National Institute for Health and Clinical Excellence

IP1048 - Occipital nerve stimulation for intractable chronic migraine

Consultation Comments table

IPAC date: 17 January 2013

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
1	Consultee 1 Charity The Migraine Trust	**1.3**	Any clinician-headache specialist should be in position to refer and give consent for ONS to intractable chronic migraine patients*. The employment of a multidisciplinary team, may delay the process and reduce the number of patients who need access to ONS. * The guidelines should include a guide to when a patient is consider to suffer intractable migraine; medication-overuse headache should be excluded and triptans, preventives and nerve blocks should be the least to be tried before classifying a patient with intractable chronic migraine and refer for ONS."	Thank you for your comment. The Committee discussed your comment and considered that in the context of this chronic condition, consideration by an MDT would not introduce a clinical significant delay. It is outside the remit of the IP Programme to make recommendations about specific patient selection criteria for an intervention.

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2	Consultee 2 Association of British Neurologists	**1.1**	The ABN welcome the provisional recommendations and wish to highlight the importance of retaining this procedure for the small but significant population of refractory chronic migraine patients who experience ongoing significant migraine related functional impairment. The ABN suggests that an additional operational consideration is added in relation to patient selection for this intervention (See below). The ABN recommends that this intervention be offered to Refractory Chronic Migraine Patients at the present time subsequent to further peer reviewed published data on longer term efficacy. This opinion is based on consensus opinion, headache literature review and the extensive clinical experience of UK Neurologists delivering complex headache assessment and treatment services at Subspecialty headache clinics within the UK. "Refractory or Intractable" Chronic Migraine does not appear to have been clearly defined in the consultation document The ABN has therefore proposed that the following operational selection criteria could be used (based on published literature and expert consensus) to select the small number of patients who may be suitable for ONS:	Thank you for your comment. It is outside the remit of the IP Programme to make recommendations about specific patient selection criteria for an intervention. The Committee noted that a variety of terms are used to describe migraine. Therefore, a general definition of migraine with reference to ICHD-2 classification of migraine was given in 2.1.1.
3	Consultee 2 Association of British Neurologists	**1.1 c.d.**	1. A confirmed diagnosis of Refractory Chronic Migraine as defined by the International Classification of Headache Disorders i.e ICHD-IIR and the Schulmann criteria. The diagnosis needs to be confirmed by a Headache Specialist (Appropriately trained and accredited) and experienced in the treatments available for the management of Chronic Migraine. The ABN suggests use of the published American Headache Society criteria to signpost and define refractory chronic migraine patients (Schulman et al. 2008 & 2009). 2. Those patients to be considered intractable need to have Analgesic Medication Overuse headache excluded or appropriately treated before consideration for ONS and fulfil the following criteria:	Thank you for your comment. See response to comment 2.

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4	Consultee 2 Association of British Neurologists	**1.1 c.d.**	3. The patient should have: - Well documented evidence of failure to benefit significantly from the 4 classes of oral preventatives used routinely in practice for migraine treatment. These agents should have been used at appropriate target dosage and for adequate duration i.e. (a) Beta-blockers; (b) Anticonvulsants - (Topiramate, Sodium valproate, Gabapentin); (c) Tricyclic anti-depressants; (d) Serotoninergic modulators (Methysergide, Pizotifen) if tolerated. - Failed to respond to Acupuncture as recommended by NICE CG 150 - Failed to respond to Cranial Botulinum Toxin as defined by NICE TA 260 - Failed to benefit from intravenous Dihydroergotamine (Nagy et al., 2011) - May have received an occipital nerve block (ONB). Some authorities recommend ONB before proceeding to ONS. It is however recognised that ONB response does not reliably predict positive or negative ONS treatment response.	Thank you for your comment See response to comment 2.

