NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT417 Axonics sacral neuromodulation system for bladder control in people with symptoms of overactive bladder

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	16/09/2019	**Manufacturer** Initial questions/requests by email.	When and where will Blok 2019 be published?	Neurourology and Urodynamics, end of 2019
2.		See Appendix 1 for further information submitted by the manufacturer.	Table 2 and 3 appear to be missing from the submission	Not missing just all in table 1 with footnote.
3.	24/09/2019	**Manufacturer** Initial teleconference – questions asked by EAC	Please describe your device and how it is used.	The main innovation with the Axonics device is that it is rechargeable, so can remain in place for much longer. We recommend that patients recharge their device weekly.
4.			Could you explain more about the need for re-programming – how frequently is this needed? How many programs are there? Does a patient need to come into clinic for this?	In the studies, patients had their devices reprogrammed at a scheduled follow-up visit during the first few weeks after implantation. The comparator (InterStim) device offers 7 programs, and relies on

				stimulation being delivered at a constant voltage. The Axonics device only needs one program because the output voltage automatically adjusts over time; it uses current-controlled stimulation which varies according to tissue impedance. See also row 11.
5.			Does available data *quantify* the different *reasons* for explantation of devices? Not only for battery replacement, but due to complications, patient choice etc?	Few devices are replaced due to complications – for InterStim this has been reported as around 5% at 5 years. Note the context - 100% of InterStim devices will need replacing within 4-5 years due to battery life limitation. See also row 11.
6.			To date, what is the longest time that an Axonics device has been in place clinically?	2.5 years (received regulatory approval in 2016).
7.			Have there been any issues with patient compliance with recharging?	No. 100% of treatment responders have been able to recharge their device at their 1 year follow-up.
8.			What are the training requirements?	Surgical training is the same as the comparator. We provide in-person support for every implantation procedure, free of charge.
9.			Could the remote control be activated accidentally? What would the implications be?	This has not been reported to us as a problem. Each remote device is paired to a single patient. The amplitude is increased/reduced by very small increments, and program settings ensure the highest limit is still comfortable. The on/off button is very clearly marked.
10.			Please would you send the instructions for use.	Received by EAC.
11.	24/09/2019	**Manufacturer** Initial teleconference – question asked by NICE	Is there any evidence (technical or anecdotal) that clinical outcomes differ depending on whether people have the 2-stage procedure (including an external trial, as used in clinical practice) or a 1-stage procedure (as used in the published studies)?	Because of cost implications, patients do not usually receive the permanent implant without first undergoing a trial with an external device – patients also value the opportunity to test it before committing. In the published studies a trial period was unnecessary. There are no changes in programming settings (between stages 1 and 2) for 80% patients. Although routinely using a single procedure is expected to be

				more cost-saving, this is not a claim that we are making with this submission. Our proposal is for a 2-stage procedure.
12.	30/09/2019	**Manufacturer** Received further information to follow-up on earlier teleconference.	See rows 4 (programming) and 5 (explantation) above.	Additional information from the manufacturer is saved in Appendix 1.
13.	Sent 9/10/19-23/10/19 Responses received 10/10/19-23/10/19	**Expert advisers** Q&A via email	Can we assume that sacral nerve stimulation (SNS) refers to exactly the same technology as sacral neuromodulation (SNM)? If not, what are the key differences and implications when appraising evidence of effectiveness and/or safety?	We tend to use the titles interchangeably (**KN**) Yes (**NT**) SNS and SNM are usually interchangeable terminology in my experience. (**NF**) I believe the two terms are used interchangeably. The use of anterior sacral nerve root stimulation is different to the technology we are discussing in this evaluation and should not be confused. (**CH**)
14.	Sent 9/10/19-23/10/19 Responses received 10/10/19-23/10/19	**Expert advisers** Q&A via email	Could you please describe a typical profile of people eligible to receive SNM treatment to improve bladder control: a) What would you expect the gender distribution to be? b) What proportion of people from the eligible population is likely to also have other important comorbidities? c) What proportion of people from the eligible population is likely to require a full-body MRI scan within 5 years of implantation? d) Does the specific type of bladder control problem matter? How would you expect effectiveness to differ between subgroups labelled: a. "(Urge) urinary incontinence (UUI)" b. "Urinary frequency (UF)" c. "Overactive bladder (OAB)"?	I only do for faecal incontinence (**KN**) Typical patient is 40, female. Have OAB and UUI and have failed medical therapy. Most would have tried Botox first. Most are female (80%). No difference in co-morbidity distribution to the general population. Low percentage (<10%) would need an MRI in the future. OAB and UF are the same and have higher success than UUI. True dry rates for UUI are probably in the region of 30% in the long term. Improvement rates for UF/OAB is in the region of 70-80% in the long term. (**NT**) a) We tend to see more female patients. OAB generally effect more female population. In regards to female retention, well that is obvious. (**NF**) One of the indications for SNM is refractory overactive bladder and the prevalence is around 15% for both

