National Institute for Health and Care Excellence

IP806/2 Deep brain stimulation for refractory epilepsy in adults

IPAC date: 14 May 2020

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Association of British Neurologists	**1.1**	We acknowledge that there is still limited published evidence of efficacy and risks of using Deep brain Stimulation in refractory epilepsy. In light of the fairly limited published data, it seems reasonable that Anterior thalamic DBS is initially offered by special arrangement, to allow collection of further data regarding safety and efficacy. It is also reasonable that the decision is taken by MDT to discuss if this is the most appropriate treatment for each patient. Regarding stimulation of sites outside the anterior thalamus, the data on hippocampal stimulation appears fairly convincing although there are fewer patients studied for this procedure than anterior thalamus and we would like NICE to consider that this procedure could be used under special arrangements as well. It would be helpful for data collection if there was a nationwide audit tool from	Thank you for your comment. The committee considered this comment but decided not to change the guidance. Section 1.2 of the guidance states that clinicians wishing to do deep brain stimulation of anterior thalamic targets for refractory epilepsy should audit and review clinical outcomes of all patients having the procedure. NICE has identified relevant audit criteria, and a NICE audit tool will be available for use.
2	Consultee 2	**General**	It is acknowledged that there is paucity of evidence for DBS in drug-resistant epilepsy in	Thank you for your comment.

	Society of British Neurological Surgeons		children. However, in view of the small but positive emerging evidence of DBS use in children with drug resistant epilepsy, DBS as an available treatment option needs to be carefully considered in children. I am keen to point out the potential life changing utility of DBS in severe refractory epilepsy in the paediatric setting. Velasco et al demonstrated significant seizure reduction and improvement of patient disability with stimulation of the centromedian thalamic nucleus in the treatment of generalized seizures of Lennox–Gastaut syndrome(1). There is anecdotal evidence of good palliative effect when used in children with FIRES (Febrile Infection-Related Epilepsy Syndrome). The review by Yan et al of DBS for the treatment of drug-resistant epilepsy in childhood found 85% of patients had a reduction in seizure frequency with DBS stimulation in a representative sample size of 40 children(2). The potential impact on the child and family of the ability to utilise DBS to help palliate (if not control) seizures in severe drug-resistant epilepsy in children, when no other surgical intervention is deemed possible, should not be underestimated and can have a positive impact on the overall quality of life for the child/family. The current treatment options in drug-resistant epilepsy in children include ketogenic diet, vagal nerve stimulation, and resective/disconnective epilepsy surgery. All the interventions are subject	Although the evidence for the draft recommendation included children in some studies, the DBS device currently available in the market is only indicated and CE marked for use in adults. The NICE interventional procedures (IP) programme **manual** states that the programme only considers the efficacy and safety of a procedure using devices that are CE marked for the proposed indication. The title of the guidance has been changed to clarify that it only refers to adults, in accordance with the IP process. Velasco et al. (2006) is a small case series (n=13) with patients who had Lennox–Gastaut syndrome. The study has been added to the appendix of the overview. Yan et al. (2019) is included in the main extraction table of the overview.

			to very rigorous, protocol based multidisciplinary assessment for determining eligibility. In view of the fact that Children's epilepsy surgery is commissioned to take place within 4 centres in England (Children's Epilepsy Surgery Service, CESS), with comprehensive processes for patients selection, investigation and MDT decision making, it would be appropriate to allow the implantation of DBS for severe drug resistant epilepsy in children this context. As patient numbers who would fit into this category are small in England, it is unlikely that a RCT based study design for research will be feasible. I think it would be useful in the above context to allow the utilisation of DBS for severe intractable drug resistant epilepsy for children who might have no other method of seizure reduction.	
3	Consultee 3 Company Medtronic	**1.1**	Dear Interventional Procedures Advisory Committee (IPAC). Thank you for the concise review for IPG IP806/2 Deep Brain Stimulation for refractory epilepsy. Section 1.1 notes: "For anterior thalamic targets the evidence is limited in quantity and quality" May the committee reconsider the wording of this statement, for the following reasons: • For patients with focal-onset, drug-resistant epilepsy (DRE), ANT-DBS is supported by Class I evidence from "The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy" (SANTE)	Thank you for your comment. The committee considered this comment but decided not to change the guidance. The SANTE trial (Fisher et al. 2010) is included in the main extraction table of the overview and was considered by the committee before they

