out of ten adverse events being classified as mild and resolving without long-term consequences. **Severe Case**: • One severe case was reported, which involved hemichorea-hemiballismus (a type of dyskinesia), but it eventually resolved with treatment adjustments.

First author, date	Efficacy outcomes	Safety outcomes
	6 months: 5.5 (IQR 4.2 to 7.5) Change in score baseline vs 6 months: p = .28 **Quality of life (assessed using PDQ39)** Baseline: 7.7 (IQR 4.0 to 13.9) 6 months: 10.5 (IQR 3.7 to 17.6) Change in score baseline vs 6 months: p = .91 **Drug changes LEDD (milligrams)** Baseline: 607.5 (IQR 406.2 to 805.0) 6 months: 552.5 (IQR 150.0 to 881.5) Change in score baseline vs 6 months: p = .52 **Drug changes Levodopa daily dose (milligrams)** Baseline: 312.5 (IQR 218.7 to 387.5) 6 months: 225.0 (IQR 25.0 to 443.7) Change in score baseline vs 6 months: p = .33 **Patient satisfaction at 3 years (assessed using global impression of change questionnaire)** All patients reported improvement after the second procedure. No specific scores provided.	
Armengou-Garcia, 2024, Spain	**MDS-UPDRS motor part III, total score (off medication state):** Baseline: 32.0 (27.0 to 40.2) 1 month: 31.5 (29.2 to 37.8) 3 months: 34.0 (25.2 to 41.5)	**Severe Weakness**: 1 patient (5%) experienced severe weakness in the treated hemibody, which improved with physical therapy and was mild at the 6-month follow-up.

First author, date	Efficacy outcomes	Safety outcomes
	6 months: 3.8 (off-medication treated side) 12 months: 5.0 (off-medication treated side) Change in score baseline vs. 12 months: -12.4, p<0.001 Change in score 6 months vs. 12 months: +1.2, p<0.001 **MDS-UPDRS III scores (for treated side, off medication state):** Baseline: 17.5 (5.0) 1 month: 16.9 (1.7) 3 months: 3.6 (4.1) 6 months: 3.8 (4.0) 12 months: 5.0 (3.7) Change in score baseline vs. 12 months: -12.4, p<0.001 Change in score 6 months vs. 12 months: +1.2, p<0.001 **Tremor (off medication state):** Baseline: 5.2 (2.6) 6 months: 0.5 (0.9) **Tremor (on medication state):**	**Moderate Dyskinesia**: 1 patient (5%) developed moderate dyskinesia, which was resolved by 6 months. **Moderate Confusional State**: 1 patient (5%) had a moderate confusional state, which completely resolved by the 6-month follow-up. **Mild Adverse Events (AEs)**: ○ **Dizziness**: 11 patients (55%) ○ **Headache**: 6 patients (30%) ○ **Nausea**: 2 patients (10%) ○ **Gait Disturbance**: 3 patients (15%) ○ **Mild Weakness**: 2 patients (10%) **Behavioural Changes (Hypomania)**: 6 patients (30%) experienced hypomania, which resolved by 6 months. **Weight Gain**: 7 patients (35%) experienced weight gain, with 1 patient still showing slight weight gain at 6 and 12 months

First author, date	Efficacy outcomes	Safety outcomes
	No significant changes were noted throughout the follow-up. **Bradykinesia (off medication state):** Baseline: 8.8 (2.9) 6 months: 2.9 (3.3) **Bradykinesia (on medication state):** No significant changes were observed throughout the study. **Rigidity (off medication state):** Baseline: 3.5 (1.4) 6 months: 0.5 (0.9) **Rigidity (on medication state):** No significant changes were noted across visits. **MDS-UPDRS III for the untreated side (off-medication state):** No significant worsening was observed.	

First author, date	Efficacy outcomes	Safety outcomes
	MDS-UPDRS III for the untreated side (on-medication state): No significant changes were recorded. **MDS-UPDRS part IV, for levodopa-related motor complications (total score):** No significant changes were recorded. **Sub-scores of Dyskinesia:** Dyskinesia was transient and mild, with one moderate case resolving by 6 months. **Sub-scores of motor fluctuations:** Motor fluctuations did not worsen. **Dystonia (off medication state):** No persistent dystonia reported. **Quality of life (assessed using PDQ39):** Improvement observed, specific values not available.	

First author, date	Efficacy outcomes	Safety outcomes
	Drug changes - LEDD (mg): Baseline: 737.5 (SD 513.8) 1 Month: 648.0 (SD 172.2); 20.2% reduction, mean difference: 146.1 (p < 0.001) 3 Months: 593.7 (SD 471.8); 27.3% reduction, mean difference: 198.6 (p < 0.001) 6 Months: 544.1 (SD 436.6); 24.8% reduction, mean difference: 194.4 (p < 0.001) 12 Months: 562.3 (SD 448.8); 13.1% reduction, mean difference: 158.9 (p = 0.002) **Drug changes - LDD (mg):** Baseline: 483.8 (SD 330.5) 1 Month: 429.5 (SD 126.0); 16.2% reduction, mean difference: 83.8 (p = 0.004) 3 Months: 400.0 (SD 252.7); 23.1% reduction, mean difference: 115.0 (p < 0.001) 6 Months: 368.8 (SD 287.0); 22.3% reduction, mean difference: 115.0 (p < 0.001)	

First author, date	Efficacy outcomes	Safety outcomes
	12 Months: 356.2 (SD 215.9); 5.8% reduction, mean difference: 81.6 (p = 0.017) **Patient satisfaction (assessed using Global Impression of Change questionnaire):** With one exception, all patients reported a subjective impression of improvement in the PGI-C scale at 6 month follow-up.	