				males and females (prevalence in women is usually a couple of percent higher – see EPIC, NOBLE and EPI-LUTS studies). Urinary incontinence which may be the driver for second or third line treatments such as SNM is usually 3 x more common in women (when the OAB population is examined). In addition the NOBLE study found that the level of "bother" was higher in women. The other main indication for SNM is non-obstructive retention which is almost exclusively seen in women. Taking all of the above into consideration I think SNM is more likely to be used in females by a ratio of at least 5:1. (**CH**) b) Unable to say (**NF**) c) Unable to say (**NF**) b) and c) – I don't think the literature can answer this – my impression from my practice is b) 30% and c) less than 10% (**CH**) d) OAB tend to get banded together as a group but the list of symptoms describe in the question could sub divide them into 'main' issue the patient experiences and finds more of a problem. All these symptoms can be elevated by SNM to some degree in the right patients. (**NF**) d) These are not mutually exclusive sub groups and rarely if ever encountered in isolation in clinical practice – OAB syndrome comprises urinary urgency often with frequency. Overall the success rates of SNM would be 60-70%. (**CH**)
15.	Sent 9/10/19-23/10/19 Response received 11/10/19-	**Expert advisers** Q&A via email	What are the most important potential study confounders to account for when assessing the effectiveness of SNM for improvement of bladder control?	Objective and subjective definitions and improvement and cure rates differ. (**NT**) The patient's ability to record and give good history of symptoms. The ability to use patient controller appropriately. (**NF**)

	28/10/19			Gender, Age, BMI, Neurological disease, baseline symptom severity, proportion of patients with urinary incontinence, faecal incontinence, concomitant medications. (**CH**)
16.	Sent 9/10/19-23/10/19 Responses received 11/10/19-28/10/19	**Expert advisers** Q&A via email	When people with symptoms of overactive bladder (OAB) undergo treatment using an SNM device in the UK NHS, is the permanent implant **always** preceded by a test period (using an external stimulator) **in all patients**? If not, what would be the circumstances or reasons?	Yes, it should be. In a new patient, I cannot see a reason why one would proceed directly to permanent implantation without a test. (**NT**) We always have a trial of SNM or a Precautious Nerve Evaluation (PNE). Occasionally if this is equivocal we main attempt a 2 stage trial of SNM using a permanent lead with an external battery. (**NF**) Yes – in my practice always a test phase as 30-40% will not respond. The devices are expensive so I believe a test phase should be mandatory. (**CH**)
17.	Sent 9/10/19-23/10/19 Responses received 10/10/19-28/10/19	**Expert advisers** Q&A via email	When implanting a permanent SNM IPG device (Implantable Pulse Generator), is the procedure normally carried out as day case, or inpatient?	Day case (**KN**) Day case (**NT**) Day case is the norm. (**NF**) Day case (**CH**)
18.	Sent 9/10/19-23/10/19 Responses received 10/10/19-28/10/19	**Expert advisers** Q&A via email	a) How much influence would you expect surgical implant technique and/or surgical equipment (eg use of curved stylets) to affect optimal lead placement and treatment response rates/therapeutic outcomes? b) How likely is it that this could account for differences in reported effectiveness between studies carried out at different sites/nations?	Curved stylet improves optimal lead placement perhaps increasing success rate by 10%. (**CH**) a) Very operator dependent. The placement of wire through the foramena – level, depth and angle are all important (**KN**) Little influence on surgical technique – it is a straightforward procedure with small learning curve. Have not seen any evidence or observed any anecdotal evidence to say curved stylet beneficial. Likely differences due to patient selection and definition of improvement/cure. (**NT**) To date we have not found a major difference in the stylets when tried them. The placement of the lead