			randomised controlled trial. • Within the Cochrane review by Sprengers et al (2017), noted in this IPG's rapid review of literature "Study 6", the study quality assessment indicated the SANTE RCT to be of high quality, with a low risk of bias regarding the study design and a moderate to high quality rating in the overall body of evidence GRADE assessment for the most important patient outcomes. • The RCTs in support of regulatory approval (CE mark or FDA) for different neuromodulation therapies for epilepsy have used similar trial designs on key reported metrics. Assessment of these published studies indicates comparable blinded phase and long-term results. • Since the initial publication of SANTE (Fisher et al, 2010) which was considered during the "IPG416 (January 2010) deep brain stimulation for refractory epilepsy" review, a greater body of long-term evidence is now available , illustrating the long-term results on safety, efficacy and patient-reported outcomes over a seven year period for ANT-DBS. Documented in two peer-reviewed journals (Salanova et al, 2015; Tröster et al,2017) and a conference publication (Sandok E et al, 2016). The long-term data indicate that the effects of ANT-DBS hold over time, with increasing improvements in reduction in seizure frequency rates. In light of the robust clinical evidence supporting ANT-DBS, could the committee consider	reached their conclusion regarding the evidence base. Sprengers et al. (2017) is included in the main extraction table of the overview and this review does identify the SANTE RCT to be of high quality with low risk of bias. Salanova et al. (2015) and Tröster et al. (2017) are included in the main extraction table of the overview and were considered by the committee. Sandok et al. (2016) is conference abstract. The NICE IP Methods Guide states that efficacy data that are unpublished or not peer reviewed are not normally selected for presentation to the committee. This includes conference abstracts,

			upgrading current recommendations from “use in special arrangements” to “use in standard / normal arrangements”? The category for normal arrangements would appear consistent with existing interventional procedure guidance for common neurostimulator therapies E.g. DBS for Parkinson’s Disease [IPG19] and gastroelectrical stimulation for gastroparesis [IPG19]. As the DBS therapy is prescribed and undertaken at specialised teaching hospitals, data collection and audit are commonly undertaken routinely to monitor clinical safety, efficacy and patient related quality of life outcomes.	which are not normally considered adequate to support decisions on efficacy. The committee makes recommendations about the procedure on the basis of the evidence relating to its efficacy and safety.
4	Consultee 3 Company Medtronic	**General**	As noted in the specialist advice questionnaire comments, the procedural safety profile for DBS implant procedures is established across several clinical indications. Over recent years there has been a moderate increase in clinical trials assessing DBS therapy for DRE, with trial size and patient enrolment numbers proportional to the eligible patient population, reflecting the practical real-world challenges’ researchers need to address when designing and running clinical trials for DRE patient groups. May the committee kindly clarify the type of additional evidence required to support a move to “standard / normal arrangements” for example greater patient numbers recruited or longer patient follow up?	Thank you for your comment. The committee considered this comment but decided not to change the guidance. The NICE IP programme **manual** describes how the committee weighs the evidence presented to it.
5	Consultee 3 Company Medtronic	**General**	The patient & medical need for alternative treatment options:	Thank you for your comment.

