National Institute for Health and Care Excellence

IP2035 MRI guided focused ultrasound subthalamotomy in Parkinson's disease

IPAC date: 10th October 2024

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1.	Consultee 2 Parkinson's UK	draft recommendations 1.2	Parkinson's UK acknowledges the NICE committee's recommendation that there was not enough research evidence to recommend MRI-guided focused ultrasound subthalamotomy be made available on the NHS outside a research setting.	Thank you for your comments.
2.	Consultee 2 Parkinson's UK	draft recommendations 1.3	We are concerned that the committee has set the bar too high in terms of research methodology for further studies, given the current availability of services in the UK. There are several challenges to conducting a randomised control trial (RCT) for this therapy. The small patient population size makes recruiting sufficient participants for the trial difficult. There are also ethical considerations to be made as an RCT would require 'sham surgery'. We have been advised that none of the focused ultrasound facilities in the UK can currently perform such research, as a vital upgrade is needed to improve image quality, making the procedure safer and more effective. This would limit the ability to hold a multicentre trial in the UK.	Thank you for your comments. Further research is not restricted to RCTs as the numbers will be small. Section 1.3 states that research can also be prospective cohort studies. It has been amended as follows: 'More research, which could be in the form of suitably-powered randomised controlled trials, or prospective cohort studies and safety data from a registry, is needed on: • patient selection, including severity of condition and symptoms • the site of the lesion • the technique used • long-term outcomes • safety outcomes

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			There is also a need for consistency in the assessment of available evidence. For example, the same procedure for essential tremor was recommended for use on the NHS with appropriate clinical governance in place on the basis of a similar quality small-scale randomised control trial ((Elias, W. J., et al (2016). A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. The New England journal of medicine, 375(8), 730–739. https://doi.org/10.1056/NEJMoa1600159)). Although in this case n=76 as opposed to n=32 in the R. Martínez-Fernández et al. 2020 trial, there is a much larger patient population of people with essential tremor. We recommend that NICE encourage the use of small open-label pilot prospective cohorts in the first instance to gather data with which to power clinical trials and see if they can replicate the findings of the Madrid RCT (R. Martínez-Fernández et al. 2023. Prospective Long-term Follow-up of Focused Ultrasound Unilateral Subthalamotomy for Parkinson Disease. Neurology. Volume 100, Number 13.).	Professional experts told the committee that trials are possible when coordinated by a group of experts in this area. The committee considered the comments about consistency of evidence and noted that the evidence for this topic was limited (only from 4 sources- 1 small RCT and 3 prospective studies) with short term follow-up. However, the evidence considered for IPG617 (essential tremor) was from 11 sources and included 1 systematic review, 1 randomised controlled trial (2 publications providing 1- and 2--year follow-up data), 2 non-randomised comparative studies and 6 case series.
3.	Consultee 2 Parkisnon's UK	Why the committee made these recommendations 1.3	We believe that in recommending future research, NICE should make clear that this is a promising area of translational research that may usher in a necessary new treatment for patients with drug-refractory Parkinson's symptoms.	Thank you for your comments. The committee considered your comment but did not make any amendment to 1.3.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
4.	Consultee 2 Parkinson's UK	Why the committee made these recommendations **1.3**	We disagree with the committee that the benefit of the treatment is short term. The trial also demonstrated a sustained improvement in controlling motor symptoms several years post-therapy (R. Martínez-Fernández et al. 2023. Prospective Long-term Follow-up of Focused Ultrasound Unilateral Subthalamotomy for Parkinson Disease. Neurology. Volume 100, Number 13.). It potentially improved quality of life and enabled people with Parkinson's to stay in work for longer. It also offers an additional treatment option, which is particularly valuable for people with advanced Parkinson's, where treatment choices are scarce.	Thank you for your comments. The long-term follow-up study (Martinez-Fernandez 2023) was included in the overview of evidence. 32 patients underwent 3 years follow-up for primary outcome and 7 (patients from the pilot study) included in the long-term follow-up underwent 5 years of follow-up. The committee noted that the risks and side effects with this procedure are high and the follow-up was short. Therefore, they recommended more research with long term outcomes in section 1.2. The committee considered your comments but did not make any change to this section.
5.	Consultee 1 UCL	draft recommendations 1.3 why the committee made these recommendations	*'But the evidence is short-term'* The evidence has 3-years follow up. This is relatively long term for a study in PD.	Thank you for your comments. The committee noted that the risks and side effects with this procedure are high and the follow-up was short. Therefore, they recommended more research with long term outcomes in section 1.2. The committee considered your comments but did not make any change to this section.
6.	Consultee 1 UCL	draft recommendations 1.3 why the committee made these recommendations	*'the benefits of this procedure are unclear'* The patients undergoing this procedure have asymmetric PD symptoms. They are poorly served by current therapies. Medication in sufficient doses to alleviate tremor, slowness and bradykinesia in the more affected side often induces dyskinesia in the less affected side. Subthalamotomy offer this	Thank you for your comments. The committee discussed about the current treatment options available for these patients. They noted that from the very little evidence for this procedure the benefits are unclear. Section 3.5 has been amended to state that 'The procedure is used unilaterally to treat Parkinson's