Procedure technique

A similar procedure technique and device was used in all studies.

Efficacy

Change in motor features

In a prospective cohort study of 32 patients who had MRgFUS unilateral subthalamotomy for asymmetrical presentation of Parkinson's, change in motor status (assessed with part III of the MDS-UPDRS) for the treated side of the body (contralateral to the subthalamotomy), in the off-medication state (that is, after a minimum 12-hour overnight withdrawal of antiparkinsonian drugs) reported that the mean part III score (ranging from 0 to 44) was statistically significantly improved by 52% from baseline to 3 years (reduced from 19.0 to 8.9, 95% CI 8.7 to 11.6, p< 0.001). The scores did not change statistically significantly from 4 to 6 months to 3 years (from 7.7 to 8.9, 95% CI −2.5 to 0.2, p=0.09). Individual improvement at 3 years was heterogeneous and ranged from 7.2% to 95.7%. The change in the MDS-UPDRS III score for the treated side in the on-medication state (assessed 45 to 60 minutes after the intake of usual medication) improved by 55% from baseline to 3 years (reduced from 13.7 to 5.8, 95% CI 6.3–9.4, p<0.001), and was maintained (from 5.5 at 4 to 6 months to 5.8 at 3 years, 95% CI −1.6 to 0.8, p=0.50).The MDS-UPDRS part III sub-scores for all specific motor features (tremor, dyskinesia and rigidity) for the treated side of the body in both off-medication and on-medication states were improved from baseline to 3 years (p<0.001 for all) and was maintained from 4 to 6 months to 3 years.

The MDS-UPDRS III for the untreated side improved statistically significantly from baseline to 3 years in both the off-medication and on-medication states (increased from 6.6 to 10.1, 95% CI −5.4 to −2.0, p<0.001 and 4.3 to 6.6, 95% CI −4.4 to −0.9, p=0.016), respectively. The total MDS-UPDRS III score was

significantly improved from baseline to 3 years in both the off-medication and on-medication states, from 36.8 to 27.4 (95% CI 6.0 to 11.5, p<0.001) and from 24.7 to 17.7 (95% CI 3.7 to 10.1, p<0.001), respectively. Scores were statistically significantly increased (worsened) at 3 years compared with 4 to 6 months in the off-medication state (from 21.8 to 27.4, 95% CI −8.6 to −2.7, p<0.001) but the increase was not statistically significant for the on-medication state (from 15.4 to 17.7, 95% CI −5.1 to 0.4, p<0.093) (Martinez-Fernandez 2023).

In a pilot study of 10 patients with asymmetric PD and medically-refractory motor features who had unilateral subthalamotomy with MRgFUS targeting the affected side of the body, the mean MDS–UPDRS III score in the treated side reduced by 53% from baseline to 6 months in the off-medication state (16.6 to 7.5) and by 47% in the on-medication state (11.9 to 5.8). All cardinal signs improved, notably tremor and rigidity. The scores in the untreated side did not change in either the off-medication or on-medication state. Total MDS–UPDRS part III score reduced by 26% in the on-medication state and by 36% in the off-medication state (Martinez-Fernandez 2018).

A randomised, sham-controlled trial of 40 patients with refractory PD and asymmetric symptoms (in which 27 patients had unilateral MRgFUS subthalamotomy and 13 had a sham procedure) reported that patients in the MRgFUS group had improvement in contralateral MDS-UPDRS part III scores in the off-medication state compared with the sham group at 4-month follow up. The mean MDS-UPDRS part III score for the more affected side decreased from 19.9 at baseline to 9.9 at 4-month follow up in the MRgFUS group (mean difference 9.8 points; 95% CI 8.6 to 11.1) and from 18.7 to 17.1 in the sham group (mean difference 1.7 points; 95% CI 0.0 to 3.5). The between-group difference was 8.1 points (95% CI 6.0 to 10.3; p<0.001). The sub-scores for all specific motor features (tremor, dyskinesia and rigidity) for the treated side of the body in the off-medication state improved from baseline to 4-month follow up (by 83%, 33%

and 60%). The MDS-UPDRS part III score for the more affected side in the on-medication state at 4-month follow up decreased by 6.4 points (95% CI 5.2 to 7.6) in the MRgFUS group and by 0.1 points (95% CI 0.3 to 0.6) in the sham group (between-group difference was 5.9 points; 95% CI 3.8 to 8.0). Total MDS–UPDRS part III score in the off-medication state reduced by 34% (mean change 15.2; 95% CI 13.5 to 17.0) in MRgFUS group compared with 6% (mean change 2.3; 95% CI−0.2 to 4.8) in the sham group. The between-group difference was 12.9% (95% CI 9.9 to 16.0).

The mean decrease in the score in the MRgFUS group at 12-month follow up was 11.6 points from baseline (95% CI 9.9 to 13.3; 25 patients). Among patients in the unblinded crossover group (controls who had MRgFUS), the mean MDS-UPDRS part III score for the more affected side decreased from 19.5 at baseline to 8.1 (mean difference 11.6 points; 95% CI 8.4 to 14.8; 11 patients) at 4-month follow up and to 9.7 at 12 months (mean difference 8.7 points; 95% CI 4.5 to 12.9; 8 patients) (Martinez-Fernandez 2020). In the sub-study of the same trial with 26 patients, the change in MDS-UPDRS III score from baseline to 4 months showed an improvement of 8.4 points, favouring the active treatment group. A Bayesian analysis indicated strong evidence supporting the effectiveness of the active treatment, with a Bayes Factor (BF+0) of 13.72, further strengthening the conclusion that the active treatment led to significant motor improvement (Guida, 2024).