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5	Consultee 2 Association of British Neurologists	**1.1 c.d.**	Based on expert consensus opinion and clinical experience with the procedure, the ABN recommends that centres offering ONS should have a multidisciplinary team to evaluate suitability before ONS implantation occurs. The ABN would propose that the core multidisciplinary team needs to include: - A suitably accredited and experienced Headache Subspecialty Neurologist or Headache specialist with access to all the operational service criteria outlined below. - A Neurosurgeon or Pain Specialist to facilitate implantation & manage devices issues, complications. - A Psychologist/Psychiatrist to optimally screen for and manage relevant issues - A Headache Nurse Specialist or back up team to support, review medication and ONS device issues.	Thank you for your comment. IP guidance is not intended to specify all the details of the procedure, such as the specific selection criteria, rather it is to provide guidance from the evidence and expert opinion. Guidance that a multi-disciplinary team including key specialists should make selection decisions was made in section 1.3. The Committee considered your comments and section 1.3 of the guidance was amended to remove the word ‘functional’ from the sentence.

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6	Consultee 2 Association of British Neurologists	**1.1c.d.**	The ABN recommends that the procedure and outcome should be mandatorily audited. Measures should include outcome variables that robustly document treatment response, device related complication and morbidity rates, and longer term sequential quality of life assessments. Such data should be made available for Speciality Headache service peer review to help guide patient referral choice from Headache clinics with no ONS provision locally. • Schulman, E. A., A. E. Lake, et al. (2008). "Defining refractory migraine and refractory chronic migraine: proposed criteria from the Refractory Headache Special Interest Section of the American Headache Society." Headache: The Journal of Head and Face Pain **48**(6): 778-782 • Schulman, E. A., B. L. Peterlin, et al. (2009). "Defining Refractory Migraine: Results of the RHSIS Survey of American Headache Society Members " Headache **49**(4): 509-518. • Nagy, A. J., S. Gandhi, et al. (2011). "Intravenous dihydroergotamine for inpatient management of refractory primary headaches." Neurology **77**(20): 1827-1832. • Afridi, S. K., K. G. Shields, et al. (2006). "Greater occipital nerve injections in primary headache syndromes - prolonged effects from a single injection." Pain **122**(1-2): 126-129.	Thank you for your comment Section 1.4 of the Guidance includes the recommendations that: 'clinicians should enter details about all patients undergoing ONS for intractable chronic migraine onto the UK Neuromodulation Register [web link] when access to that database is available. They should audit and review clinical outcomes locally and should document and consider their relationship to patient characteristics'. The IP team is informed that the Neuromodulation Society for the UK and Ireland is developing a national register for this procedure. The Team will pass on your comments to those working on the dataset.

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7	Consultee 3 Manufacturer	**1.1**	"1.1 ONS therapy is indicated in those patients who are refractive to multiple preventative classes of medications at maximal doses and therefore are very complex. There Â are a number of studies that report long-term results & adverse events from one year follow-up to 916 cumulative therapy months (Silberstein et al 2012; Serra et al 2012; Brewer et al 2012; Schwedt et al 2007; Ellens Â et al 2011; Magis et al 2011; Saper et al 2010; Fontaine et al 2011; Burns et al 2009). Â The most common adverse event is electrode lead migration due to the flexibility of the neck, however, improvements in technologies, anchoring techniques & implant techniques have reduced this frequency	Thank you for your comment IP guidance is not intended to specify all the details of the procedure, such as the specific selection criteria, rather it is to provide guidance from the evidence and expert opinion. With reference to the papers you have suggested: • Silberstein et al 2012 was included in the addendum report to the systematic review. • Serra et al 2012 is included in the updated search. • Brewer et al 2012 was published after the original search. It has been added to the summary of updated search outcomes. • Schwedt et al 2007 was identified in the original search and is listed in section 6.2.1.1.2 of the systematic review. • Ellens A et al 2011 was excluded because it is a narrative review. • Magis et al 2011 was identified in the original search but was not included because there were limited clinical outcomes reported. • Saper et al 2010 is listed in table 13 of the systematic review. • Fontaine et al 2011 was identified in the original search and is listed in section 6.2.1.1.2 of the review. • Burns et al 2009 was identified in the original search and is listed in section 6.2.1.1.2 of the review. Lead migration is covered in section 2.4.3. of the guidance . The incidence in the more recent Silberstein paper is less than older evidence. Cross reference to comment 25.