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			relatively small proportion of PD patients (but still a large number of patients) to enjoy a better quality of life.	disease with asymmetric symptoms and there have been some reports of bilateral use.
7.	Consultee 1 UCL	draft recommendations 1.3 why the committee made these recommendations	*'The evidence is mostly for advanced Parkinson's in people who had not had symptoms for long. They were also younger than most people with Parkinson's having treatment in the NHS. So, it is unclear who might benefit from this procedure'.* If the patients who benefit from this procedure are younger and have not had symptoms for long, it means they will have a reduced quality of life for many decades ahead. It is very clear that this subgroup of patients may benefit most from focused ultrasound subthalamotomy. Just because they do not represent the majority of people with PD, they nevertheless represent an important and substantial number of patients.	Thank you for your comment. The committee noted that the evidence was very limited and only from one centre. Therefore, they recommended more research in section 1.3 to gather more evidence on: • patient selection, including severity of condition and symptoms • the site of the lesion • the technique used • long-term outcomes • safety outcomes.
8.	Consultee 1 UCL	2.3 the procedure	"minimally invasive" is misleading. This procedure creates a lesion in the brain. "incisionless" is a better term	Thank you for your comment. 2.3 has been amended as follows: *MRI-guided focused ultrasound subthalamotomy is an incisionless procedure that aims to treat tremor, slowness and stiffness associated with Parkinson's.*
9.	Consultee 1 UCL	2.3 the procedure	"""some of the symptoms of"" is vague ""tremor, slowness and stiffness associated with"" is more appropriate"	Thank you for your comments. 2.3 has been amended as follows:

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
				MRI-guided focused ultrasound subthalamotomy is an incisionless procedure that aims to treat tremor, slowness and stiffness associated with Parkinson's
10.	Consultee 1 UCL	3.5 committee comments	To improve accuracy, the sentence should read"The procedure is used to treat unilateral symptoms of Parkinson disease in patients with asymmetric symptoms."	Thank you for your comments. The committee considered your comments and amended 3.5 as follows: The procedure is used to treat Parkinson's disease with asymmetric symptoms and there have been some reports of staged bilateral use.
11.	Consultee 1 UCL	3.6 committee comments	But a high incidence of undesirable neurological side effects, which may be permanent, have been reported in the literature. Should read: But a high incidence of mild undesirable side effects, which may be permanent, have been reported in the literature.	Thank you for your comments. The committee considered your comments but did not amend 3.6.
12.	Consultee 1 UCL	unmet need	MRI-guided focused ultrasound subthalamotomy is a non-invasive procedure that may be beneficial to a subgroup of patients 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. Consider replacing "non-invasive" with "incisionless" through the document. Also, the unmet need here is patients who have asymmetric motor symptoms that cannot be managed properly with medication alone. This should be stated clearly.	Thank you for your comments. The text in this section has been amended as follows: 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. The term 'non-invasive' or 'minimally invasive' has been replaced with 'incisionless' in the document.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
13.	Consultee 1 UCL	existing assessments of the procedure	"Long-term data beyond 1 year are lacking". This is no longer correct. 3 year outcome data has been published. 1.Martínez-Fernández, R. et al. Prospective Long-term Follow-up of Focused Ultrasound Unilateral Subthalamotomy for Parkinson Disease. Neurology 100, e1395–e1405 (2023).	Thank you for your comments. This statement is from an existing assessment published by the European Academy of Neurology and the European section of the Movement Disorder Society (Deuschl 2022). The long term follow-up study by (Martinez-Fernandez 2023) is already included in the overview of evidence.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."