Another pilot study of 12 patients who had MRgFUS subthalamotomy for early PD (less than 5 years from diagnosis) reported 68% mean improvement in MDS-UPDRS part III motor scores in the off-medication state at 12-month follow up (from 14.5 to 4.0, p=0.002). Sub-scores for motor features improved statistically significantly by 70% for rigidity, 64% for bradykinesia and 90% for tremor (p<0.001, p=0.002, and p<0.001 respectively). In the on-medication state, the treated side showed 69% improvement in part III motor scores (from 9.5 to 2.5,

p=0.001) at 12-month follow up. The total motor MDS-UPDRS part III score also improved statistically significantly by 49% and 43% in both the off-medication states (from 26.5 to 13.0, p=0.002) and on-medication states (from 18.0 to 8.0, p=0.016) (Martinez-Fernandez 2024).

In the prospective open label case-series study of 6 participants, MDS-UPDRS III total score, assessing motor function, showed statistically significant improvements both on and off medication over time. In the on-medication state, the baseline score of 27.0 improved to 12.5 at 6 months, with a mean change of 11.0 points (95% CI, 0.9 to 23.7; p = 0.03). Off medication, the baseline score of 37.5 decreased to 20.5 at 6 months, with a change of 23.0 points (95% CI, 7.0 to 33.7; p = 0.03). For the treated side, off-medication scores improved by 9.5 points (95% CI, 3.2 to 17.7; p = 0.02) at 6 months, and on-medication scores improved by 6.5 points (95% CI, 0.2 to 13.1; p = 0.02), indicating notable motor improvements with and without medication (Martínez-Fernández, 2024).

Another prospective study of 20 people reported that MDS-UPDRS III scores for patients in the off-medication state demonstrate a significant decline in motor function over a 12-month period. Initially, the total score at baseline was 32.0 (ranging from 27.0 to 40.2), which showed a slight decrease to 31.5 at 1 month, but then increased to 34.0 at 3 months, indicating some fluctuations in symptoms. By 6 months, the score dropped significantly to 3.8 for the treated side and further decreased to 5.0 by 12 months, resulting in an overall reduction of 12.4 points from baseline ($p < 0.001$). Additionally, the scores for the treated side also reflected this trend, starting at 17.5 (with a standard deviation of 5.0) at baseline, declining gradually to 16.9 at 1 month, and then showing marked decreases at 3 months (3.6) and 6 months (3.8), before slightly increasing to 5.0 at 12 months. The changes from baseline to 12 months and from 6 months to 12 months were both statistically significant, further highlighting the evolving nature of the patient's motor function over time (Armengou-Garcia, 2024, Spain).

Motor complications

In the prospective cohort study of 32 patients, the total score for motor complications of treatment (MDS-UPDRS part IV) did not change from baseline to 3 years (2.9 to 2.6, 95% CI −1.2 to 1.3, p=0.64). The scores for main motor complications (dyskinesias, motor fluctuations and off-medication dystonia) were similar at baseline and at 3-year follow up (Martinez-Fernandez 2023).

In the pilot study of 10 patients, the total score for motor complications of treatment (MDS-UPDRS part IV) decreased by 45% from baseline to 6 months (4.2 to 1.7) (Martinez-Fernandez 2018).

In the RCT, the total score for motor complications of treatment (MDS-UPDRS part IV) decreased by 40% in the MRgFUS group from 4.0 to mean 1.1 (95% CI 0.0 to 2.1) and in the sham group from 5.1 to −1.2 (95% CI −2.7 to 0.3). The between-group difference was 2.3 (95% CI 0.5 to 4.1). The score for dyskinesia and dystonia did not differ between the MRgFUS and sham groups at 4-month follow up (between-group differences 0.3 points [95% CI −0.3 to 1.0] and 0.4 points [95% CI −0.1 to 1.0]). The between-group difference for motor fluctuations was 1.5 points (95% CI 0.2 to 2.7) (Martinez-Fernandez 2020).

In the pilot study of 12 patients, the total score for motor complications of treatment (MDS-UPDRS part IV) did not change from baseline to 12-month follow up (p=0.408). The scores of main motor complications (dyskinesias, motor fluctuations and off-medication dystonia) were similar at baseline and at 1-year follow up (p=0.392, p=0.102, p=0.275) (Martinez-Fernandez 2024).

The prospective open label case-series study of 6 participants who went through staged bilateral FUS-STN procedures documented that MDS-UPDRS IV scores related to the second procedure show changes in motor function over 6 months. The total score decreased from 3.5 (IQR 2.2–4.0) at baseline to 1.0 (IQR 1.0–2.5) after the procedure, but this change was not statistically significant (p =

0.10). The dyskinesia sub-score at 6 months was 1.0 (IQR 0.2–1.0), with no significant change from baseline (p = 0.70). Motor fluctuations improved from 1.5 (IQR 1.0–2.7) at baseline to 0.0 (IQR 0.0–0.7) at 6 months, but this change was also not significant (p = 0.23). Dystonia scores decreased from 0.5 (IQR 0.0–1.0) to 0.0 (IQR 0.0–0.7), with no significant change (p = 0.47), indicating some improvement in symptoms post-procedure, though not statistically significant (Martínez-Fernández, 2024).

Functional impairment in activities of daily living

In the prospective cohort study of 32 patients, scores for functional impairment in activities of daily living (MDS-UPDRS part II) in the on-medication state did not show statistically significant improvement from baseline to 3 years (from 10.0 to 10.3, 95% CI −1.0 to 3.7, p=0.352) (Martinez-Fernandez 2023).

In the pilot study of 10 patients, scores for functional impairment in activities of daily living (MDS-UPDRS parts I and II) were slightly decreased at 6-month follow up compared with baseline (MDS-UPDRS part I 5.9 to 5.5, MDS–UPDRS part II 7.9 to 6.6) (Martinez-Fernandez 2018).