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8	Consultee 3 Manufacturer	**1.3**	1.3 It is not necessary to require a ""functional"" neurosurgeon but a neurosurgeon or pain interventionalist to implant the neurostimulator hardware such as those experienced in spinal cord stimulation	Thank you for your comment See response to comment 5
9	Consultee 3 Manufacturer	**1.5**	1.5 The full results of the 157 patient Silberstein study will be submitted for publication at the end of 2012. In addition St Jude Medical will be conducting an additional 100 patient study (RELIEF) to examine long-term ONS therapy safety & efficacy"	Thank you for your comment The IP team is informed that the Silberstein study (reporting 1 year results) is not yet published. There was some uncertainty over the data consistency with respect to information received. As a consequence, the IP process requires that safety data from such a source should not be included.
10	Consultee 4 NHS Professional Chairman British Association for the Study of Headache	**1.1**	The procedure must be undertaken at a last resort. This means patients with Chronic Migraine should have tried a range of preventive treatments including the first line i.e. tricyclic, anticonvulsant topiramate, beta-blockers and 2nd line treatments i.e. sodium valproate, methysergide, gabapentin, pizotifen, Botox, Greater Occipital Nerve block and if applicable non-invasive neurostimulation such as transcranial magnetic stimulation as these generally involes the least risk to the patient. Once all options are exhausted by the headache specialist the patient must be evaluated by a multidisciplinary team comprising of a Neurologist, and Neurosurgeon and when appropriate a psychologist to weigh the pros and cons of the procedure, anticipated success rate and jointly inform patients on the published literature regards to the outcome, adverse events and need for frequent monitoring. Â Clinical experience suggests that patients do not prefer surgical intervention if there is an option of managing the condition with non-invasive treatment. Â There is lack of robust long term data on the outcome and the procedure is very expensive and only available in a few centres.	Thank you for your comment IP guidance is not intended to specify all the details of the procedure, such as the specific selection criteria, rather it is to provide guidance from the evidence and expert opinion.
11	Consultee 1 Charity The Migraine Trust	**2.1.1**	2.1.1 The Migraine Trust encourages the use of the International Headache Classification definitions for migraine. We recommend "Migraine is a severe headache, accompanied by nausea, sensitivity to light and sounds". It should be clear that migraine is not attributed to another disorder such as depression. Sleep disturbances are recognised as common triggers for migraine. Additionally migraine aura should be better defined as unusual sensory symptoms such as visual perception, speech disturbances and motor weakness.	Thank you for your comment The Committee considered your comments and section 2.1 of the guidance was amended.

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12	Consultee 2 Association of British Neurologists	**2.1**	**Section 2 - The Procedure** Based on expert knowledge, literature review and clinical practice specialist headache clinics, the ABN would like to highlight that this section is too simplistic in its description of indications and current treatments or the extent of disability associated with chronic migraine. It lists acute abortive treatments i.e. "painkillers, anti-emetics and triptans" with no recognition of the other commonly initiated interventions (CG 150; TA 260; SIGN 107). It does not consider the importance of excluding analgesic overuse as a maintaining factor for chronic headache, which may obviate the need to proceed to ONS - See our suggested Operational criteria above relating to the typical treatment pathway. It does not emphasise the important fact that Chronic Migraine is experienced in up to 2% of Migraine sufferers and has a significantly greater impact on health related quality of life in both physical and emotional functioning compared with episodic migraine. Chronic migraine has been shown to produce more Healthcare consultations and thus costs (Blumenfield et al. 2011). • Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, Manack A, Goadsby PJ, Lipton (2011) RBDisability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). Cephalalgia. Feb;**31**(3):301-15. • NICE Clinical Guideline 150 (2012) • NICE Technology Assessment 260 (2012) • SIGN Guideline 107 (2008)	Thank you for your comment Section 2.1 is designed to be a succinct summary of the indication and current treatments. The guidance makes reference to other relevant NICE guidance: CG150 and TA 260 in section 2.1.2.