				needs to be accurate to gain best results. (**NF**) b) Very – also infection rate varies dependent on how fastidious the surgeon is (**KN**) Couldn't say without a review of lead placement and results being audited. (**NF**)
19.	Sent 9/10/19-23/10/19 Responses received 11/10/19-28/10/19	**Expert advisers** Q&A via email	When people with symptoms of OAB have an SNM device removed because of limited battery life: a) Do they usually choose to have the device replaced? Why/why not? b) Is the replacement device implanted during the same procedure as the removal?	All those that present will have device replaced with a new IPG. There may be some patients whose symptom control tailed off and they have not re-attended for device reprogramming or IPG replacement but I think these numbers are small. (**NT**) a) Yes generally they have a replacement battery fitted. (**NF**) Yes most have it replaced – more than 90%. (**CH**) b) Yes, we swap the old for the new during the procedure. (**NF**) It is implanted at the same time as removal of the old battery but the lead is usually left in position. (**CH**)
20.	Sent 9/10/19-23/10/19 Responses received 11/10/19-28/10/19	**Expert advisers** Q&A via email	Are you aware of any high-quality published evidence specifically relating to use of the Axonics SNM device in people with symptoms of OAB, other than that produced as a result of: • the ARTISAN-SNM study (McCrery, Lane et al.) • the RELAX-OAB study (Blok, van Kerrebroek, de Wachter, et al.)? If yes, please provide the full reference(s).	No (**NT**) No, currently I am unaware of any independent date to battery life and efficacy of the device. (**NF**) No (**CH**)
21.	Sent 9/10/19-23/10/19 Responses received 10/10/19-	**Expert advisers** Q&A via email	If a person with symptoms of OAB had an Axonics SNM device implanted and subsequently required an MRI scan: a) What is your opinion of the likelihood of device-related imaging artefacts proving	a/b) Any metal device can cause a scatter or obscure an area (**KN**) Would need radiologist to comment on this. (**NT**) a) I guess it depends on the location the MRI is

	28/10/19		problematic? b) Could device positioning obscure details in the image that are important in the diagnosis/treatment of other conditions? c) Do you have real-world experience of people undergoing MRI scans whilst an Axonics device is in situ?	targeting. (**NF**) I do not have the expertise to answer these questions accurately – perhaps a radiologists opinion would be useful. (**CH**) b) This is possible (**NF**) The device itself is unlikely to obscure the relevant areas to be examined with MRI. (**CH**) c) No (**KN**) No (**NT**) No, to date none of our patients with Axonics devices have had MRI scans that I am aware of. (**NF**) I have no experience of the axonics system (**CH**)
22.	Sent 9/10/19-23/10/19 Responses received 10/10/19-28/10/19	**Expert advisers** Q&A via email	If you have experience of managing symptoms of OAB using the Axonics SNM device, how does it compare to other (non-rechargeable) devices with respect to: a) Differences in the number/frequency of outpatient appointments required specifically for the purpose of reprogramming the device? b) Differences in the number/frequency of device replacements carried out specifically because of adverse experiences such as wound infection, discomfort or pain?	Only do faecal (**KN**) Nil experience (**NT**) No experience. (**CH**) a) We have only just started to use the device so too early to say. (**NF**) b) No adverse issue to date requiring intervention, however only been implanting since June and a small number. (**NF**)
23.	Sent 9/10/19-23/10/19 Responses received 10/10/19-28/10/19	**Expert advisers** Q&A via email	According to the Axonics device manufacturer's instructions for use, caution is advised when using in specific populations in whom safety and effectiveness has not been established: • pregnant women • patients under the age of 16 • patients with neurological disease origins (such as multiple sclerosis or diabetes)	a) I would not for a pregnant woman. I would advise women who have an implant and become pregnant to turn off the device. I have implanted an SNS (Medtronic) in children with overactive bladder and had good results. I would consider in neurological patients if they had relevant symptoms and had a good response with a temporary wire. (**KN**) Nil, currently SNS not recommended in these situations and would not change due to Axonics