In the RCT, scores for functional activities of daily living (MDS-UPDRS part II) improved from baseline in the MRgFUS group (mean change 4.1, 95% CI 2.2 to 5.9) but not in the sham group (mean change -1.4, 95% CI −4.0 to 1.2) at 4-month follow up. The between-group difference was 5.5 points (95% CI 2.2 to 8.7) (Martinez-Fernandez 2020).

In the pilot study of 12 patients, non-motor and motor symptoms' impact on daily living activities (MDS-UPDRS parts I and II) improved statistically significantly at 12-month follow up (p=0.023, p=0.022, respectively) (Martinez-Fernandez 2020).

The prospective open-label study of 6 patients reported that, after the second FUS-STN, MDS-UPDRS part I scores decreased from a median of 3.5 (IQR 2.0–

7.2) at baseline (before 2nd procedure) to 3.0 (IQR 0.2–9.5) at 3 months and 2.5 (IQR 1.0–4.0) at 6 months, with no significant change (p = 0.14). In part II, scores dropped from 7.5 (IQR 6.2–10.2) at baseline (before 2nd procedure) to 6.0 (IQR 3.5–7.0) at 3 months and 5.5 (IQR 4.2–7.5) at 6 months, also not significant (p = 0.28). Though, improvements were observed in both parts, they were not statistically significant (Martínez-Fernández, 2024).

Quality of life

In the prospective cohort study of 32 patients, quality-of-life scores (PDQ-39SI) were comparable from baseline to 3-year follow up and were not statistically significantly different (from 17.7 to 16.1, 95% CI −0.8 to 6.6, p=0.10) (Martinez-Fernandez 2023).

In the pilot study of 10 patients, quality-of-life scores (PDQ-39SI) reduced by 19% from baseline to 6-month follow up (12.6 to 10.4) (Martinez-Fernandez 2018).

In the RCT, quality-of-life scores (PDQ-39SI) improved from baseline in the MRgFUS group (mean change 7.4, 95% CI 4.1 to 10.6) at 4-month follow up. The mean change in the sham group was 1.6 (95% CI −3.1 to 6.2). The between-group difference was 5.8 points (95% CI 0.1 to 11.4) (Martinez-Fernandez 2020).

In the pilot study of 12 patients, quality-of-life scores (PDQ-39SI) improved significantly from baseline (11.6 to 6.7, p=0.035) at 12-month follow up (Martinez-Fernandez 2024).

In another open label, prospective study with 6 patients, quality of life (PDQ-39), showed a median score of 7.7 (IQR 4.0–13.9) at baseline (before 2nd procedure), which increased to 10.5 (IQR 3.7–17.6) at the 6-month follow-up. However, this change was not statistically significant, with a p-value of 0.91, indicating that there was no meaningful difference in quality of life over the 6-month period (Martínez-Fernández, 2024).

Medication usage

In the prospective cohort study of 32 patients, drug changes (assessed as LEDD and as levodopa daily dose) at 3-year follow up were comparable with those at baseline (LEDD from 728.2 to 835.4 mg, 95% CI −5.4 to 220.1, p=0.06; levodopa dose 453.9 to 515.7 mg, 95% CI −29.9 to 162.9; p=0.17) (Martinez-Fernandez 2023).

In the pilot study of 10 patients, drug usage (LEDD) reduced by 24% after 6 months compared with baseline (from 732.7 to 564.4 mg) (Martinez-Fernandez 2018).

In the RCT, drug usage (LEDD, mg) from baseline was statistically significantly reduced in the MRgFUS group (mean change -94.5, 95% CI −151.9 to −37.2) at 4-month follow up. The mean change in the sham group was 22.5 (95% CI −60.2 to 106.4). The between-group difference was −117.0 points (95% CI −218.0 to −16.0) (Martinez-Fernandez 2020).

In the pilot study of 12 patients, a non-significant reduction in anti-parkinsonian drug requirements of both LEDD and levodopa dosage was reported (Martinez-Fernandez 2024).

In the open label prospective case series study of 6 patients, LEDD showed a median of 607.5 mg (IQR 406.2–805.0) at baseline, which decreased to 552.5 mg (IQR 150.0–881.5) at the 6-month follow-up; however, this change was not statistically significant (p = 0.52). Similarly, the daily dose of levodopa decreased from a baseline median of 312.5 mg (IQR 218.7–387.5) to 225.0 mg (IQR 25.0–443.7) at 6 months, with no significant difference observed (p = 0.33). These results suggest a trend towards reduced medication doses, but neither change reached statistical significance (Martínez-Fernández, 2024).

In another prospective single centre study with 20 patients, it is observed that, over 12 months, there were significant reductions in LEDD and levodopa. Total LEDD decreased at each follow-up, with changes of 20.2% at 1 month ($p < 0.001$), 27.3% at 3 months ($p < 0.001$), 24.8% at 6 months ($p < 0.001$), and 13.1% at 12 months ($p = 0.002$). For levodopa, the baseline dose dropped significantly, with changes of 16.2% at 1 month ($p = 0.004$), 23.1% at 3 months ($p < 0.001$), 22.3% at 6 months ($p < 0.001$), and 5.8% at 12 months ($p = 0.017$). Both total LEDD and levodopa doses decreased significantly throughout the study (Armengou-Garcia, 2024).

Patient's or clinician's impression of change and patient satisfaction

In the prospective cohort study of 32 patients, 83% (24/29) of patients who completed the self-assessed P-GIC questionnaire 3 years after treatment (ranges from "very much improved" to "very much worsened") reported a better global status than before baseline. 90% (26/29) of patients reported overall satisfaction with the treatment (self-assessed with an adapted satisfaction scale) (Martinez-Fernandez 2023).