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13	Consultee 3 Manufacturer	**2.1.1**	2.1.1 Migraine is a headache disorder and among the most common of the neurological disorders in the developed world more prevalent than diabetes, epilepsy & asthma combined. Â The International Headache Society (ICHD-2) classifies chronic migraine as a complication of migraine with migraineurs suffering ≥15 headache days per month for ≥3 months without medication overuse. Â Migraine is an idiopathic, recurring headache disorder with attacks lasting 4-72 hours. Â For diagnosis the sufferer must also fulfill two additional criteria (diagnostic criteria C & D for 1.1 Migraine without aura) namely ? 1. Headache has a minimum of two of the following characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity 2. During headache a minimum of one of the following: 1. Nausea and / or vomiting 2. Photophobia and phonophobia 3. Osmophobia In addition, the migraine must not be attributed to another disorder.Despite therapeutic options the migraine of some sufferers becomes chronic & refractory to treatment estimated at 1.3 -2.4% in population-based studies	Thank you for your comment. See response to comment 11.
14	Consultee 5 Pharmaceutical Industry	**2.1**	please note that onabotulinum toxin type A (BOTOXÂ®) is recommended by NICE as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine) TA260	Thank you for your comment. The guidance makes reference to other relevant NICE guidance including TA 260 in section 2.1.2.

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15	Consultee 4 NHS Professional Chairman British Association for the Study of Headache	**2.1**	Chronic Migraine affects 2% of the population. A considerable proportion would respond to first line treatments; the remaining will respond either to Botox or other abovementioned 2nd line treatments. A significant number would have medication overuse and will respond to appropriate intervention with withdrawal. Other intervention like acupuncture may be used to obviate the need for surgical intervention. Those intractable to all available treatments may well be considered for occipital nerve stimulation as a last resort. Â The response is based on clinical experience, the recent NICE guidelines and the BASH guidelines.	Thank you for your comment
16	Consultee 1 Charity The Migraine Trust	**2.2**	The outline should also involve that patient may experience perception of paresthesia (tingling) which is used to optimize placement of the contacts on the lead	Thank you for your comment. The Committee considered your comments and section 2.2.1 of the guidance was amended.
17	Consultee 2 Association of British Neurologists	**2.2**	**Section 2.2 Outline of the Procedure** The procedure used varies between centers. This is work in progress. New techniques are being developed to minimise post procedural lead migration and device failure. The types of stimulator paddles may vary. Some use flat paddles rather than round. Neurosurgeons who routinely perform this procedure might advise about such technical details	Thank you for your comment The Committee considered your comments and section 2.2.1 of the guidance was amended.
18	Consultee 6 NHS Professional Consultant Functional Neurosurgeon	**2.2**	We are increasingly moving towards a single stage operation under general anaesthetic. The correlation between test stimulation findings and long term efficiacy is limited and poor, with many patients reporting significant improvment occuring after months of continued stimulation. Furthermore from a technical point of view, occipital nerve, compared to many other targets that we as functional neurosurgeons operate on,is large and so in expereinced hands is relatively easily reached. Last, but not least, patients find the operation under general anaestheric much more comfortable and easier to tolerate.	Thank you for your comment See response to comment 17.
19	Consultee 3 Manufacturer	**2.2.1**	2.2.1 Dependent on the ONS therapy centre?s protocol the implanting team may decide to implant the total neurostimulation system in one operating session after first confirming the accuracy of the electrode lead position(s) by intraoperative test stimulation	Thank you for your comment See response to comment 17.