			• bilateral stimulation. a) How likely is it that you would consider implanting the device in any of these populations? b) What key factors would influence your decision?	device. (**NT**) Unlikely. Not worth the risk to patient during pregnancy. Do not operate on under 16's at this hospital. Neurological conditions such as MS are generally not seen to benefit over the long period in this treatment. Diabetes would not be an issue. Never under taken bilateral stimulation to date. (**NF**) Moderately likely to use SNS in those with common neurological disease especially diabetes. Rarely use in children and never if women are pregnant – I advise women who become pregnant to turn off their stimulators until they have delivered. (**CH**) b) Influencing factors include – literature, peer experiences, manufactures advice. (**NF**)
24.	Sent 9/10/19-23/10/19 Responses received 10/10/19-28/10/19	**Expert advisers** Q&A via email	a) What is the likelihood of buttons on the Axonics Patient Remote Control being pressed unintentionally? b) What might be the implications of accidental activation/deactivation of wireless remote control functions?	Not had any patients do this. (**KN**) Depends on where they keep it. Accidental deactivation would lead to loss of symptom control. Accidental activation may lead to recurrent symptoms of why the patient deactivated the device, such as leg pain. (**NT**) No experience with Axonics system. (**CH**) a) This can happen. Education of the patient on their patient controller is essential. (**NF**) b) Again this can happen but the patient needs to be educated enough to spot and trouble shoot issues like this. (**NF**)
25.	Sent 9/10/19-23/10/19 Responses received 11/10/19-28/10/19	**Expert advisers** Q&A via email	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	There is no real world data on longevity of device, the data is extrapolated and therefore used with caution. I do not know enough about batteries but I am aware there is a degradation over time. (**NT**)

26.	Sent 23/10/19 Response received 23/10/19	**Expert adviser (NF only)** Q&A via email	Please describe your level of experience with the technology, for example: a) Are you familiar with the technology? Have you used it? b) Are you currently using it? c) Have you been involved in any research or development on this technology? d) Do you know how widely used this technology is in the NHS?	A) I have been involved with the treatment of OAB through Sacral Neuromodulation (SNM) for approx. 18 years. This has been through Theatre, Clinic and as operator. (**NF**) B) In regards to Axonics device we have been implanting the permanent device since June. (**NF**) C) No. (**NF**) D) The use of SNM across both urological and Colorectal has been option for 20+ years and 15 approx respectively. The technology is limited to specific sites. We receive referrals for Urological patients for consideration for SNM from across the North West. (**NF**)
27.	Sent 22/10/19-23/10/19 Responses received 27/10/19-28/10/19	**Expert advisers** Q&A via email	Marcelissen et al. (2018) describe the usual options for managing overactive bladder syndrome as: • First-line: behavioural (eg bladder training) • Second-line: pharmacotherapy • Third-line: surgical procedures (such as augmentation cystoplasty or urinary diversion), or minimally-invasive therapies (botox, percutaneous tibial nerve stimulation – PTNS, or SNM) Does this accurately reflect the treatment pathway and options in the NHS? If not, how does it differ?	In part yes. I would say that augmentation and urinary diversion are arguably in a Fourth-line of treatments as they are more invasive and life changing surgical procedures. (**NF**) Yes – v accurate and representative of UK NHS practice. (**CH**)
28.	Sent 22/10/19-23/10/19 Responses received 27/10/19-28/10/19	**Expert advisers** Q&A via email	SNM is recommended for patients whose condition (urge urinary incontinence) is refractory (after conservative treatment has failed). a) Is it likely that people who fall into this category would still be taking concomitant medication to treat the condition?	These patients have usually failed medications therefore almost always do not continue to take them. However studies reporting SNM success should detail the numbers taking and types of medications. (**CH**) a) it is possible but most people who have failed that treatment usually stop the medication due to side effect verse successfulness of it. (**NF**)