In the RCT, clinical improvement (P-GIC) was reported by 85% (23/27) of patients in the MRgFUS group and 15% (2/13) of patients in the sham group (Martinez-Fernandez 2020). In the sub-study of 26 patients within the same trial, except for one patient from the intervention arm (n=18), all others reported a subjective feeling of improvement on the PGI-C scale at the 6-month follow-up (Guida, 2024).

In the pilot study of 10 patients, all patients except one experienced clinical improvement after 6 months according to the P-GIC and neurologists found all patients very much improved as per C-GIC scores (Martinez-Fernandez 2018).

In the pilot study of 12 patients, 92% (11/12) reported a better global status compared with baseline (P-GIC). All patients reported being satisfied with the treatment (Martinez-Fernandez 2024).

Safety

Complications

In the prospective study of 32 patients with Parkinson's who had MRgFUS for subthalamotomy, adverse events were mostly mild including:

- At 4 to 6 month follow up,
  - drug induced dyskinesias in 25% (8/32) of patients
  - speech impairment in 9% (3 patients)
  - weight gain in 9% (3 patients)
  - contralateral limb weakness, facial asymmetry and unsteady gait in 1 patient each.
- At 6-month follow up,
  - off-medication dyskinesia in the treated arm (1 patient, almost resolved by 6 months)
  - on-medication dyskinesia in the treated arm (1 patient, resolved after levodopa dose reduction)
  - subjective speech disturbance (1 patient)
  - anxiety and fatigue (1 patient each) and weight gain (2 patients)
  - transient gait ataxia (related to subthalamotomy, in 6 patients)
  - transient pin-site head pain (related to the head frame, in 6 patients)
  - transient high blood pressure (during the procedure, in 5 patients)
  - transient facial asymmetry (in 1 patient)
  - moderate impulsivity (in 2 patients).
- At 3-year follow up,

- reduced verbal fluency, mild dysarthria and clumsy hand in 1 patient each were reported (Martinez-Fernandez 2023).

In the RCT, reported adverse events in the MRgFUS group included:

- dyskinesia in the off-medication state in 22% (6/27) of patients, which was transient and mostly resolved within 6 months (of these 5 were chorea and 1 was ballism movement)
- new-onset dyskinesia in the on-medication state in 22% (6/27) of patients, which persisted in 2 patients at 12 months
- weakness on the treated side in 19% (5/27) of patients, which persisted in 2 patients at 12 months
- isolated facial asymmetry or weakness in 11% (3/27) of patients, which mostly resolved within 4 months
- speech difficulties in 56% (15/27) of patients, which were mainly transient. These include dysarthria in 7 patients (which persisted in 1 patient at 1-year follow up) and slurred speech in 8 patients
- gait disturbances in 48% (13/27) of patients. These included unsteady gait in 10 patients (which persisted in 1 patient at 1-year follow up) and ataxia in 3 patients
- other events included upper limb dysmetria in 2 patients, impulsive binge eating in 1 patient (which resolved after 2 months), weight gain in 2 patients and somnolence in 1 patient (that resolved after 24 hours)
- perilesional oedema was reported by all patients in the treatment group but resolved by 4 months
- intraprocedural adverse events occurred in both groups but more frequently in the treatment group. These included nausea, emesis, dizziness, head tilting, head discomfort, pin-site head pain, headache, back or neck pain, high blood pressure and fatigue. These events resolved after the procedure. Anxiety (in 6

patients) and right inner ear pain (in 1 patient) were only reported in the treatment group (Martinez-Fernandez 2020)

- The sib-study of 26 patients within the same trial primarily focused on the efficacy of improving motor symptoms and found no adverse motor outcomes or significant neuropsychiatric issues (Guida, 2024).

In the pilot study of 12 patients who had STN-FUS for early PD (less than 5 years from diagnosis):

- 17% (2/12) of patients developed foot dystonia that needed treatment with botulinum toxin
- weight gain was reported in 58% (7/12) of patients and persisted after 12 months. Isolated facial asymmetry was reported in 50% (6/12) patients at different follow-up periods (1 persisted at 12-month follow up)
- transient gait instability was reported in 42% (5/12) of patients and resolved within 2 weeks
- new-onset drug induced dyskinesia on the treated side (3 in upper limb and 1 in lower limb) was reported in 33% (4/12) of patients and persisted in 1 patient at 3 months. Dyskinesia on the treated side (off-medication state) was reported in 1 patient at 3 months
- speech abnormalities (mild slur) were reported in 17% (2/12) of patients and persisted in 1 patient at 12 months
- cheerfulness, hiccups and pericranial hypothesia were reported in 1 patient each (Martinez-Fernandez 2024).

In the prospective open label study of 6 patients, who had a 2nd procedure:

- four out of six patients experienced contralateral dyskinesia within the first week after the second FUS-STN; three had mild dyskinesia (upper limb choreiform movements during levodopa intake), while one patient experienced

severe hemichorea-hemiballismus that significantly interfered with daily activities

- four patients developed speech disturbances post-FUS-STN; three had dysarthria, and one experienced reduced verbal fluency. Gradual improvement was noted; by 6 months, one patient still had mild dysarthria, and another continued to show reduced verbal fluency, but neither significantly affected communication
- one patient had transient worsening of preexisting dysphagia and mild gait imbalance. Symptoms appeared within the first week post-FUS-STN and resolved by the 3-month follow-up.
- neuropsychological testings conducted before and after the second FUS-STN. No behavioral or cognitive disturbances were detected across various cognitive domains and behaviour-related issues
- post-treatment MRIs showed no significant brain lesions or radiological complications
- majority were mild, with nine out of ten adverse events classified as mild and resolving without long-term consequences
- one severe case of hemichorea-hemiballismus was reported (Martinez-Fernandez 2024).