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20	Consultee 4 NHS Professional Chairman British Association for the Study of Headache	**2.2**	The procedure appears simple but dependent on the expertise and experience of the operating neurosurgeon. Â Neurosurgeons are best placed to comment on the actual procedure. Ã However, there is added cost for having two procedures requiring admission followed by close post-operative monitoring.	Thank you for your comment See response to comment 17.
21	Consultee 3 Manufacturer	**2.3.1**	"2.3.1 Data has been presented on the 1-year efficacy of the 157 patient study. Â Headache days were significantly reduced by 6.7 (+8.4) days per 28 days in the Intention to Treat group (p<0.001) and by 7.7 (+8.7) days in the Intractable Chronic Migraine group sub-analysis (n=125) (p<0.001) at 1 year Mean baseline MIDAS score in the ITT group fell from 156.6 (+75.3) points to a mean score of 106.7 (+85.4) points (p<0.001). Â For the ICM group MIDAS scores fell by 57.9 (+71.8) points from a baseline score of 169.7 (+70.6) points (p<0.001) The Zung PAD scores reduced, both the total score & pain, mood & behavioural subcomponent scores. The ITT group score significantly reduced 10.3 (+14.8) points from baseline (p<0.001). The ICM group also had a significant reduction of 11.2 (+15.2) 65.4% of the patients reported excellent or good headache relief in the ITT group and 67.9% of patient in the ICM group reported the same. Less than 20% reported poor pain relief in both populations. The ITT group rated mean pain relief of 49.5% (+30.7) & ICM group 50.4% (+30.5) QoL was reported as improved in 68.4% & 69.8% in the ITT & ICM groups respectively 83% & 73% were willing to repeat"	Thank you for your comment The reference quoted is an unpublished paper. The NICE IP Methods Guide highlights that efficacy outcomes from non peer-reviewed studies are not normally presented to the Committee.

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22	Consultee 2 Association of British Neurologists	**2.3**	**Section 2.3 Efficacy** It has been identified that the ONSTIM study was set up initially as a feasibility study and was not powered to determine clinical response. The responder rate was however 39% with optimum stimulation compared with 0% improvement in the persistent medically treatment alone group. This was considered potentially clinically meaningful given this was considered an intractable patient group. Similarly Silberstein and colleagues have recently reported a significant number experiencing a 30% treatment response (Silberstein et al. 2012). The recent NICE TA 260 appraisal for Botulinum Toxin determined that a 30% reduction in such populations was clinically meaningful. A similar 30% reduction in pain has been suggested as a reasonable endpoint by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (Dworkin et al, 2012). Thus in retrospect, the choice of primary endpoint in these trials could be considered over ambitious, particularly as they were originally designed as proof of concept studies only. The ABN recognises the need for further ONS research studies both to provide more robust treatment response data and longer follow-up data. The ABN does believe that access to this interventional treatment for medically intractable/refractory chronic migraine is important, given the fact that clinically significant benefits have been seen. Dworkin RH, Turk DC, Peirce-Sandner S, et al. (2012) Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations**.** Pain.;**153(6):**1148-58	Thank you for your comment With reference to the publications listed in your comment: Silberstein et al 2012 is included in the addendum to the systematic review. The ONSTIM study (Saper et al 2011) is included in table 13 of the systematic review. The Committee considered your comments and section 2.5.2.of the guidance was included which acknowledges that research faces challenges including choice of outcome measures and participant blinding.

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23	Consultee 4 NHS Professional Chairman British Association for the Study of Headache	**2.3**	The three RCTs for ONS in CM reporting a 56% success. ONSTIM was a single blind multicentre study in patients responded to GON injection was in favour of those receiving adjustable stimulation compared to preset stimulation or medical treatment. (Saper et al Cephalalgia, 2011;31:271-85). PRISM was a prospective double-blind multicentre study randomised 1:1 with active or sham stimulation was negative. An important finding from this study was that the sub-group with medication overuse performed worse than those without medication overuse, reinforcing the need for specialist assessment and treatment of medication overuse before ONS (Lipton et al, Cephalalgia;2009:29:30:abstract). Another RCT on 157 patients randomised 1:1 to sham or active stimulation followed up for 3 months showed a reduction of MIDAS and improved quality of life (Silberstein et al,Cephalalgia 2011;31:117 abstract). There is need for a larger double-blind PC study that is followed up for a longer duration due to a delayed therapeutic response to neuromodulation. It is acknowledged that setting such study will be difficult and expensive but in its absence it is difficult to justify ahead of other treatments.	Thank you for your comment With reference to the publications listed in your comment: The ONSTIM study (Saper et al 2011) is included in table 13 of the systematic review. Lipton et al 2009 is included in table 13 of the systematic review. Silberstein et al 2012 is included in the addendum to the systematic review.
24	Consultee 3 Manufacturer	**2.4.1**	"2.4.1 At 1-year follow-up in the open label phase of the 157 RCT patient study 11 infections were recorded.	Thank you for your comment The reference quoted is to an unpublished paper. The NICE IP Methods Guide highlights that efficacy outcomes from non peer-reviewed studies are not normally presented to the Committee. With regard to safety data please see response to comment 9.