			While open resective surgery is the standard of care treatment option for DRE (NICE CG137, 2012), a need exists for neuromodulation treatment options: • Open resective surgery may not be an option in some patients due to the invasive procedure and high risk of complications or loss of eloquent brain function. Even when eligible, some patients do not proceed with open resection surgery due to fear of surgery or little awareness (Lim et al, 2013; Anderson et al, 2013). • Of those patients having undergone open resection surgery, a proportion may still experience seizures afterwards requiring further treatment for seizure control. • In SANTE, 25% of patients had previous resective surgery (Fisher et al, 2010) and the clinical benefits of ANT-DBS were observed in this subgroup of patients, providing an effective next line treatment. Considering neuromodulation options for DRE and following the shared decision-making concept, while access to Vagus Nerve Stimulation (VNS) has been established in the NHS, there is a patient & medical need for improved access to ANT-DBS: • A proportion of patients cannot have or will fail to improve seizure outcomes with VNS. In SANTE,	The IP programme does not assess the efficacy and safety of comparator interventions. Lim et al. (2013) and Anderson et al (2013) are not included in the overview because they are not relevant to the procedure. Gooneratne et al (2016) is a review article and has been added to the appendix of the overview.

			a representative DRE patient population, 45% of patients had a prior VNS system that did not provide effective seizure control. Responder rates in the two VNS RCTs ranged from 23-31% (Gooneratne et al, 2016), demonstrating a clinical need to provide a next line treatment for VNS non-responders. • For patients failing to respond to VNS in the absence of DBS, they will have limited treatment alternatives aside from continuing with anti-epileptic drugs (AEDs). Yet success rates with AEDs decline with every attempt of adding another AED: % seizure freedom after 3 attempts of AEDs: 3rd medication: 3.7%, 4th medication: 1% (Brodie et al, 2012) • In SANTE, ANT-DBS has been shown to be an effective option in patients considered VNS failures: Safety and efficacy outcomes for ANT-DBS were similar in patient groups with or without prior VNS (Fisher et al, 2010). • Hospital Episode Statistics (HES) data shows 360 VNS procedures for epilepsy occurred between April 2018 – March 2019 within the NHS in England, 57 % were adults = approximately 200 procedures (Data source - NHS Digital (Harvey Walsh Ltd, Data Sharing Agreement: DARS-NIC-05934-M7V9K). Considering the VNS responder rates (23-31%) - see above. The data highlights a need for treatment alternatives for a defined proportion of patients after experiencing poor VNS response in the NHS. The recent evidence reviews by Gooneratne et al (2016) commented on the role of neuromodulation therapies,	The review compares the outcomes for 3 different neuromodulations techniques (including DBS) without any statistical analysis. The study for DBS (Fisher et al. 2010) in the review is included in main extraction table of the overview. Brodie et al. (2012) is not included in the overview because it is not relevant to the procedure. The median seizure reduction for subjects with or without previous vagus nerve stimulation (VNS) and previous resective surgery is presented in the main extraction table (Study 2) of the overview.

			including DBS, from a UK perspective. The authors state that “ANT-DBS and VNS have a role in patients who are not seizure free after resective surgery while ANT-DBS has a role for patients with VNS failure.”	
6	Consultee 3 Company Medtronic	**General**	Additional Clinical Study information: MORE Registry. ClinicalTrials.gov Identifier: NCT01521754: A Post Market European Registry for Deep Brain Stimulation in Epilepsy, >190 patients enrolled. Results expected in 2021. EPAS, Epilepsy Post Approval Study: ClinicalTrials.gov Identifier: NCT03900468. A prospective, multicentre, open-label, post-market clinical study to further evaluate the long-term safety and effectiveness of DBS therapy for epilepsy on seizure reduction in newly implanted patients through 3 years of follow-up. Expected to commence early 2020.	Thank you for your comment. The committee is pleased to note the existence of the post-market surveillance MORE registry and the EPAS study. This information has been added to the page 46 of the overview. NICE may review the guidance when substantial new evidence is published.
7	Consultee 3 Company Medtronic	**General**	References (Per comments above 1 &2): Anderson CT, Noble E, Mani R, et al. Epilepsy Surgery: Factors That Affect Patient Decision-Making in Choosing or Deferring a Procedure. Epilepsy Research and Treatment. 2013;2013:309284. doi:10.1155/2013/309284.	Anderson et al. (2013) is not included in the overview because it does not present data on the efficacy or safety of the procedure.