In another prospective, open-label study of 20 patients:

- 1 patient (5%) experienced severe weakness in the treated hemibody, which improved with physical therapy and was mild at the 6-month follow-up
- 1 patient (5%) developed moderate dyskinesia, which resolved by 6 months
- 1 patient (5%) had a moderate confusional state, which completely resolved by the 6-month follow-up.
- Mild Adverse Events (AEs) observed:
  - Dizziness: 11 patients (55%)

- Headache: 6 patients (30%)
- Nausea: 2 patients (10%)
- Gait disturbance: 3 patients (15%)
- Mild weakness: 2 patients (10%)
- 6 patients (30%) experienced hypomania, which resolved by 6 months
- 7 patients (35%) experienced weight gain, with 1 patient still showing slight weight gain at 6 and 12 months (Armengou-Garcia, 2024).

Anecdotal and theoretical adverse events

NICE sought expert advice from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed no anecdotal adverse events.

They listed the following theoretical adverse events:

- stroke
- sensory side effects
- permanent side effects.

Two professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

MRI-guided focused ultrasound subthalamotomy is intended for unilateral treatment in Parkinson's:

- there is limited evidence on MRgFUS for unilateral subthalamotomy with short-term follow up, predominantly for advanced Parkinson's. Patients were young with short duration of symptoms
- there is a small RCT, comparing against sham. Although it was double blinded, all patients and assessors correctly guessed the group assignments,
- studies were mainly done in 1 centre in Spain. These studies were sponsored by the device company.

Ongoing studies:

- NCT03964272: A feasibility study on the safety and preliminary efficacy of bilateral subthalamotomy using the ExAblate transcranial system to treat the cardinal motor features of Parkinson's. Feasibility study (3 enrolled); primary outcome: mean change (from baseline to 6 months) in the motor MDS-UPDRS score, adverse events; Study location: Spain; study completion date: June 2023.
- NCT06584383: Early Focus II- a prospective, multicentre RCT to test safety and effectiveness of unilateral Exablate MR-guided focused ultrasound subthalamotomy in patients with early-stage Parkinson's disease. randomised (ratio 2:1), n=54 patients (36 in Exablate arm versus 18 in control arm and up to 18 patients in a reference arm); primary outcome MDS-UPDRS Part III OFF Medication at 12 months; follow-up 12 to 36 months, study location Spain, study completion date September 2029.
- NCT02246374: ExAblate Transcranial MRgFUS of the Subthalamic Nucleus for Treatment of Parkinson's Disease: A randomised feasibility clinical trial of the management of the medically refractory motor symptoms of advanced idiopathic Parkinson's with unilateral lesioning of the subthalamic nucleus using the ExAblate transcranial system. N=7, crossover assignment; exablate subthalamotomy compared with sham subthalamotomy; primary outcome: incidence and severity of adverse events, mean change in MDS-UPDRS Part

III scores; study completion date December 2023; location US; study status active, not recruiting.

Existing assessments of this procedure

The treatment guidelines on Parkinson's (invasive therapies) by the European Academy of Neurology and the European section of the Movement Disorder Society recommend *'using unilateral MRgFUS of the STN in people with distinctly unilateral PD only within clinical studies or registries due to the limited data on this new treatment'.*

The guidelines task force considered that '*this treatment is new, and only one RCT is available. The results are promising regarding the standard outcomes for advanced PD. The adverse events are frequent, but longer-term sequela are mild and rare. Many key questions, however, remain open regarding this treatment: Long-term data beyond 1 year are lacking. The treatment was applied unilaterally in a highly selected group of people with unilaterally dominant PD. Therefore, preliminary data suggesting that MRgFUS may be cost-effective compared with DBS should be interpreted with caution. The majority of people with advanced PD have bilateral disease, but it is unknown whether MRgFUS subthalamotomy can be safely and efficiently performed bilaterally. Despite initial promising results, currently the treatment cannot be recommended outside clinical studies' (Deuschl G 2022).*

The multidisciplinary consensus paper for safe implementation and standardized practice of MRgHiFUS treatments for functional neurosurgery in Switzerland states that '*good clinical evidence is presently only available for unilateral thalamic lesioning in treating essential tremor or tremor-dominant Parkinson's disease and, to a minor extent, for unilateral subthalamotomy for Parkinson's disease motor features. However, the workgroup unequivocally recommends further exploration and adaptation of MRgHiFUS-based functional lesioning*

interventions and confirms the need for outcome-based evaluation of these approaches based on a unified registry. MRgHiFUS and DBS should be evaluated by experts familiar with both methods, as they are mutually complementing therapy options to be appreciated for their distinct advantages and potential' (Stieglitz LH 2021).

Related NICE guidance

Interventional procedures

- Overview | Unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor | Guidance | NICE IPG617 (June 2018)
- Overview | Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids | Guidance | NICE IPG413 (November 2011)
- Overview | Subthalamotomy for Parkinson's disease | Guidance | NICE IPG65 (June 2004)
- Overview | Deep brain stimulation for Parkinson's disease | Guidance | NICE IPG19 (November 2003)

NICE guidelines

Parkinson's disease in adults, NICE guideline NG71 (July 2017)

Professional societies

- British Society for Stereotactic and Functional Neurosurgery (BSSFN)
- British Society of Interventional Radiology (BSIR)
- British Society of Neurological Surgeons (BSNS)
- Association of British Neurologists (ABN).

Evidence from patients and patient organisations

NICE received no submissions from patient organisations about this procedure.

NICE received no questionnaires from patients who had the procedure (or their carers).

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received no completed submissions.