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25	Consultee 2 Association of British Neurologists	**2.4**	**Section 2.4 Safety** The ABN would wish to highlight that the adverse events in earlier clinical studies and trials may have been in part due to a learning effect. This especially applies to lead migration. By comparison, the ONS lead migration rates in the earlier ONSTIM study were 24% compared with only 5.9% in the Silberstein et al. later study. Furthermore, the development of newer anchoring techniques and flat or narrow stimulation paddles may further reduce device revision issues. These data further support the ABN view that robust audit of device insertion types and complication rates is needed. It also highlights the importance of a multidisciplinary team not only for pre-insertion assessment but longer term follow up and patient support. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ; ONSTIM Investigators (2011) Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia. **31(3)**:271-85 Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, Reed K, Narouze S, Mogilner A, Goldstein J, Trentman T, Vaisma J, Ordia J, Weber P, Deer T, Levy R, Diaz RL, Washburn SN, Mekhail N (2012) Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia. **32(16)**:1165-79. Abhinav K, Park ND, Prakash SK, Love-Jones S, Patel NK (2012) Novel Use of Narrow Paddle Electrodes for Occipital Nerve Stimulation-Technical Note. Neuromodulation. 2012 Oct 25. doi: 10.1111/j.1525-1403.2012.00524.x. [Epub ahead of print]	Thank you for your comment The IP team is informed that the Neuromodulation Society for the UK and Ireland is developing a national register for this procedure. The Team will pass on your comments to those working on the register. The stated lead migration data being drawn from an unpublished paper cannot be considered by the IP programme. Please see the response to comment 7. With reference to the publications listed in your comment: Saper et al 2010 is listed in table 13 of the systematic review. Silberstein et al 2012 is included in the addendum to the systematic review. Abhinay et al 2012 would not be included because it is a technical note.
26	Consultee 6 NHS Professional Consultant Functional Neurosurgeon	**2.4**	It is important to clarify that not in all instances the operations were performed by sub-specialist functional neurosurgeons, who are arguably more skilled and expereinced in handeling neuro-stimulator devices and equipments than general neurosurgeons	Thank you for your comment

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27	Consultee 4 NHS Professional Chairman British Association for the Study of Headache	**2.4**	The procedure is not without risk with lead infection and lead migration reported in 1 in 7 patients in addition to persistent pain and numbness with skin erosion in 17% cases. There are problems of ineffective device programming. Serious adverse events are rare; however, there is considerable cost attached to the management of the common side effects; requirement of close monitoring of the patient for programming of the device and need for frequent visits due to delayed therapeutic response in majority of patients. This is based on the clinical experience of referring patients for this procedure.	Thank you for your comment With reference to the publications listed in your comment: Silberstein et al (2012) reports a rate of 4% for skin erosion.
28	Consultee 3 Manufacturer	**2.4.2**	2.4.2 There were 8 skin erosions recorded at 1-year follow-up in the 157 RCT patient study.	Thank you for your comment The stated data on skin erosion was reported in an unpublished paper which cannot be considered by the IP programme. Please also see response to comment 9.
29	Consultee 3 Manufacturer	**2.4.3**	2.4.3 There were a total of 29 lead migrations, 1 IPG migration and 7 lead breakages or fractures in the 1-year 157 RCT patient study.	Thank you for your comment The stated data was reported in an unpublished paper which cannot be considered by the IP programme. Please also see response to comment 9.
30	Consultee 3 Manufacturer	**2.4.5**	2.4.5 There were 38 patients reporting persistent pain and/or numbness at the IPG/lead site during the 1-year open label phase of the 157 RCT patient study	Thank you for your comment The stated data was reported in an unpublished paper which cannot be considered by the IP programme. Please also see response to comment 9.
31	Consultee 3 Manufacturer	**2.4.6**	2.4.6 During the 1-year open label phase of the 157 RCT patient study stimulation-related events accounted for 45 cases including 1 case of unintended changes in headache severity, type, or frequency; 17 cases of undesirable changes in stimulation; 21 cases of lack of efficacy or return of symptoms; 1 case of unintended stimulation effects-muscle spasms/cramping; 4 cases of nausea/vomiting; and 1 case of diminished or loss of motor or musculoskeletal control."	Thank you for your comment The stated data was reported in an unpublished paper which cannot be considered by the IP programme. Please also see response to comment 9