			Brodie MJ, Barry SJE, Bamagous GA, Norrie JD,Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 012;78(20):1548-1554.	Brodie et al. (2012) is not included in the overview because it does not present data on the efficacy or safety of the procedure.
			Fisher R, Salanova V, Witt T et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899-908.	Fisher et al. (2010) is included in the main extraction table of the overview.
			Gooneratne IK, Green AL, Dugan P, et al.Comparing neurostimulation technologies in refractory focal-onset epilepsy J Neurol Neurosurg Psychiatry Published Online First: 11 August 2016]doi:10.1136/ jnnp-2016-313297	Gooneratne et al (2016) is a review article and has been added to the appendix of the overview. The review compares the outcomes for 3 different neuromodulations techniques (including DBS) without any statistical analysis.
			Lim ME, Bowen JM, Snead OC 3rd, et al. Access to surgery for paediatric patients with medically refractory epilepsy: a systems analysis. Epilepsy Res. 2013 Dec;107(3):286-96.	Lim et al. (2013) is not included in the overview because it does not present data on the efficacy or safety of the procedure.
			Salanova V, Witt T, Worth R et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84(10):1017-1025.	Salanova et al. (2015) is included in the main extraction table of the overview.
			Sandok E, Sperling M, Gross R, Fisher R. Long	

			Term Outcomes of the SANTE Trial: 7-year Follow-up. 2016 Dec 2-2016. Sprengers M, Vonck K, Carrette E et al (2017) Deep brain and cortical stimulation for epilepsy. Cochrane Database of Systematic Reviews Tröster AI, Meador KJ, Irwin CP, Fisher RS. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure.2017;45:133-141.	This is a conference abstract. The NICE IP Methods Guide states that efficacy data that are unpublished or not peer reviewed are not normally selected for presentation to the committee. This includes conference abstracts, which are not normally considered adequate to support decisions on efficacy but can be included if they present new safety data. Sprengers et al. (2017) is included in the main extraction table of the overview. Tröster et al. (2017) included in the main extraction table of the overview.
8	Consultee 4 Epilepsy Action	**1**	Epilepsy Action supports the draft NICE recommendations on the use of deep brain stimulation (DBS) for refractory epilepsy. In light of some high quality clinical evidence that has shown limited improvements in long-term efficacy of DBS against other comparable neuromodulation procedures, Epilepsy Action would encourage DBS for refractory epilepsy to be added to the NHS tariff.	Thank you for your comment. The Interventional Procedures programme at NICE assesses the safety and efficacy of new interventional procedures. The committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. It does not have a remit to determine the placement of a procedure in the NHS National tariff.
9	Consultee 4 Epilepsy Action	**General**	DBS and refractory epilepsy:	Thank you for your comments about the unmet need for alternative treatment options, and which patients may be most likely to benefit.

			Given the prevalence of refractory epilepsy and associated increased risks of status epilepticus and sudden unexpected death in epilepsy (SUDEP) there is a clear unmet need for alternative treatment options for this patient cohort, including neuromodulation procedures. The complexity and variation within refractory epilepsy similarly calls for as wider variety of safe and efficacious treatment options as possible. This point is echoed by clinicians and people affected by the condition. Deep brain stimulation (DBS) offers an alternative treatment option for some patients with refractory epilepsy. Current evidence suggests that DBS could be particularly beneficial for some refractory epilepsy patients with focal onset seizures or where anterior thalamic (ANT) targets have been identified. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4352097/)	The committee considered this comment but decided not to change the guidance. Salanova et al. (2015) is included in the main extraction table of the overview.
10	Consultee 4 Epilepsy Action	**General**	Seizure frequency: The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial was a double blind randomised controlled trial (RCT) of DBS of anterior thalamic target (ANT DBS). The trial was followed up to the seven year period with long term outcomes reported. The SANTE trial provides high quality clinical evidence of ANT DBS. Similar high quality clinical data for other	The SANTE trial (Fisher et al. 2010) is included in the main extraction table of the overview and was considered by the committee in their deliberations.