References

1. Martínez-Fernández R, Rodríguez-Rojas R, Del Álamo M et al. (2018) Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study. Lancet Neurol 17: 54–63.
2. Martínez-Fernández R, Máñez-Miró JU, RodríguezRojas R et al. (2020) Randomized trial of focused ultrasound subthalamotomy for Parkinson's disease. N Engl J Med. 383 (26): 2501-2513.
3. Martinez-Fernandez R, Natera-Villalba E, Manez Miro JU et al. (2023) Prospective long-term follow-up of focused ultrasound unilateral subthalamotomy for Parkinson disease. Neurology. 100, 13: E1395–405. doi: 10.1212/WNL.0000000000206771
4. Fernández RM, Villalba EN, Rodriguez-Rojas R et al. (2024) Unilateral focused ultrasound sub-thalamotomy in early Parkinson's disease: a pilot study. J Neurol Neurosurg Psychiatry. 95, 206-213.
5. Guida, Pasqualina; Martinez-Fernandez, Raul; Manez-Miro, Jorge U; et al. (2024) Social Cognition in Parkinson's Disease after Focused Ultrasound Subthalamotomy: A Controlled Study. Movement disorders: official journal of the Movement Disorder Society; 2024. Social Cognition in Parkinson's Disease after Focused Ultrasound Subthalamotomy: A Controlled Study - Guida - Movement Disorders - Wiley Online Library
6. Martínez-Fernández R, Natera-Villalba E, Rodríguez-Rojas R et al. (2024) Staged Bilateral MRI-Guided Focused Ultrasound Subthalamotomy for Parkinson Disease. JAMA neurology; 81 (6); 638-644.
7. Armengou-Garcia L, Sanchez-Catasus CA, Aviles-Olmos I, Jiménez-Huete A, Montoya-Murillo G, Gorospe A, Martin-Bastida A, Gonzalez-Quarante LH, Guridi J, Rodriguez-Oroz MC. Unilateral Magnetic Resonance-Guided Focused Ultrasound Lesion of the Subthalamic Nucleus in Parkinson's Disease: A Prospective Study. Mov Disord. 2024 Sep 18. doi: 10.1002/mds.30020. Epub ahead of print. PMID: 39295191.

8. Deuschl G, Antonini A, Costa J et al. (2022). European Academy of Neurology/Movement Disorder Society-European Section Guideline on the Treatment of Parkinson's Disease: I. Invasive Therapies. Mov Disord. 37(7):1360-1374.
9. Stieglitz LH, Oertel MF, Accolla EA et al. (2021) Consensus Statement on High-Intensity Focused Ultrasound for Functional Neurosurgery in Switzerland. Frontiers in Neurology, 12, PP 722762

Methods

NICE identified studies and reviews relevant to MRI-guided focused ultrasound subthalamotomy from the medical literature. The following databases were searched between the date they started to 19-08-2024: MEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search:

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that are not available in the published literature.
- Patients with Parkinson’s disease.
- Intervention or test: MRI-guided focused ultrasound for subthalamotomy.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

- If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE ALL (Ovid)	19/08/2024	1946 to August 15, 2024
EMBASE (Ovid)	19/08/2024	1974 to August 16, 2024
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	19/08/2024	Issue 7 of 12, July 2024
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	19/08/2024	Issue 7 of 12, July 2024
International HTA database (INAHTA)	19/08/2024	-

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 Parkinson Disease/ 86952
2 Parkinsonian Disorders/ 9621
3 PD.tw. 203681
4 parkinson*.tw. 153012
5 Tremor/ or Essential Tremor/ 13530
6 Tremor*.tw. 27679
7 Movement Disorders/ 17125
8 ((movement* or motor) adj4 (disord* or diseas* or dysfunct*)).tw. 59971
9 (shaking palsy or shaking palsies).tw. 83
10 (Paralysis adj4 agitans).tw. 204
11 or/1-10 370280
12 Subthalamus/ 282
13 ((Thalamic* adj4 Fasciculus) or (Field adj4 (H1 or H2) adj4 Forel*) or (Forel* adj4 Field adj4 (H1 or H2)) or (Nucleus adj4 "Field H") or (Nucleus adj4 Campi adj4 Forel*) or (Campi adj4 Forel* adj4 Nucleus) or (Forel* adj4 Nucleus adj4 Campi) or (Lenticular adj4 Fasciculus) or (Nucleus adj4 Ansa adj4 Lenticularis) or (Ansa adj4 Lenticularis adj4 Nucleus)).tw. 267
14 Subthalamic Nucleus/ 4937
15 ((Body adj4 Luys) or (Corpus adj4 Luysi) or (Nucleus adj4 Luys)).tw. 49
16 (Subthalamotom* or Subthalam*).tw. 8858
17 or/12-16 9804
18 exp Ultrasonic Therapy/ 14450
19 exp Ultrasonography, Interventional/ 33146
20 Ultrasonic Surgical Procedures/ 464
21 High-Intensity Focused Ultrasound Ablation/ 2368
22 HIFU.tw. 3134
23 ((ultraso* or ultra-so*) adj4 (unilateral or intervention*)).tw. 3291
24 (MRgFUS or MRgHIFU or FUS-STN).tw. 776
25 or/18-24 51458
26 17 and 25 45
27 ((High-intensity or focus*) adj4 subthalam*).tw. 27
28 ((ultraso* or ultra-so*) adj4 subthalam*).tw. 19
29 or/26-28 60
30 11 and 29 57
31 animals/ not humans/ 5215368
32 30 not 31 57
33 limit 32 to english language 54
34 limit 33 to ed=20240403-20240831 3
35 limit 33 to dt=20240403-20240831 4
36 34 or 35 5

