National Institute for Health and Care Excellence

IP778/2 Implanted vagus nerve stimulation for treatment-resistant depression

IPAC date: 19/03/20

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company electroCore	**General**	The vagus nerve can also be stimulated by non-invasive medical devices, and a surgical procedure is not always necessary. Stimulation of the auricular branch of the vagus nerve (aVNS), or the cervical region of the vagus nerve (nVNS) should be considered as viable techniques throughout this guidance document as they are cheaper and a much safer option for stimulating the vagus.	Thank you for your comment. The committee were aware that non-implanted stimulation is also used, but this guidance is not for non-invasive stimulation.
2	Consultee 2 NHS professionals NHS Foundation Trust	**General**	I would raise ethical issues in accepting an invasive surgical procedure on the current evidence for NICE guidelines for treatment resistant depression. The evidenced 'success rate' is not sufficient, in my opinion, to warrant surgery for service users and would suggest further evidence required for invasive practice before NICE guidelines allow research across active patients.	Thank you for your comment. This is NICE Interventional Procedures guidance and not the NICE guideline for treatment resistant depression. Interventional Procedures guidance considers the safety and efficacy of a procedure and not its relative place in the clinical pathway. When NICE guidelines are reviewed, they will take into account the recommendation of the Interventional Procedures guidance. The guidance recommendation states that "evidence on its efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."

3	Consultee 2 NHS professionals NHS Foundation Trust	**General**	Informed consent could be an issue, and I would like reassurance that any surgical procedure is given only under informed consent – understanding all potential side effects and/or potential adverse effects from surgery/complications. This includes not allowing non-consensual treatment on grounds of lack of mental capacity – i.e. this treatment should not be forced on patients under section or under mental capacity act.	Thank you for your comment. For this procedure, as for all interventional procedures, the standard processes for seeking informed patient consent should be followed.
4	Consultee 2 NHS professionals NHS Foundation Trust	**General**	I am concerned about potential conflicts of interest arising from research funding, and would consider informed consent to also include awareness of any financial or other benefits the clinic/clinician/Trust may be in receipt of by being part of a funded trial.	Thank you for your comment. For this procedure, as for all interventional procedures, the standard processes for seeking informed patient consent should be followed. The committee were aware of who had funded the research studies which were considered in the evidence overview.
5	Consultee 2 NHS professionals NHS Foundation Trust	**General**	There is an ethical issue of whether the patient can withdraw consent if the device is operated remotely, and I would want reassurance that the patient is able to turn the device off (i.e. withdraw consent) at any time, and that understanding the timescale for removal of the device (via surgery) is part of informed consent prior to the device being implanted – i.e. the patient needs to know that the device can be turned off immediately on withdrawing consent and then that it can be removed within 2 weeks (for example) via surgery, regardless of whether the patient can be seen as having capacity to withdraw consent.	Thank you for your comment. Text has been added to the 'committee comments' section which states that patients can temporarily disable the device themselves, prior to requesting permanent removal by a clinician.
6	Consultee 3 Company Livanova UK Ltd	**2.2**	On behalf of patients with treatment-resistant depression who have no other alternatives, LivaNova appreciates that NICE have assessed VNS Therapy through this consultation process to define the appropriate pathway by which patients can obtain access VNS Therapy.	Thank you for your comment.

			We have the following suggestions that we feel will add clarity to the document. Section 2.2 states that “When 2 or more conventional treatments do not work, neurostimulation (for example, electroconvulsive therapy, transcranial magnetic stimulation, or transcranial direct current stimulation) may be considered.” This is misleading because it implies that transcranial direct current stimulation (TDCS) has similar arrangements as ECT and TMS. Per NICE guidance 530, TDCS is covered only via special arrangements. For consistency, we recommend eliminating TDCS from the list or adding VNS since, like TDCS, it too is a neuromodulation treatment that is available under special arrangements and is recommended as part of the treatment algorithm. Recommended revision: “When 2 or more conventional treatments do not work, neurostimulation (for example, electroconvulsive therapy, transcranial magnetic stimulation, transcranial direct current stimulation, or vagus nerve stimulation) may be considered.” Reference: R.H. McAllister-Williams , C. Arango , P. Blier , K. Demyttenaere , P. Falkai , P. Gorwood , M. Hopwood , A. Javed , S. Kasper , G.S. Malhi , J.C. Soares , E. Vieta , A.H. Young , A. Papadopoulos , A.J. Rush , The identification, assessment and management of difficult-	Relevant wording in section 2.2 has been changed. McAllister-Williams et al. (2020) has been added to the appendix in the overview.