			targets is limited. Clinical evidence generated by the SANTE trial demonstrated statistically significant reductions in median seizure frequency in years 1 – 7. The SANTE trial showed a 41% reduction in median seizure frequency at year 1, 69% at year 5 and 75% at year 7. The SANTE trial demonstrated that 18% of participants were seizure free for at least 6 months at any time up to year 7. Trial participants were experiencing at least 6 partial or secondarily generalized seizures per month at baseline and had failed at least 3 antiepileptic drugs (AEDs).	
11	Consultee 4 Epilepsy Action	**General**	Quality of life: When assessed according to the 31-item Quality of Life in Epilepsy Inventory (QOLIE-31) participants in the SANTE trial reported statistically significant improvements from baseline for years 1-7.	The SANTE trial (Fisher et al. 2010) is included in the main extraction table of the overview and was considered by the committee in their deliberations.
12	Consultee 4 Epilepsy Action	**General**	Alternative neuromodulation devices: When assessed against alternative neuromodulation devices such as vagus nerve stimulation (VNS) there is some evidence that	IP guidance assess the efficacy and safety of a procedure, it does not cover comparative effectiveness of alternative procedures. Wong et al. (2019) was identified in the updated literature search and has been added to the appendix of the overview. The review compared

			DBS provides slightly improved long-term efficacy. DBS has been shown to increase in efficacy over time while other comparable devices have been shown to plateau in the longer term. (https://www.ncbi.nlm.nih.gov/pubmed/31062294)	three implantable anti-epileptic devices including DBS, without any statistical analysis. The study for DBS (Fisher et al. 2010) is included in the main extraction table of the overview.
13	Consultee 4 Epilepsy Action	**General**	Adverse events: Due consideration should be given to the potential for adverse events associated with this procedure. The SANTE trial identified some adverse events related to the device including implant site infection and implant site pain. There was also a high incidence of depression (39.1%) and memory impairment (30.9%) reported by trial participants. It is of note that a significant proportion of trial participants who reported depression, 66%, had previously experienced depression and of those who reported memory impairment, none were considered serious. (https://www.ncbi.nlm.nih.gov/pubmed/27516384) These potential adverse and serious adverse events necessitate additional monitoring and this is recognised in the draft NICE recommendations. They should also be considered alongside the quality of life reporting noted above and the risks associated with inadequate seizure control or other potential treatment options.	Thank you for your comments regarding adverse events and in particular the incidence of depression. These adverse events are described in the overview and were considered by the committee. Gooneratne et al (2016) is a review article and has been added to the appendix of the overview.

14	Consultee 4 Epilepsy Action	**1**	Epilepsy Action position on DBS refractory epilepsy: In light of the limited high quality clinical evidence outlined above and the market approval of the procedure from the Food and Drug Admistration (FDA) in the United States (https://www.fda.gov/medical-devices/recently-approved-devices/medtronic-dbs-system-epilepsy-p960009s219), amongst other considerations, Epilepsy Action supports the use of DBS for refractory epilepsy on the terms set out in the draft NICE guidelines. There is also a strong case for the procedure to be made available on an NHS tariff to increase the number of patients who could potentially benefit and to support clinicians who deem the process to be clinically appropriate for patients with refractory epilepsy.	Thank you for your comment. The committee considered this comment but decided not to change the guidance. The Interventional Procedures programme at NICE assesses the safety and efficacy of new interventional procedures. The committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. It does not have a remit to determine the placement of a procedure in the NHS National tariff.
15	Consultee 4 Epilepsy Action	**General**	Additional references (all comments) Sandok: “Long Term Outcomes of the SANTE Trial: 7-year Follow-up”. Abstract presented at the American Epilepsy Society Meeting (2016)	Thank you for your comment. This is a conference abstract. The NICE IP Methods Guide states that efficacy data that are unpublished or not peer reviewed are not normally selected for presentation to the

				committee. This includes conference abstracts, which are not normally considered adequate to support decisions on efficacy although they may be included if they include new safety data.
			https://www.ncbi.nlm.nih.gov/pubmed/20331461	Fisher et al. (2010) is included the main extraction table of the overview.
			https://www.ncbi.nlm.nih.gov/pubmed/25663221	Salanova et al. (2015) is included the main extraction table of the overview.

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