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32	Consultee 1 Charity The Migraine Trust	**2.5**	Research in the field is additionally the correct blinding in study designs, a common problem in neuromodulation approaches	Thank you for your comment The Committee comment has been added to section 2.5 of the Guidance.
33	Consultee 2 Association of British Neurologists	**2.5**	**Other Comments - Section 2.5** The ABN views ONS as a new, potentially valuable intervention that should be offered to selected chronic migraine patients who fulfill previously defined intractability - see above (i.e. Refractory Chronic Migraine). In addition to ensure good governance and be clinically and cost effective, ONS should be delivered within the framework of a structured, appropriately trained, knowledgeable multidisciplinary headache service. The ABN recognises that this patient group may not be large but note that they are usually female, of working age, and often otherwise fit and well.	Thank you for your comment The Committee considered your comments and section 2.5.2.of the guidance was included which acknowledges that research faces challenges including choice of outcome measures and participant blinding. This conclusion also underpins the committee recommendation in section 1.
34	Consultee 4 NHS Professional Chairman British Association for the Study of Headache	**2.5**	BASH would advoate that ONS should be considered for intractable chronic migraine patients as a last resort. Â We feel that such numbers would be extremely small. Â To ascertain that patients are chosen carefully, they must be evaluated by a trained headache physician ensuring that further referrals are appropriate. Â In the absence of robust evidence, it is vital that patients are counselled appropriately on the outcome, possible adverse events and the need for long term close monitoring. Â It is important that the patient has the right expectations from the procedure.	Thank you for your comment
35	Consultee 3 Manufacturer	**2.5.2**	2.5.2 Prevention of headache days is clinically relevant for chronic migraineurs especially those that are resistant to medications both acute & prophylactic and alternative therapies hence patients seek treatment such as ONS. Â Patients recruited in the 157 RCT patient study will continue to be followed for safety & efficacy. Â In addition there will shortly begin a further 100 industry sponsored patient study (RELIEF) plus there are additional studies in progress that seek to better clarify clinical efficacy including optimizing patient selection for ONS.	Thank you for your comment