			b) How might this impact on study outcomes?	b) if they have failed then the impact on a trial will be limited at best. At worse it maybe an adjuvant treatment to the SNM going forward to further improve result potentially. (**NF**)
29.	Sent 22/10/19-23/10/19 Responses received 27/10/19-28/10/19	**Expert advisers** Q&A via email	Is the Medtronic Interstim system the only alternative SNM device for treatment of OAB that is currently commercially available in the UK?	That I am aware of. The other alternatives are PTNS in nature. (**NF**) Yes to my knowledge. (**CH**) As far as I am aware (**KN**)
30.	Sent 22/10/19-23/10/19 Responses received 27/10/19-28/10/19	**Expert advisers** Q&A via email	The Axonics IPG has regulatory approval for implantation up to (and beyond) 15 years. a) Are there are likely to be any new adverse events, or greater risk of AEs, from this longer term implantation (compared with existing non-rechargeable devices)? *If yes, please describe.* b) Is tolerability likely to change over the long term? *How?*	a) Not that I am aware of at this time. (**NF**) None that I can think of… (**CH**) Not that I am aware. There may be issues with long term implantation of a lithium device but I am not aware of any. (**KN**) b) Some people will change their mind on the treatment like with another type of treatment, but to date most patient that are receiving benefit from a SNM device tolerate it well. (**NF**) No I don't think so. (**CH**) No (**KN**)
31.	Sent 22/10/19-23/10/19 Responses received 27/10/19-28/10/19	**Expert advisers** Q&A via email	a) When devices are replaced, are the leads checked? b) Do the leads get routinely replaced at all? *If yes, how often?*	Yes in my practice I check the lead responses and the leads are most often not replaced. (**CH**) a) Not at time of surgery generally, but beforehand at clinic where would be listed for battery change. (**NF**) Yes – before attaching a new battery the lead is checked for fracture and whether still working (**KN**) c) Leads are occasionally replaced due to damage from fall etc… (**NF**) Get replaced 1 in 3 (**KN**)

32.	Sent 22/10/19-23/10/19 Responses received 27/10/19-28/10/19	**Expert advisers** Q&A via email	Is lead migration/dislodgement or failure likely to only occur immediately after implantation (within 3 months), OR is it just as likely to occur at any point over the device lifetime?	No obviously time scale to lead damage and/or replacements of leads noted at this site. (**NF**) Any point in time in my opinion. (**CH**) Anecdotally – I would say it can happen at anytime but more likely early on (**KN**)
33.	Sent 22/10/19-23/10/19 Responses received 27/10/19-28/10/19	**Expert advisers** Q&A via email	Once the Axonics IPG is implanted, would there be any further monitoring of patients in the long-term (for example, annual check-up with GP)?	We would see them annually in the Urology OPD to check on function and troubles shoot any patient issues. This is how we have dealt with Medtronic patients, however may review given 15yr potential battery life of Axonics. (**NF**) No extra monitoring needed. (**CH**) No – we have an open access policy for patients to return to our unit to a nurse led clinic if the device stops working or the patient needs more advice (**KN**)
34.	Sent 22/10/19-23/10/19 Responses received 27/10/19-28/10/19	**Expert advisers** Q&A via email	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	Not at this time (**NF**) No (**CH**)

Appendix 1.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from questions 1-2:

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Additional 1.pdf

File attachments/additional information from questions 4,5,12:

20190930
Additional 2.pdf