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Cummins DD, Bernabei JM, Wang DD. (2024) Focused ultrasound for treatment of movement disorders: A review of non-food and drug administration approved indications. Stereotact Funct Neurosurg; 102:93–108.	Review on FUS for non-FDA approved movement disorders.	Subthalamic nucleus (STN)-FUS for PD gave approximately 50% improvement in PD motor symptoms, with dystonia and mild dyskinesias as possible adverse effects that required medical management.	Review
Jung NY, Chang JW. (2018) Magnetic resonance-guided focused ultrasound in neurosurgery: taking lessons from the past to inform the future. J Korean Med Sci. 33(44): e279.	Review	MRgFUS for subthalomotomy is an emerging procedure and a pilot study found that the mean UPDRS part III scores in the treated hemibody improved by 53% from baseline to 6 months in the off-medication state and by 47% in the on-medication state.	Review
Jorge U. Máñez-Miró, Rafael Rodríguez-Rojas,	Systematic review on	Unilateral subthalamotomy for the treatment of PD	Evidence regarding subthalamotomy

Marta Del Álamo, R. Martínez-Fernández & José A. Obeso (2021) Present and future of subthalamotomy in the management of Parkinson´s disease: a systematic review, Expert Review of Neurotherapeutics, 21:5,533-545,	subthalamotomy for PD	motor features can be considered a viable option in asymmetric patients, particularly with FUS which allows a minimally invasive safe and effective ablation of the STN. Risk of inducing dyskinesia (i.e., hemichorea/ballism) may be strikingly reduced when lesions enlarge dorsally to impinge on pallidothalamic fibres	both with radiofrequency and FUS assessed together.
Lin SJ, Rodriguez-Rojas R, Baumeister TR et al. (2022) Neuroimaging signatures predicting motor improvement to focused ultrasound subthalamotomy in Parkinson's disease. NPJ Parkinsons Dis; 8(1):70. doi: 10.1038/s41531-022-00332-9.	Functional and structural neuroimaging and extensive clinical data from thirty-five PD patients enrolled in a double-blind MRgFUS-subthalamotomy clinical trial were analysed.	findings reveal specific quantitative brain signatures highly predictive of MRgFUS-subthalamotomy responsiveness in PD. The unanticipated weight of a cortical-subcortical-cerebellar subnetwork in defining clinical outcome extends the current biological understanding of the mechanisms associated with clinical benefits.	Assesses brain imaging features.
Maesawa S, Nakatsubo D, Tsugawa T et al. (2021) Techniques, indications, and outcomes in magnetic resonance-guided focused ultrasound	Review	A small pilot study reported that the motor score of the UPDRS improved postoperatively by 53% during on-medication and by 47% during off-medication. A RCT	Review

thalamotomy for tremor. Neurol Med Chir (Tokyo). 15;61(11):629-639.		for subthalamotomy demonstrated promising results.	
Máñez-Miró JU, Rodríguez-Rojas R, Del Álamo M, et al. (2021) Present and future of subthalamotomy in the management of Parkinson´s disease: a systematic review. Expert Rev Neurother. 21(5):533-545.	Systematic review and expert opinion.	Unilateral subthalamotomy for the treatment of PD motor features can be considered a viable option in asymmetric patients, particularly with FUS which allows a minimally invasive safe and effective ablation of the STN. Risk of inducing dyskinesia (hemichorea/ballism) may be strikingly reduced when lesions enlarge dorsally to impinge on pallidothalamic fibres.	evidence regarding subthalamotomy both with radiofrequency and, with FUS assessed.
Martínez-Fernández R, Matarazzo M, Máñez-Miró JU et al. (2021) The role of focused ultrasound in the management of movement disorders: Insights after 5 Years of experience. Mov Disord Clin Pract. 23;8(5):681-687.	review	provides insights into the current evidence as well as a perspective for the potential future applications of FUS ablation in movement disorders, considering experience since 2015.	covers all movement disorders.
Rodriguez-Rojas R, Pineda-Pardo JA, Martinez-Fernandez R et al. (2020) Functional impact of subthalamotomy by magnetic	n=8 patients with unilateral MRgFUS-subthalamotomy hybrid [^{18}F] FDG-PET/MR imaging study	MRgFUS-subthalamotomy induced metabolic alterations in distributed nodes of the motor, associative, and limbic circuits.	effect on brain metabolism.

resonance-guided focused ultrasound in Parkinson's disease: a hybrid PET/MR study of resting-state brain metabolism. Eur J Nucl Med Mol Imaging. 47(2):425-436.		Clinical improvement was associated with reduction in the PD-related covariance pattern expression. This treatment-induced modulation of the metabolic network is likely to mediate the clinical benefit achieved.	
Tian X, Hu R, He P et al. (2023) Efficacy and safety of magnetic resonance-guided focused ultrasound for Parkinson's disease: a systematic review and meta-analysis. Frontiers in Neurology, 14:1301240.	Systematic review and meta-analysis 20 studies involving 258 patients with drug-resistant Parkinson's disease.	MRgFUS offers an effective and relatively safe treatment option for patients with drug-resistant PD-related tremor.	Study includes different ablation targets (VIM, GPI, PTT and STN). There is no sub-group analysis of different ablation targets.
Tzu-Hsiang K, Yu-Hsuan L, Lung C et al. (2023) Magnetic resonance–guided focused ultrasound surgery for Parkinson's disease: A mini-review and comparison between deep brain stimulation. Parkinsonism & Related Disorders Volume 111, June 2023, 105431	Review	The present study reviews the literature on conventional surgical interventions for PD, discusses recent studies on MRgFUS, and the comparison between DBS and MRgFUS for PD. The reviews aims to provide an essential reference for neurologists to select the appropriate treatments for patients with PD.	Review