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36	Consultee 3 Manufacturer	**General**	I have been given permission to provide NICE with the 1 year open label phase results of our 157 RCT which is the largest current study in the management of refractory migraine by Occipital Nerve Stimulation The results are currently in preparation for journal submission with an expected publication early New Year (possibly when you publish your Guideline) You may wish to consider these results too for you consultation, in particular, understanding the design of the study. **Evidence for Long-term Safety and Efficacy of Peripheral Nerve Stimulation of the Occipital Nerves for the Management of Chronic Migraine** 52 Week Draft 10 30 2012.doc The PNS document makes the suggestion that perhaps the Saper Study & the Silberstein Study may have an overlap on the basis of centre & investigator choices. I can confirm that the Saper Study and the Silberstein Study are entirely separate. The former was a Medtronic sponsored study and the latter a St. Jude Medical (SJM) Study using the corresponding company's neurostimulation systems. The SJM Study required a neurostimulation trial of all patients where the patient experienced parasthesia to insure correct coverage over the painful migraine areas to optimize the likelihood of therapy success (since all patients after 12 weeks would have active therapy). However, after the trial the Control Group of patients (n=52) were informed that patients may receive sub-threshold stimulation as part of the therapy evaluation. In fact all the Control Group had their neurostimulators switched off during the 12 week randomization complete with provision of "dummy" patient programmers which would not communicate with the pulse generator to change therapy settings despite patient education implicating it would.	Thank you for your comment. The study referred to is not yet published. The NICE IP Methods Guide highlights that efficacy outcomes from non peer-reviewed studies are not normally presented to the Committee. The IP team is informed that the Silberstein study (reporting 1 year results) is not yet published. There was some uncertainty over the data consistency with respect to information received. As a consequence, the IP process requires that safety data from such a source should not be included.
37	Consultee 3 Manufacturer	**General**	The proposed 50% pain reduction as a primary endpoint was eventually determined to be unrealistic and based on the FDA evaluation & decision of neurostimulation per se that a definition of success is a minimum of 50% pain reduction. Subsequent to the study initiation the International Headache Experts determined that a 30% reduction was clinically meaningful & relevant to CHRONIC migraine patients and are since primary endpoints in multiple drug trials and botulinum toxin. The SJM Study reached clinical significance on pain	Thank you for your comment. The study referred to is not yet published. The NICE IP Methods Guide highlights that efficacy outcomes from non peer-reviewed studies are not normally presented to the Committee.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			reduction at 10%, 20% & 30% at the 95% confidence limits and indeed at 40% (p=0.04) but not at 95% with a 10% confidence limit through the study design. Neuromodulation blinding is difficult on the account of parasthesia but this seemed the optimal option and one Control Group patient complained of unpleasant parasthesia despite not receiving therapy. I am welcome to continue dialogue and be helpful at all times.	
38	Consultee 3 Manufacturer	**Notes**	I would like the attached clinical papers to be considered for review for the following consultation as I believe they match the literature search criteria 1 Fontaine et al (2011) 'Treatment of refractory chronic cluster headache by chronic occipital nerve stimulation. 2 Schewdt et al (2007) Occipital nerve stimulation for chronic headache - long term safety and efficacy. 3 Burns, Watkins & Goadsby (2009) Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. 4. Silberstein et al (2012) Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Results from a randomised, multicenter, double blinded, control study. *Cephalalgia* 2012 DOI: 10.1177/033310241246242, 5. Serra et al (2012) Occipital nerve stimulation for chronic migraine: a randomized trial. 6.Magis D et al (2011) Central modulation in cluster headache patients treated with occipital nerve stimulation: an FDG-PET study. 7. Slavin K et al (2006) Trigeminal and occipital peripheral nerve stimulation for craniofacial pain: a single-institution experience and review of the literature. 8. Brewer A et al (2012) Long-Term Outcome in Occipital Nerve Stimulation PatientsWith Medically Intractable Primary Headache Disorders. 9. Wolter T and Kaube H (2012) Neurostimulation for chronic cluster headache. 10. Ellens D and Levy R (2011) Peripheral Neuromodulation for Migraine Headache.	Thank you for your comment With reference to the publications listed in your comment: References 1,2,3 and 7 are already included in the systematic review. Reference 4 is included in the addendum. Reference 5 is included in the update search. Reference 6 was identified in the original search but was not included because the paper primarily concerns results from PET study and there were limited clinical outcomes reported. Reference 8 was published after the original search. This reference has been added to the summary of updated search. References 9 and 12 were identified in the update search but excluded because they are narrative reviews. Reference 10 was identified in the original search but excluded because it is a narrative review. Reference 11 was identified in the original search but excluded because it is mainly a technical rather than clinical study.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
			11. Trentman et al (2008) Stimulation Ranges, Usage Ranges, and Paresthesia Mapping During Occipital Nerve Stimulation. 12. Young and Silberstein (2012) Occipital nerve stimulation for primary headaches. SilbersteinPPTpresentation_FINAL6.16.11.pptx	

"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."