			to-treat depression: An international consensus statement, Journal of Affective Disorders (2020), doi: https://doi.org/10.1016/j.jad.2020.02.023.	
7	Consultee 3 Company Livnanova UK Ltd	**Overview**	Section 3.1 describes the literature search. However, the rationale for choice of studies included in the evidence review is unclear as it favors the inclusion of smaller case series over larger, longer term studies. For example, three small case studies (Studies 7-9) were included, whereas relevant larger and longer duration studies (e.g., Christmas et al. 2013, Tisi et al. 2014, Müller et al. 2017, and Kumar et al 2019) were not. Failure to present these more relevant and robust studies may have biased the committee's decision. We recommend that, prior to finalizing the document, the committee review these studies.	Thank you for your comment. The committee has considered this comment but decided not to change the guidance. The selection of studies was in line with the interventional procedures programme manual, section 9.2, and Müller et al. 2017 has been added to the appendix in the overview.
8	Consultee 3 Company Livnanova UK Ltd	**3.5**	Section 3.5 states that there is a high incidence of side effects. We recommend revising this statement to note that evidence indicates the therapy is well-tolerated and the incidence of these side effects decreases over time. We note that this is also consistent with the patients with epilepsy who are treated with vagus nerve stimulation. Recommended revision: "The committee noted that there was a high incidence of side effects associated with the procedure including voice change, cough and dyspnoea. However, these side effects decreased with time and the therapy was well-tolerated. The overall side effect burden when VNS is added to conventional therapy is no greater than conventional therapy alone." Reference:	Thank you for your comment. Relevant wording has been added to section 3.5.

			The Safety Summary, specifically Studies 1, 2, and 3, along with specialist advice all describe the decreasing incidence over time. Tolerability of the procedure is described by the specialist advice and in the conclusions of multiple articles cited in the Appendix. The CE Mark and FDA approved product labeling (https://symmetryvns.com/resources.html, Section 2.3.2.1.1 of VNS Therapy® System Depression Physician's Manual) that was updated based on Study 4 demonstrates that "…adding VNS Therapy does not impart a clinically greater side effect burden than what is seen with medication (TAU) treatment alone, and VNS Therapy is tolerable with multiple adjunctive medication regimens." For some reason, the labeling was not captured in the rapid review of the literature, which, as discussed previously has some deficiencies.	
9	Consultee 3 Company Livnanova UK Ltd	**3.6**	4. Section 3.6 is partially misleading because, although patients who responded to ECT did respond better to VNS than conventional therapy, patients who did not respond to ECT also responded better to VNS than conventional therapy. The reference supporting this statement shows that patient response is better when VNS is added to conventional therapy, irrespective of whether or not the patient has responded to ECT (see Figure 4 of Study 4). Recommended revision: "The committee was informed that, among patients who were previously treated with ECT, regardless of their response, there may be a better response to this intervention." Reference:	Thank you for your comment. The committee considered this comment but decided not to change section 3.6. They considered that the evidence from Aaronson et al., 2017 (figure 4) supported the current wording (participants with a history of response to ECT in this study showed a greater response to VNS than participants with a history of non-response to ECT).

			Aaronson AT, Sears P, Ruvuna F et al. (2017) A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: Comparison of response, remission, and suicidality. The American journal of psychiatry 174(7): 640-648	
10	Consultee 3 Company Livnanova UK Ltd	**3.7**	Section 3.7 is misleading because the placebo effect is a well-documented issue for all depression therapies, including those currently funded (e.g., transcranial magnetic stimulation) not just therapy under consideration. Recommended Revision: “The committee noted that, consistent with other therapies for depression, studies on this procedure show a placebo effect.” References: Brunoni AR, Lopes M, Kaptchuk TJ, Fregni F (2009) Placebo Response of Non-Pharmacological and Pharmacological Trials in Major Depression: A Systematic Review and Meta-Analysis. PLoS ONE 4(3): e4824. doi:10.1371/journal.pone.0004824. Gaynes BN, Asher G, Gartlehner G, Hoffman V, Green J, Boland J, Lux L, Weber RP, Randolph C, Bann C, Coker-Schwimmer E, Viswanathan M, Lohr KN. Definition of Treatment-Resistant Depression in the Medicare Population. Technology Assessment Program. Project ID: PSYT0816. (Prepared by RTI—UNC Evidence-Based Practice Center under Contract No. HHSA290201500011I_HHSA29032006T). Rockville, MD: Agency for Healthcare Research and Quality. February 2018. http://www.ahrq.gov/clinic/epcix.htm.	Thank you for your comment. Relevant wording has been added to section 3.7.

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